National Institute for Health and Care Excellence

Final

Post-traumatic stress disorder

[F] Evidence reviews for pharmacological interventions for the prevention and treatment of PTSD in adults

NICE guideline NG116

Evidence reviews

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Final

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Pharmacological interventions for PTSD in adults

This evidence report contains information on 2 reviews relating to the treatment of PTSD.

- Review question 4.1 For adults at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?
- Review question 4.2 For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?

Review question For adults at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?

Introduction

PTSD is a potentially debilitating condition. Secondary prevention (intervention following exposure to a traumatic event) is an area of potential clinical and economic benefit. Pharmacological interventions may be beneficial for the secondary prevention of PTSD symptoms.

No drugs are currently licenced in the UK for the secondary prevention of PTSD. Two selective serotonin reuptake inhibitors (SSRIs), paroxetine and sertraline, are currently licenced for the treatment of PTSD in adults.

Pharmacological interventions will be considered as classes of drugs (SSRIs, anticonvulsants, benzodiazepines and other drugs) and form subsections below.

Evidence for tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), other antidepressant drugs, antipsychotics and anxiolytics was also searched for but none was found.

Summary of the protocol (PICO table)

Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: PICO table for review of pharmacological interventions versus comparator treatments for PTSD prevention in adults

Population	Adults at risk of PTSD (defined in accordance with DSM as exposure to actual or threatened death, serious injury or sexual violation) This population includes people with a diagnosis of acute stress disorder/acute stress reaction (according to DSM, ICD or similar criteria), people with clinically important PTSD symptoms within a month of the traumatic event, and people with subthreshold symptoms
Intervention	• SSRIs: o fluoxetine o paroxetine o sertraline • TCAs: o amitriptyline o imipramine • MAOIs: o brofaromine o phenelzine • SNRIs: o venlafaxine • Other antidepressant drugs: o mirtazapine o nefazodone

	• Anticonvulsants o carbamazepine o divalproex o lamotrigine o tiagabine o topiramate • Antipsychotics o olanzapine o risperidone • Anxiolytics: o buspirone • Benzodiazepines o alprazolam o clonazepam o diazepam o lorazepam • Other drugs: o clonidine o cortisol o d-cycloserine o ketamine o MDMA o neuropeptide-Y o oxytocin o prazosin o propranolol
Comparison	• Any other intervention • Placebo
Outcome	**Critical outcomes:** • Efficacy (PTSD symptoms/diagnosis) • Acceptability/tolerability of the intervention (discontinuation for any reason and discontinuation due to adverse events used as a proxy) **Important outcomes:** • Dissociative symptoms • Personal/social/occupational functioning (including global functioning/functional impairment) • Sleeping difficulties • Quality of life • Symptoms of a coexisting condition (including anxiety and depression)

For full details see review protocol in Appendix A.

Methods and processes

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 and 2018 conflicts of interests policies.

Clinical evidence

Selective serotonin reuptake inhibitors (SSRIs): clinical evidence

Included studies

Eight studies of SSRIs for the prevention of PTSD in adults were identified for full-text review. Of these 8 studies, 1 RCT (N=31) was included in a single comparison for SSRIs (Suliman 2015). This RCT compared escitalopram with placebo for the early prevention (intervention initiated within 1 month of traumatic event) of PTSD in adults.

Excluded studies

Seven studies were reviewed at full text and excluded from this review. Reasons for exclusion included non-randomised group assignment, small sample size (N<10 per arm), or the paper was a systematic review with no new useable data and any meta-analysis results not appropriate to extract.

Studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of the included study and evidence from this study is summarised in the clinical GRADE evidence profile below (Table 3).

See also the study selection flow chart in Appendix C, forest plots in Appendix E and study evidence tables in Appendix D.

Table 2: Summary of included studies: SSRIs for early prevention (<1 month)

Comparison	Escitalopram versus placebo
Total no. of studies (N randomised)	1 (31)
Study ID	Suliman 2015
Country	South Africa
Diagnostic status	Clinically important PTSD symptoms (scoring above a threshold on validated scale)
Mean age (range)	29.5 (range NR)
Sex (% female)	34
Ethnicity (% BME)	100
Coexisting conditions	Depression (34%); other anxiety disorders (21%); alcohol dependence or abuse (17%); antisocial personality disorder (3%)
Mean months since traumatic event	NR (≤1 month)
Type of traumatic event	Mixed: Physical or sexual assault (69%); other, including motor vehicle accident or witnessing event (31%)
Single or multiple incident index trauma	Single
Lifetime experience of trauma	NR
Intervention details	Escitalopram, 10-20mg/day
Intervention format	Oral
Actual intervention intensity	NR
Comparator	Placebo
Intervention length (weeks)	24

Comparison	Escitalopram versus placebo
Note. None	

BME – Black and minority ethnic; NR-Not reported; PTSD-Post-traumatic stress disorder; SSRI – Selective serotonin reuptake inhibitors.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review (SSRIs for the prevention of PTSD in adults) are presented in Table 3.

Table 3: Summary clinical evidence profile: Escitalopram versus placebo for the early prevention (<1 month) of PTSD in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Escitalopram			
PTSD symptomatology clinician-rated CAPS change score Follow-up: mean 24 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.9 standard deviations higher (0.12 to 1.68 higher)		29 (1 study)	very low[1,2,3]
Depression symptoms MADRS change score Follow-up: mean 24 weeks		The mean depression symptoms in the intervention groups was 0.5 standard deviations higher (0.25 lower to 1.25 higher)		29 (1 study)	very low[1,3,4]
Functional impairment SDS change score Follow-up: mean 24 weeks		The mean functional impairment in the intervention groups was 0.49 standard deviations higher (0.26 lower to 1.24 higher)		29 (1 study)	very low[3,4,5]
Discontinuation due to any reason (including adverse events) - Clinically important PTSD symptoms at baseline Number of participants lost to follow-up for any reason Follow-up: mean 24 weeks	59 per 1000	84 per 1000 (6 to 1000)	RR 1.42 (0.1 to 20.49)	29 (1 study)	very low[5,6]

CI, Confidence Interval; CAPS, Clinician Administered PTSD Scale; PTSD, Post-traumatic stress disorder; SDS, Sheehan Disability Scale, RR, Risk ratio.

[1] *Significant group difference at baseline and non-blind outcome assessment*
[2] *OIS not met (N<400)*
[3] *Funding from pharmaceutical company*
[4] *95% CI crosses line of no effect and threshold for clinically important harm*
[5] *Significant group difference at baseline*
[6] *95% CI crosses line of no effect and thresholds for both clinically important benefit and harm*

See Appendix F for full GRADE tables.

Anticonvulsants: clinical evidence

Included studies

One study of anticonvulsants for the prevention of PTSD in adults was identified for full-text review, and this 1 RCT (N=48) compared gabapentin with placebo for the early prevention (intervention initiated within 1 month of traumatic event) of PTSD in adults (Stein 2007). This RCT had three arms and also compared gabapentin with propranolol (see other drugs section below).

Excluded studies

No studies on anticonvulsants were reviewed at full text and excluded.

Summary of clinical studies included in the evidence review

Table 4 provides a brief summary of the included study and evidence from this study is summarised in the clinical GRADE evidence profile below (Table 5).

See also the study selection flow chart in Appendix C, forest plots in Appendix E and study evidence tables in Appendix D.

Table 4: Summary of included studies: Anticonvulsants for early prevention (<1 month)

Comparison	Gabapentin versus placebo
Total no. of studies (N randomised)	1 (48)
Study ID	Stein 2007
Country	US
Diagnostic status	Non-significant symptoms (below threshold and <50% maximum score on scale)
Mean age (range)	Median 29 (18-61)
Sex (% female)	46
Ethnicity (% BME)	65
Coexisting conditions	NR
Mean months since traumatic event	0.066 (within 48 hours)
Type of traumatic event	Motor Vehicle Collision: Motor vehicle collisions (58%); falls (21%); burns (6%); pedestrian versus automobile (4%); assault (4%); other (6%)
Single or multiple incident index trauma	Single
Lifetime experience of trauma	NR
Intervention details	Gabapentin, 900-1200mg/day (starting at 3 daily doses of 300mg and titrated upwards after 2 days to 3 daily doses of 400mg)
Intervention format	Oral
Actual intervention intensity	NR

Comparison	Gabapentin versus placebo
Comparator	Placebo
Intervention length (weeks)	2
Note. None	

BME, Black and minority ethnic; NR, Not reported.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review (anticonvulsants for the prevention of PTSD in adults) are presented in Table 5.

Table 5: Summary clinical evidence profile: Gabapentin versus placebo for the early prevention (<1 month) of PTSD in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Gabapentin			
PTSD/ASD symptomatology ASDS endpoint score Follow-up: mean 1 months		The mean PTSD/ASD symptomatology in the intervention groups was 0.16 standard deviations higher (0.57 lower to 0.89 higher)		29 (1 study)	low[1]
Diagnosis of PTSD at 3-month follow-up CIDI Follow-up: mean 3 months	294 per 1000	429 per 1000 (165 to 1000)	RR 1.46 (0.56 to 3.78)	31 (1 study)	low[1]
Discontinuation due to any reason (including adverse events) - Non-significant PTSD symptoms at baseline Number of participants lost to follow-up for any reason Follow-up: mean 1 months	118 per 1000	28 per 1000 (1 to 544)	RR 0.24 (0.01 to 4.62)	31 (1 study)	low[1]

ASD, Acute Stress Disorder; CI, Confidence Interval; CIDI, Composite International Diagnostic Interview; PTSD, post-traumatic stress disorder
[1] 95% CI crosses both line of no effect and thresholds for both clinically important benefit and harm

See Appendix F for full GRADE tables.

Benzodiazepines: clinical evidence

Included studies

Two studies of benzodiazepines for the prevention of PTSD in adults were identified for full-text review. Of these 2 studies, 1 RCT (N=22) was included in a single comparison for benzodiazepines (Mellman 2002). This RCT compared temazepam with placebo for the early prevention (intervention initiated within 1 month of traumatic event) of PTSD in adults.

Excluded studies

One study was reviewed at full text and excluded from this review because the study was unpublished (registered on clinical trials.gov and author contacted for full trial report but author confirmed that this study had never reached 'operational stage').

Studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 6 provides a brief summary of the included study and evidence from this study is summarised in the clinical GRADE evidence profile below (Table 7).

See also the study selection flow chart in Appendix C, forest plots in Appendix E and study evidence tables in Appendix D.

Table 6: Summary of included studies: Benzodiazepines for early prevention (<1 month)

Comparison	Temazepam versus placebo
Total no. of studies (N randomised)	1 (22)
Study ID	Mellman 2002
Country	US
Diagnostic status	Clinically important PTSD symptoms (scoring above a threshold on validated scale)
Mean age (range)	36.1 (range NR)
Sex (% female)	36
Ethnicity (% BME)	91
Coexisting conditions	All participants had sleep disturbance
Mean months since traumatic event	0.47 (mean 14.3 days)
Type of traumatic event	Motor Vehicle Collision: Motor vehicle accident (68%); industrial accidents (9%); impersonal assaults (23%)
Single or multiple incident index trauma	Single
Lifetime experience of trauma	NR
Intervention details	Temazepam, 30mg at bedtime for 5 nights followed by 15mg for 2 nights
Intervention format	Oral
Actual intervention intensity	NR
Comparator	Placebo
Intervention length (weeks)	1
Note. None	

BME – Black and minority ethnic; NR-Not reported; PTSD-Post-traumatic stress disorder;

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review (benzodiazepines for the prevention of PTSD in adults) are presented in Table 7.

Table 7: Summary clinical evidence profile: Temazepam versus placebo for the early prevention (<1 month) of PTSD in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Temazepam			
PTSD symptomatology clinician-rated at endpoint CAPS change score Follow-up: mean 1 weeks		The mean PTSD symptomatology clinician-rated at endpoint in the intervention groups was 0.55 standard deviations higher (0.35 lower to 1.45 higher)		20 (1 study)	low[1,2]
PTSD symptomatology clinician-rated at 1-month follow-up CAPS change score Follow-up: mean 1 months		The mean PTSD symptomatology clinician-rated at 1-month follow-up in the intervention groups was 0.18 standard deviations higher (0.65 lower to 1.02 higher)		22 (1 study)	very low[1,3]
Diagnosis of PTSD at 1-month follow-up CAPS Follow-up: mean 1 months	273 per 1000	545 per 1000 (180 to 1000)	RR 2 (0.66 to 6.04)	22 (1 study)	very low[1,3]

CAPS, Clinician Administered PTSD Scale; CI, Confidence Interval; PTSD, post-traumatic stress disorder
[1] Risk of bias is unclear across multiple domains
[2] 95% CI crosses both line of no effect and threshold for clinically important harm
[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

See Appendix F for full GRADE tables.

Other drugs: clinical evidence

Included studies

Thirty-four studies of other drugs for the prevention of PTSD in adults were identified for full-text review. Of these 34 studies, 6 RCTs (N=354) were included. There were 5 comparisons for other drugs. 1 RCT had 3 arms and was included in 2 comparisons.

For the early prevention (intervention initiated within 1 month of traumatic event) of PTSD in adults, there were 4 relevant comparisons: 1 RCT (N=68) compared hydrocortisone with placebo (Delahanty 2013); 1 RCT (N=120) compared oxytocin with placebo (van Zuiden 2017); 3 RCTs (N=132) compared propranolol with placebo (Hoge 2012; Pitman 2002; Stein 2007); and 1 RCT (N=48) compared propranolol with gabapentin (Stein 2007).

For the delayed treatment (>3 months) of non-significant PTSD symptoms in adults, there was 1 relevant comparison: 1 RCT (N=34) compared prazosin with placebo (Germain 2012).

Excluded studies

Twenty-eight studies were reviewed at full text and excluded from this review. The most common reasons for exclusion were that the paper was a systematic review with no new useable data and any meta-analysis results not appropriate to extract, or the intervention was outside protocol.

Studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 8 and *BME – Black and minority ethnic; NR-Not reported; PTSD-Post-traumatic stress disorder.*

Table 9 provide brief summaries of the included studies and evidence from these are summarised in the clinical GRADE evidence profiles below (Table 10, Table 11, Table 12, Table 13 and Table 14).

See also the study selection flow chart in Appendix C, forest plots in Appendix E and study evidence tables in Appendix D.

Table 8: Summary of included studies: Other drugs for early prevention (<1 month)

Comparison	Hydrocortisone versus placebo	Oxytocin versus placebo	Propranolol versus placebo	Propranolol versus gabapentin
Total no. of studies (N randomised)	1 (68)	1 (120)	3 (132)	1 (48)
Study ID	Delahanty 2013	van Zuiden 2017	Hoge 2012[1] Pitman 2002[2] Stein 2007[3]	Stein 2007
Country	US	Netherlands	US	US
Diagnostic status	Unclear	Subthreshold symptoms (below threshold but ≥50% maximum score on scale)	Unclear[1,2] Non-significant symptoms (below threshold and <50% maximum score on scale)[3]	Non-significant symptoms (below threshold and <50% maximum score on scale)
Mean age (range)	30.6 (18-56)	35.5 (range NR)	33.5 (range NR)[1] 34.3 (range NR)[2] Median 29 (18-61)[3]	Median 29 (18-61)
Sex (% female)	34	50	56[1] 51[2] 46[3]	46
Ethnicity (% BME)	16	NR	NR[1,2] 65[3]	65
Coexisting conditions	NR	NR	NR	NR
Mean months since	0.016 (within 12 hours)	0.29 (mean 8.9 days, inclusion criterion within 12 days)	0.006 (mean 4.44 hours)[1] 0.008 (within 6 hours)[2]	0.066 (within 48 hours)

Comparison	Hydrocortisone versus placebo	Oxytocin versus placebo	Propranolol versus placebo	Propranolol versus gabapentin
traumatic event			0.066 (within 48 hours)[3]	
Type of traumatic event	Motor Vehicle Collision: Motor vehicle accident (58%); fall (19%); assault (17%); other (6%)	Unintentional injury: 80% accidental; 20% assault	Motor Vehicle Collision: Motor vehicle accident (63%); work injury (10%); burn/electric shock (10%); falls (7%); physical assault (5%); hit by bicycle (2%); fire (2%)[1] Motor Vehicle Collision: Motor vehicle accident (71%)[2] Motor Vehicle Collision: Motor vehicle collisions (58%); falls (21%); burns (6%); pedestrian versus automobile (4%); assault (4%); other (6%)[3]	Motor Vehicle Collision: Motor vehicle collisions (58%); falls (21%); burns (6%); pedestrian versus automobile (4%); assault (4%); other (6%)
Single or multiple incident index trauma	Single	Single	Single	Single
Lifetime experience of trauma	NR	NR	NR	NR
Intervention details	Low dose hydrocortisone (40mg/day; 20mg every 12 hours)	Oxytocin, 40 IU/dose twice daily (5 puffs of 4 IU per nostril per dose)	Propranolol, initial dose of 40mg short-acting propranolol followed by 60mg long-acting propranolol 1-hour later, and then continued long-acting propranolol 240mg/day (120mg morning and evening) for 10 days and then tapering for 9 days[1] Propranolol, 160mg/day (in 4 doses of 40mg)[2] Propranolol, 60-120mg/day (starting at 3 daily doses of 20mg and titrated upwards	Propranolol, 60-120mg/day (starting at 3 daily doses of 20mg and titrated upwards after 2 days to 3 daily doses of 40mg)

Comparison	Hydrocortisone versus placebo	Oxytocin versus placebo	Propranolol versus placebo	Propranolol versus gabapentin
			after 2 days to 3 daily doses of 40mg) [3]	
Intervention format	Oral	Intranasal	Oral	Oral
Actual intervention intensity	NR	Mean doses administered 14.24 (SD=2.18)	49% showed high drug compliance (defined as taking ≥90% of medication doses as indicated by participant's log, pill count by staff and Medication Event Monitoring System [MES]) [1] NR[2,3]	NR
Comparator	Placebo	Placebo	Placebo	Gabapentin, 900-1200mg/day (starting at 3 daily doses of 300mg and titrated upwards after 2 days to 3 daily doses of 400mg)
Intervention length (weeks)	1.4 (+ 0.9 taper period)	1.1	1.4 (+ 1.3 taper period) [1,2] 2[3]	2
Note. [1]Hoge 2012; [2]Pitman 2002; [3]Stein 2007				

BME – Black and minority ethnic; NR-Not reported; PTSD-Post-traumatic stress disorder.

Table 9: Summary of included studies: Other drugs for delayed treatment (>3 months) of non-significant PTSD symptoms

Comparison	Prazosin versus placebo
Total no. of studies (N randomised)	1 (34)
Study ID	Germain 2012
Country	US
Diagnostic status	Non-significant symptoms (below threshold and <50% maximum score on scale)
Mean age (range)	41.3 (range NR)
Sex (% female)	6
Ethnicity (% BME)	12
Coexisting conditions	All participants had sleep complaints. SCID primary diagnosis: 3% Generalized anxiety disorder; 24% Primary insomnia or insomnia related to another disorder; 6% no diagnosis on axis I
Mean months since traumatic event	NR
Type of traumatic event	Military combat. Combat Theatre: 48% Operations Iraqi/Enduring Freedom; 18% Persian Gulf War; 12% Vietnam; 6% Other theatre of operations; 15% No conflict

Comparison	Prazosin versus placebo
Single or multiple incident index trauma	Multiple
Lifetime experience of trauma	NR
Intervention details	Prazosin (1-15mg/day)
Intervention format	Oral
Actual intervention intensity	Mean final dose 8.9 mg (SD=5.7 mg; range 1-15 mg)
Comparator	Placebo
Intervention length (weeks)	8
Note. None	

BME – Black and minority ethnic; NR-Not reported; SCID – Semi-structured interview for making the major DSM-IV Axis I Diagnoses.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review (other drugs for the prevention of PTSD in adults) are presented in Table 10, Table 11, Table 12, Table 13 and Table 14.

Table 10: Summary clinical evidence profile: Hydrocortisone versus placebo for the early prevention (<1 month) of PTSD in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Hydrocortisone			
PTSD symptomatology clinician-rated at endpoint CAPS endpoint score Follow-up: mean 1 months		The mean PTSD symptomatology clinician-rated at endpoint in the intervention groups was 2.62 standard deviations lower (3.38 to 1.86 lower)		51 (1 study)	very low[1,2]
PTSD symptomatology clinician-rated at 2-month follow-up CAPS endpoint score Follow-up: mean 2 months		The mean PTSD symptomatology clinician-rated at 2-month follow-up in the intervention groups was 2.96 standard deviations lower (3.85 to 2.07 lower)		43 (1 study)	very low[1,2]
Diagnosis of PTSD at endpoint CAPS Follow-up: mean 1 months	111 per 1000	83 per 1000 (16 to 458)	RR 0.75 (0.14 to 4.12)	51 (1 study)	very low[1,3]
Diagnosis of PTSD at 2-month follow-up CAPS	125 per 1000	22 per 1000 (1 to 407)	RR 0.18 (0.01 to 3.26)	43 (1 study)	very low[1,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Hydrocortisone			
Follow-up: mean 2 months					
Depression symptoms at endpoint CES-D endpoint score Follow-up: mean 1 months		The mean depression symptoms at endpoint in the intervention groups was 3.57 standard deviations lower (4.48 to 2.66 lower)		51 (1 study)	very low[1,2]
Depression symptoms at 2-month follow-up CES-D endpoint score Follow-up: mean 2 months		The mean depression symptoms at 2-month follow-up in the intervention groups was 3.71 standard deviations lower (4.73 to 2.69 lower)		43 (1 study)	very low[1,2]
Quality of life SF-36 General health change score Follow-up: mean 1 months Better indicated by higher values		The mean quality of life in the intervention groups was 3.51 standard deviations higher (2.61 to 4.41 higher)		51 (1 study)	very low[1,2]
Discontinuation due to adverse events Number of participants who dropped out due to adverse events Follow-up: mean 1 months	0 per 1000	0 per 1000 (0 to 0)	RR 3.19 (0.13 to 75.43)	64 (1 study)	very low[1,3]

CI, Confidence Interval; PTSD, post-traumatic stress disorder; CAPS, Clinician Administered PTSD Scale.
[1] Risk of bias is high or unclear across multiple domains
[2] OIS not met (N<400)
[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Table 11: Summary clinical evidence profile: Oxytocin versus placebo for the early prevention (<1 month) of PTSD in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Oxytocin			
PTSD symptomatology		The mean PTSD symptomatology self-		107 (1 study)	moderate[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Oxytocin			
self-rated at 1-month follow-up IES-R change score Follow-up: mean 1 months		rated at 1-month follow-up in the intervention groups was 0.39 standard deviations lower (0.78 to 0.01 lower)			
PTSD symptomatology self-rated at 2-month follow-up IES-R change score Follow-up: mean 2 months		The mean PTSD symptomatology self-rated at 2-month follow-up in the intervention groups was 0.27 standard deviations lower (0.65 lower to 0.11 higher)		107 (1 study)	moderate[2]
PTSD symptomatology self-rated at 5-month follow-up IES-R change score Follow-up: mean 5 months		The mean PTSD symptomatology self-rated at 5-month follow-up in the intervention groups was 0.08 standard deviations lower (0.46 lower to 0.3 higher)		107 (1 study)	moderate[1]
PTSD symptomatology clinician-rated at 1-month follow-up CAPS change score Follow-up: mean 1 months		The mean PTSD symptomatology clinician-rated at 1-month follow-up in the intervention groups was 0.2 standard deviations lower (0.58 lower to 0.18 higher)		107 (1 study)	low[2,3]
PTSD symptomatology clinician-rated at 2-month follow-up CAPS change score Follow-up: mean 2 months		The mean PTSD symptomatology clinician-rated at 2-month follow-up in the intervention groups was 0.44 standard deviations lower (0.83 to 0.06 lower)		107 (1 study)	low[1,3]
PTSD symptomatology clinician-rated at 5-month follow-up CAPS change score Follow-up: mean 5 months		The mean PTSD symptomatology clinician-rated at 5-month follow-up in the intervention groups was 0.16 standard deviations lower		107 (1 study)	low[2,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Oxytocin			
		(0.54 lower to 0.22 higher)			
Anxiety symptoms at 1-month follow-up HADS-A change score Follow-up: mean 1 months		The mean anxiety symptoms at 1-month follow-up in the intervention groups was 0.31 standard deviations lower (0.7 lower to 0.07 higher)		107 (1 study)	moderate[2]
Anxiety symptoms at 2-month follow-up HADS-A change score Follow-up: mean 2 months		The mean anxiety symptoms at 2-month follow-up in the intervention groups was 0.33 standard deviations lower (0.71 lower to 0.05 higher)		107 (1 study)	moderate[2]
Anxiety symptoms at 5-month follow-up HADS-A change score Follow-up: mean 5 months		The mean anxiety symptoms at 5-month follow-up in the intervention groups was 0.51 standard deviations lower (0.89 to 0.12 lower)		107 (1 study)	moderate[1]
Depression symptoms at 1-month follow-up HADS-D change score Follow-up: mean 1 months		The mean depression symptoms at 1-month follow-up in the intervention groups was 0.13 standard deviations lower (0.51 lower to 0.25 higher)		107 (1 study)	moderate[2]
Depression symptoms at 2-month follow-up HADS-D change score Follow-up: mean 2 months		The mean depression symptoms at 2-month follow-up in the intervention groups was 0.07 standard deviations lower (0.45 lower to 0.31 higher)		107 (1 study)	moderate[1]
Depression symptoms at 5-month follow-up HADS-D change score Follow-up: mean 5 months		The mean depression symptoms at 5-month follow-up in the intervention groups was 0.13 standard deviations lower		107 (1 study)	moderate[2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Oxytocin			
		(0.51 lower to 0.25 higher)			
Discontinuation due to any reason (including adverse events) - Subthreshold symptoms (below threshold but ≥50% maximum score on scale) at baseline Number of participants lost to follow-up for any reason Follow-up: mean 1 months	293 per 1000	340 per 1000 (199 to 574)	RR 1.16 (0.68 to 1.96)	120 (1 study)	low[4]

CI, Confidence Interval; HADS-A, Hospital anxiety and depression scale; HADS-D, German version of hospital anxiety and depression scale; CAPS, Clinician Administered PTSD Scale; PTSD, post-traumatic stress disorder; SMD, Standard mean difference, RR, Risk Ratio.
[1] OIS not met (N<400)
[2] 95% CI crosses both line of no effect and threshold for clinically important benefit
[3] Non-blind outcome assessment
[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Table 12: Summary clinical evidence profile: Propranolol versus placebo for the early prevention (<1 month) of PTSD in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Propranolol			
PTSD/ASD symptomatology self-rated ASDS endpoint score Follow-up: mean 1 months		The mean PTSD/ ASD symptomatology self-rated in the intervention groups was 0.36 standard deviations lower (1.11 lower to 0.39 higher)		28 (1 study)	moderate[1]
PTSD symptomatology clinician-rated at endpoint CAPS endpoint score Follow-up: mean 1 months		The mean PTSD symptomatology clinician-rated at endpoint in the intervention groups was 0.16 standard deviations lower (0.63 lower to 0.31 higher)		72 (2 studies)	low[1,2]
PTSD symptomatology clinician-rated		The mean PTSD symptomatology clinician-rated at 2-		41 (1 study)	very low[2,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Propranolol			
at 2-month follow-up CAPS endpoint score Follow-up: mean 2 months		month follow-up in the intervention groups was 0.08 standard deviations higher (0.53 lower to 0.7 higher)			
Diagnosis of PTSD at endpoint CAPS Follow-up: mean 1 months	366 per 1000	388 per 1000 (223 to 670)	RR 1.06 (0.61 to 1.83)	81 (2 studies)	very low[2,3]
Diagnosis of PTSD at 2-3 month follow-up CAPS/CIDI Follow-up: 2-3 months	344 per 1000	406 per 1000 (255 to 651)	RR 1.18 (0.74 to 1.89)	118 (3 studies)	very low[2,3]
Discontinuation due to any reason (including adverse events) Number of participants lost to follow-up for any reason Follow-up: mean 1 months	98 per 1000	226 per 1000 (92 to 557)	RR 2.3 (0.94 to 5.66)	118 (3 studies)	moderate[4]

ASD, Acute Stress Disorder; CAPS, Clinician Administered PTSD Scale; CI, Confidence Interval; CIDI, Composite International Diagnostic Interview; PTSD, post-traumatic stress disorder
[1] 95% CI crosses both line of no effect and threshold for clinically important benefit
[2] Risk of bias is high or unclear across multiple domains
[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm
[4] 95% CI crosses both line of no effect and threshold for clinically important harm

Table 13: Summary clinical evidence profile: Propranolol versus gabapentin for the early prevention (<1 month) of PTSD in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Gabapentin	Corresponding risk Propranolol			
PTSD/ASD symptomatology self-rated ASDS endpoint score Follow-up: mean 1 months		The mean PTSD/ASD symptomatology self-rated in the intervention groups was 0.48 standard deviations lower		27 (1 study)	moderate[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Gabapentin	Corresponding risk Propranolol			
		(1.25 lower to 0.29 higher)			
Diagnosis of PTSD at 3-month follow-up CIDI Follow-up: mean 3 months	429 per 1000	471 per 1000 (214 to 1000)	RR 1.1 (0.5 to 2.41)	31 (1 study)	low[2]
Discontinuation due to any reason (including adverse events) - Non-significant PTSD symptoms at endpoint Number of participants lost to follow-up for any reason Follow-up: mean 1 months	0 per 1000	0 per 1000 (0 to 0)	RR 7.5 (0.44 to 128.4)	31 (1 study)	low[2]

ASD, Acute Stress Disorder; CI, Confidence Interval; CIDI, Composite International Diagnostic Interview; PTSD, post-traumatic stress disorder;
[1] 95% CI crosses both line of no effect and threshold for clinically important benefit
[2] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Table 14: Summary clinical evidence profile: Prazosin versus placebo for the delayed treatment (>3 months) of non-significant PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Prazosin			
PTSD symptomatology self-rated at endpoint PCL change score Follow-up: mean 8 weeks		The mean PTSD symptomatology self-rated at endpoint in the intervention groups was 0.94 standard deviations lower (1.72 to 0.15 lower)		28 (1 study)	moderate[1]
PTSD symptomatology self-rated at 4-month follow-up PCL change score Follow-up: mean 4 months		The mean PTSD symptomatology self-rated at 4-month follow-up in the intervention groups was 1.12 standard deviations lower (2.02 to 0.23 lower)		23 (1 study)	moderate[1]
Anxiety symptoms at		The mean anxiety symptoms at		27 (1 study)	moderate[2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Prazosin			
endpoint BAI change score Follow-up: mean 8 weeks		endpoint in the intervention groups was 0.32 standard deviations lower (1.08 lower to 0.45 higher)			
Anxiety symptoms at 4-month follow-up BAI change score Follow-up: mean 4 months		The mean anxiety symptoms at 4-month follow-up in the intervention groups was 0.76 standard deviations lower (1.61 lower to 0.1 higher)		23 (1 study)	moderate[2]
Depression symptoms at endpoint BDI change score Follow-up: mean 8 weeks		The mean depression symptoms at endpoint in the intervention groups was 0.54 standard deviations lower (1.3 lower to 0.22 higher)		28 (1 study)	moderate[2]
Depression symptoms at 4-month follow-up BDI change score Follow-up: mean 4 months		The mean depression symptoms at 4-month follow-up in the intervention groups was 0.96 standard deviations lower (1.83 to 0.09 lower)		23 (1 study)	moderate[1]
Functional impairment at endpoint SDS change score Follow-up: mean 8 weeks		The mean functional impairment at endpoint in the intervention groups was 0.23 standard deviations lower (0.98 lower to 0.52 higher)		28 (1 study)	low[3]
Functional impairment at 4-month follow-up SDS change score Follow-up: mean 4 months		The mean functional impairment at 4-month follow-up in the intervention groups was 0.52 standard deviations lower		22 (1 study)	moderate[2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Prazosin			
		(1.38 lower to 0.33 higher)			
Sleeping difficulties at endpoint PSQI change score Follow-up: mean 8 weeks		The mean sleeping difficulties at endpoint in the intervention groups was 1.01 standard deviations lower (1.82 to 0.2 lower)		27 (1 study)	moderate[1]
Sleeping difficulties at 4-month follow-up PSQI change score Follow-up: mean 4 months		The mean sleeping difficulties at 4-month follow-up in the intervention groups was 1.15 standard deviations lower (2.04 to 0.25 lower)		23 (1 study)	moderate[1]
Discontinuation due to any reason (including adverse events) Number of participants lost to follow-up for any reason Follow-up: mean 8 weeks	250 per 1000	278 per 1000 (90 to 860)	RR 1.11 (0.36 to 3.44)	34 (1 study)	low[3]
Discontinuation due to adverse events Number of participants who dropped out due to adverse events Follow-up: mean 8 weeks	125 per 1000	55 per 1000 (5 to 556)	RR 0.44 (0.04 to 4.45)	34 (1 study)	low[3]

BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CI, Confidence Interval; PTSD, Post-traumatic stress disorder; PC, Self-report measure; PSQI-Pittsburgh Sleep Quality Index; SDS, Sheehan Disability Scale.
[1] OIS not met (N<400)
[2] 95% CI crosses both line of no effect and threshold for clinically important benefit
[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

See Appendix F for full GRADE tables.

Economic evidence

Included studies

No economic studies assessing the cost effectiveness of pharmacological interventions for the prevention of PTSD in adults identified from the systematic search of economic literature. The search strategy for economic studies is provided in Appendix B.

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Resource impact

The recommendation made by the committee based on this review is not expected to have a substantial impact on resources. However, the recommendation may save resources by reducing the use of non-evidence-based interventions and also improve consistency of practice.

Clinical evidence statements

- Very low quality single-RCT (N=29) evidence suggests a large and statistically significant harm of escitalopram relative to placebo on PTSD symptomatology for adults exposed to trauma within the last month, with significantly greater improvement observed for placebo participants. Evidence from this study also suggested a trend for higher discontinuation due to any reason associated with escitalopram, although absolute numbers are small and this effect is not statistically significant. Evidence from this same RCT suggests non-significant effects of escitalopram on depression symptoms or functional impairment.
- Low quality single-RCT (N=29-31) evidence suggests non-significant effects of gabapentin relative to placebo on acute stress disorder symptomatology, diagnosis of PTSD at 3-month follow-up and discontinuation, for adults exposed to trauma within the last month.
- Low to very low quality single-RCT (N=20-22) evidence suggests non-significant effects of temazepam relative to placebo on PTSD symptomatology at endpoint or 1-month follow-up or diagnosis of PTSD at 1-month follow-up, for adults exposed to trauma within the last month. No evidence on discontinuation is available.
- Very low quality single-RCT (N=43-51) evidence suggests large and statistically significant benefits of hydrocortisone relative to placebo on PTSD symptomatology and depression symptoms at endpoint and 2-month follow-up, and quality of life at endpoint, for adults exposed to trauma within the last month. However, evidence from the same RCT suggests clinically important but not statistically significant effects on the number of participants meeting criteria for a diagnosis of PTSD at endpoint or 2-month follow-up. Evidence from this study suggests a trend for a higher rate of discontinuation due to adverse events associated with hydrocortisone, although absolute numbers are small and this effect is not statistically significant.
- Low to moderate quality single-RCT (N=107) evidence suggests small but statistically significant benefits of oxytocin relative to placebo on self-rated PTSD symptomatology at endpoint and clinician-rated PTSD symptomatology at 2-month follow-up, for adults exposed to trauma within the last month. However, effects at other time points (up to 5-month follow-up) are neither clinically important nor statistically significant. Moderate quality evidence from this same RCT suggests a delayed benefit of oxytocin on anxiety symptoms at 5-month follow-up, however effects at endpoint and 2-month follow-up, and on depression symptoms at all time points, and discontinuation are non-significant.
- Very low to moderate quality evidence from 1-3 RCTs (N=28-118) suggests non-significant effects of propranolol relative to placebo on PTSD symptomatology (self-rated or clinician-rated), or diagnosis of PTSD, at endpoint or 2-3 month follow-up for adults exposed to trauma within the last month. Moderate quality evidence from all 3 RCTs

(N=118) suggests a trend for a higher rate of discontinuation associated with propranolol relative to placebo, although this effect is not statistically significant.

- Low to moderate quality single-RCT (N=27-31) evidence suggests non-significant differences between propranolol and gabapentin on acute stress disorder symptomatology or diagnosis of PTSD at 3-month follow-up for adults exposed to trauma within the last month. Evidence from this same RCT suggests a trend for a higher rate of discontinuation associated with propranolol relative to gabapentin, although this effect is not statistically significant.
- Moderate quality single-RCT (N=23-28) evidence suggests large and statistically significant benefits of prazosin relative to placebo on PTSD symptomatology and sleeping difficulties (at endpoint and 4-month follow-up) for adults exposed to trauma more than 3 months ago with non-significant PTSD symptoms. Evidence from this same RCT suggests a delayed benefit of prazosin on depression symptoms at 4-month follow-up (non-significant at endpoint). Non-significant effects are observed on anxiety symptoms, functional impairment and discontinuation (due to any reason and due to adverse events).

Economic evidence statements

- No economic evidence on pharmacological interventions for the prevention of PTSD in adults was identified and no economic modelling was undertaken.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Critical outcomes were measures of PTSD symptom improvement on validated scales and prevention of PTSD (as measured by the number of people with a diagnosis or scoring above clinical threshold on a validated scale at endpoint or follow-up). Attrition from treatment (for any reason) was also considered an important outcome as a proxy for the acceptability of treatment, and discontinuation due to adverse events was considered as particularly important as an indicator of potential harm in terms of tolerability. The committee considered dissociative symptoms, personal/social/occupational functioning (including global functioning/functional impairment, sleeping or relationship difficulties, and quality of life), and symptoms of a coexisting condition (including anxiety and depression symptoms) as important but not critical outcomes. This distinction was based on the primacy of targeting the core PTSD symptoms, whilst acknowledging that broader symptom measures may be indicators of a general pattern of effect. Change scores were favoured over final scores as although in theory randomisation should balance out any differences at baseline, this assumption can be violated by small sample sizes. The committee also expressed a general preference for self-rated PTSD symptomatology, particularly for pharmacological interventions where the participant is likely to be blinded and may be less susceptible to bias than the study investigator(s). However, the committee discussed potential threats to blinding of the participant, for example in the context of side effects, and therefore triangulation with blinded clinician-rated outcome measures was also regarded as important.

The quality of the evidence

The evidence for this review was of moderate to very low quality, and of limited volume with most comparisons consisting of single studies with relatively few participants. There were also considerable gaps in the evidence, including widespread reporting of only endpoint data, very limited data reported for discontinuation due to adverse events (only reported by a single study), most comparisons including either self-rated or clinician-rated PTSD symptomatology measures but not both so triangulation not possible, relatively short-term follow-up periods, and less breadth in terms of effects on associated symptoms.

Consideration of clinical benefits and harms

The committee considered the evidence for harm associated with escitalopram, namely that patients treated with placebo appeared to show greater improvement in PTSD symptomatology than those receiving the drug. There were also higher rates of discontinuation in patients treated with escitalopram, hydrocortisone and propranolol than those treated with placebo. The committee also considered that providing a treatment that had no clinical benefit over placebo was harmful, as this prevents someone from accessing a treatment that could improve their condition. Such harms were evident in patients treated with an anticonvulsant, a benzodiazepine, or propranolol.

There was some limited evidence of benefit for hydrocortisone, oxytocin and prazosin, however this came from single studies and benefits were not observed consistently across outcomes. On this basis the committee did not consider a positive recommendation appropriate.

Taken together, the committee agreed that the potential harms outweighed the benefits for drug treatments in order to prevent PTSD.

Cost effectiveness and resource use

No evidence on the cost effectiveness of pharmacological interventions for the prevention of PTSD in adults was identified and no economic modelling was undertaken in this area. As there was limited evidence of clinical benefit and evidence of harm associated with pharmacological interventions for the prevention of PTSD in adults, a negative recommendation ('do not offer') for pharmacological interventions was made. This recommendation is anticipated to result in a moderate change in practice. The previous guideline made only a 'consider' recommendation for hypnotic medication for the short-term management of sleep disturbance as an early pharmacological intervention. However, the committee expressed the view that pharmacological treatment within the first month of trauma may be common in clinical practice, although there is variation across settings; therefore implementation of this recommendation may save resources by reducing the use of non-evidence-based interventions, and also improve consistency of practice.

Other factors the committee took into account

The committee noted their knowledge of harm arising from the prescription of benzodiazepines for PTSD, although they pointed out that much of this data was not of sufficient quality to have been included within this review.

References for the included studies

SSRI

Suliman 2015

Suliman S, Seedat S, Pingo J, et al. (2015) Escitalopram in the prevention of posttraumatic stress disorder: a pilot randomized controlled trial. BMC psychiatry 15(1), 24

Anticonvulsants

Stein 2007

Stein M, Kerridge C, Dimsdale J and Hoyt D (2007) Pharmacotherapy to prevent PTSD: Results from a randomized controlled proof-of-concept trial in physically injured patients, Journal of Traumatic Stress 20, 923-932

Benzodiazepines

Mellman 2002

Mellman TA (2002) Hypnotic medication in the aftermath of trauma. Journal of Clinical Psychiatry 63, 1183-1184

Other drugs

Delahanty 2013

Delahanty DL, Gabert-Quillen C, Ostrowski SA, et al. (2013) The efficacy of initial hydrocortisone administration at preventing posttraumatic distress in adult trauma patients: a randomized trial. CNS Spectr 18(2), 103-11

Germain 2012

Germain A, Richardson R, Moul DE, et al. (2012) Placebo-controlled comparison of prazosin and cognitive-behavioral treatments for sleep disturbances in US Military Veterans. Journal of psychosomatic research 72(2), 89-96

Hoge 2012

Hoge EA, Worthington JJ, Nagurney JT, et al. (2012) Effect of acute posttrauma propranolol on PTSD outcome and physiological responses during script-driven imagery. CNS neuroscience & therapeutics 18(1), 21-7

Pitman 2002

Pitman RK, Sanders KM, Zusman RM, et al. (2002) Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. Biological Psychiatry 51, 189-192

Stein 2007

Stein M, Kerridge C, Dimsdale J and Hoyt D (2007) Pharmacotherapy to prevent PTSD: Results from a randomized controlled proof-of-concept trial in physically injured patients, Journal of Traumatic Stress 20, 923-932

van Zuiden 2017

van Zuiden M, Frijling JL, Nawijn L, et al. (2017) Intranasal oxytocin to prevent posttraumatic stress disorder symptoms: A randomized controlled trial in emergency department patients. Biological psychiatry 81(12), 1030-40

Review question For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?

Introduction

In the UK, only two drugs are currently licensed for the treatment of PTSD, paroxetine and sertraline. However, other drugs have been tested in randomised clinical trials for the treatment of PTSD and are considered within this review.

Pharmacological interventions will be considered as classes of drugs (SSRIs, TCAs, MAOIs, SNRIs, other antidepressant drugs, anticonvulsants, antipsychotics, benzodiazepines, and other drugs) and form subsections below.

Evidence for anxiolytics was also searched for but none was found.

Summary of the protocol (PICO table)

Please see Table 15 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 15: Summary of the protocol (PICO table)

Population	Adults with PTSD (as defined by a diagnosis of PTSD according to DSM, ICD or similar criteria, or clinically-significant PTSD symptoms as indicated by baseline scores above threshold on a validated scale more than one month after the traumatic event)
Intervention	• SSRIs: o fluoxetine o paroxetine o sertraline • TCAs: o amitriptyline o imipramine • MAOIs: o brofaromine o phenelzine • SNRIs: o venlafaxine • Other antidepressant drugs: o mirtazapine o nefazodone • Anticonvulsants: o carbamazepine o divalproex o lamotrigine o tiagabine o topiramate • Antipsychotics: o olanzapine o risperidone • Anxiolytics: o buspirone • Benzodiazepines: o alprazolam o clonazepam o diazepam o lorazepam • Other drugs: o clonidine o cortisol o d-cycloserine o ketamine o MDMA o neuropeptide-Y o oxytocin o prazosin

	o propranolol
Comparison	• Any other intervention • Placebo
Outcome	Critical outcomes: • Efficacy (PTSD symptoms/diagnosis/response/remission/relapse) • Acceptability/tolerability of the intervention (discontinuation for any reason and discontinuation due to adverse events used as a proxy) Important outcomes: • Dissociative symptoms • Personal/social/occupational functioning (including global functioning/functional impairment) • Sleeping difficulties • Quality of life • Symptoms of a coexisting condition (including anxiety and depression)

For full details see review protocol in Appendix A.

Methods and processes

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 and 2018 conflicts of interests policies.

Clinical Evidence

Selective serotonin reuptake inhibitors (SSRIs): clinical evidence

Included studies

Eighty studies of SSRIs for the treatment of PTSD in adults were identified for full-text review. Of these 80 studies, 35 RCTs (N=5892) were included. Many of these 80 RCTs were three- or four-armed trials and as such were included in more than one comparison. There were 11 comparisons for SSRIs.

There were no studies for early treatment (intervention initiated 1-3 months post-trauma) of PTSD symptoms.

For delayed treatment (intervention initiated more than 3 months post-trauma) of PTSD symptoms, 20 RCTs (N=4547) compared SSRIs with placebo (Brady 2000; Connor et al. 1999b; Davidson 2001b; Davidson 2004a; Davidson 2006b/Davidson unpublished [one study reported across two papers]; Friedman 2007; GSK 29060 627 [unpublished data]; Li 2017; Marshall 2001; Marshall 2007; Martenyi 2002a; Martenyi 2007; Panahi 2011; Pfizer 588 [unpublished data]; Pfizer 589 [unpublished data]; SKB627, Bryson [unpublished data]; Tucker 2001; Tucker 2003/2004 [one study reported across two papers]; Van der Kolk 2007; Zohar 2002). 3 RCTs (N=292) compared SSRI augmentation of trauma-focused CBT with trauma-focused CBT alone or in addition to placebo (Buhmann 2016; Popiel 2015; Schneier 2012). 1 RCT (N=69) compared augmentation of non-trauma-focused cognitive therapy with sertraline relative to placebo (Hien 2015/Ruglass 2015 [one study reported across two papers]).1 RCT (N=50) compared paroxetine with amitriptyline (Celik 2011). 2 RCTs (N=153) compared an SSRI with paroxetine (Chung 2004/2005 [one study reported across two papers]; Seo 2010).

1 RCT (N=538) compared sertraline with venlafaxine (Davidson 2006b/Davidson unpublished [one study reported across two papers]). 1 RCT (N=207) compared augmentation of trauma-focused CBT with sertraline relative to augmentation with venlafaxine (Sonne 2016). 2 RCTs (N=97) compared sertraline with nefazodone (McRae 2004; Saygin 2002). 1 RCT (N=103) compared fluoxetine with moclobemide (Önder 2006), and the same RCT (N=103) also compared fluoxetine with tianeptine (Önder 2006). 1 RCT (N=40) compared fluvoxamine with reboxetine (Spivak et al. 2006). Finally, 3 RCTs (N=334) compared maintenance treatment with SSRIs relative to placebo (Davidson 2001a; Davidson 2005a; SKB650, Bryson [unpublished data]).

Sub-analyses were possible for the SSRIs versus placebo comparison, comparing effects by multiplicity of trauma and specific drug.

Excluded studies

Forty-five studies were reviewed at full text and excluded from this review. The most common reasons for exclusion were non-randomised group assignment, efficacy or safety data could not be extracted, or the paper was a systematic review with no new useable data and any meta-analysis results not appropriate to extract.

Studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 16, BME, Black and Minority Ethnic; DSM, Diagnostic and Statistical Manual of mental disorders; GAD, generalised anxiety disorder; ICD, International Classification of Disease; MDD, major depressive disorder; NA, not applicable; NR, not reported; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors;

[1]*Brady 2000;*
[2]*Connor 1999b;*
[3]*Davidson 2001b;*
[4]*Davidson 2004a;*
[5]*Davidson 2006b/Davidson unpublished;*
[6]*Friedman 2007;*
[7]*GSK 29060 627;*
[8]*Li 2017;*
[9]*Marshall 2001;*
[10]*Marshall 2007;*
[11]*Martenyi 2002a;*
[12]*Martenyi 2007;*
[13]*Panahi 2011;*
[14]*Pfizer 588;*
[15]*Pfizer 589;*
[16]*SKB627;*
[17]*Tucker 2001;*
[18]*Tucker 2003/2004;*
[19]*van der Kolk 2007;*
[20]*Zohar 2002*

Table 17, AUD, alcohol use disorders; BME, Black and Minority Ethnic; CBT, cognitive behavioural therapy; DSM, Diagnostic and Statistical Manual of mental disorders; ICD, International Classification of Disease; MDD, major depressive disorder; MVA, motor vehicle accidents; NA, not applicable; NR, not reported; PE, psychoeducation; PTSD, post-traumatic stress disorder; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors; SUD, substance use disorder; TF-CBT, trauma-focused-cognitive behavioural therapy

[1]*Buhmann 2016;*
[2]*Popiel 2015;*
[3]*Schneier 2012;*
[4]*Chung 2004/2005;*
[5]*Seo 2010*

Table 18, and Table 19 provide brief summaries of the included studies and evidence from these are summarised in the clinical GRADE evidence profiles below (Table 20,Table 21, Table 22, Table 23, Table 24, Table 25, Table 26, Table 27, Table 28, Table 29, Table 30 and Table 31).

See also the study selection flow chart in Appendix C, forest plots in Appendix E and study evidence tables in Appendix D.

Table 16: Summary of included studies: SSRIs for delayed treatment (>3 months)-part 1

Comparison	SSRIs versus placebo
Total no. of studies (N randomised)	20 (4547)
Study ID	Brady 2000[1] Connor 1999b[2] Davidson 2001b[3] Davidson 2004a[4] Davidson 2006b/Davidson unpublished[5] Friedman 2007[6] GSK 29060627[7] Li 2017[8] Marshall 2001[9] Marshall 2007[10] Martenyi 2002a[11] Martenyi 2007[12] Panahi 2011[13] Pfizer 588[14] Pfizer 589[15] SKB627[16] Tucker 2001[17] Tucker 2003/2004[18] van der Kolk 2007[19] Zohar 2002[20]
Country	US[1,2,3,4,5,6,9,10,12,14,15,18,19] Austria, Belgium, Canada, France, Germany, Ireland, Netherlands, South Africa, UK, Italy, Israel, and Switzerland[7] China[8] Belgium, Bosnia, Croatia, Israel, South Africa, Yugoslavia[11] Iran[13] Unclear[16] US and Canada[17] Israel[20]
Diagnostic status	PTSD diagnosis according to ICD/DSM criteria
Mean months since onset of PTSD	146[1] Median 6 years[2] 147[3] NR (pooled data from Brady 2000 and Davidson 2001b)[4] NR (≥6 months)[5] 219[6] NR (≥3 months inclusion criterion)[7,10] 238.8[8] 188.4[9] NR[11,12,18,19]

Comparison	SSRIs versus placebo
	289[13] 126[14] 216[15] NR ('chronic')[16,17] 88[20]
Mean age (range)	39.9 (18-69)[1] Median 37 (range NR)[2] 37.1 (18-69)[3] 38.4 (range NR)[4] NR[5,16] 45.3 (range NR)[6] 39.2 (range NR)[7] 46 (range NR)[8] 41.8 (range NR)[9] 39.8 (range NR)[10] 37.9 (range NR)[11] 40.7 (range NR)[12] 45.6 (range NR)[13] 37 (range NR)[14] 45 (range NR)[15] 40.8 (18-78)[17] 38.7 (range NR)[18] 36.1 (range NR)[19] 39.6 (range NR)[20]
Sex (% female)	73[1] 91[2] 78[3] 76[4] NR[5,6,9] 54[7,16] 13[8] 67[10] 19[11] 72[12] 0[13] 75[14] 20[15] 66[17] 74[18] 83[19] 12[20]
Ethnicity (% BME)	15[1] 7[2] 16[3,4] NR[5,8,9,13,14,15,16,20] 31[6] 8[7] 75[10] 9[11] 23[12] 28[17]

Comparison	SSRIs versus placebo
	14[18] 33[19]
Coexisting conditions	Major depression (33%); anxiety disorder (16%)[1] NR[2,4,5,7,8,11,12,13,14,15,16,20] Major depression (40%); anxiety disorder (20%)[3] Major depression (47%); anxiety disorder (19%)[6] 45% met DSM-IV criteria for MDD. Other comorbid diagnoses (across the three treatment groups) included generalized anxiety disorder (28%–32%), agoraphobia (21%–25%), panic disorder (14%–17%), and dysthymia (9%–12%)[9] 81% had at least one additional Axis I diagnosis: social phobia (23%); major depressive disorder (63%); and panic disorder (15%). At least one personality disorder diagnosis was observed in 41%[10] 35% MDD; 16% GAD; 11% panic disorder; 9% social anxiety disorder; 2% OCD[17] Axis I diagnoses (secondary to PTSD): 76% MDD; 3% dysthymia; 12% both MDD and panic disorder[18] Mean 3.2 comorbid Axis I/II diagnoses[19]
Mean months since traumatic event	224[1] NR[2,5,7,8,10,11,12,13,16,18,20] 221[3] NR (pooled data from Brady 2000 and Davidson 2001b)[4] 278[6] 188.4[9] 180[14] 216[15] 178.3[17] 154.8[19]
Type of traumatic event	Mixed: 61% physical or sexual assault; 9% serious unintentional injury or fire; 9% seeing someone hurt or die; 6% being in war or combat; 15% miscellaneous other events[1] Mixed. Civilian trauma: Rape (26%); incest or spousal sexual abuse (15%); physical abuse (11%); traumatic bereavement (13%); violent crime (13%); accident (8%); other (13%)[2] Mixed: 62% physical or sexual assault; 12% seeing someone hurt or die; 12% serious accident/fire/injury; 5% being in a war or combat; 9% other event[3] Mixed: NR (pooled data from Brady 2000 and Davidson 2001b)[4] Mixed: Most common types of primary trauma were nonsexual abuse (26%), adult sexual abuse (16%), childhood sexual abuse (15%), unexpected death (13%), accidental injury (12%), and combat (9%)[5] Military combat: 71% being in war or combat; 15% physical or sexual assault; 8% seeing someone hurt or die; 2% serious accident, injury or fire; 4% miscellaneous other events[6] Unclear (no details reported)[7,16] Mixed: Presence of chemical burn (33%); military-related trauma (19%)[8] Mixed: The most common trauma types in the three treatment groups were physical or sexual assault (48%–54%), witnessing injury or death (17%–18%), serious accident or injury (6%–12%), and combat (5%–8%)[9]

Comparison	SSRIs versus placebo
	Mixed: Sexual assault or abuse (15%); both sexual and physical assault/abuse (21%); physical assault or abuse (48%); and other (witnessing events, fire, accident; 15%)[10] Mixed: Multiple traumas of combat-related type (48%) and/or as a victim of war or witness of war event (47%)[11] Mixed: 5% Combat-related; 27% Sexual assault; 16% Domestic violence; 12% Accident; 11% Incest; 10% Witnessed another person's death[12] Military combat: Iranian Iran–Iraq war veteran[13] Mixed: Physical/sexual assault[14] Military combat. Most common trauma: war/combat (71%)[15] Mixed: Most common trauma types: Physical or sexual assault (49%); seeing someone hurt or die (19%); serious accident or injury (10%); combat exposure (7%)[17] Mixed: Physical abuse, assault (31%); sexual abuse, rape (24%); witness violent death (14%); life-threatening event (12%); tornado (5%); terrorist bomb (5%); combat (3%); motor vehicle accident (3%); nuclear bomb exposure (2%)[18] Mixed: 28% child sexual abuse; 5% child physical abuse; 9% child sexual and physical abuse; 9% adult sexual assault; 6% adult physical assault; 8% domestic violence; 7% other adult victimization; 9% traumatic loss; 3% war/terrorism/violence; 16% injury/accident[19] Military combat: Combat-related PTSD in Israeli military veterans. The index traumatic event, defined as the event that was currently most distressing to the patient, consisted of combat-related violence (76%), motor vehicle accident (19%), and captivity (5%)[20]
Single or multiple incident index trauma	Single[1,2,3,4,5,9,14,17,18] Multiple[6,11,13,15,19,20] Unclear[7,8,10,12,16]
Lifetime experience of trauma	NR[1,3,4,5,6,7,8,9,10,12,13,14,15,16,17,18,19,20] Lifetime experience of trauma: 4% 1 trauma; 8% 2 traumas; 15% 3 traumas; 23% 4-6 traumas; 30% 7-9 traumas; 21% >9 traumas[2] 53% 1 trauma; 47% ≥2 traumas[11]
Intervention details	Sertraline, titrated up to 200mg/day[1] Fluoxetine, up to a maximum of 60mg/day[2] Sertraline, 25-200mg/day [3,5,6] NA (Pooled data analysis of Brady 2000 and Davidson 2001b) [4] Paroxetine, 20-50mg/day[7,16,17] Sertraline, 135mg/day[8] Paroxetine: Two fixed dose arms combined (20mg and 40mg) [9] Paroxetine, 10-60mg/day[10] Fluoxetine, 20-80mg/day[11] Fluoxetine: Two fixed dose arms combined, 20mg/day and 40mg/day[12] Sertraline, 50-200mg/day[13,20] Sertraline (planned dosage NR) [14,15] Two arms combined: sertraline (50-200mg/day) and citalopram (20-50mg/day) [18] Fluoxetine, 10-60mg/day[19]
Intervention format	Oral
Actual intervention intensity	Mean final dose 133.3mg/day (SD=59.2) [1] Median daily dose 30mg[2]

Comparison	SSRIs versus placebo
	Mean final dose 146.3mg/day (SD=49.3) [3] NA (Pooled data analysis of Brady 2000 and Davidson 2001b) [4] The mean average prescribed daily dose was 110.2 mg/d for sertraline and the mean maximum prescribed daily dose was 151.4 mg/d (range, 25.0–200.0 mg/d). 49% (85/173) of patients in the sertraline group achieved maximum dosing[5] Mean final dose 135mg/day (SD=61.9) [6] NR[7,8,9,12,16] Mean final dose 40.4 mg/day (SD=17.7) [10] Mean final dose 57mg/day[11] Mean final dose 140mg/day (SD=33) [13] Mean final dose 156 mg/day[14] Mean final dose 135mg/day[15] Mean dosage during the study 27.6mg/day (SD=6.72) [17] Mean final dose 134.1mg/day for sertraline and 36.2mg/day for citalopram[18] Mean dose during study 30mg/day and final modal dose 40mg/day[19] Mean final dose 120mg/day (SD=60) [20]
Comparator	Placebo (actual intensity, dose equivalent, NR) [1,3,4,5,7,8,9,11,12,14,15,16,17,19] Placebo. Median daily dose 40mg[2] Placebo. Mean final dose 172mg/day (SD=49) [6] Placebo. Mean final dose 43.2mg (SD=17.3) [10] Placebo. Mean final dose 131mg/day (SD=29) [13] Placebo. Mean final dose 2.1 tablets/day[18] Placebo. Mean final dose 147mg/day (SD=56) [20]
Intervention length (weeks)	12[1,2,3,5,6,7,8,9,11,12,16,17] NA (Pooled data analysis of Brady 2000 and Davidson 2001b) [4] 10[10,13,15,18,20] 11[14] 8[19]

BME, Black and Minority Ethnic; DSM, Diagnostic and Statistical Manual of mental disorders; GAD, generalised anxiety disorder; ICD, International Classification of Disease; MDD, major depressive disorder; NA, not applicable; NR, not reported; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors;

[1]Brady 2000;
[2]Connor 1999b;
[3]Davidson 2001b;
[4]Davidson 2004a;
[5]Davidson 2006b/Davidson unpublished;
[6]Friedman 2007;
[7]GSK 29060 627;
[8]Li 2017;
[9]Marshall 2001;
[10]Marshall 2007;
[11]Martenyi 2002a;
[12]Martenyi 2007;
[13]Panahi 2011;
[14]Pfizer 588;
[15]Pfizer 589;
[16]SKB627;
[17]Tucker 2001;
[18]Tucker 2003/2004;
[19]van der Kolk 2007;
[20]Zohar 2002

Table 17: Summary of included studies: SSRIs for delayed treatment (>3 months)-part 2

Comparison	SSRI + TF-CBT versus (+/- placebo +) TF-CBT	Sertraline (+ non-TF-CBT) versus placebo (+ non-TF-CBT)	Paroxetine versus amitriptyline	SSRI versus mirtazapine
Total no. of studies (N randomised)	3 (292)	1 (69)	1 (50)	2 (153)
Study ID	Buhmann 2016[1] Popiel 2015[2] Schneier 2012[3]	Hien 2015/Ruglass 2015	Celik 2011	Chung 2004/2005[4] Seo 2010[5]
Country	Denmark[1] Poland[2] US[3]	US	Turkey	Korea
Diagnostic status	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria
Mean months since onset of PTSD	166[1] NR[2] 77.8[3]	205	NR ('chronic')	414[4] NR[5]
Mean age (range)	45.5 (range NR) [1] 35.4 (range NR) [2] 50.3 (range NR) [3]	42.4 (range NR)	30.8 (range NR)	59.8 (range NR) [4] 37.3 (range NR) [5]
Sex (% female)	45[1] NR[2] 54[3]	81	NR	0[4] 70[5]
Ethnicity (% BME)	NR[1,2] 32[3]	77	NR	NR
Coexisting conditions	Patients were not excluded solely based on psychotic symptoms (12% psychotic during treatment). 94% depression according to ICD-10. 27% Personality change after catastrophic events (ICD-10 code F62.0). 23% report traumatic brain injury[1] 61% Comorbid Axis I disorder; 45% Comorbid personality disorder; 18% traumatic brain injury in MVA[2] 70% current axis I disorder (66% mood disorder);	Alcohol dependence: 88% alcohol dependence; 4% alcohol abuse; 42% early-onset AUD. Drug dependence: 12% cannabis dependence; 30% cocaine dependence; 55% comorbid AUD and SUD. 61% current major depression	NR	17% MDD, 79% dysthymia and 4% dysthymia and MDD[4] None of the participants had current diagnosis of any other DSM-IV axis I disorder (exclusion criterion) [5]

Comparison	SSRI + TF-CBT versus (+/- placebo +) TF-CBT	Sertraline (+ non-TF-CBT) versus placebo (+ non-TF-CBT)	Paroxetine versus amitriptyline	SSRI versus mirtazapine
	16% current axis II disorder[3]			
Mean months since traumatic event	NR[1,3] 18.3[2]	NR	NR (26% 0-6 months; 12% 6 months-3 years; 62% >3 years)	NR[4] 15.6[5]
Type of traumatic event	Mixed: 39% torture; 22% refugee camp; 57% Danish asylum centre; 27% ex-combatant[1] Motor Vehicle Collision. Status during MVC: Driver (34%); Passenger (33%); Cyclist (5%); Pedestrian (16%); Found out about death (7%); Other (4%). Patient considered MVA perpetrator (10%)[2] Terrorist attack: World Trade Centre attack. All participants reported having been in the vicinity of the World Trade Centre at the time of the attack or building collapse (in the World Trade Centre [22%], in nearby lower Manhattan [65%], arrived in immediate aftermath to help [14%]). 84% were emergently evacuated; 32% reported loss of an immediate family member or close friend[3]	Index trauma not reported	Military combat. Combat-related PTSD: 86% gun battle; 10% mine; 5% hand grenade	Military combat: Veterans of the Korean or Vietnam war[4] Motor Vehicle Collision: Traffic accident (78%); physical assault (10%); sexual assault (3%); witnessing a trauma (3%); other accidents (8%)[5]
Single or multiple incident index trauma	Multiple[1] Single[2,3]	Unclear	Multiple	Multiple[4] Single[5]

Comparison	SSRI + TF-CBT versus (+/- placebo +) TF-CBT	Sertraline (+ non-TF-CBT) versus placebo (+ non-TF-CBT)	Paroxetine versus amitriptyline	SSRI versus mirtazapine
Lifetime experience of trauma	NR[1] Number of previous traumatic events (before current MVA): 2.1 (SD=1.2). 4% childhood trauma[2] 38% had history of prior trauma[3]	Lifetime traumatic experiences: 46% child physical; 46% adult physical; 39% child sexual; 36% adult sexual; 67% transportation accident; 22% life-threatening illness; 35% exposed to violent death	NR	NR
Intervention details	Sertraline (titrated up to 200mg/day). Participants reporting problems sleeping were supplemented with mianserin in doses of 10–30mg at night, with doses titrated weekly by 10 mg. Patients who had too many side-effects from sertraline were switched to mianserin solely. After 2 months sertraline was combined with manualised CBT treatment and included methods from acceptance and commitment therapy (ACT), mindfulness exercises and in vivo and visualised exposure for 4 months of weekly CBT sessions[1] Paroxetine 20mg/day (standard dose) + prolonged exposure (PE; following manual by Foa et al. 2007; 10-12x weekly 90-min sessions)[2] Paroxetine (12.5-50mg/day) + prolonged exposure (following protocol	Sertraline (50-200mg/day) combined with integrated, present-Focused CBT, Seeking Safety (Najavits, 2002)	Paroxetine, titrated up to 60mg/day	Sertraline (planned intensity NR)[4] Paroxetine, 10-60mg/day[5]

Comparison	SSRI + TF-CBT versus (+/- placebo +) TF-CBT	Sertraline (+ non-TF-CBT) versus placebo (+ non-TF-CBT)	Paroxetine versus amitriptyline	SSRI versus mirtazapine
	of Foa & Rothbaum, 1998; 10x weekly 90-min sessions)[3]			
Intervention format	Oral	Oral	Oral	Oral
Actual intervention intensity	The mean maximum dose of sertraline was 132.1 mg (+/– 56 mg) and 20.0 (+/– 10 mg) of mianserin. The end dose of both drugs was slightly lower at 119.3 mg sertraline (+/– 66 mg) and 15.7 mg (+/– 12 mg) mianserin. The mean number of sessions with a physician was nine. CBT consisted of, on average, 12 sessions[1] Mean attended PE sessions 8.0 (SD = 3.4)[2] NR[3]	Mean attendance rates for CBT were 6.7 sessions	NR	Mean daily dose was 101.5 mg/day[4] Mean final dose 38.9mg/day (SD=10.2)[5]
Comparator	Trauma-focused cognitive therapy[1] Prolonged exposure (PE; following manual by Foa et al. 2007)[2] Placebo + prolonged exposure[3]	Placebo combined with integrated, present-Focused CBT, Seeking Safety (Najavits, 2002)	Amitriptyline, 75-200mg/day	Mirtazapine (planned intensity NR). Mean daily dose 34.1mg[4] Mirtazapine, 15-60mg/day. Mean final dose 43.9mg/day (SD=15.0)[5]
Intervention length (weeks)	26[1] 12[2] 10[3]	12	12	6[4] 8[5]

AUD, alcohol use disorders; BME, Black and Minority Ethnic; CBT, cognitive behavioural therapy; DSM, Diagnostic and Statistical Manual of mental disorders; ICD, International Classification of Disease; MDD, major depressive disorder; MVA, motor vehicle accidents; NA, not applicable; NR, not reported; PE, psychoeducation; PTSD, post-traumatic stress disorder; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors; SUD, substance use disorder; TF-CBT, trauma-focused-cognitive behavioural therapy

[1]*Buhmann 2016;*
[2]*Popiel 2015;*
[3]*Schneier 2012;*
[4]*Chung 2004/2005;*
[5]*Seo 2010*

Table 18: Summary of included studies: SSRIs for delayed treatment (>3 months)-part 3

Comparison	Sertraline versus venlafaxine	Sertraline (+ TF-CBT) versus venlafaxine (+ TF- CBT)	Sertraline versus nefazodone
Total no. of studies (N randomised)	1 (538)	1 (207)	2 (97)
Study ID	Davidson 2006b/Davidson unpublished	Sonne 2016	McRae 2004[1] Saygin 2002[2]
Country	US	Denmark	US[1] Turkey[2]
Diagnostic status	PTSD diagnosis according to ICD/DSM criteria	Clinically important PTSD symptoms (scoring above a threshold on validated scale)	Clinically important PTSD symptoms (scoring above a threshold on validated scale) [1] PTSD diagnosis according to ICD/DSM criteria[2]
Mean months since onset of PTSD	NR (≥6 months)	NR	NR (≥3 months inclusion criterion) [1] NR[2]
Mean age (range)	NR	43.7 (range NR)	40.3 (18-65) [1] 41.5 (range NR) [2]
Sex (% female)	NR	40	77[1] 76[2]
Ethnicity (% BME)	NR	NR	NR
Coexisting conditions	NR	99% depression; 41% enduring personality change	NR[1] 40% of sertraline group and 25% of nefazodone group had another psychiatric diagnosis: 9% OCD; 9% MDD; 6% GAD; 2% Panic Disorder; 2% Social Phobia; 2% Specific Phobia; 4% Conversion Disorder[2]
Mean months since traumatic event	NR	NR (mean 14.6 years since arrival in Denmark)	264[1] NR[2]
Type of traumatic event	Mixed: Most common types of primary trauma were nonsexual abuse (26%), adult sexual abuse (16%), childhood sexual abuse (15%), unexpected death (13%), accidental injury (12%), and combat (9%)	Witnessing war as a civilian: Refugees who had experienced imprisonment (53%), torture (48%) and/or refugee camp (26%). Country of origin: Iraq (35%); Iran (14%); Afghanistan (14%); Lebanon (13%); Ex-Yugoslavia (10%); other (16%)	Mixed: 15% Childhood physical or sexual abuse; 19% Physical assault; 31% Sexual assault; 15% Accident; 19% Other[1] Natural disaster: Marmara Earthquake (1999) [2]

Comparison	Sertraline versus venlafaxine	Sertraline (+ TF-CBT) versus venlafaxine (+ TF- CBT)	Sertraline versus nefazodone
Single or multiple incident index trauma	Single	Multiple	
Lifetime experience of trauma	NR	NR	NR
Intervention details	Sertraline, 25-200mg/day	Sertraline (25-200mg/day) + manualised psychotherapy (16 sessions) and social counselling. Psychotherapy was flexible CBT, including elements from trauma-focused cognitive behavioural therapy (TF-CBT), acceptance and commitment therapy (ACT), stress management and mindfulness	Sertraline, 50-200mg/day[1] Sertraline, 50-100mg/day[2]
Intervention format	Oral	Oral	Oral
Actual intervention intensity	The mean average prescribed daily dose was 110.2 mg/d for sertraline and the mean maximum prescribed daily dose was 151.4 mg/d (range, 25.0–200.0 mg/d). 49% (85/173) of patients in the sertraline group achieved maximum dosing	Mean dose 96.2mg/day	Mean final dose 153mg/day[1] Mean dose 68.33mg/day (SD=21.70) [2]
Comparator	Venlafaxine, 37.5-300 mg/day. Mean daily dose 164.4mg	Venlafaxine (slow-release, 37.5-375mg/day) + manualised psychotherapy (16 sessions) and social counselling. Mean dose 225mg/day	Nefazodone, 100-600mg/day. Mean final dose 463mg/day[1] Nefazodone, 200-400mg/day. Mean dose 332.35mg/day (SD=63.5)[2]
Intervention length (weeks)	12	30	12[1] 22[2]

BME, Black and Minority Ethnic; CBT, cognitive behavioural therapy; DSM, Diagnostic and Statistical Manual of mental disorders; GAD, generalised anxiety disorder; ICD, International Classification of Disease; MDD, major depressive disorder; NR, not reported; PE, psychoeducation; PTSD, post-traumatic stress disorder; SD, standard deviation; TF-CBT, trauma-focused-cognitive behavioural therapy
[1]McRae 2004;
[2]Saygin 2002

Table 19: Summary of included studies: SSRIs for delayed treatment (>3 months)-part 4

Comparison	Fluoxetine versus moclobemide	Fluoxetine versus tianeptine	Fluvoxamine versus reboxetine	Maintenance SSRIs versus placebo
Total no. of studies (N randomised)	1 (103)	1 (103)	1 (40)	3 (334)
Study ID	Onder 2006	Onder 2006	Spivak 2006	Davidson 2001a[1] Davidson 2005a[2] SKB650[3]
Country	Turkey	Turkey	Israel	US[1,2] Unclear[3]
Diagnostic status	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria	Responders (in relapse prevention study)
Mean months since onset of PTSD	NR	NR	NR	157[1] NR[2] NR ('chronic')[3]
Mean age (range)	31.4 (range NR)	31.4 (range NR)	40.1 (range NR)	43.4 (21-69)[1] 44.1 (range NR)[2] 43 (18-82)[3]
Sex (% female)	50	50	48	70[1] 50[2] 66[3]
Ethnicity (% BME)	NR	NR	NR	NR[1,3] 19[2]
Coexisting conditions	NR	NR	NR	40% secondary depressive disorder; 20% secondary anxiety disorder[1] NR[2,3]
Mean months since traumatic event	NR	NR	NR	NR
Type of traumatic event	Natural disaster: Marmara Earthquake (1999)	Natural disaster: Marmara Earthquake (1999)	Motor vehicle collision (no further detail reported)	Mixed: 55% physical or sexual assault; 13% seeing someone hurt or die; 9% being in a war or combat; 6% serious accident, injury, or fire; 17% miscellaneous other events Mixed: 32% combat; 16% sexual trauma; 16% other violence; 19% death

Comparison	Fluoxetine versus moclobemide	Fluoxetine versus tianeptine	Fluvoxamine versus reboxetine	Maintenance SSRIs versus placebo
				[bereavement]; 18% other[2] Unclear (no details reported)[3]
Single or multiple incident index trauma	Single	Single	Single	Single[1] Unclear[2,3]
Lifetime experience of trauma	NR	NR	NR	NR
Intervention details	Fluoxetine, 20-40mg/day	Fluoxetine, 20-40mg/day	Fluvoxamine, 150mg/day	Sertraline (planned dose NR)[1] Fluoxetine, maximum of 60mg/day (open-label dose maintained)[2] Paroxetine, up to maximum dose of 50mg/day[3]
Intervention format	Oral	Oral	Oral	Oral
Actual intervention intensity	NR	NR	NR	Mean dose 137mg/day (SD=52)[1] Mean dose at randomisation 48.6mg/day (SD=15.4)[2] NR[3]
Comparator	Moclobemide, 450-900mg/day	Tianeptine, 37.5-50mg/day	Reboxetine, 8mg/day	Placebo. Mean dose 145mg/day (SD=58)[1] Mean dose at randomisation 42.1mg/day (SD=13.9)[2] Placebo (actual intensity, dose equivalent, NR)[3]
Intervention length (weeks)	12	12	8	28[1] 26[2] 24[3]

BME, Black and Minority Ethnic; DSM, Diagnostic and Statistical Manual of mental disorders; ICD, International Classification of Disease; NR, not reported; PTSD, post-traumatic stress disorder; SD, standard deviation; SSRI, selective serotonin reuptake disorder
[1]Davidson 2001a;
[2]Davidson 2005a;
[3]SKB650

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review (SSRIs for the treatment of PTSD in adults) are presented in Table 20, Table 21, Table 22, Table 23, Table 24, Table 25, Table 26, Table 27, Table 28, Table 29, Table 30 and Table 31.

Table 20: Summary clinical evidence profile: SSRIs versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk SSRIs			
PTSD symptomatology self-rated DTS/IES-R change score Follow-up: 10-12 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 0.26 standard deviations lower (0.39 to 0.14 lower)		3593 (16 studies)	low[1,2]
PTSD symptomatology clinician-rated CAPS/SI–PTSD change score Follow-up: 8-12 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.28 standard deviations lower (0.4 to 0.16 lower)		3475 (17 studies)	very low[1,2,3]
Remission clinician-rated Number of people scoring <20 on CAPS/no longer meeting diagnostic criteria for PTSD Follow-up: 8-12 weeks	192 per 1000	251 per 1000 (205 to 305)	RR 1.31 (1.07 to 1.59)	1527 (5 studies)	low[2,4]
Remission self-rated Number of people scoring <18 on DTS	149 per 1000	247 per 1000 (163 to 375)	RR 1.65 (1.09 to 2.51)	384 (1 study)	low[2,5]
Response Number of people showing ≥30% improvement on CAPS or IES-R/≥50% improvement on TOP-8 and/or CGI-I much or very much improved Follow-up: 10-12 weeks	410 per 1000	553 per 1000 (492 to 623)	RR 1.35 (1.2 to 1.52)	2155 (11 studies)	low[2,3]
Anxiety symptoms HAM-A change score Follow-up: 10-12 weeks		The mean anxiety symptoms in the intervention groups was 0.15 standard deviations lower (0.37 lower to 0.06 higher)		1060 (5 studies)	very low[1,2,3]
Depression symptoms HAM-		The mean depression		3135 (14 studies)	very low[1,2,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk SSRIs			
D/MADRS/BDI/BDI-II change score Follow-up: 8-12 weeks		symptoms in the intervention groups was 0.24 standard deviations lower (0.37 to 0.11 lower)			
Dissociative symptoms DES change score Follow-up: mean 10 weeks		The mean dissociative symptoms in the intervention groups was 0.86 standard deviations lower (1.62 to 0.1 lower)		30 (1 study)	low[2,6]
Functional impairment SDS change score Follow-up: mean 12 weeks		The mean functional impairment in the intervention groups was 0.33 standard deviations lower (0.49 to 0.17 lower)		1506 (5 studies)	low[1,2]
Global functioning GAF change score Follow-up: mean 12 weeks Better indicated by higher values		The mean global functioning in the intervention groups was 0.32 standard deviations higher (0.11 to 0.53 higher)		352 (1 study)	low[2,6]
Quality of life Q-LES-Q-SF change score Follow-up: mean 12 weeks Better indicated by higher values		The mean quality of life in the intervention groups was 0.59 standard deviations higher (0.16 to 1.03 higher)		535 (2 studies)	very low[2,7]
Sleeping difficulties PSQI change score Follow-up: mean 12 weeks		The mean sleeping difficulties in the intervention groups was 0.04 standard deviations higher (0.25 lower to 0.32 higher)		368 (2 studies)	low[2,6]
Relationship difficulties IIP change score Follow-up: mean 10 weeks		The mean relationship difficulties in the intervention groups was 0.73 standard deviations lower		30 (1 study)	low[2,6]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk SSRIs			
		(1.48 lower to 0.02 higher)			
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: 8-12 weeks	301 per 1000	304 per 1000 (276 to 337)	RR 1.01 (0.92 to 1.12)	3569 (17 studies)	moderate[2]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: 10-12 weeks	67 per 1000	95 per 1000 (74 to 122)	RR 1.42 (1.1 to 1.82)	3074 (13 studies)	low[2,5]

BDI, Beck Depression Inventory; CAPS, Clinician Administered PTSD Scale; CGI-I, Clinical Global Impression scale-Global Improvement; CI, confidence interval; DES, Dissociative Experiences Scale; DTS, Davidson Trauma Scale; GAF, Global Assessment of Functioning; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; IES-R, Impact of Event Scale-Revised; IIP, Inventory of Interpersonal Problems; MADRS, Montgomery-Asberg Depression Rating Scale; PTSD, post-traumatic stress disorder; PSQI, Pittsburgh Sleep Quality Index; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; RR, risk ratio; SDS, Sheehan Disability Scale; SI-PTSD, Structured Interview for PTSD; SMD, standard mean difference; SSRIs, Selective Serotonin Reuptake Inhibitors; TOP-8, Treatment Outcome PTSD scale

[1] *Substantial heterogeneity (I2>50%)*
[2] *Funding from pharmaceutical company*
[3] *Unclear blinding of outcome assessor(s) and unclear risk of attrition bias*
[4] *Unclear blinding of outcome assessor(s)*
[5] *OIS not met (events<300)*
[6] *OIS not met (N<400)*
[7] *Considerable heterogeneity (I2>80%)*

Table 21: Summary clinical evidence profile: Sertraline (+ non-trauma-focused cognitive therapy) versus placebo (+ non-trauma-focused cognitive therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ non-trauma-focused cognitive therapy)	Corresponding risk Sertraline (+ non-trauma-focused cognitive therapy)			
PTSD symptomatology clinician-rated at endpoint CAPS change score Follow-up: mean 12 weeks		The mean PTSD symptomatology clinician-rated at endpoint in the intervention groups was 0.6 standard deviations lower		49 (1 study)	moderate[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ non-trauma-focused cognitive therapy)	Corresponding risk Sertraline (+ non-trauma-focused cognitive therapy)			
		(1.17 to 0.02 lower)			
PTSD symptomatology clinician-rated at 6-month follow-up CAPS change score Follow-up: mean 26 weeks		The mean PTSD symptomatology clinician-rated at 6-month follow-up in the intervention groups was 0.82 standard deviations lower (1.41 to 0.23 lower)		49 (1 study)	moderate[1]
PTSD symptomatology clinician-rated at 12-month follow-up CAPS change score Follow-up: mean 52 weeks		The mean PTSD symptomatology clinician-rated at 12-month follow-up in the intervention groups was 0.83 standard deviations lower (1.46 to 0.21 lower)		43 (1 study)	moderate[1]
Response at endpoint Number of people showing improvement of at least 15 points on CAPS Follow-up: mean 12 weeks	486 per 1000	783 per 1000 (535 to 1000)	RR 1.61 (1.1 to 2.34)	69 (1 study)	moderate[2]
Response at 6-month follow-up Number of people showing improvement of at least 15 points on CAPS Follow-up: mean 26 weeks	649 per 1000	811 per 1000 (610 to 1000)	RR 1.25 (0.94 to 1.67)	69 (1 study)	moderate[3]
Response at 12-month follow-up Number of people showing improvement of at least 15 points on	649 per 1000	941 per 1000 (726 to 1000)	RR 1.45 (1.12 to 1.86)	69 (1 study)	moderate[2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ non-trauma-focused cognitive therapy)	Corresponding risk Sertraline (+ non-trauma-focused cognitive therapy)			
CAPS Follow-up: mean 52 weeks					
Alcohol use: Number of heavy drinking days in the past 7 days at endpoint TLFB HDD (≥5 drinks/day for men and ≥4 drinks/day for women) change score Follow-up: mean 12 weeks		The mean alcohol use: number of heavy drinking days in the past 7 days at endpoint in the intervention groups was 0.22 standard deviations higher (0.36 lower to 0.79 higher)		47 (1 study)	moderate[4]
Alcohol use: Number of heavy drinking days in the past 7 days at 6-month follow-up TLFB HDD (≥5 drinks/day for men and ≥4 drinks/day for women) change score Follow-up: mean 26 weeks		The mean alcohol use: number of heavy drinking days in the past 7 days at 6-month follow-up in the intervention groups was 0.08 standard deviations lower (0.64 lower to 0.47 higher)		50 (1 study)	moderate[3]
Alcohol use: Number of heavy drinking days in the past 7 days at 12-month follow-up TLFB HDD (≥5 drinks/day for men and ≥4 drinks/day for women) change score Follow-up: mean 52 weeks		The mean alcohol use: number of heavy drinking days in the past 7 days at 12-month follow-up in the intervention groups was 0.09 standard deviations lower (0.7 lower to 0.52 higher)		41 (1 study)	low[5]
Alcohol use: Drinks per drinking day at endpoint TLFB DDD change score Follow-up: mean 12 weeks		The mean alcohol use: drinks per drinking day at endpoint in the intervention groups was 0.27 standard		47 (1 study)	moderate[4]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ non-trauma-focused cognitive therapy)	Corresponding risk Sertraline (+ non-trauma-focused cognitive therapy)			
		deviations higher (0.31 lower to 0.85 higher)			
Alcohol use: Drinks per drinking day at 6-month follow-up TLFB DDD change score Follow-up: mean 26 weeks		The mean alcohol use: drinks per drinking day at 6-month follow-up in the intervention groups was 0.25 standard deviations lower (0.81 lower to 0.31 higher)		50 (1 study)	moderate[3]
Alcohol use: Drinks per drinking day at 12-month follow-up TLFB DDD change score Follow-up: mean 52 weeks		The mean alcohol use: drinks per drinking day at 12-month follow-up in the intervention groups was 0.06 standard deviations lower (0.67 lower to 0.55 higher)		41 (1 study)	low[5]
Alcohol use: Abstinence at endpoint Number of participants abstinent from alcohol (in the prior 7 days; TLFB) Follow-up: mean 12 weeks	600 per 1000	456 per 1000 (258 to 792)	RR 0.76 (0.43 to 1.32)	47 (1 study)	low[5]
Alcohol use: Abstinence at 6-month follow-up Number of participants abstinent from alcohol (in the prior 7 days; TLFB) Follow-up: mean 26 weeks	464 per 1000	543 per 1000 (316 to 947)	RR 1.17 (0.68 to 2.04)	50 (1 study)	low[5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ non-trauma-focused cognitive therapy)	Corresponding risk Sertraline (+ non-trauma-focused cognitive therapy)			
Alcohol use: Abstinence at 12-month follow-up Number of participants abstinent from alcohol (in the prior 7 days; TLFB) Follow-up: mean 52 weeks	571 per 1000	400 per 1000 (206 to 766)	RR 0.7 (0.36 to 1.34)	41 (1 study)	low[5]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 12 weeks	324 per 1000	250 per 1000 (117 to 535)	RR 0.77 (0.36 to 1.65)	69 (1 study)	low[5]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 12 weeks	54 per 1000	31 per 1000 (3 to 329)	RR 0.58 (0.05 to 6.08)	69 (1 study)	low[5]

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference; TLFB-DDD/HDD, alcohol timeline feedback-drinks per drinking days/heavy drinking days

[1] OIS not met (N<400)

[2] OIS not met (events<300)

[3] 95% CI crosses both line of no effect and threshold for clinically important benefit

[4] 95% CI crosses both line of no effect and threshold for clinically important harm

[5] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Table 22: Summary clinical evidence profile: SSRI versus mirtazapine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Mirtazapine	Corresponding risk SSRI			
PTSD symptomatology clinician-rated CAPS change score Follow-up: 6-8 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.29 standard deviations higher (0.34 lower to 0.93 higher)		140 (2 studies)	very low[1,2,3,4]
Response Number of people showing ≥30% improvement on CAPS Follow-up: 6-8 weeks	756 per 1000	734 per 1000 (484 to 1000)	RR 0.97 (0.64 to 1.47)	153 (2 studies)	very low[1,2,4,5]
Depression symptoms HAM-D/BDI-II change score Follow-up: 6-8 weeks		The mean depression symptoms in the intervention groups was 0.15 standard deviations higher (0.32 lower to 0.63 higher)		140 (2 studies)	very low[1,3,4]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: 6-8 weeks	167 per 1000	107 per 1000 (42 to 270)	RR 0.64 (0.25 to 1.62)	153 (2 studies)	very low[1,4,5]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: 6-8 weeks	38 per 1000	17 per 1000 (3 to 111)	RR 0.44 (0.07 to 2.88)	153 (2 studies)	low[5]

BDI, Beck Depression Inventory; CI, confidence interval; CAPS, clinician administered PTSD scale; HAM-D, Hamilton Depression Rating Scale-Depression; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference; SSRI, selective serotonin reuptake inhibitor

[1] Risk of bias is high or unclear across multiple domains

[2] Substantial heterogeneity (I2>50%)

[3] 95% CI crosses both line of no effect and threshold for clinically important effect

[4] *Funding from pharmaceutical company*
[5] *95% CI crosses line of no effect and thresholds for both clinically important benefit and harm*

Table 23: Summary clinical evidence profile: Sertraline versus nefazodone for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Nefazodone	Corresponding risk Sertraline			
PTSD symptomatology self-rated DTS change score Follow-up: mean 12 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 0.46 standard deviations higher (0.32 lower to 1.24 higher)		26 (1 study)	low[1,2]
PTSD symptomatology clinician-rated CAPS/TOP-8 change score Follow-up: 12-22 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.7 standard deviations lower (1.47 lower to 0.07 higher)		80 (2 studies)	very low[1,2,3,4]
Anxiety symptoms HAM-A change score Follow-up: mean 12 weeks		The mean anxiety symptoms in the intervention groups was 0.4 standard deviations higher (0.37 lower to 1.18 higher)		26 (1 study)	very low[1,2,3]
Depression symptoms MADRS change score Follow-up: mean 12 weeks		The mean depression symptoms in the intervention groups was 0.28 standard deviations higher (0.49 lower to 1.05 higher)		26 (1 study)	very low[1,2,3]
Functional impairment SDS change score Follow-up: mean 12 weeks		The mean functional impairment in the intervention groups was 0.09 standard deviations higher (0.68 lower to 0.86 higher)		26 (1 study)	very low[2,5]
Sleeping difficulties		The mean sleeping		26 (1 study)	very low[2,5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Nefazodone	Corresponding risk Sertraline			
PSQI change score Follow-up: mean 12 weeks		difficulties in the intervention groups was 0.06 standard deviations lower (0.83 lower to 0.71 higher)			
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: 12-22 weeks	229 per 1000	89 per 1000 (5 to 1000)	RR 0.39 (0.02 to 7.14)	97 (2 studies)	very low[2,4,5]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 12 weeks	111 per 1000	106 per 1000 (17 to 670)	RR 0.95 (0.15 to 6.03)	37 (1 study)	very low[2,5]

CAPS, clinical administered PTSD scale; CI, confidence interval; DTS, Davidson Trauma Scale; PSQI, Pittsburgh Sleep Quality Index; RR, risk ration; SDS, Sheehan Disability Scale; TOP-8, Treatment Outcome PTSD scale; SMD, standard mean difference

[1] 95% CI crosses both line of no effect and threshold for clinically important effect

[2] Funding from pharmaceutical company

[3] Risk of bias is high or unclear across multiple domains

[4] Substantial heterogeneity (I2>50%)

[5] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Table 24: Summary clinical evidence profile: Fluoxetine versus moclobemide for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Moclobemide	Corresponding risk Fluoxetine			
PTSD symptomatology clinician-rated CAPS change score Follow-up: mean 12 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.13 standard deviations lower (0.59 lower to 0.33 higher)		73 (1 study)	very low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Moclobemide	Corresponding risk Fluoxetine			
Response Number of people showing >50% improvement on CAPS Follow-up: mean 12 weeks	629 per 1000	761 per 1000 (559 to 1000)	RR 1.21 (0.89 to 1.66)	73 (1 study)	very low[1,2]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 12 weeks	143 per 1000	184 per 1000 (64 to 527)	RR 1.29 (0.45 to 3.69)	73 (1 study)	very low[1,3]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 12 weeks	29 per 1000	105 per 1000 (12 to 897)	RR 3.68 (0.43 to 31.4)	73 (1 study)	very low[1,3]

CAPS, clinician administered PTSD scale; CI, confidence interval; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] Open-label
[2] 95% CI crosses both line of no effect and threshold for clinically important effect
[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Table 25: Summary clinical evidence profile: Fluoxetine versus tianeptine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Tianeptine	Corresponding risk Fluoxetine			
PTSD symptomatology clinician-rated CAPS change score Follow-up: mean 12 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.03 standard deviations higher (0.45 lower to 0.51 higher)		68 (1 study)	very low[1,2]
Response Number of people showing >50%	767 per 1000	767 per 1000 (583 to 997)	RR 1 (0.76 to 1.3)	68 (1 study)	very low[1,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Tianeptine	Corresponding risk Fluoxetine			
improvement on CAPS Follow-up: mean 12 weeks					
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 12 weeks	200 per 1000	184 per 1000 (70 to 490)	RR 0.92 (0.35 to 2.45)	68 (1 study)	very low[1,3]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 12 weeks	67 per 1000	105 per 1000 (21 to 537)	RR 1.58 (0.31 to 8.05)	68 (1 study)	very low[1,3]

CAPS, clinician administered PTSD scale; CI, confidence interval; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] Open-label
[2] 95% CI crosses line of no effect and threshold for clinically important effect
[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Table 26: Summary clinical evidence profile: Fluvoxamine versus reboxetine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Reboxetine	Corresponding risk Fluvoxamine			
PTSD symptomatology clinician-rated CAPS change score Follow-up: mean 8 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.57 standard deviations lower (1.34 lower to 0.21 higher)		28 (1 study)	very low[1,2,3]
Anxiety symptoms HAM-A change score Follow-up: mean 8 weeks		The mean anxiety symptoms in the intervention groups was 0 standard deviations higher		28 (1 study)	very low[1,3,4]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Reboxetine	Corresponding risk Fluvoxamine			
		(0.76 lower to 0.76 higher)			
Depression symptoms HAM-D change score Follow-up: mean 8 weeks		The mean depression symptoms in the intervention groups was 0.24 standard deviations lower (1 lower to 0.52 higher)		28 (1 study)	very low[1,3,4]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 8 weeks	450 per 1000	149 per 1000 (49 to 472)	RR 0.33 (0.11 to 1.05)	40 (1 study)	low[2,3]

CAPS, clinician-administered PTSD scale; CI, confidence interval; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference;

[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses both line of no effect and threshold for clinically important effect
[3] Funding from pharmaceutical company
[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Table 27: Summary clinical evidence profile: Sertraline versus venlafaxine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Venlafaxine	Corresponding risk Sertraline			
PTSD symptomatology self-rated DTS change score Follow-up: mean 12 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 0.25 standard deviations higher (0.04 to 0.46 higher)		352 (1 study)	low[1,2]
PTSD symptomatology clinician-rated CAPS change score		The mean PTSD symptomatology clinician-rated in the intervention groups was		352 (1 study)	very low[1,2,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Venlafaxine	Corresponding risk Sertraline			
Follow-up: mean 12 weeks		0.15 standard deviations higher (0.06 lower to 0.35 higher)			
Remission Number of people scoring <20 on CAPS Follow-up: mean 12 weeks	302 per 1000	241 per 1000 (172 to 344)	RR 0.8 (0.57 to 1.14)	352 (1 study)	very low[2,3,4]
Depression symptoms HAM-D change score Follow-up: mean 12 weeks		The mean depression symptoms in the intervention groups was 0.19 standard deviations higher (0.02 lower to 0.4 higher)		352 (1 study)	very low[1,2,3]
Functional impairment SDS change score Follow-up: mean 12 weeks		The mean functional impairment in the intervention groups was 0.09 standard deviations higher (0.12 lower to 0.3 higher)		352 (1 study)	low[1,2]
Global functioning GAF change score Follow-up: mean 12 weeks Better indicated by higher values		The mean global functioning in the intervention groups was 0.08 standard deviations lower (0.29 lower to 0.13 higher)		352 (1 study)	low[1,2]
Quality of life Q-LES-Q-SF change score Follow-up: mean 12 weeks Better indicated by higher values		The mean quality of life in the intervention groups was 0.06 standard deviations lower (0.27 lower to 0.15 higher)		352 (1 study)	low[1,2]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events	302 per 1000	359 per 1000 (265 to 483)	RR 1.19 (0.88 to 1.6)	352 (1 study)	low[2,4]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Venlafaxine	Corresponding risk Sertraline			
Follow-up: mean 12 weeks					
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 12 weeks	95 per 1000	127 per 1000 (70 to 231)	RR 1.34 (0.74 to 2.43)	352 (1 study)	very low[2,5]

CAPS, clinician administered PTSD scale; CI, confidence interval; DTS, Davidson Trauma Scale; GAF, Global Assessment of Functioning; HAM-D, Hamilton Anxiety Rating scale-Depression; PTSD, post-traumatic stress disorder; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; RR, risk ratio; SMD, standard mean difference

[1] OIS not met (N<400)

[2] Funding from pharmaceutical company

[3] Risk of bias is unclear across multiple domains

[4] 95% CI crosses both line of no effect and threshold for clinically important effect

[5] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Table 28: Summary clinical evidence profile: Sertraline (+ trauma-focused CBT) versus venlafaxine (+ trauma-focused CBT) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Venlafaxine (+ trauma-focused CBT)	Corresponding risk Sertraline (+ trauma-focused CBT)			
PTSD symptomatology self-rated HTQ change score Follow-up: mean 30 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 0.15 standard deviations lower (0.43 lower to 0.13 higher)		195 (1 study)	low[1,2]
Anxiety symptoms HAM-A change score Follow-up: mean 30 weeks		The mean anxiety symptoms in the intervention groups was 0.08 standard deviations higher (0.2 lower to 0.36 higher)		195 (1 study)	low[1,2]
Depression symptoms HAM-D change score		The mean depression symptoms in the intervention groups was		195 (1 study)	low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Venlafaxine (+ trauma-focused CBT)	Corresponding risk Sertraline (+ trauma-focused CBT)			
Follow-up: mean 30 weeks		0.02 standard deviations lower (0.3 lower to 0.27 higher)			
Functional impairment SDS change score Follow-up: mean 30 weeks		The mean functional impairment in the intervention groups was 0.39 standard deviations lower (0.68 to 0.11 lower)		195 (1 study)	low[1,2]
Quality of life WHO-5 change score Follow-up: mean 30 weeks Better indicated by higher values		The mean quality of life in the intervention groups was 0.29 standard deviations higher (0.01 to 0.58 higher)		195 (1 study)	low[1,2]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 30 weeks	306 per 1000	193 per 1000 (119 to 312)	RR 0.63 (0.39 to 1.02)	207 (1 study)	moderate[3]

CBT, cognitive behavioural therapy; CI, confidence interval; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; HTQ, Harvard Trauma Questionnaire; PTSD, post-traumatic stress disorder; RR, risk ratio; SDS, Sheehan Disability Scale; SMD, standard mean difference

[1] Open-label

[2] OIS not met (N<400)

[3] 95% CI crosses both line of no effect and threshold for clinically important effect

Table 29: Summary clinical evidence profile: Paroxetine versus amitriptyline for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Amitriptyline	Corresponding risk Paroxetine			
PTSD symptomatology clinician-rated CAPS change		The mean PTSD symptomatology clinician-rated in the intervention		42 (1 study)	very low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Amitriptyline	Corresponding risk Paroxetine			
score Follow-up: mean 12 weeks		groups was 0.66 standard deviations higher (0.03 to 1.28 higher)			
Response Number of people showing ≥30% improvement on CAPS & CGI-I much or very much improved Follow-up: mean 12 weeks	440 per 1000	282 per 1000 (132 to 603)	RR 0.64 (0.3 to 1.37)	50 (1 study)	very low[1,3]
Anxiety symptoms BAI change score Follow-up: mean 12 weeks		The mean anxiety symptoms in the intervention groups was 0.61 standard deviations higher (0.01 lower to 1.23 higher)		42 (1 study)	low[1,4]
Depression symptoms BDI change score Follow-up: mean 12 weeks		The mean depression symptoms in the intervention groups was 0.04 standard deviations lower (0.65 lower to 0.56 higher)		42 (1 study)	very low[1,3]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 12 weeks	200 per 1000	120 per 1000 (32 to 450)	RR 0.6 (0.16 to 2.25)	50 (1 study)	low[3]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 12 weeks	200 per 1000	120 per 1000 (32 to 450)	RR 0.6 (0.16 to 2.25)	50 (1 study)	low[3]

BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CAPS, clinician-administered PTSD scale; CGI-I, Clinical Global Impression scale-Global Improvement; CI, confidence interval; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] Open-label (no blinding)
[2] OIS not met (N<400)
[3] 95% CI crosses line of no effect and threshold for both clinically important benefit and harm
[4] 95% CI crosses both line of no effect and threshold for clinically important effect

Table 30: Summary clinical evidence profile: SSRIs versus placebo for maintenance treatment of PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk SSRIs			
Relapse Number of participants who relapsed Follow-up: 24-28 weeks	386 per 1000	197 per 1000 (96 to 409)	RR 0.51 (0.25 to 1.06)	322 (3 studies)	very low[1,2,3,4]
PTSD symptomatology self-rated DTS change score Follow-up: 24-28 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 0.24 standard deviations lower (0.87 lower to 0.39 higher)		211 (2 studies)	very low[3,4,5]
PTSD symptomatology clinician-rated CAPS change score Follow-up: mean 24 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.19 standard deviations higher (0.15 lower to 0.54 higher)		129 (1 study)	very low[1,4,6]
Depression symptoms HAM-D change score Follow-up: mean 28 weeks		The mean depression symptoms in the intervention groups was 3.19 standard deviations lower (3.85 to 2.54 lower)		84 (1 study)	very low[1,4,7]
Quality of life Q-LES-Q-SF change score Follow-up: mean 28 weeks Better indicated by higher values		The mean quality of life in the intervention groups was 3.47 standard deviations higher (2.78 to 4.16 higher)		84 (1 study)	low[4,7]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk SSRIs			
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: 24-28 weeks	416 per 1000	254 per 1000 (175 to 370)	RR 0.61 (0.42 to 0.89)	322 (3 studies)	low[4,8]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: 26-28 weeks	38 per 1000	70 per 1000 (19 to 257)	RR 1.81 (0.49 to 6.69)	146 (2 studies)	very low[4,9]

CAPS, clinician administered PTSD scale; CI, confidence interval; DTS, Davidson Trauma Scale; HAM-D, Hamilton Anxiety Rating scale-Depression; PTSD, post-traumatic stress disorder; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; RR, risk ratio; SMD, standard mean difference; SSRIs, selective serotonin reuptake inhibitors

[1] Risk of bias is high or unclear across multiple domains
[2] Substantial heterogeneity (I2>50%)
[3] 95% CI crosses both line of no effect and threshold for clinically important benefit
[4] Funding from pharmaceutical company
[5] Considerable heterogeneity (I2=>80%)
[6] 95% CI crosses both line of no effect and threshold for clinically important harm
[7] OIS not met (N<400)
[8] OIS not met (events<300)
[9] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Table 31: Summary clinical evidence profile: SSRI + trauma-focused CBT versus (+/- placebo +) trauma-focused CBT for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Trauma-focused CBT (+/- placebo)	Corresponding risk SSRI + trauma-focused CBT			
PTSD symptomatology self-rated at endpoint HTQ/PDS change score Follow-up: 12-26 weeks		The mean PTSD symptomatology self-rated at endpoint in the intervention groups was 0.1 standard deviations lower (0.39 lower to 0.18 higher)		222 (2 studies)	low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Trauma-focused CBT (+/- placebo)	Corresponding risk SSRI + trauma-focused CBT			
PTSD symptomatology self-rated at 1-year follow-up PDS change score Follow-up: mean 52 weeks		The mean PTSD symptomatology self-rated at 1-year follow-up in the intervention groups was 0.21 standard deviations lower (0.65 lower to 0.23 higher)		115 (1 study)	low[1,3]
PTSD symptomatology clinician-rated CAPS/SI–PTSD change score Follow-up: 10-12 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.6 standard deviations lower (1.39 lower to 0.19 higher)		141 (2 studies)	very low[1,3,4]
Remission Number of people no longer meeting diagnostic criteria for PTSD/scoring ≤20 on CAPS & CGI-I score=1 Follow-up: 10-12 weeks	568 per 1000	608 per 1000 (136 to 1000)	RR 1.07 (0.24 to 4.69)	208 (2 studies)	very low[1,5,6]
Response Number of people rated as 'much' or 'very much' improved on CGI-I Follow-up: mean 10 weeks	389 per 1000	630 per 1000 (323 to 1000)	RR 1.62 (0.83 to 3.18)	37 (1 study)	low[1,3]
Anxiety symptoms at endpoint HAM-A/STAI State change score Follow-up: 12-26 weeks		The mean anxiety symptoms at endpoint in the intervention groups was 0.23 standard deviations lower (0.52 lower to 0.06 higher)		222 (2 studies)	very low[1,3]
Anxiety symptoms at 1-year follow-up STAI State change score Follow-up: mean 52 weeks		The mean anxiety symptoms at 1-year follow-up in the intervention groups was 0.08 standard deviations lower (0.52 lower to 0.35 higher)		115 (1 study)	low[1,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Trauma-focused CBT (+/- placebo)	Corresponding risk SSRI + trauma-focused CBT			
Depression symptoms at endpoint HAM-D/BDI-II change score Follow-up: 10-26 weeks		The mean depression symptoms at endpoint in the intervention groups was 0.61 standard deviations lower (0.88 to 0.34 lower)		249 (3 studies)	very low[1,2]
Depression symptoms at 1-year follow-up BDI-II change score Follow-up: mean 52 weeks		The mean depression symptoms at 1-year follow-up in the intervention groups was 0.74 standard deviations lower (1.19 to 0.3 lower)		115 (1 study)	low[1,2]
Functional impairment SDS change score Follow-up: mean 26 weeks		The mean functional impairment in the intervention groups was 0.39 standard deviations lower (0.77 to 0.01 lower)		107 (1 study)	low[1,2]
Quality of life WHO-5 change score Follow-up: mean 26 weeks Better indicated by higher values		The mean quality of life in the intervention groups was 0.13 standard deviations higher (0.24 lower to 0.51 higher)		107 (1 study)	low[1,3]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: 10-26 weeks	198 per 1000	307 per 1000 (156 to 598)	RR 1.55 (0.79 to 3.02)	349 (3 studies)	very low[1,4,6]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: 10-26 weeks	23 per 1000	11 per 1000 (1 to 121)	RR 0.49 (0.05 to 5.31)	178 (2 studies)	very low[1,6]

BDI, Beck Depression Inventory; CAPS, Clinician Administered PTSD Scale; CBT, cognitive behavioural therapy; CGI, Clinical Global Impression scale; CI, confidence interval; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; HTQ, Harvard Trauma Questionnaire; PDS, Post-traumatic Diagnostic Scale; PTSD, post-traumatic stress disorder; RR, risk ratio; SDS, Sheehan Disability Scale; SI-PTSD, Structured Interview for PTSD; SMD, standard mean difference; SSRI, selective serotonin reuptake inhibitor; STAI, State-Trait Anxiety Inventory

[1] *Risk of bias is high or unclear across multiple domains*
[2] *OIS not met (N<400)*
[3] *95% CI crosses both line of no effect and threshold for clinically important benefit*
[4] *Substantial heterogeneity (I2>50%)*
[5] *Considerable heterogeneity (I2>80%)*
[6] *95% CI crosses line of no effect and threshold for both clinical benefit and harm*

Sensitivity and subgroup analysis

Sub-analysis of the comparison, SSRIs versus placebo for delayed treatment (>3 months) of clinically important symptoms/PTSD, by multiplicity of trauma revealed non-significant differences for PTSD outcomes and discontinuation due to adverse events. However, the test for subgroup differences on discontinuation due to any reason is statistically significant ($Chi^2 = 6.50$, $p = 0.04$), and suggests a relatively higher rate of discontinuation due to any reason for those who have experienced multiple incident index trauma (RR 1.52 [1.08, 2.15]) relative to those who have experienced single incident index trauma (RR 1.00 [0.89, 1.14]) or where the multiplicity of index trauma is unclear (RR 0.90 [0.73, 1.11]).

Sub-analysis by specific drug revealed non-significant differences for all PTSD outcomes and discontinuation (due to any reason or adverse events).

Tricyclic antidepressants (TCAs): clinical evidence

Included studies

Four studies of TCAs for the treatment of PTSD in adults were identified for full-text review. Of these 4 studies, 2 RCTs (N=106) were included in a single comparison for TCAs.

There were no studies for early treatment (intervention initiated 1-3 months post-trauma) of PTSD symptoms.

For delayed treatment (intervention initiated more than 3 months post-trauma) of PTSD symptoms, both RCTs (N=106) compared TCAs with placebo (Davidson 1990; Kosten 1991).

Comparisons with SSRIs are presented in the SSRI section above.

Excluded studies

Two studies were reviewed at full text and excluded from this review because the paper was a secondary analysis of an RCT that had already been included, or due to small sample size (N<10 per arm).

Studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 32 provides brief summaries of the included studies and evidence from these are summarised in the clinical GRADE evidence profile below (Table 33).

See also the study selection flow chart in Appendix C, forest plots in Appendix E and study evidence tables in Appendix D.

Table 32: Summary of included studies: TCAs for delayed treatment (>3 months)

Comparison	TCAs versus placebo
Total no. of studies (N randomised)	2 (106)
Study ID	Davidson 1990[1]

Comparison	TCAs versus placebo
	Kosten 1991[2]
Country	US
Diagnostic status	PTSD diagnosis according to ICD/DSM criteria
Mean months since onset of PTSD	NR ('chronic')[1] NR[2]
Mean age (range)	NR[1] 39 (range NR)[2]
Sex (% female)	NR[1] 0[2]
Ethnicity (% BME)	NR[1] 13[2]
Coexisting conditions	67% any other diagnosis: 20% MDD; 30% intermittent depression; 13% panic disorder; 35% GAD; 15% alcohol or drug abuse; 11% phobic disorder[1] 47% met RDC for diagnosis of minor depression[2]
Mean months since traumatic event	NR
Type of traumatic event	Military combat: 41% World War II; 2% Korean war; 43% Vietnam; 13% NR[1] Military combat: Vietnam veterans[2]
Single or multiple incident index trauma	Multiple
Lifetime experience of trauma	NR
Intervention details	Amitriptyline, 50-300mg/day[1] Imipramine, target dose 200-300mg/day (titrated up from 50mg/day)[2]
Intervention format	Oral
Actual intervention intensity	Mean final dose 169mg/day[1] Mean maximal dose 225mg/day (SD=55mg)[2]
Comparator	Placebo. Mean final dose 237mg/day[1] Placebo. Mean maximal dose 4.4 tablets/day (SD=1.4)[2]
Intervention length (weeks)	8

BME, Black and Minority Ethnic; DSM, Diagnostic and Statistical Manual of mental disorders; GAD, generalised anxiety disorder; ICD, International Classification of Disease; MDD, major depressive disorder; NR, not reported; PTSD, post-traumatic stress disorder; RDC, research diagnostic criteria; SD, standard deviation; TCA, tricyclic anti-depressants
[1]Davidson 1990;
[2]Kosten 1991

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review (TCAs for the treatment of PTSD in adults) are presented in Table 33.

Table 33: Summary clinical evidence profile: TCAs versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk TCAs			
PTSD symptomatology self-rated IES change score Follow-up: mean 8 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 0.64 standard deviations lower (1.11 to 0.16 lower)		74 (2 studies)	very low[1,2]
PTSD symptomatology clinician-rated SI–PTSD change score Follow-up: mean 8 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.35 standard deviations lower (1.04 lower to 0.33 higher)		33 (1 study)	low[1,3]
Response Number of people showing ≥50% improvement on SI–PTSD/rated as 'much or very much improved' on CGI-I Follow-up: mean 8 weeks	205 per 1000	437 per 1000 (222 to 859)	RR 2.13 (1.08 to 4.19)	87 (2 studies)	very low[1,4]
Anxiety symptoms HAM-A/CAS change score Follow-up: mean 8 weeks		The mean anxiety symptoms in the intervention groups was 0.43 standard deviations lower (0.9 lower to 0.03 higher)		74 (2 studies)	very low[1,3]
Depression symptoms HAM-D change score Follow-up: mean 8 weeks		The mean depression symptoms in the intervention groups was 0.62 standard deviations lower (1.18 to 0.07 lower)		74 (2 studies)	very low[1,2]
Discontinuation due to any reason Number of people who dropped out of the study for any	436 per 1000	388 per 1000 (244 to 619)	RR 0.89 (0.56 to 1.42)	87 (2 studies)	very low[1,5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk TCAs			
reason, including adverse events Follow-up: mean 8 weeks					
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 8 weeks	167 per 1000	173 per 1000 (45 to 680)	RR 1.04 (0.27 to 4.08)	41 (1 study)	very low[1,5]

CAS, Clinical Anxiety Scale; CI, confidence interval; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; IES, Impact of Event Scale; PTSD, post-traumatic stress disorder; RR, risk ratio; SI-PTSD, Structured Interview for PTSD; SMD, standard mean difference; TCA, tricyclic antidepressant

[1] Risk of bias is high or unclear across multiple domains

[2] OIS not met (N<400)

[3] 95% CI crosses both line of no effect and threshold for clinically important benefit

[4] OIS not met (events<300)

[5] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Serotonin and norepinephrine reuptake inhibitors (SNRIs): clinical evidence

Included studies

Six studies of SNRIs for the treatment of PTSD in adults were identified for full-text review. Of these 6 studies, 2 RCTs (N=867) were included in a single comparison for SNRIs.

There were no studies for early treatment (intervention initiated 1-3 months post-trauma) of PTSD symptoms.

For delayed treatment (intervention initiated more than 3 months post-trauma) of PTSD symptoms, both RCTs (N=867) compared SNRIs with placebo (Davidson 2006a/2008/2012 [one study reported across three papers]; Davidson 2006b/Davidson unpublished [one study reported across two papers]).

Comparisons with SSRIs are presented in the SSRI section above.

Excluded studies

Four studies were reviewed at full text and excluded from this review. The reasons for exclusion were non-randomised group assignment, conference abstract, or non-English-language paper.

Studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 34 provides brief summaries of the included studies and evidence from these are summarised in the clinical GRADE evidence profile below (Table 35).

See also the study selection flow chart in Appendix C, forest plots in Appendix E and study evidence tables in Appendix D.

Table 34: Summary of included studies: SNRIs for delayed treatment (>3 months)

Comparison	SNRIs versus placebo
Total no. of studies (N randomised)	2 (867)
Study ID	Davidson 2006a/2008/2012[1] Davidson 2006b/Davidson unpublished[2]
Country	Argentina, Chile, Colombia, Denmark, Finland, Mexico, Norway, Portugal, South Africa, Spain, Sweden, UK[1] US[2]
Diagnostic status	PTSD diagnosis according to ICD/DSM criteria
Mean months since onset of PTSD	NR (≥6 months)
Mean age (range)	41.3 (range NR) [1] NR[2]
Sex (% female)	54[1] NR[2]
Ethnicity (% BME)	NR
Coexisting conditions	NR
Mean months since traumatic event	NR
Type of traumatic event	Mixed: Nonsexual abuse (29%); accidental injury (18%); unexpected death (13%); combat (12%); sexual assault in adulthood (12%); witnessing (7%); natural disaster (2%); childhood sexual abuse (1%); other (5%); unknown (1%)[1] Mixed: Most common types of primary trauma were nonsexual abuse (26%), adult sexual abuse (16%), childhood sexual abuse (15%), unexpected death (13%), accidental injury (12%), and combat (9%)[2]
Single or multiple incident index trauma	Single
Lifetime experience of trauma	NR
Intervention details	Venlafaxine extended release, 37.5-300mg/day
Intervention format	Oral
Actual intervention intensity	Mean dose 181.7mg/day[1] Mean dose 164.4 mg/day and mean maximum dose 224.6 mg/day (range, 37.5–375.0 mg/d). 47% achieved maximum dosing[2]
Comparator	Placebo (actual intensity, dose equivalent, NR)
Intervention length (weeks)	26[1] 12[2]

BME, Black and Minority Ethnic; DSM, Diagnostic and Statistical Manual of mental disorders; ICD, International Classification of Disease; NR, not reported; PTSD, post-traumatic stress disorder; SNRIs, serotonin and norepinephrine reuptake inhibitors
[1]Davidson 2006a/2008/2012;
[2]Davidson 2006b/Davidson unpublished

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review (SNRIs for the treatment of PTSD in adults) are presented in Table 35.

Table 35: Summary clinical evidence profile: Venlafaxine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Venlafaxine			
PTSD symptomatology self-rated DTS change score Follow-up: mean 12 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 0.52 standard deviations lower (0.73 to 0.31 lower)		358 (1 study)	low[1,2]
PTSD symptomatology clinician-rated CAPS change score Follow-up: 12-26 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.44 standard deviations lower (0.59 to 0.29 lower)		687 (2 studies)	low[2,3]
Remission Number of people scoring <20 on CAPS Follow-up: 12-26 weeks	282 per 1000	398 per 1000 (325 to 491)	RR 1.41 (1.15 to 1.74)	687 (2 studies)	very low[2,3,4]
Depression symptoms HAM-D change score Follow-up: 12-26 weeks		The mean depression symptoms in the intervention groups was 0.49 standard deviations lower (0.64 to 0.33 lower)		687 (2 studies)	low[2,3]
Functional impairment SDS change score Follow-up: 12-26 weeks		The mean functional impairment in the intervention groups was 0.42 standard deviations lower (0.57 to 0.27 lower)		687 (2 studies)	moderate[2]
Global functioning GAF change score Follow-up: 12-26 weeks Better indicated by higher values		The mean global functioning in the intervention groups was 0.4 standard deviations higher (0.24 to 0.55 higher)		687 (2 studies)	moderate[2]
Quality of life Q-LES-Q-SF		The mean quality of life in the		687 (2 studies)	moderate[2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Venlafaxine			
change score Follow-up: 12-26 weeks Better indicated by higher values		intervention groups was 0.46 standard deviations higher (0.3 to 0.61 higher)			
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: 12-26 weeks	349 per 1000	303 per 1000 (244 to 377)	RR 0.87 (0.7 to 1.08)	687 (2 studies)	low[2,5]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: 12-26 weeks	81 per 1000	96 per 1000 (50 to 182)	RR 1.19 (0.62 to 2.26)	687 (2 studies)	very low[2,6]

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; DTS, Davidson Trauma Scale; GAF, Global Assessment of Functioning; HAM-D, Hamilton Anxiety Rating scale-Depression; PTSD, post-traumatic stress disorder; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; RR, risk ratio; SDS, Sheehan Disability Scale; SMD, standard mean difference

[1] OIS not met (N<400)
[2] Funding from pharmaceutical company
[3] Blinding of outcome assessor(s) unclear
[4] OIS not met (events<300)
[5] 95% CI crosses both line of no effect and threshold for clinically important benefit
[6] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Monoamine oxidase inhibitors (MAOIs): clinical evidence

Included studies

Five studies of MAOIs for the treatment of PTSD in adults were identified for full-text review. Of these 5 studies, 2 RCTs (N=105) were included. There were 2 comparisons for MAOIs, one of the RCTs was a three-armed trial and included in both comparisons.

There were no studies for early treatment (intervention initiated 1-3 months post-trauma) of PTSD symptoms.

For delayed treatment (intervention initiated more than 3 months post-trauma) of PTSD symptoms, 2 RCTs (N=105) compared MAOIs with placebo (Katz 1994; Kosten 1991), and 1 of these RCTs (N=60) compared phenelzine with imipramine.

Excluded studies

Three studies were reviewed at full text and excluded from this review because efficacy or safety data could not be extracted, or due to non-randomised group assignment or small sample size (N<10 per arm).

Studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 36 provides brief summaries of the included studies and evidence from these are summarised in the clinical GRADE evidence profiles below (Table 37 and Table 38).

See also the study selection flow chart in Appendix C, forest plots in Appendix E and study evidence tables in Appendix D.

Table 36: Summary of included studies: MAOIs for delayed treatment (>3 months)

Comparison	MAOIs versus placebo	Phenelzine versus imipramine
Total no. of studies (N randomised)	2 (105)	1 (60)
Study ID	Katz 1994[1] Kosten 1991[2]	Kosten 1991
Country	US	US
Diagnostic status	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria
Mean months since onset of PTSD	Medians: 32 (brofaromine); 36 (placebo) [1] NR[2]	NR
Mean age (range)	Median: 36 (brofaromine); 42 (placebo). Range 22-62[1] 39 (range NR) [2]	39 (range NR)
Sex (% female)	76[1] 0[2]	0
Ethnicity (% BME)	NR[1] 13[2]	13
Coexisting conditions	NR[1] 47% met RDC for diagnosis of minor depression[2]	47% met RDC for diagnosis of minor depression
Mean months since traumatic event	NR	NR
Type of traumatic event	Mixed: Sexual assault (9%); physical (non-sexual; 38%); accident (22%); combat-related (18%); other (13%)[1] Military combat: Vietnam veterans[2]	Military combat: Vietnam veterans
Single or multiple incident index trauma	Single[1] Multiple[2]	Multiple
Lifetime experience of trauma	NR	NR
Intervention details	Brofaromine, 50mg/day titrated to a maximum of 150mg/day[1]	Phenelzine, target dose 60-75mg/day (titrated up from 15mg/day)

Comparison	MAOIs versus placebo	Phenelzine versus imipramine
	Phenelzine, target dose 60-75mg/day (titrated up from 15mg/day) [2]	
Intervention format	Oral	Oral
Actual intervention intensity	Modal dose 100mg/day[1] Mean maximal dose 68mg/day (SD=20mg) [2]	Mean maximal dose 68mg/day (SD=20mg)
Comparator	Placebo. Modal dose 2 tablets (100mg equivalent) [1] Placebo. Mean maximal dose 4.4 tablets/day (SD=1.4) [2]	Imipramine, target dose 200-300mg/day (titrated up from 50mg/day). Mean maximal dose 225mg/day (SD=55mg)
Intervention length (weeks)	14[1] 8[2]	8

BME, Black and Minority Ethnic; DSM, Diagnostic and Statistical Manual of mental disorders; ICD, International Classification of Disease; MAOIs, monoamine oxidase inhibitors; NR, not reported; PTSD, post-traumatic stress disorder; RDC, research diagnostic criteria; SD, standard deviation;
[1]Katz 1994;
[2]Kosten 1991

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review (MAOIs for the treatment of PTSD in adults) are presented in Table 37 and Table 38.

Table 37: Summary clinical evidence profile: MAOIs versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk MAOIs			
PTSD symptomatology self-rated IES change score Follow-up: mean 8 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 1.15 standard deviations lower (1.85 to 0.45 lower)		37 (1 study)	low[1,2]
PTSD symptomatology clinician-rated CAPS change score Follow-up: mean 14 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.58 standard deviations lower (1.18 lower to 0.02 higher)		45 (1 study)	low[1,3]
Remission Number of people no longer meeting diagnostic criteria for PTSD Follow-up: mean 14 weeks	194 per 1000	343 per 1000 (147 to 803)	RR 1.77 (0.76 to 4.15)	66 (1 study)	very low[1,4]

	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk MAOIs			
Response Number of people rated as 'much' or 'very much' improved on CGI-I Follow-up: mean 8 weeks	278 per 1000	683 per 1000 (306 to 1000)	RR 2.46 (1.1 to 5.51)	37 (1 study)	very low[1,5]
Anxiety symptoms CAS change score Follow-up: mean 8 weeks		The mean anxiety symptoms in the intervention groups was 0.53 standard deviations lower (1.19 lower to 0.12 higher)		37 (1 study)	low[1,3]
Depression symptoms HAM-D change score Follow-up: mean 8 weeks		The mean depression symptoms in the intervention groups was 0.29 standard deviations lower (0.94 lower to 0.36 higher)		37 (1 study)	very low[1,3]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: 8-14 weeks	408 per 1000	282 per 1000 (65 to 1000)	RR 0.69 (0.16 to 3.07)	103 (2 studies)	very low[4,6]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 8 weeks	167 per 1000	53 per 1000 (7 to 460)	RR 0.32 (0.04 to 2.76)	37 (1 study)	very low[1,4]

CAPS, Clinician Administered PTSD Scale; CAS, Clinical Anxiety Scale; CGI-I, Clinical Global Impression scale-Global Improvement; CI, confidence interval; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; IES, Impact of Event Scale; MAOIs, monoamine oxidase inhibitors; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference

[1] Risk of bias is high or unclear across multiple domains

[2] OIS not met (N<400)

[3] 95% CI crosses both line of no effect and threshold for clinically important benefit

[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

[5] OIS not met (events<300)

[6] Considerable heterogeneity (I2>80%)

Table 38: Summary clinical evidence profile: Phenelzine versus imipramine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Imipramine	Corresponding risk Phenelzine			
PTSD symptomatology self-rated IES change score Follow-up: mean 8 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 0.4 standard deviations lower (1.02 lower to 0.21 higher)		42 (1 study)	low[1,2]
Response Number of people rated as 'much' or 'very much' improved on CGI-I Follow-up: mean 8 weeks	652 per 1000	685 per 1000 (443 to 1000)	RR 1.05 (0.68 to 1.61)	42 (1 study)	very low[1,3]
Anxiety symptoms CAS change score Follow-up: mean 8 weeks		The mean anxiety symptoms in the intervention groups was 0 standard deviations higher (0.61 lower to 0.61 higher)		42 (1 study)	very low[1,3]
Depression symptoms HAM-D change score Follow-up: mean 8 weeks		The mean depression symptoms in the intervention groups was 0.09 standard deviations higher (0.52 lower to 0.7 higher)		42 (1 study)	very low[1,3]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 8 weeks	522 per 1000	209 per 1000 (83 to 548)	RR 0.4 (0.16 to 1.05)	42 (1 study)	low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Imipramine	Corresponding risk Phenelzine			
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 8 weeks	174 per 1000	52 per 1000 (7 to 431)	RR 0.3 (0.04 to 2.48)	42 (1 study)	very low[1,3]

CAS, Clinical Anxiety Scale; CGI-I, Clinical Global Impression scale-Global Improvement; CI, confidence interval; HAM-D, Hamilton Anxiety Rating scale-Depression; IES, Impact of Event Scale; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses both line of no effect and threshold for clinically important benefit
[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Other antidepressant drugs: clinical evidence

Included studies

Ten studies of other antidepressant drugs for the treatment of PTSD in adults were identified for full-text review. Of these 10 studies, 3 RCTs (N=175) were included in 3 comparisons for other antidepressants drugs.

There were no studies for early treatment (intervention initiated 1-3 months post-trauma) of PTSD symptoms.

For delayed treatment (intervention initiated more than 3 months post-trauma) of PTSD symptoms, 1 RCT (N=42) compared nefazodone with placebo (Davis et al. 2004). 1 RCT (N=30) compared bupropion in addition to TAU with placebo in addition to TAU (Becker et al. 2007), and 1 RCT (N=103) compared moclobemide with tianeptine (Önder et al. 2006).

Excluded studies

Seven studies were reviewed at full text and excluded from this review. The most common reasons for exclusion were that the study was unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided) or non-randomised group assignment.

Studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 39 provides brief summaries of the included studies and evidence from these are summarised in the clinical GRADE evidence profiles below (Table 40, Table 41 and Table 42).

See also the study selection flow chart in Appendix C, forest plots in Appendix E and study evidence tables in Appendix D.

Table 39: Summary of included studies: Other antidepressant drugs for delayed treatment (>3 months)

Comparison	Nefazodone versus placebo	Bupropion (+ TAU) versus placebo (+ TAU)	Moclobemide versus tianeptine
Total no. of studies (N randomised)	1 (42)	1 (30)	1 (103)
Study ID	Davis 2004	Becker 2007	Onder 2006
Country	US	US	Turkey
Diagnostic status	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria
Mean months since onset of PTSD	358.3	NR	NR
Mean age (range)	53.8 (32-75)	50.4 (range NR)	31.4 (range NR)
Sex (% female)	2	21	50
Ethnicity (% BME)	41	71	NR
Coexisting conditions	35% MDD; 24% dysthymia; 2% panic with agoraphobia; 4% panic without agoraphobia	NR	NR
Mean months since traumatic event	NR	NR	NR
Type of traumatic event	Military combat: Combat trauma (98%); sexual trauma (2%)	Military combat: 50% war trauma; 11% medical illness; 7% domestic violence; 7% motor vehicle accident; 7% homicide; 7% death/suicide of a love one; 7% childhood physical or sexual abuse; 4% rape	Natural disaster: Marmara Earthquake (1999)
Single or multiple incident index trauma	Multiple	Multiple	Single
Lifetime experience of trauma	NR	NR	NR
Intervention details	Nefazodone 200-600mg/day	Bupropion SR titrated up to a maximum dose of 300mg/day + TAU (39% SSRIs [22% citalopram; 6% paroxetine; 6% fluoxetine; 6% nefazodone]; 6% trazodone; 22% antipsychotics	Moclobemide, 450-900mg/day

Comparison	Nefazodone versus placebo	Bupropion (+ TAU) versus placebo (+ TAU)	Moclobemide versus tianeptine
		[risperidone or olanzapine])	
Intervention format	Oral	Oral	Oral
Actual intervention intensity	Mean final dose 435 mg/day	Mean final dose 300mg	NR
Comparator	Placebo	Placebo + TAU (50% SSRIs [20% citalopram; 20% fluoxetine; 10% sertraline]; 10% trazodone)	Tianeptine, 37.5-50mg/day
Intervention length (weeks)	12	8	12

BME, Black and Minority Ethnic; DSM, Diagnostic and Statistical Manual of mental disorders; ICD, International Classification of Disease; MDD, major depressive disorder; NR, not reported; PTSD, post-traumatic stress disorder; SD, standard deviation; SR, slow release; TAU, treatment as usual
None

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review (other antidepressant drugs for the treatment of PTSD in adults) are presented in Table 40, Table 41 and Table 42.

Table 40: Summary clinical evidence profile: Nefazodone versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Nefazodone			
PTSD symptomatology self-rated PCL change score Follow-up: mean 12 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 0.2 standard deviations lower (0.84 lower to 0.43 higher)		41 (1 study)	very low[1,2,3]
PTSD symptomatology clinician-rated CAPS change score Follow-up: mean 12 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.23 standard deviations lower (0.86 lower to 0.41 higher)		41 (1 study)	very low[1,2,3]
Response Number of people showing ≥30%	333 per 1000	333 per 1000 (137 to 813)	RR 1 (0.41 to 2.44)	42 (1 study)	very low[1,3,4]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Nefazodone			
improvement on CAPS Follow-up: mean 12 weeks					
Depression symptoms HAM-D change score Follow-up: mean 12 weeks		The mean depression symptoms in the intervention groups was 0.27 standard deviations lower (0.91 lower to 0.37 higher)		41 (1 study)	very low[1,2,3]
Dissociative symptoms CADSS change score Follow-up: mean 12 weeks		The mean dissociative symptoms in the intervention groups was 0.07 standard deviations lower (0.71 lower to 0.57 higher)		41 (1 study)	very low[1,3,4]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 12 weeks	400 per 1000	480 per 1000 (232 to 1000)	RR 1.2 (0.58 to 2.51)	42 (1 study)	very low[1,3,4]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 12 weeks	67 per 1000	185 per 1000 (24 to 1000)	RR 2.78 (0.36 to 21.62)	42 (1 study)	very low[1,3,4]

CADSS, Clinician Administered Dissociative States Scale; CAPS, Clinician Administered PTSD Scale; CI, confidence interval; HAM-D, Hamilton Anxiety Rating scale-Depression; PCL, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; RR, relative risk; SMD, standard mean difference

[1] Risk of bias is high or unclear across multiple domains

[2] 95% CI crosses both line of no effect and threshold for clinically important benefit

[3] Funding from pharmaceutical company

[4] 95% CI crosses line of no effect and threshold for both clinically important benefit and harm

Table 41: Summary clinical evidence profile: Bupropion (+ TAU) versus placebo (+ TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ TAU)	Corresponding risk Bupropion (+ TAU)			
PTSD symptomatology self-rated DTS change score Follow-up: mean 8 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 0.1 standard deviations lower (0.88 lower to 0.67 higher)		28 (1 study)	very low[1,2]
Depression symptoms BDI change score Follow-up: mean 8 weeks		The mean depression symptoms in the intervention groups was 0.05 standard deviations higher (0.72 lower to 0.83 higher)		28 (1 study)	very low[1,2]

BDI=Beck Depression Inventory; CI=confidence interval; DTS=Davidson Trauma Scale; PTSD=post-traumatic stress disorder; TAU=treatment as usual; SMD=standard mean difference

[1] 95% CI crosses line of no effect and threshold for both clinically important benefit and harm

[2] Funding from pharmaceutical company

Table 42: Summary clinical evidence profile: Moclobemide versus tianeptine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Tianeptine	Corresponding risk Moclobemide			
PTSD symptomatology clinician-rated CAPS change score Follow-up: mean 12 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.1 standard deviations higher (0.39 lower to 0.59 higher)		65 (1 study)	very low[1,2]
Response Number of people showing >50% improvement on CAPS Follow-up: mean 12 weeks	767 per 1000	629 per 1000 (452 to 866)	RR 0.82 (0.59 to 1.13)	65 (1 study)	very low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Tianeptine	Corresponding risk Moclobemide			
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 12 weeks	200 per 1000	142 per 1000 (48 to 422)	RR 0.71 (0.24 to 2.11)	65 (1 study)	very low[1,3]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 12 weeks	67 per 1000	29 per 1000 (3 to 300)	RR 0.43 (0.04 to 4.5)	65 (1 study)	very low[1,3]

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] Open-label
[2] 95% CI crosses both line of no effect and threshold for clinically important effect
[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Anticonvulsants: clinical evidence

Included studies

Thirty-three studies of anticonvulsants for the treatment of PTSD in adults were identified for full-text review. Of these 33 studies, 6 RCTs (N=496) were included in 4 comparisons for anticonvulsants.

There were no studies for early treatment (intervention initiated 1-3 months post-trauma) of PTSD symptoms.

For delayed treatment (intervention initiated more than 3 months post-trauma) of PTSD symptoms, 3 RCTs (N=142) compared topiramate with placebo (Akuchekian & Amanat 2004; Tucker 2007; Yeh 2011/Mello 2008 [published study and trial protocol]). 1 RCT (N=85) compared divalproex with placebo (Davis 2008a), and 1 RCT (N=232) compared tiagabine with placebo (Davidson 2007). Finally, 1 RCT (N=37) compared augmentation of routine medications with pregabalin relative to placebo (Baniasadi 2014).

Excluded studies

Twenty-seven studies were reviewed at full text and excluded from this review. The most common reasons for exclusion was non-randomised group assignment.

Studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 43 provide brief summaries of the included studies and evidence from these are summarised in the clinical GRADE evidence profiles below (Table 44, Table 45, Table 46 and Table 47).

See also the study selection flow chart in Appendix C, forest plots in Appendix E and study evidence tables in Appendix D.

Table 43: Summary of included studies: Anticonvulsants for delayed treatment (>3 months)

Comparison	Topiramate versus placebo	Divalproex versus placebo	Tiagabine versus placebo	Pregabalin (+ routine med.) versus placebo (+ routine med.)
Total no. of studies (N randomised)	3 (142)	1 (85)	1 (232)	1 (37)
Study ID	Akuchekian 2004[1] Tucker 2007[2] Yeh 2011/Mello 2008[3]	Davis 2008a	Davidson 2007	Banisadi 2014
Country	Iran[1] US[2] Brazil[3]	US	US	Iran
Diagnostic status	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria
Mean months since onset of PTSD	214.8[1] NR (≥6 months)[2] 43.8[3]	292.8	157.2	210
Mean age (range)	39.5 (30-50)[1] 41.5 (18-64)[2] 40.5 (18-62)[3]	55.2 (range NR)	42.6 (18-64)	48.2 (40-60)
Sex (% female)	0[1] 79[2] 68[3]	2	66	0
Ethnicity (% BME)	NR[1,3] 11[2]	NR	NR	NR
Coexisting conditions	NR[1,3] 61% MDD; 29% MDD + panic; 3% MDD + dysthymia[2]	NR	51% had at least 1 comorbid psychiatric disorder: MDD most prevalent comorbidity (38%)	NR
Mean months since traumatic event	NR	NR	NR	340
Type of traumatic event	Military combat: Explosion wave (58.2%), chemical weapons exposure	Military combat: Combat-related trauma (95%)	Mixed: Physical and sexual assault/violence (53%); witnessing	Military combat: Iran-Iraq war (1980-1988)

Comparison	Topiramate versus placebo	Divalproex versus placebo	Tiagabine versus placebo	Pregabalin (+ routine med.) versus placebo (+ routine med.)
	(10.4%), captivity and torture (7.5%), injury (20.9%), and witnessing the death of their fellow soldiers (3%)[1] Mixed: Non-combat-related PTSD (24% childhood sexual abuse; 8% childhood physical abuse; 18% domestic/other violence; 11% rape; 11% motor vehicle accident; 16% death/injury of loved one; 5% witness death; 8% tornado; 16% other)[2] Unclear: Civilian sample (no details of trauma type reported)[3]		harm or death (15%); serious accident/fire/injury (9%); combat (9%); natural or technological disaster (2%); other (11%)	
Single or multiple incident index trauma	Multiple[1] Unclear[2,3]	Multiple	Single	Multiple
Lifetime experience of trauma	NR	NR	Mean number of lifetime traumas was 7.3 (SD=3.1)	NR
Intervention details	Topiramate, 50-500mg/day[1] Topiramate, 25-400mg/day[2] Topiramate, 25-200mg/day[3]	Divalproex sodium 1000-3000mg/day (enteric-coated, delayed-release)	Tiagabine, 4-16mg/day	Pregabalin (75-300mg/day). All patients recruited into the study were treated with SSRIs (citalopram 20–40 mg/day or sertraline 50–200 mg/day) and sodium valproate (1000–1800mg/day) for at least 1 month
Intervention format	Oral	Oral	Oral	Oral
Actual intervention intensity	NR[1] Median final dose 150mg/day[2] Mean dose 102.94 mg/day (range 50–200 mg/day)[3]	Mean final dose 2309mg/day (SD=508)	Mean final dose 11.2 mg/day (range 2–16mg/day)	NR

Comparison	Topiramate versus placebo	Divalproex versus placebo	Tiagabine versus placebo	Pregabalin (+ routine med.) versus placebo (+ routine med.)
Comparator	Placebo	Placebo	Placebo. Mean final dose 11.8 mg/day (range 2–16mg/day)	Placebo (+ citalopram [20–40mg/day] or sertraline [50–200mg/day] + sodium valproate [1000–1800 mg/day])
Intervention length (weeks)	12	8	12	6

BME, Black and Minority Ethnic; DSM, Diagnostic and Statistical Manual of mental disorders; ICD, International Classification of Disease; MDD, major depressive disorder; NR, not reported; PTSD, post-traumatic stress disorder; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors.
[1]Akuchekian 2004;
[2]Tucker 2007;
[3]Yeh 2011/Mello 2008

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review (anticonvulsants for the treatment of PTSD in adults) are presented in Table 44, Table 45, Table 46 and Table 47.

Table 44: Summary clinical evidence profile: Topiramate versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Topiramate			
PTSD symptomatology self-rated DTS change score Follow-up: mean 12 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 0.6 standard deviations lower (1.26 lower to 0.05 higher)		38 (1 study)	low[1,2]
PTSD symptomatology clinician-rated CAPS change score Follow-up: mean 12 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 1.25 standard deviations lower (2.61 lower to 0.11 higher)		136 (3 studies)	very low[1,3,4]
Response Number of people showing ≥30% improvement on CAPS	500 per 1000	825 per 1000 (495 to 1000)	RR 1.65 (0.99 to 2.75)	35 (1 study)	moderate[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Topiramate			
Follow-up: mean 12 weeks					
Anxiety symptoms HAM-A change score Follow-up: mean 12 weeks		The mean anxiety symptoms in the intervention groups was 0.31 standard deviations lower (0.95 lower to 0.33 higher)		38 (1 study)	very low[1,2,3]
Depression symptoms HAM-D/BDI change score Follow-up: mean 12 weeks		The mean depression symptoms in the intervention groups was 0.44 standard deviations lower (0.92 lower to 0.04 higher)		69 (2 studies)	very low[1,2,3]
Functional impairment SDS change score Follow-up: mean 12 weeks		The mean functional impairment in the intervention groups was 0.08 standard deviations higher (0.56 lower to 0.72 higher)		38 (1 study)	very low[2,5]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 12 weeks	169 per 1000	144 per 1000 (66 to 314)	RR 0.85 (0.39 to 1.86)	142 (3 studies)	low[5]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 12 weeks	70 per 1000	94 per 1000 (33 to 267)	RR 1.33 (0.47 to 3.79)	142 (3 studies)	low[5]

BDI, Beck Depression Inventory; CAPS, Clinician Administered PTSD Scale; CI, confidence interval; DTS, Davidson Trauma Scale; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; PTSD, post-traumatic stress disorder; RR, risk ratio; SDS, Sheehan Disability Scale; SMD, standard mean difference

[1] 95% CI crosses both line of no effect and threshold for clinically important benefit

[2] Funding from pharmaceutical company

[3] Blinding of outcome assessor(s) is unclear

[4] *Considerable heterogeneity (I2>80%)*
[5] *95% CI crosses line of no effect and thresholds for both clinically important benefit and harm*

Table 45: Summary clinical evidence profile: Divalproex versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Divalproex			
PTSD symptomatology clinician-rated CAPS change score Follow-up: mean 8 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.08 standard deviations higher (0.35 lower to 0.51 higher)		82 (1 study)	low[1,2]
Anxiety symptoms HAM-A change score Follow-up: mean 8 weeks		The mean anxiety symptoms in the intervention groups was 0.28 standard deviations lower (0.72 lower to 0.15 higher)		82 (1 study)	low[2,3]
Depression symptoms MADRS change score Follow-up: mean 8 weeks		The mean depression symptoms in the intervention groups was 0.09 standard deviations lower (0.52 lower to 0.35 higher)		82 (1 study)	low[2,3]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 8 weeks	171 per 1000	227 per 1000 (96 to 541)	RR 1.33 (0.56 to 3.17)	85 (1 study)	very low[2,4]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 8 weeks	24 per 1000	68 per 1000 (7 to 630)	RR 2.8 (0.3 to 25.81)	85 (1 study)	very low[2,4]

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; HAM-A, Hamilton Anxiety Rating scale-Anxiety; MADRS, Montgomery-Asberg Depression Rating Scale; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference

[1] *95% CI crosses both line of no effect and threshold for clinically important harm*
[2] *Funding from pharmaceutical company*
[3] *95% CI crosses both line of no effect and threshold for clinically important benefit*
[4] *95% CI crosses line of no effect and thresholds for both clinically important benefit and harm*

Table 46: Summary clinical evidence profile: Tiagabine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Tiagabine			
PTSD symptomatology clinician-rated CAPS change score Follow-up: mean 12 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.02 standard deviations lower (0.3 lower to 0.26 higher)		202 (1 study)	very low[1,2,3]
Response Number of people rated as 'much' or 'very much' improved on CGI-I Follow-up: mean 12 weeks	448 per 1000	439 per 1000 (332 to 587)	RR 0.98 (0.74 to 1.31)	232 (1 study)	very low[1,3,4]
Remission Number of people scoring <20 on CAPS Follow-up: mean 12 weeks	121 per 1000	146 per 1000 (76 to 284)	RR 1.21 (0.63 to 2.35)	232 (1 study)	very low[1,3,4]
Depression symptoms MADRS change score Follow-up: mean 12 weeks		The mean depression symptoms in the intervention groups was 0.01 standard deviations higher (0.27 lower to 0.29 higher)		202 (1 study)	very low[1,2,3]
Functional impairment SDS change score Follow-up: mean 12 weeks		The mean functional impairment in the intervention groups was 0.05 standard deviations higher (0.22 lower to 0.33 higher)		202 (1 study)	low[2,3]
Discontinuation due to any reason Number of people who dropped out of the study for any	448 per 1000	336 per 1000 (242 to 466)	RR 0.75 (0.54 to 1.04)	232 (1 study)	low[3,5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Tiagabine			
reason, including adverse events Follow-up: mean 12 weeks					
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 12 weeks	78 per 1000	78 per 1000 (32 to 189)	RR 1 (0.41 to 2.43)	232 (1 study)	very low[3,4]

CAPS, Clinician Administered PTSD Scale; CGI-I, Clinical Global Impression scale-Global Improvement; CI, confidence interval; MADRS, Montgomery-Asberg Depression Rating Scale; PTSD, post-traumatic stress disorder; RR, risk ratio; SDS, Sheehan Disability Scale; SMD, standard mean difference
[1] Blinding of outcome assessor(s) is unclear
[2] OIS not met (N<400)
[3] Funding from pharmaceutical company
[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm
[5] 95% CI crosses both line of no effect and threshold for clinically important benefit

Table 47: Summary clinical evidence profile: Pregabalin (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (augmentation of routine medications)	Corresponding risk Pregabalin (augmentation of routine medications)			
PTSD symptomatology self-rated PCL change score Follow-up: mean 6 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 0.71 standard deviations lower (1.38 to 0.04 lower)		37 (1 study)	moderate[1]
Anxiety symptoms HAM-A change score Follow-up: mean 6 weeks		The mean anxiety symptoms in the intervention groups was 0.39 standard deviations lower (1.04 lower to 0.26 higher)		37 (1 study)	moderate[2]
Depression symptoms		The mean depression		37 (1 study)	low[3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (augmentation of routine medications)	Corresponding risk Pregabalin (augmentation of routine medications)			
HAM-D change score Follow-up: mean 6 weeks		symptoms in the intervention groups was 0.1 standard deviations lower (0.74 lower to 0.55 higher)			
Quality of life Spitzer Quality of Life Index change score Follow-up: mean 6 weeks Better indicated by higher values		The mean quality of life in the intervention groups was 0.21 standard deviations lower (0.86 lower to 0.44 higher)		37 (1 study)	moderate[4]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 6 weeks	-	-	Not estimable	37 (1 study)	moderate[5]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 6 weeks	-	-	Not estimable	37 (1 study)	moderate[5]

CI, confidence interval; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; PCL, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference

[1] OIS not met (N<400)

[2] 95% CI crosses both line of no effect and threshold for clinically important benefit

[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

[4] 95% CI crosses both line of no effect and threshold for clinically important harm

[5] OIS not met (events<300)

Antipsychotics: clinical evidence

Included studies

Twenty-nine studies of antipsychotics for the treatment of PTSD in adults were identified for full-text review. Of these 28 studies, 5 RCTs (N=505) were included in 2 comparisons for antipsychotics.

There were no studies for early treatment (intervention initiated 1-3 months post-trauma) of PTSD symptoms.

For delayed treatment (intervention initiated more than 3 months post-trauma) of PTSD symptoms, 3 RCTs (N=410) compared antipsychotic monotherapy with placebo (Carey 2012; Krystal 2011/2016 [one study reported across two papers]; Villarreal 2016). 2 RCTs (N=95) compared augmentation of routine medications with antipsychotics relative to placebo (Bartzokis 2005; Ramaswamy 2016).

Sub-analyses were possible for the antipsychotic monotherapy versus placebo comparison, comparing effects on different subscales of the Clinician-Administered PTSD Scale for DSM–IV (CAPS) and by multiplicity of trauma. Sub-analysis by specific drug was not meaningful as there was only 1 study in each subgroup.

Excluded studies

Twenty-four studies were reviewed at full text and excluded from this review. The most common reasons for exclusion were small sample size (N<10 per arm), the paper was a systematic review with no new useable data and any meta-analysis results not appropriate to extract, or the study was unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided).

Studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 48 provide brief summaries of the included studies and evidence from these are summarised in the clinical GRADE evidence profiles below (Table 49 and Table 50).

See also the study selection flow chart in Appendix C, forest plots in Appendix E and study evidence tables in Appendix D.

Table 48: Summary of included studies: Antipsychotics for delayed treatment (>3 months)

Comparison	Antipsychotic monotherapy versus placebo	Antipsychotic (+ routine med.) versus placebo (+ routine med.)
Total no. of studies (N randomised)	3 (410)	2 (95)
Study ID	Carey 2012[1] Krystal 2011/2016[2] Villarreal 2016[3]	Bartzokis 2005[4] Ramaswamy 2016[5]
Country	South Africa[1] US[2,3]	US
Diagnostic status	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria
Mean months since onset of PTSD	NR (≥3 months) [1] 'NR ('chronic') [2,3]	NR[4] NR ('chronic') [5]

Comparison	Antipsychotic monotherapy versus placebo	Antipsychotic (+ routine med.) versus placebo (+ routine med.)
Mean age (range)	40.8 (range NR) [1] 54.4 (range NR) [2] 53 (range NR) [3]	51.6 (38-63) [4] 38.9 (range NR) [5]
Sex (% female)	61[1] 3[2] 6[3]	0[4] 87[5]
Ethnicity (% BME)	NR[1] 34[2] 48[3]	32[4] NR[5]
Coexisting conditions	NR[1,3] 70% above threshold for MDD, 10% above threshold for dysthymia and 10% above threshold for generalized anxiety disorder. 6% over threshold for antisocial personality disorder[2]	NR
Mean months since traumatic event	NR	NR
Type of traumatic event	Mixed: Non-combat PTSD. Trauma types reflect the profile of trauma in South Africa (i.e. domestic violence and criminal violence) [1] Military combat: Most patients served during the Vietnam war or earlier (72%) or the wars in Iraq and Afghanistan (24%), their PTSD symptoms were attributed principally to direct participation in combat (78%) or other combat-related events (11%)[2] Military combat: Veterans (no further details reported) [3]	Military combat: 97% Vietnam veterans; 3% Persian Gulf War veterans[4] Unclear (NR) [5]
Single or multiple incident index trauma	Unclear[1] Multiple[2,3]	Multiple[4] Unclear[5]
Lifetime experience of trauma	NR	NR
Intervention details	Olanzapine, 5-15mg/day[1] Risperidone, 1-4mg/day[2] Quetiapine, 25-800mg/day[3]	Risperidone (1-3mg/day). All participants receiving VA residential psychosocial treatment program for PTSD. 92% on stable psychotropic medications: 88% antidepressants, 32% anxiolytics, 28% hypnotics. 9% on both anxiolytics and hypnotics and 51% on either anxiolytic or hypnotic medications[4] Ziprasidone, 40-160mg/day (concomitant psychotropic medication permitted) [5]
Intervention format	Oral	Oral
Actual intervention intensity	NR[1] Mean final dose 2.74mg/day[2]	NR

Comparison	Antipsychotic monotherapy versus placebo	Antipsychotic (+ routine med.) versus placebo (+ routine med.)
	Mean dose 258mg/day (range 50-800mg)[3]	
Comparator	Placebo. Actual intensity, dose equivalent, NR[1] Placebo. Mean final dose 3.35 mg/day[2] Placebo. Mean final dose 463mg/day (range 50-800mg)[3]	Placebo + routine medications
Intervention length (weeks)	8[1] 24[2] 12[3]	16[4] 9[5]

BME, Black and Minority Ethnic; DSM, Diagnostic and Statistical Manual of mental disorders; ICD, International Classification of Disease; MDD, major depressive disorder; NR, not reported; PTSD=post-traumatic stress disorder; SD=standard deviation.
[1]Carey 2012;
[2]Krystal 2011/2016;
[3]Villarreal 2016;
[4]Bartzokis 2005;
[5]Ramaswamy 2016

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review (antipsychotics for the treatment of PTSD in adults) are presented in Table 49 and Table 50.

Table 49: Summary clinical evidence profile: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Antipsychotic monotherapy			
PTSD symptomatology self-rated DTS change score Follow-up: 8-12 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 0.84 standard deviations lower (1.23 to 0.44 lower)		108 (2 studies)	very low[1,2,3]
PTSD symptomatology clinician-rated CAPS change score Follow-up: 8-24 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.75 standard deviations lower (1.38 to 0.11 lower)		355 (3 studies)	very low[2,3,4]
Remission Number of people scoring <50 on CAPS	214 per 1000	714 per 1000 (249 to 1000)	RR 3.33 (1.16 to 9.59)	28 (1 study)	very low[1,3,5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Antipsychotic monotherapy			
Follow-up: mean 8 weeks					
Response Number of people showing >50% improvement on CAPS Follow-up: mean 8 weeks	214 per 1000	714 per 1000 (249 to 1000)	RR 3.33 (1.16 to 9.59)	28 (1 study)	very low[1,3,5]
Anxiety symptoms HAM-A change score Follow-up: 12-24 weeks		The mean anxiety symptoms in the intervention groups was 0.54 standard deviations lower (1.11 lower to 0.04 higher)		327 (2 studies)	very low[3,6,7]
Depression symptoms MADRS/HAM-D change score Follow-up: 8-24 weeks		The mean depression symptoms in the intervention groups was 0.75 standard deviations lower (1.19 to 0.31 lower)		355 (3 studies)	very low[2,3,6]
Functional impairment SDS change score Follow-up: mean 8 weeks		The mean functional impairment in the intervention groups was 0.81 standard deviations lower (1.59 to 0.04 lower)		28 (1 study)	low[2,3]
Quality of life BLSI change score Follow-up: mean 24 weeks Better indicated by higher values		The mean quality of life in the intervention groups was 0.14 standard deviations higher (0.11 lower to 0.39 higher)		247 (1 study)	low[2,3]
Sleeping difficulties PSQI change score Follow-up: 12-24 weeks		The mean sleeping difficulties in the intervention groups was 0.3 standard deviations lower (0.52 to 0.08 lower)		327 (2 studies)	low[2,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Antipsychotic monotherapy			
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: 12-24 weeks	230 per 1000	175 per 1000 (106 to 285)	RR 0.76 (0.46 to 1.24)	376 (2 studies)	low[3,7]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: 12-24 weeks	21 per 1000	49 per 1000 (16 to 152)	RR 2.31 (0.75 to 7.1)	376 (2 studies)	very low[3,8]

BLSI, Boston Life Satisfaction Inventory; CAPS, Clinician Administered PTSD Scale; CI, confidence interval; DTS, Davidson Trauma Scale; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; MADRS, Montgomery-Asberg Depression Rating Scale; PSQI, Sleep Quality Assessment; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference

[1] Risk of bias is high or unclear across multiple domains
[2] OIS not met (N<400)
[3] Funding from pharmaceutical company
[4] Considerable heterogeneity (I2>80%)
[5] OIS not met (events<300)
[6] Substantial heterogeneity (I2=50-80%)
[7] 95% CI crosses both line of no effect and threshold for clinically important benefit
[8] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Table 50: Summary clinical evidence profile: Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (augmentation of routine medications)	Corresponding risk Antipsychotic (augmentation of routine medications)			
PTSD symptomatology clinician-rated CAPS change score Follow-up: 9-16 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.51 standard deviations lower		72 (2 studies)	very low[1,2,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (augmentation of routine medications)	Corresponding risk Antipsychotic (augmentation of routine medications)			
		(0.98 to 0.04 lower)			
Response Number of people showing ≥ 20/50% improvement on CAPS Follow-up: 9-16 weeks	85 per 1000	226 per 1000 (24 to 1000)	RR 2.66 (0.28 to 24.82)	95 (2 studies)	very low[1,3,4,5]
Anxiety symptoms HAM-A change score Follow-up: 9-16 weeks		The mean anxiety symptoms in the intervention groups was 0.66 standard deviations lower (1.17 to 0.16 lower)		66 (2 studies)	very low[1,2,3]
Depression symptoms HAM-D change score Follow-up: 9-16 weeks		The mean depression symptoms in the intervention groups was 0.35 standard deviations lower (0.84 lower to 0.14 higher)		66 (2 studies)	very low[1,3,6]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 16 weeks	188 per 1000	334 per 1000 (141 to 793)	RR 1.78 (0.75 to 4.23)	65 (1 study)	very low[3,5]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: 9-16 weeks	128 per 1000	123 per 1000 (43 to 347)	RR 0.96 (0.34 to 2.72)	95 (2 studies)	very low[3,5]

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; PTSD, post-traumatic stress disorder; RR risk ratio; SMD, standard mean difference

[1] *Risk of bias is high or unclear across multiple domains*

[2] *OIS not met (N<400)*

[3] *Funding from pharmaceutical company*

[4] *Substantial heterogeneity (I2>50%)*

[5] *95% CI crosses line of no effect and thresholds for both clinically important benefit and harm*
[6] *95% CI crosses both line of no effect and threshold for clinically important benefit*

Sensitivity and subgroup analysis

Sub-analysis of the comparison, antipsychotic monotherapy versus placebo for delayed treatment (>3 months) of clinically important symptoms/PTSD, by CAPS subscale revealed no significant differences in the effects across the CAPS-B (re-experiencing), CAPS-C (avoidance/numbing), and CAPS-D (hyperarousal) subscales. Sub-analyses by multiplicity of trauma also revealed non-significant differences in efficacy across PTSD outcomes and on discontinuation for those who had experienced multiple incident index trauma relative to those where multiplicity of trauma was unclear.

Benzodiazepines: clinical evidence

Included studies

Five studies of benzodiazepines for the treatment of PTSD in adults were identified for full-text review. Of these 5 studies, 1 RCT (N=156) was included, and had three-arms meaning there were 2 comparisons for benzodiazepines.

There were no studies for early treatment (intervention initiated 1-3 months post-trauma) of PTSD symptoms.

For delayed treatment (intervention initiated more than 3 months post-trauma) of PTSD symptoms, 1 RCT (N=156) compared the augmentation of virtual reality exposure therapy with alprazolam relative to placebo, and the same study also compared alprazolam augmentation with d-cycloserine augmentation (Rothbaum 2014/ Norrholm 2016 [one study reported across two papers]).

Excluded studies

Four studies were reviewed at full text and excluded from this review. Reasons for exclusion were: small sample size (N<10 per arm); non-randomised group assignment; systematic review with no new useable data and any meta-analysis results not appropriate to extract; population outside scope (inoculation interventions for people who may be at risk of experiencing but have not experienced, a traumatic event).

Studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 51 provides a brief summary of the included study and evidence from this study is summarised in the clinical GRADE evidence profiles below (Table 52 and Table 53).

See also the study selection flow chart in Appendix C, forest plots in Appendix E and study evidence tables in Appendix D.

Table 51: Summary of included studies: Benzodiazepines for delayed treatment (>3 months)

Comparison	Alprazolam (+ virtual reality exposure therapy) versus placebo (+ virtual reality exposure therapy)	Alprazolam (+ virtual reality exposure therapy) versus d-cycloserine (+ virtual reality exposure therapy)
Total no. of studies (N randomised)	1 (156)	1 (156)
Study ID	Rothbaum 2014/Norrholm 2016	Rothbaum 2014/Norrholm 2016
Country	US	US
Diagnostic status	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria
Mean months since onset of PTSD	NR	NR
Mean age (range)	35.1 (32-38)	35.1 (32-38)
Sex (% female)	5	5
Ethnicity (% BME)	58	58
Coexisting conditions	28% comorbid mood disorder	28% comorbid mood disorder
Mean months since traumatic event	NR	NR
Type of traumatic event	Military combat: Iraq/Afghanistan veterans	Military combat: Iraq/Afghanistan veterans
Single or multiple incident index trauma	Multiple	Multiple
Lifetime experience of trauma	NR	NR
Intervention details	Alprazolam (0.25mg; taken 30-mins prior to virtual reality exposure therapy [5x 90-min sessions])	Alprazolam (0.25mg; taken 30-mins prior to virtual reality exposure therapy [5x 90-min sessions])
Intervention format	Oral	Oral
Actual intervention intensity	NR	NR
Comparator	Placebo (+ virtual reality exposure therapy [5x 90-min sessions])	D-cycloserine (50mg; taken 30-mins prior to virtual reality exposure therapy [5x 90-min sessions])
Intervention length (weeks)	6	6

Note.
BME=Black and Minority Ethnic; DSM=Diagnostic and Statistical Manual of mental disorders; ICD=International Classification of Disease; NR=not reported; PTSD=post-traumatic stress disorder;

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review (benzodiazepines for the treatment of PTSD in adults) are presented in Table 52 and Table 53.

Table 52: Summary clinical evidence profile: Alprazolam (+ virtual reality exposure therapy) versus placebo (+ virtual reality exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ virtual reality exposure therapy)	Corresponding risk Alprazolam (+ virtual reality exposure therapy)			
PTSD symptomatology self-report at endpoint PSS-SR change score Follow-up: mean 6 weeks		The mean PTSD symptomatology self-report at endpoint in the intervention groups was 0.11 standard deviations higher (0.28 lower to 0.49 higher)		103 (1 study)	moderate[1]
PTSD symptomatology self-report at 3-month follow-up PSS-SR change score Follow-up: mean 13 weeks		The mean PTSD symptomatology self-report at 3-month follow-up in the intervention groups was 0.35 standard deviations higher (0.04 lower to 0.74 higher)		103 (1 study)	moderate[2]
PTSD symptomatology self-report at 6-month follow-up PSS-SR change score Follow-up: mean 26 weeks		The mean PTSD symptomatology self-report at 6-month follow-up in the intervention groups was 0.49 standard deviations higher (0.09 to 0.88 higher)		103 (1 study)	moderate[1]
PTSD symptomatology self-report at 1-year follow-up PSS-SR change score Follow-up: mean 52 weeks		The mean PTSD symptomatology self-report at 1-year follow-up in the intervention groups was 0.19 standard deviations higher (0.19 lower to 0.58 higher)		103 (1 study)	moderate[2]
PTSD symptomatology clinician-rated at endpoint CAPS change score Follow-up: mean 6 weeks		The mean PTSD symptomatology clinician-rated at endpoint in the intervention groups was 0.02 standard deviations higher		103 (1 study)	low[1,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ virtual reality exposure therapy)	Corresponding risk Alprazolam (+ virtual reality exposure therapy)			
		(0.37 lower to 0.41 higher)			
PTSD symptomatology clinician-rated at 3-month follow-up CAPS change score Follow-up: mean 13 weeks		The mean PTSD symptomatology clinician-rated at 3-month follow-up in the intervention groups was 0.54 standard deviations higher (0.15 to 0.94 higher)		103 (1 study)	low[1,3]
PTSD symptomatology clinician-rated at 6-month follow-up CAPS change score Follow-up: mean 26 weeks		The mean PTSD symptomatology clinician-rated at 6-month follow-up in the intervention groups was 0.57 standard deviations higher (0.18 to 0.97 higher)		103 (1 study)	low[1,3]
PTSD symptomatology clinician-rated at 1-year follow-up CAPS change score Follow-up: mean 52 weeks		The mean PTSD symptomatology clinician-rated at 1-year follow-up in the intervention groups was 0.2 standard deviations higher (0.19 lower to 0.59 higher)		103 (1 study)	low[2,3]
Remission at endpoint Number of people no longer meeting diagnostic criteria for PTSD Follow-up: mean 6 weeks	170 per 1000	180 per 1000 (78 to 416)	RR 1.06 (0.46 to 2.45)	103 (1 study)	very low[3,4]
Remission at 3-month follow-up Number of people no longer meeting diagnostic criteria for PTSD Follow-up: mean 13 weeks	226 per 1000	100 per 1000 (38 to 263)	RR 0.44 (0.17 to 1.16)	103 (1 study)	low[2,3]
Remission at 6-month follow-up Number of people	245 per 1000	120 per 1000 (49 to 292)	RR 0.49 (0.2 to 1.19)	103 (1 study)	low[2,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ virtual reality exposure therapy)	Corresponding risk Alprazolam (+ virtual reality exposure therapy)			
no longer meeting diagnostic criteria for PTSD Follow-up: mean 26 weeks					
Remission at 1-year follow-up Number of people no longer meeting diagnostic criteria for PTSD Follow-up: mean 52 weeks	170 per 1000	160 per 1000 (66 to 382)	RR 0.94 (0.39 to 2.25)	103 (1 study)	very low[3,4]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 6 weeks	358 per 1000	301 per 1000 (172 to 523)	RR 0.84 (0.48 to 1.46)	103 (1 study)	low[4]

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; PSS-SR, PTSD Symptom Scale-Self Report; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] OIS not met (N<400)
[2] 95% CI crosses both line of no effect and threshold for clinically important harm
[3] Blinding of outcome assessor(s) is unclear
[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Table 53: Summary clinical evidence profile: Alprazolam (+ virtual reality exposure therapy) versus d-cycloserine (+ virtual reality exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk D-cycloserine (+ virtual reality exposure therapy)	Corresponding risk Alprazolam (+ virtual reality exposure therapy)			
PTSD symptomatology self-report at endpoint PSS-SR change score Follow-up: mean 6 weeks		The mean PTSD symptomatology self-report at endpoint in the intervention groups was 0.08 standard deviations lower		103 (1 study)	moderate[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk D-cycloserine (+ virtual reality exposure therapy)	Corresponding risk Alprazolam (+ virtual reality exposure therapy)			
		(0.47 lower to 0.31 higher)			
PTSD symptomatology self-report at 3-month follow-up PSS-SR change score Follow-up: mean 13 weeks		The mean PTSD symptomatology self-report at 3-month follow-up in the intervention groups was 0.11 standard deviations higher (0.28 lower to 0.5 higher)		103 (1 study)	moderate[2]
PTSD symptomatology self-report at 6-month follow-up PSS-SR change score Follow-up: mean 26 weeks		The mean PTSD symptomatology self-report at 6-month follow-up in the intervention groups was 0.21 standard deviations higher (0.17 lower to 0.6 higher)		103 (1 study)	moderate[2]
PTSD symptomatology self-report at 1-year follow-up PSS-SR change score Follow-up: mean 52 weeks		The mean PTSD symptomatology self-report at 1-year follow-up in the intervention groups was 0.16 standard deviations higher (0.22 lower to 0.55 higher)		103 (1 study)	moderate[2]
PTSD symptomatology clinician-rated at endpoint CAPS change score Follow-up: mean 6 weeks		The mean PTSD symptomatology clinician-rated at endpoint in the intervention groups was 0.07 standard deviations higher (0.32 lower to 0.45 higher)		103 (1 study)	low[1,3]
PTSD symptomatology clinician-rated at 3-month follow-up CAPS change score Follow-up: mean 13 weeks		The mean PTSD symptomatology clinician-rated at 3-month follow-up in the intervention groups was 0.23 standard deviations higher		103 (1 study)	low[2,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk D-cycloserine (+ virtual reality exposure therapy)	Corresponding risk Alprazolam (+ virtual reality exposure therapy)			
		(0.16 lower to 0.62 higher)			
PTSD symptomatology clinician-rated at 6-month follow-up CAPS change score Follow-up: mean 26 weeks		The mean PTSD symptomatology clinician-rated at 6-month follow-up in the intervention groups was 0.27 standard deviations higher (0.12 lower to 0.66 higher)		103 (1 study)	low[2,3]
PTSD symptomatology clinician-rated at 1-year follow-up CAPS change score Follow-up: mean 52 weeks		The mean PTSD symptomatology clinician-rated at 1-year follow-up in the intervention groups was 0.39 standard deviations higher (0 to 0.78 higher)		103 (1 study)	low[1,3]
Remission at endpoint Number of people no longer meeting diagnostic criteria for PTSD Follow-up: mean 6 weeks	113 per 1000	180 per 1000 (69 to 469)	RR 1.59 (0.61 to 4.14)	103 (1 study)	very low[3,4]
Remission at 3-month follow-up Number of people no longer meeting diagnostic criteria for PTSD Follow-up: mean 13 weeks	132 per 1000	100 per 1000 (34 to 295)	RR 0.76 (0.26 to 2.23)	103 (1 study)	very low[3,4]
Remission at 6-month follow-up Number of people no longer meeting diagnostic criteria for PTSD Follow-up: mean 26 weeks	132 per 1000	120 per 1000 (44 to 333)	RR 0.91 (0.33 to 2.52)	103 (1 study)	very low[3,4]
Remission at 1-year follow-up Number of people no longer meeting diagnostic criteria	170 per 1000	160 per 1000 (66 to 382)	RR 0.94 (0.39 to 2.25)	103 (1 study)	very low[3,4]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk D-cycloserine (+ virtual reality exposure therapy)	Corresponding risk Alprazolam (+ virtual reality exposure therapy)			
for PTSD Follow-up: mean 52 weeks					
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 6 weeks	472 per 1000	302 per 1000 (179 to 500)	RR 0.64 (0.38 to 1.06)	103 (1 study)	moderate[2]

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; PSS-SR, Post-traumatic Symptom Scale-Self-Report; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] OIS not met (N<400)
[2] 95% CI crosses both line of no effect and threshold for clinically important effect
[3] Blinding of outcome assessor(s) is unclear
[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Other drugs: clinical evidence

Included studies

One hundred and fourteen studies of other drugs for the treatment of PTSD in adults were identified for full-text review. Of these 114 studies, 12 RCTs (N=979) were included. One of these RCTs was included in more than one comparison (three-armed trial where each arm was relevant to this section of the review). There were 8 comparisons for other drugs.

There were no studies for early treatment (intervention initiated 1-3 months post-trauma) of PTSD symptoms.

For delayed treatment (intervention initiated more than 3 months post-trauma) of PTSD symptoms, 4 RCTs (N=542) compared prazosin (alone or in addition to TAU) with placebo (alone or in addition to TAU) (Ahmadpanah 2014; Petrakis 2016; Raskind 2007; Raskind 2018/Ventura 2007 [published paper and trial protocol]). 1 of these RCTs (N=102) also compared prazosin with hydroxyzine, and hydroxyzine with placebo (Ahmadpanah et al. 2014). 1 RCT (N=27) compared eszopiclone versus placebo (Pollack 2011). 1 RCT (N=41) compared augmentation of routine medications with propranolol relative to placebo (Mahabir et al. 2016), 1 RCT (N=24) compared augmentation of routine medications with rivastigmine relative to placebo (Ardani 2017), and 1 RCT (N=63) compared augmentation of routine medications with guanfacine relative to placebo (Neylan 2006). Finally, 4 RCTs (N=282) compared augmentation of exposure therapy with d-cycloserine relative to placebo (de Kleine et al. 2012/2014/2015 [one study reported across three papers]; Difede 2014/ Difede 2008 [published paper and trial protocol]; Litz 2012; Rothbaum 2014/ Norrholm 2016 [one study reported across two papers).

Excluded studies

Forty-five studies were reviewed at full text and excluded from this review. The most common reasons for exclusion were non-randomised group assignment, efficacy or safety

data could not be extracted, or the paper was a systematic review with no new useable data and any meta-analysis results not appropriate to extract.

Studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 54, *BME, Black and Minority Ethnic; DSM, Diagnostic and Statistical Manual of mental disorders; ICD, International Classification of Disease; MDD, major depressive disorder; NR, not reported; PTSD, post-traumatic stress disorder; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; TAU, treatment as usual; TCA, tricyclic anti-depressants.*
[1]Ahmadpanah 2014;
[2]Petrakis 2016;
[3]Raskind 2007;
[4]Raskind 2018/Ventura 2007

Table 55 and *BME, Black and Minority Ethnic; DSM, Diagnostic and Statistical Manual of mental disorders; GAD, generalised anxiety disorder; ICD, International Classification of Disease; MINI, Mini-International Neuropsychiatric Interview; MDD, major depressive disorder; NR, not reported; PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitor*

Table 56 provide brief summaries of the included studies and evidence from these are summarised in the clinical GRADE evidence profiles below (Table 57, Table 58, Table 59, Table 60, Table 61, Table 62, Table 63 and Table 64).

See also the study selection flow chart in Appendix C, forest plots in Appendix E and study evidence tables in Appendix D.

Table 54: Summary of included studies: Other drugs for delayed treatment (>3 months)-part 1

Comparison	Prazosin (+/- TAU) versus placebo (+/- TAU)	Prazosin versus hydroxyzine	Hydroxyzine versus placebo
Total no. of studies (N randomised)	4 (542)	1 (102)	1 (102)
Study ID	Ahmadpanah 2014[1] Petrakis 2016[2] Raskind 2007[3] Raskind 2018/Ventura 2007[4]	Ahmadpanah 2014	Ahmadpanah 2014
Country	Iran[1] US[2,3,4]	Iran	Iran
Diagnostic status	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria
Mean months since onset of PTSD	94.2[1] NR[2] NR ('chronic')[3,4]	94.2	94.2
Mean age (range)	35.4 (18-45)[1] 44 (range NR)[2] 56 (range NR)[3] 51.8 (range NR)[4]	35.4 (18-45)	35.4 (18-45)
Sex (% female)	29[1] 6[2] 5[3]	29	29

Comparison	Prazosin (+/- TAU) versus placebo (+/- TAU)	Prazosin versus hydroxyzine	Hydroxyzine versus placebo
	2[4]		
Ethnicity (% BME)	NR[1] 19[2] 35[3] 27[4]	NR	NR
Coexisting conditions	NR[1] 100% comorbid alcohol dependence, 39% current major depression, 19% had another anxiety disorder, 11% had current marijuana abuse/dependence, and 18% had current cocaine abuse/dependence[2] All participants had sleeping difficulties[3] All participants had frequent nightmares. 38% MDD[4]	NR	NR
Mean months since traumatic event	NR	NR	NR
Type of traumatic event	Military combat: 51% Persian gulf war, 37% Car accident, 4% Disaster, 7% Other[1] Military combat: 'Veterans' (no further detail reported)[2] Military combat: 80% veterans of the Vietnam War, 5% veterans of World War II, 8% of the Korean War, 3% of the Panama invasion, and 5% of the first Gulf War[3] Military combat: War zone trauma exposure[4]	Military combat: 51% Persian gulf war, 37% Car accident, 4% Disaster, 7% Other	Military combat: 51% Persian gulf war, 37% Car accident, 4% Disaster, 7% Other
Single or multiple incident index trauma	Multiple	Multiple	Multiple
Lifetime experience of trauma	NR	NR	NR
Intervention details	Prazosin, 1-15mg/day[1] Prazosin, target dose 16mg/day + TAU (98% enrolled in other treatments: 59% in substance abuse	Prazosin, 1-15mg/day	Hydroxyzine, 10-100mg/day

Comparison	Prazosin (+/- TAU) versus placebo (+/- TAU)	Prazosin versus hydroxyzine	Hydroxyzine versus placebo
	treatment only, 22% in treatment for PTSD only, and 19% enrolled in both)[2] Prazosin, 1-15mg/day + TAU (68% receiving group and/or individual psychotherapy; 33%) SSRIs; 5% venlafaxine; 5% TCA; 5% nefazodone; 5% bupropion; 10% benzodiazepine; 13% sedating antihistamine hydroxyzine; 8% zolpidem; 3% perphenazine; 3% quetiapine; 3% divalproex) [3] Prazosin, titrated up to a maximum of 20mg in men and 12mg in women + TAU (78% maintained on any antidepressant: 74% on SSRI) [4]		
Intervention format	Oral	Oral	Oral
Actual intervention intensity	NR[1] Average maintenance dose 14.5 mg[2] Mean dose 13mg/day[3] Mean dose (for both men and women) 14.8mg/day (SD=6.1) [4]	NR	NR
Comparator	Placebo[1] Placebo + TAU[2] Placebo + TAU. Mean dose 14mg/day[3] Placebo + TAU. Mean dose 16.4mg/day (SD=5.9) [4]	Hydroxyzine, 10-100mg/day	Placebo
Intervention length (weeks)	8[1] 12[2] 16[3] 26[4]	8	8

BME, Black and Minority Ethnic; DSM, Diagnostic and Statistical Manual of mental disorders; ICD, International Classification of Disease; MDD, major depressive disorder; NR, not reported; PTSD, post-traumatic stress disorder; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; TAU, treatment as usual; TCA, tricyclic anti-depressants.
[1]Ahmadpanah 2014;
[2]Petrakis 2016;
[3]Raskind 2007;
[4]Raskind 2018/Ventura 2007

Table 55: Summary of included studies: Other drugs for delayed treatment (>3 months)-part 2

Comparison	Eszopiclone versus placebo	Propranolol (+ routine med.) versus placebo (+ routine med.)	Rivastigmine (+ routine med.) versus placebo (+ routine med.)
Total no. of studies (N randomised)	1 (27)	1 (41)	1 (24)
Study ID	Pollack 2011	Mahabir 2016	Ardani 2017
Country	US	Canada	Iran
Diagnostic status	PTSD diagnosis according to ICD/DSM criteria	Clinically important PTSD symptoms (scoring above a threshold on validated scale)	PTSD diagnosis according to ICD/DSM criteria
Mean months since onset of PTSD	228	Mean NR (36-144)	NR ('chronic' ≥10 years)
Mean age (range)	42 (range NR)	43.4 (range NR)	50.2 (40-65)
Sex (% female)	71	73	0
Ethnicity (% BME)	26	NR	NR
Coexisting conditions	All participants had sleep disturbance. 46% MDD; 13% dysthymia; 4% agoraphobia; 21% social anxiety disorder; 13% GAD; 8% panic disorder	29% co-morbid Major Depressive Disorder and 51% other anxiety disorders (assessed with MINI)	NR
Mean months since traumatic event	NR	NR	NR
Type of traumatic event	Mixed: Sexual assault or abuse (41%); physical abuse or assault (25%); observed violence to or death of a loved one (17%); other (17%)	Mixed: 66% physical and sexual assaults; 20% accidents; 10% violent or unexpected deaths of close ones; 2% combat exposure; 2% other stressors	Military combat: The aetiology of the PTSD in all cases was the 8-year Iran-Iraq war, which lasted from September 1980 to August 1988
Single or multiple incident index trauma	Unclear	Single	Multiple
Lifetime experience of trauma	NR	NR	NR
Intervention details	Eszopiclone, 3mg at bedtime	Propranolol (single dose of 1mg/kg of short-acting propranolol) + routine medications (24% anxiolytics, 58% antidepressants, 22% antipsychotics)	Rivastigmine (3mg-6mg/day) in addition to routine medications (citalopram and sodium valproate). All patients received citalopram (40 mg/d) and sodium valproate (20 mg/kg per

Comparison	Eszopiclone versus placebo	Propranolol (+ routine med.) versus placebo (+ routine med.)	Rivastigmine (+ routine med.) versus placebo (+ routine med.)
			day). Sodium valproate was added to citalopram mainly due to the fact that all the patients had at least 1 history of failed monotherapy with SSRI
Intervention format	Oral	Oral	Oral
Actual intervention intensity	NR	NR	NR
Comparator	Placebo	Placebo + routine medications	Placebo + routine medications
Intervention length (weeks)	3	0.1	12

BME, Black and Minority Ethnic; DSM, Diagnostic and Statistical Manual of mental disorders; GAD, generalised anxiety disorder; ICD, International Classification of Disease; MINI, Mini-International Neuropsychiatric Interview; MDD, major depressive disorder; NR, not reported; PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitor

Table 56: Summary of included studies: Other drugs for delayed treatment (>3 months)-part 3

Comparison	Guanfacine (+ routine med.) versus placebo (+ routine med.)	d-cycloserine (+ exposure therapy) versus placebo (+ exposure therapy)
Total no. of studies (N randomised)	1 (63)	4 (282)
Study ID	Neylan 2006	de Kleine 2012/2014/2015[1] Difede 2008/2014[2] Litz 2012[3] Rothbaum 2014/Norrholm 2016[4]
Country	US	Netherlands[1] US[2,3,4]
Diagnostic status	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria
Mean months since onset of PTSD	NR ('chronic')	NR
Mean age (range)	NR	38.3 (range NR) [1] 45.8 (25-70) [2] 32.2 (range NR) [3] 35.1 (32-38) [4]
Sex (% female)	NR	81[1] 24[2] NR[3] 5[4]
Ethnicity (% BME)	NR	NR[1] 16[2]

Comparison	Guanfacine (+ routine med.) versus placebo (+ routine med.)	d-cycloserine (+ exposure therapy) versus placebo (+ exposure therapy)
		23[3] 58[4]
Coexisting conditions	NR	70% had at least one additional diagnosis: the most common current coexisting Axis I disorders were depressive disorder (54%) and anxiety disorders (42%)[1] 40% comorbid major depression[2] 27% comorbid MDD, 8% comorbid social anxiety, 19% current alcohol use[3] 28% comorbid mood disorder[4]
Mean months since traumatic event	NR	NR
Type of traumatic event	Military combat: 'Veterans' (no further details reported)	Mixed: 52% sexual assault including childhood sexual abuse; 30% violent nonsexual assault; 4% a road traffic or other accident; 3% war-zone experiences; 10% other[1] Terrorist attack: World Trade Centre attacks (44% from occupations-at-risk for PTSD [16% firefighters, 24% police, and 4% EMT/paramedic] and 56% were civilians) [2] Military combat: Veterans of the Iraq and Afghanistan wars[3,4]
Single or multiple incident index trauma	Multiple	Unclear[1] Single[2] Multiple[3,4]
Lifetime experience of trauma	NR	NR
Intervention details	Guanfacine, target dose 1-3mg/day + routine medications (75% taking concurrent psychotropic medication: 33% antidepressants only; 41% multiple classes of psychiatric medications)	d-cycloserine (50mg; taken 1 hour prior to start of prolonged exposure session [10x weekly 30-min sessions])[1] d-cycloserine (100mg; taken 90-min before weekly exposure therapy sessions 2-11 [12x 90-min sessions]) [2] d-cycloserine (50mg; taken 30-min before weekly exposure therapy sessions 2-5 [6x 60-90-min sessions])[3] d-cycloserine (50mg; taken 30-mins prior to virtual reality exposure therapy [5x 90-min sessions]) [4]
Intervention format	Oral	Oral
Intervention intensity	Mean dose 2.4 mg/day	NR
Comparator	Placebo + routine medications	Placebo + exposure therapy
Intervention length (weeks)	8	10[1] 9[2]

Comparison	Guanfacine (+ routine med.) versus placebo (+ routine med.)	d-cycloserine (+ exposure therapy) versus placebo (+ exposure therapy)
		3[3] 6[4]

BME, Black and Minority Ethnic; DSM, Diagnostic and Statistical Manual of mental disorders; ICD, International Classification of Disease; NR, not reported; PTSD, post-traumatic stress disorder; RDC, research diagnostic criteria.
[1]de Kleine 2012/2014/2015;
[2]Difede 2008/2014;
[3]Litz 2012;
[4]Rothbaum 2014/Norrholm 2016

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review (SSRIs for the treatment of PTSD in adults) are presented in Table 57, Table 58, Table 59, Table 60, Table 61, Table 62, Table 63 and Table 64.

Table 57: Summary clinical evidence profile: Prazosin (+/- TAU) versus placebo (+/- TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+/- TAU)	Corresponding risk Prazosin (+/- TAU)			
PTSD symptomatology self-rated at endpoint PCL change score Follow-up: mean 26 weeks		The mean PTSD symptomatology self-rated at endpoint in the intervention groups was 0.11 standard deviations higher (0.13 lower to 0.34 higher)		284 (1 study)	moderate[1]
PTSD symptomatology clinician-rated CAPS/MINI change score Follow-up: 8-26 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.81 standard deviations lower (1.71 lower to 0.1 higher)		480 (4 studies)	very low[2,3,4]
Response Number of people rated as 'much' or 'very much' improved on CGI-I Follow-up: mean 16 weeks	118 per 1000	706 per 1000 (186 to 1000)	RR 6 (1.58 to 22.86)	34 (1 study)	moderate[5]
Depression symptoms HAM-D/PHQ-9 change score Follow-up: 16-26 weeks		The mean depression symptoms in the intervention groups was 0.4 standard deviations lower		318 (2 studies)	very low[2,3,6]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+/- TAU)	Corresponding risk Prazosin (+/- TAU)			
		(1.56 lower to 0.76 higher)			
Alcohol use TLFB: Number of participants abstinent from alcohol during the trial Follow-up: mean 12 weeks	348 per 1000	459 per 1000 (278 to 755)	RR 1.32 (0.8 to 2.17)	96 (1 study)	moderate[4]
Alcohol craving/consumption OCDS/AUDIT-C change score Follow-up: 12-26 weeks		The mean alcohol craving/consumption in the intervention groups was 2.4 standard deviations higher (2.33 lower to 7.13 higher)		380 (2 studies)	very low[3,6]
Sleeping difficulties PSQI change score Follow-up: 8-26 weeks		The mean sleeping difficulties in the intervention groups was 0.48 standard deviations lower (2.06 lower to 1.09 higher)		480 (4 studies)	very low[3,6]
Quality of life QOLI change score Follow-up: mean 26 weeks Better indicated by higher values		The mean quality of life in the intervention groups was 0 standard deviations higher (0.23 lower to 0.23 higher)		284 (1 study)	moderate[1]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: 8-26 weeks	183 per 1000	156 per 1000 (90 to 271)	RR 0.85 (0.49 to 1.48)	508 (4 studies)	low[6]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: 8-26 weeks	32 per 1000	47 per 1000 (20 to 112)	RR 1.47 (0.62 to 3.51)	508 (4 studies)	low[6]

AUDIT-C, Alcohol Use Disorders Identification Test; CAPS, Clinician Administered PTSD Scale; CGI-I, Clinical Global Impression scale-Global Improvement; CI, confidence interval; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; MINI, Mini-International Neuropsychiatric Interview; OCDS, Obsessive Compulsive Drinking Scale; PCL, PTSD checklist; PHQ-9,Patient Health Questionnaire; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference; QOLI=Quality of life inventory; TAU, treatment as usual; TLFB, Timeline Follow back Method

[1] *OIS not met (N<400)*
[2] *Blinding of outcome assessor(s) is unclear*
[3] *Considerable heterogeneity (I2>80%)*
[4] *95% CI crosses both line of no effect and threshold for clinically important benefit*
[5] *OIS not met (events<300)*
[6] *95% CI crosses line of no effect and thresholds for both clinically important benefit and harm*

Table 58: Summary clinical evidence profile: Prazosin versus hydroxyzine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Hydroxyzine	Corresponding risk Prazosin			
PTSD symptomatology clinician-rated MINI change score Follow-up: mean 8 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.3 standard deviations lower (0.78 lower to 0.18 higher)		67 (1 study)	low[1,2]
Sleeping difficulties PSQI change score Follow-up: mean 8 weeks		The mean sleeping difficulties in the intervention groups was 1.26 standard deviations lower (1.79 to 0.74 lower)		67 (1 study)	moderate[3]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 8 weeks	0 per 1000	0 per 1000 (0 to 0)	RR 4.86 (0.24 to 97.69)	69 (1 study)	low[4]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 8 weeks	0 per 1000	0 per 1000 (0 to 0)	RR 4.86 (0.24 to 97.69)	69 (1 study)	low[4]

CI, confidence interval; MINI, Mini-International Neuropsychiatric Interview; PSQI, Pittsburgh Sleep Quality Index; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] *Blinding of outcome assessor(s) is unclear*
[2] *95% CI crosses both line of no effect and threshold for clinically important benefit*
[3] *OIS not met (N<400)*
[4] *95% CI crosses line of no effect and thresholds for both clinically important benefit and harm*

Table 59: Summary clinical evidence profile: Hydroxyzine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Hydroxyzine			
PTSD symptomatology clinician-rated MINI change score Follow-up: mean 8 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 2.05 standard deviations lower (2.65 to 1.46 lower)		67 (1 study)	low[1,2]
Sleeping difficulties PSQI change score Follow-up: mean 8 weeks		The mean sleeping difficulties in the intervention groups was 2.01 standard deviations lower (2.6 to 1.41 lower)		67 (1 study)	moderate[2]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 8 weeks	-	-	Not estimable	67 (1 study)	moderate[3]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 8 weeks	-	-	Not estimable	67 (1 study)	moderate[3]

CI, confidence interval; MINI, Mini-International Neuropsychiatric Interview; PSQI, Pittsburgh Sleep Quality Index; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference

[1] Blinding of outcome assessor(s) is unclear

[2] OIS not met (N<400)

[3] OIS not met (events<300)

Table 60: Summary clinical evidence profile: Eszopiclone versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Eszopiclone			
PTSD symptomatology clinician-rated CAPS change score Follow-up: mean 3 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 1.49 standard deviations lower (2.41 to 0.57 lower)		24 (1 study)	very low[1,2,3]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 3 weeks	143 per 1000	77 per 1000 (9 to 751)	RR 0.54 (0.06 to 5.26)	27 (1 study)	very low[3,4]

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] Blinding of outcome assessor(s) is not reported
[2] OIS not met (N<400)
[3] Funding from pharmaceutical company
[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Table 61: Summary clinical evidence profile: Propranolol (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (augmentation of routine medications)	Corresponding risk Propranolol (augmentation of routine medications)			
PTSD symptomatology self-rated IES-R change score Follow-up: mean 0.1 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 0.1 standard deviations lower (0.72 lower to 0.52 higher)		40 (1 study)	low[1]

CI, confidence interval; IES-R, Impact of Event Scale-Revised; PTSD, post-traumatic stress disorder; SMD, standard mean difference

[1] *95% CI crosses line of no effect and thresholds for both clinically important benefit and harm*

Table 62: Summary clinical evidence profile: Rivastigmine (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (augmentation of routine medications)	Corresponding risk Rivastigmine (augmentation of routine medications)			
PTSD symptomatology self-rated PCL change score Follow-up: mean 12 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 0.08 standard deviations higher (0.72 lower to 0.88 higher)		24 (1 study)	low[1]

CI, confidence interval; PCL, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; SMD, standard mean difference

[1] *95% CI crosses line of no effect and thresholds for both clinically important benefit and harm*

Table 63: Summary clinical evidence profile: Guanfacine (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (augmentation of routine medications)	Corresponding risk Guanfacine (augmentation of routine medications)			
PTSD symptomatology self-rated IES-R change score Follow-up: mean 8 weeks		The mean PTSD symptomatology self-rated in the intervention groups was 0.39 standard deviations higher (0.16 lower to 0.94 higher)		53 (1 study)	moderate[1]
PTSD symptomatology clinician-rated CAPS change score Follow-up: mean 8 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.11 standard deviations higher (0.43 lower to 0.66 higher)		53 (1 study)	low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (augmentation of routine medications)	Corresponding risk Guanfacine (augmentation of routine medications)			
Depression symptoms HAM-D change score Follow-up: mean 8 weeks		The mean depression symptoms in the intervention groups was 0.27 standard deviations higher (0.28 lower to 0.82 higher)		53 (1 study)	low[1,2]
Quality of life QOLI change score Follow-up: mean 8 weeks Better indicated by higher values		The mean quality of life in the intervention groups was 0.32 standard deviations higher (0.23 lower to 0.86 higher)		53 (1 study)	moderate[3]
Sleeping difficulties Sleep Quality Index change score Follow-up: mean 8 weeks		The mean sleeping difficulties in the intervention groups was 0.14 standard deviations higher (0.41 lower to 0.68 higher)		53 (1 study)	moderate[1]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: mean 8 weeks	118 per 1000	207 per 1000 (65 to 662)	RR 1.76 (0.55 to 5.63)	63 (1 study)	low[4]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 8 weeks	0 per 1000	0 per 1000 (0 to 0)	RR 8.17 (0.44 to 151.84)	63 (1 study)	low[4]

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; HAM-D, Hamilton Anxiety Rating scale-Depression; IES-R, Impact of Event Scale-Revised; PTSD, post-traumatic stress disorder; QOLI, Quality of Life Inventory; RR, risk-ratio; SMD, standard mean difference

[1] 95% CI crosses both line of no effect and threshold for clinically important harm

[2] Blinding of outcome assessor(s) is unclear

[3] *95% CI crosses both line of no effect and threshold for clinically important benefit*
[4] *95% CI crosses line of no effect and thresholds for both clinically important benefit and harm*

Table 64: Summary clinical evidence profile: d-cycloserine (+ exposure therapy) versus placebo (+ exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ exposure therapy)	Corresponding risk D-cycloserine (+ exposure therapy)			
PTSD symptomatology self-rated at endpoint PCL/PSS-SR change score Follow-up: 3-10 weeks		The mean PTSD symptomatology self-rated at endpoint in the intervention groups was 0.17 standard deviations higher (0.45 lower to 0.78 higher)		199 (3 studies)	low[1,2]
PTSD symptomatology self-rated at 3-month follow-up PSS-SR change score Follow-up: mean 13 weeks		The mean PTSD symptomatology self-rated at 3-month follow-up in the intervention groups was 0.17 standard deviations higher (0.22 lower to 0.57 higher)		173 (2 studies)	moderate[2]
PTSD symptomatology self-rated at 6-month follow-up PSS-SR change score Follow-up: mean 26 weeks		The mean PTSD symptomatology self-rated at 6-month follow-up in the intervention groups was 0.38 standard deviations higher (0 to 0.77 higher)		106 (1 study)	moderate[3]
PTSD symptomatology self-rated at 1-year follow-up PSS-SR change score Follow-up: mean 52 weeks		The mean PTSD symptomatology self-rated at 1-year follow-up in the intervention groups was 0.04 standard deviations higher (0.34 lower to 0.43 higher)		106 (1 study)	moderate[3]
PTSD symptomatology clinician-rated at endpoint CAPS change score Follow-up: 3-10 weeks		The mean PTSD symptomatology clinician-rated at endpoint in the intervention groups was 0.03 standard deviations lower		224 (4 studies)	very low[1,4]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ exposure therapy)	Corresponding risk D-cycloserine (+ exposure therapy)			
		(0.64 lower to 0.58 higher)			
PTSD symptomatology clinician-rated at 3-month follow-up CAPS change score Follow-up: mean 13 weeks		The mean PTSD symptomatology clinician-rated at 3-month follow-up in the intervention groups was 0.18 standard deviations higher (0.2 lower to 0.55 higher)		173 (2 studies)	low[2,5]
PTSD symptomatology clinician-rated at 6-month follow-up CAPS change score Follow-up: mean 26 weeks		The mean PTSD symptomatology clinician-rated at 6-month follow-up in the intervention groups was 0.55 standard deviations lower (2.42 lower to 1.32 higher)		131 (2 studies)	very low[4,5,6]
PTSD symptomatology clinician-rated at 1-year follow-up CAPS change score Follow-up: mean 52 weeks		The mean PTSD symptomatology clinician-rated at 1-year follow-up in the intervention groups was 0.17 standard deviations lower (0.55 lower to 0.21 higher)		106 (1 study)	low[5,7]
Remission at endpoint Number of people scoring <20 on CAPS/no longer meeting diagnostic criteria Follow-up: 6-10 weeks	192 per 1000	238 per 1000 (100 to 562)	RR 1.24 (0.52 to 2.93)	198 (3 studies)	low[4]
Remission at 3-month follow-up Number of people scoring <20 on CAPS/no longer meeting diagnostic criteria Follow-up: mean 13 weeks	218 per 1000	251 per 1000 (68 to 928)	RR 1.15 (0.31 to 4.25)	173 (2 studies)	very low[4,6]
Remission at 6-month follow-up Number of people	231 per 1000	323 per 1000 (44 to 1000)	RR 1.4 (0.19 to 10.39)	131 (2 studies)	very low[4,5,6]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ exposure therapy)	Corresponding risk D-cycloserine (+ exposure therapy)			
scoring <20 on CAPS/no longer meeting diagnostic criteria Follow-up: mean 26 weeks					
Remission at 1-year follow-up Number of people no longer meeting diagnostic criteria Follow-up: mean 52 weeks	170 per 1000	170 per 1000 (73 to 394)	RR 1 (0.43 to 2.32)	106 (1 study)	very low[4,5]
Response at endpoint Number of people showing improvement of at least 10 points on CAPS Follow-up: mean 10 weeks	382 per 1000	635 per 1000 (386 to 1000)	RR 1.66 (1.01 to 2.74)	67 (1 study)	moderate[8]
Response at 3-month follow-up Number of people showing improvement of at least 10 points on CAPS Follow-up: mean 13 weeks	500 per 1000	695 per 1000 (465 to 1000)	RR 1.39 (0.93 to 2.09)	67 (1 study)	moderate[7]
Anxiety symptoms at endpoint STAI State change score Follow-up: mean 10 weeks		The mean anxiety symptoms at endpoint in the intervention groups was 0.55 standard deviations lower (1.04 to 0.07 lower)		67 (1 study)	moderate[3]
Anxiety symptoms at 3-month follow-up STAI State change score Follow-up: mean 13 weeks		The mean anxiety symptoms at 3-month follow-up in the intervention groups was 0.06 standard deviations lower (0.53 lower to 0.42 higher)		67 (1 study)	moderate[7]
Depression symptoms at endpoint BDI/BDI-II change		The mean depression symptoms at endpoint in the		93 (2 studies)	very low[4,6]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ exposure therapy)	Corresponding risk D-cycloserine (+ exposure therapy)			
score Follow-up: 3-10 weeks		intervention groups was 0.42 standard deviations higher (0.89 lower to 1.72 higher)			
Depression symptoms at 3-month follow-up BDI change score Follow-up: mean 13 weeks		The mean depression symptoms at 3-month follow-up in the intervention groups was 0.02 standard deviations lower (0.5 lower to 0.45 higher)		67 (1 study)	moderate[7]
Discontinuation due to any reason Number of people who dropped out of the study for any reason, including adverse events Follow-up: 3-10 weeks	330 per 1000	337 per 1000 (188 to 608)	RR 1.02 (0.57 to 1.84)	224 (4 studies)	low[4]
Discontinuation due to adverse events Number of people who dropped out of the study due to adverse events Follow-up: mean 10 weeks	29 per 1000	30 per 1000 (2 to 465)	RR 1.03 (0.07 to 15.8)	67 (1 study)	low[4]

BDI, Beck Depression Inventory; CAPS, Clinician Administered PTSD Scale; CI, confidence interval; PCL, PTSD Checklist for DSM-5; PSS-SR, PTSD Symptom Scale-Self-Report; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference; STAI, State-Trait Anxiety Inventory

[1] Substantial heterogeneity (I2=50-80%)
[2] 95% CI crosses both line of no effect and threshold for clinically important harm
[3] OIS not met (N<400)
[4] 95% CI crosses both line of no effect and threshold for both clinically important benefit and harm
[5] Blinding of outcome assessor(s) is unclear
[6] Considerable heterogeneity (I2>80%)
[7] 95% CI crosses both line of no effect and threshold for clinically important benefit
[8] OIS not met (events<300)

Economic evidence

Included studies

One cost-utility analysis assessing the cost effectiveness of SSRIs for the treatment of adults with PTSD was identified (Mihalopoulos et al., 2015). The search strategy for economic studies is provided in Appendix B.

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Summary of studies included in the economic evidence review

Mihalopoulos and colleagues (2015) developed an economic model to assess the cost effectiveness of SSRIs versus non-evidence-based treatment with medication (treatment as usual) for adults with PTSD in Australia. Eligible study population comprised prevalent cases (12-month prevalence) of PTSD among the adult Australian population in 2012, who were currently seeking care, had consulted any health professional for a mental health problem during the previous 12 months and had been receiving medication but not evidence-based care (i.e. no SSRIs). The perspective of the analysis was that of the health sector (government and service user out-of-pocket expenses). Only intervention costs were included; it was assumed that the number of medical visits and mix of providers were the same in the SSRI and the treatment as usual arms of the model.

Efficacy data were taken from meta-analysis of trial data comparing SSRIs with other drugs. Resource use data were based on trial and epidemiological data and expert opinion; national unit costs were used. The measure of outcome was the QALY, estimated using utility scores elicited from the Australian population using the Assessment of Quality of Life (AQoL-4D) instrument. The Disability-Adjusted Life Year (DALY) was also used. The time horizon of the analysis was 5 years; a 3% annual discount rate was used. However, only benefits were measured for a period of 5 years; costs were measured over the duration of treatment (i.e. 9 months).

SSRIs were found to be more costly and more effective than pharmacological treatment as usual, with an ICER of Aus$230/QALY in 2012 prices (£89/QALY in 2016 prices). Results were quite uncertain and ranged from SSRIs being dominant to an ICER of Aus$4900/QALY (£2,177 in 2016 prices). The probability of SSRIs being dominant (i.e. more effective and less costly than other medications) was 0.27. Results were most sensitive to utility scores and participation rates among the prevalent population. The study is partially applicable to the NICE decision-making context as it was conducted in Australia and the method of QALY estimation is not consistent with NICE recommendations. The study is characterised by potentially serious limitations, including the short time horizon for costs (until end of treatment) and the fact that only intervention costs (drug acquisition costs) were considered.

The references of included studies and the economic evidence tables are provided in Appendix H. The economic evidence profiles are shown in Appendix I.

Economic model

No separate economic analysis of pharmacological interventions for the treatment of PTSD in adults was undertaken, as other areas were agreed as higher priorities for economic evaluation. However, SSRIs were included as one of the interventions assessed in the economic model that was developed to explore the cost effectiveness of psychological interventions for the treatment of adults with clinically important PTSD symptoms more than 3 months after trauma. The analysis was informed by the results of a network meta-analysis (NMA) conducted for this purpose. The economic model included any effective active intervention that had been compared with psychological interventions and was connected to the network of evidence, if they had been tested on at least 50 people across the RCTs included in the NMAs. Five studies compared SSRIs with psychological interventions, alone or combined with SSRIs. No other pharmacological treatments were included in the economic analysis.

The results of the analyses suggested that SSRIs were among the top 6 most cost-effective interventions considered in the model. The order of interventions, from the most to the least cost-effective, in the guideline base-case economic analysis was: TF-CBT individual < 8

sessions, psychoeducation, EMDR, combined somatic and cognitive therapies, self-help with support, SSRI, self-help without support, TF-CBT individual 8-12 sessions, IPT, non-TF-CBT, present-centred therapy, TF-CBT group 8-12 sessions, combined TF-CBT individual 8-12 sessions + SSRI, no treatment, TF-CBT individual >12 sessions, and counselling. It should be noted that the NMA that informed the base-case analysis was characterised by high between-study heterogeneity, as well as large effects and considerable uncertainty for some interventions, and this should be taken into account when interpreting the results of the economic analysis.

Details of the methods employed in the economic analysis and full results are provided in Appendix J of Evidence Report D.

Resource impact

The committee has made 'consider' recommendations on pharmacological interventions for adults with PTSD based on this review. Unlike for stronger ('offer') recommendations that interventions should be adopted, it is not possible to make a judgement about the potential resource impact to the NHS, as uptake of 'consider' recommendations is difficult to predict.

Details on the committee's discussion on the anticipated resource impact of recommendations are included under the 'Cost effectiveness and resource use' in 'The committee's discussion of the evidence' section.

Clinical evidence statements

SSRIs

- Very low to low quality evidence from 11-17 RCTs (N=2155-3593) suggests a small but statistically significant benefit of SSRIs relative to placebo, on improving PTSD symptomatology (self-rated and clinician-rated) and on the rate of response, in adults with PTSD over 3 months after trauma. There is also low quality evidence for clinically important and statistically significant effects on remission as assessed with clinician-rated (K=5; N=1527) or self-rated (K=1; N=384) measures. Very low to low quality evidence from 5-14 RCTs (N=1506-3135) suggests small but statistically significant effects on depression symptoms and functional impairment, and very low to low quality evidence from 1-2 RCT analyses (N=30-535) suggests statistically significant benefits for dissociative symptoms, global functioning and quality of life and a clinically important benefit (that just misses statistical significance) for relationship difficulties. However, very low to low quality evidence from 2-5 RCTs (N=368-1060) suggests non-significant effects on anxiety symptoms or sleeping difficulties. Low quality evidence from 13 RCTs (N=3074) suggests SSRIs are associated with harm with significantly higher discontinuation due to adverse events observed for SSRIs relative to placebo. Effect on discontinuation for any reason (K=17; N=3569) are neither clinically important nor statistically significant. Sub-analysis by multiplicity of trauma suggests no significant differences on PTSD outcomes or discontinuation due to adverse events, but a relatively higher rate of discontinuation (for any reason) from SSRIs for adults who have experienced multiple trauma. Sub-analysis by specific drug suggests no significant differences on PTSD outcomes or discontinuation.
- Very low to low quality evidence from 1-2 RCTs (N=37-141) suggests a clinically important but not statistically significant benefit of SSRI augmentation of trauma-focused CBT relative to trauma-focused CBT (alone or with placebo) on improving clinician-rated PTSD symptomatology and the rate of response, in adults with PTSD over 3 months after trauma. Very low to low quality evidence from 1-3 RCTs (N=107-249) suggests moderate and statistically significant benefits of SSRI augmentation on depression symptoms at endpoint and 1-year follow-up and a small but statistically significant benefit on functional impairment. However, very low to low quality evidence from 1-2 RCTs (N=107-222) suggests neither clinically important nor statistically significant effects of SSRI augmentation on self-rated PTSD symptomatology or anxiety symptoms at endpoint or 1-year follow-up or on the rate

of remission or quality of life. Very low quality evidence from 2-3 RCTs (N=178-349) suggests a trend for more discontinuation due to any reason and less discontinuation due to adverse effects associated with SSRI augmentation, but neither effect is statistically significant.

- Moderate quality single-RCT (N=43-49) evidence suggests moderate-to-large benefits of augmenting non-trauma-focused cognitive therapy with sertraline, relative to placebo, on improving clinician-rated PTSD symptomatology at endpoint and 6- and 12-month follow-up, in adults with PTSD over 3 months after trauma. Moderate quality evidence from this same RCT (N=69) also suggests clinically important and statistically significant benefits of sertraline augmentation on the rate of response at endpoint and 1-year follow-up (the effect at 6-month follow-up is clinically important but not statistically significant). Whereas, moderate to low quality evidence from this RCT (N=41-50) suggests non-significant effects of sertraline augmentation on alcohol use (at endpoint and 6- and 12-month follow-up), as measured by the number of heavy drinking days in the past 7 days, drinks per drinking day, and the number of participants abstinent from alcohol in the prior 7 days. Low quality evidence from this RCT (N=69) suggests a trend for higher discontinuation (due to any reason or adverse events) associated with placebo relative to sertraline augmentation, however these effects are not statistically significant.
- Very low quality evidence from 2 RCTs (N=140-153) suggests non-significant differences between an SSRI (sertraline or paroxetine) and mirtazapine for clinician-rated PTSD symptomatology, the rate of response, and depression symptoms, in adults with PTSD over 3 months after trauma. There was no evidence for self-rated PTSD symptomatology. Evidence from these same 2 RCTs suggests a trend for higher discontinuation (for any reason and due to adverse events) with mirtazapine, relative to an SSRI, however effects are not statistically significant.
- Low quality single-RCT (N=195) evidence suggests small but statistically significant benefits of sertraline in addition to trauma-focused CBT relative to venlafaxine in addition to trauma-focused CBT on improving functional impairment and quality of life in adults with PTSD over 3 months after trauma. Moderate quality evidence from this same RCT also suggests a trend (that just misses statistical significance) for less discontinuation (for any reason) associated with sertraline relative to venlafaxine augmentation. However, non-significant differences were observed for self-rated PTSD symptomatology, anxiety or depression symptoms.
- Very low quality evidence from 2 RCTs (N=80) suggests a clinically important benefit, that just misses statistical significance, of sertraline relative to nefazodone on improving clinician-rated PTSD symptomatology in adults with PTSD over 3 months after trauma. However, low to very low quality evidence from 1 of these RCTs (N=26) suggests non-significant differences for self-rated PTSD symptomatology, anxiety or depression symptoms, functional impairment, sleeping difficulties, or discontinuation due to adverse events. Very low quality evidence from both RCTs (N=97) suggests a trend for higher discontinuation due to any reason associated with nefazodone but this effect is not statistically significant.
- Very low quality single-RCT (N=73) evidence suggests non-significant differences between fluoxetine and moclobemide for clinician-rated PTSD symptomatology and the rate of response in adults with PTSD over 3 months after trauma. Evidence from this same RCT suggests a trend for a higher rate of discontinuation (due to any reason or adverse events) associated with fluoxetine relative to moclobemide, however these effects are not statistically significant.
- Very low quality single-RCT (N=68) evidence suggests non-significant differences between fluoxetine and tianeptine for clinician-rated PTSD symptomatology, the rate of response or discontinuation due to any reason, in adults with PTSD over 3 months after trauma. Evidence from this same RCT suggests a trend for a higher rate of discontinuation due to adverse events associated with fluoxetine relative to tianeptine, however this effect is not statistically significant.

- Very low to low quality single-RCT (N=28-40) evidence suggests clinically important but not statistically significant benefits of fluvoxamine relative to reboxetine on clinician-rated PTSD symptomatology and discontinuation due to any reason in adults with PTSD over 3 months after trauma. Very low quality evidence from this same RCT suggests non-significant differences between fluvoxamine and reboxetine for anxiety or depression symptoms.
- Very low quality evidence from 3 RCTs (N=322) suggests a clinically important benefit that just misses statistical significance of maintenance treatment with SSRIs relative to placebo for preventing relapse in adults with PTSD over 3 months after trauma. Very low to low quality evidence from 1-3 of these RCTs (N=84-322) also suggests large and statistically significant benefits of maintenance SSRI treatment on improving depression symptoms and quality of life, and less discontinuation due to any reason. However, very low quality evidence from 1-2 of these RCTs (N=129-211) suggests no significant effect of maintenance SSRI treatment on improving PTSD symptomatology (self-rated or clinician-rated). Very low quality evidence from 2 of these RCTs (N=146) suggests a trend for higher discontinuation due to adverse events associated with maintenance SSRI treatment relative to placebo, however this effect is not statistically significant.

TCAs

- Very low quality evidence from 2 RCTs (N=74-87) suggests moderate and statistically significant benefits of a TCA (amitriptyline or imipramine) relative to placebo on improving self-rated PTSD symptomatology, the rate of response and depression symptoms, in adults with PTSD over 3 months after trauma. However, low to very low quality evidence from 1-2 of these RCTs (N=33-74) suggests non-significant effects of a TCA on clinician-rated PTSD symptomatology or anxiety symptoms. Very low quality evidence from 1-2 of these RCTs (N=41-87) suggests non-significant effects on discontinuation (due to any reason or adverse events).
- Very low to low quality single-RCT (N=42-50) evidence suggests a moderate and statistically significant benefit of amitriptyline relative to paroxetine on improving clinician-rated PTSD symptomatology, and clinically important (but not statistically significant) benefits of amitriptyline on the rate of response and anxiety symptoms, in adults with PTSD over 3 months after trauma. Very low quality evidence from this same RCT suggests a non-significant difference for depression symptoms. There was no evidence for self-rated PTSD symptomatology. Evidence from this RCT suggests a trend for higher discontinuation (for any reason and due to adverse events) with amitriptyline, relative to paroxetine, however effects are not statistically significant.

MAOIs

- Low to very low quality single-RCT (N=37) evidence suggests large and statistically significant benefits of phenelzine relative to placebo on improving self-rated PTSD symptomatology and the rate of response in adults with PTSD over 3 months after trauma. Low to very low quality evidence from the same RCT suggests a clinically important but not statistically significant benefit of phenelzine on anxiety symptoms, but non-significant effect on depression symptoms. Low to very low quality evidence from another single RCT (N=45) suggests clinically important but not statistically significant benefits of brofaromine relative to placebo on improving clinician-rated PTSD symptomatology and the rate of remission. Very low quality evidence from 1-2 of these RCTs (N=37-103) suggests a trend for higher discontinuation (due to any reason or adverse events) associated with placebo relative to an MAOI, however these effects are not statistically significant.
- Low to very low quality single-RCT (N=42) evidence suggests non-significant differences between phenelzine and imipramine on self-rated PTSD symptomatology, the rate of response, anxiety and depression symptoms, in adults with PTSD over 3 months after trauma. Very low to low quality evidence from this same RCT suggests a trend for higher discontinuation (due to any reason or adverse events) associated with imipramine relative to phenelzine, however these effects are not statistically significant

SNRIs

- Very low to moderate quality evidence from 1-2 RCTs (N=358-687) suggests small-to-moderate and statistically significant benefits of venlafaxine relative to placebo on improving PTSD symptomatology (self-rated and clinician-rated), the rate of remission, depression symptoms, functional impairment, global functioning and quality of life, in adults with PTSD over 3 months after trauma. Very low to low quality evidence from both RCTs (N=687) suggests non-significant effects of venlafaxine on discontinuation (due to any reason or adverse events).
- Low quality single-RCT (N=352) evidence suggests a small but statistically significant benefit of venlafaxine relative to sertraline on improving self-rated PTSD symptomatology in adults with PTSD over 3 months after trauma. However, very low to low quality evidence from this same RCT suggests non-significant differences for clinician-rated PTSD symptomatology, remission, depression symptoms, functional impairment, global functioning, quality of life, or discontinuation due to any reason. Evidence from this RCT suggests a trend for higher discontinuation due to adverse events with sertraline relative to venlafaxine, however, this effect is not statistically significant.

Other antidepressant drugs

- Very low quality single-RCT (N=41-42) evidence suggests non-significant effects of nefazodone relative to placebo on PTSD symptomatology (self-rated or clinician-rated), the rate of response, depression symptoms, dissociative symptoms or discontinuation due to any reason, in adults with PTSD over 3 months after trauma. Evidence from this same RCT suggests a trend for higher discontinuation due to adverse events with nefazodone, however, this effect is not statistically significant.
- Very low quality single-RCT (N=28) evidence suggests non-significant effects of bupropion (in addition to TAU) relative to placebo (in addition to TAU) on self-rated PTSD symptomatology or depression symptoms, in adults with PTSD over 3 months after trauma. No evidence on discontinuation is available.
- Very low quality single-RCT (N=65) evidence suggests non-significant effects of moclobemide relative to tianeptine on clinician-rated PTSD symptomatology and the rate of response in adults with PTSD over 3 months after trauma. Evidence from this same RCT suggests a higher rate of discontinuation (due to any reason or adverse events) associated with tianeptine relative to moclobemide, however these effects are not statistically significant.

Anticonvulsants

- Very low to low quality evidence from 1-3 RCTs (N=35-136) suggests moderate-to-large benefits, that just miss statistical significance, of topiramate relative to placebo on improving PTSD symptomatology (self-rated and clinician-rated) and the rate of response in adults with PTSD over 3 months after trauma. Very low quality evidence from 1-2 of these RCTs (N=38-69) suggests neither clinically important nor statistically significant effects of topiramate on anxiety or depression symptoms or functional impairment. Low quality evidence from all 3 of these RCTs (N=142) suggests a trend for higher discontinuation due to adverse events with topiramate relative to placebo, although this effect is not statistically significant. A non-significant effect was observed on discontinuation for any reason.
- Low quality single-RCT (N=82) evidence suggests non-significant effects of divalproex relative to placebo on clinician-rated PTSD symptomatology, anxiety or depression symptoms, in adults with PTSD over 3 months after trauma. Very low quality evidence from this same RCT (N=85) suggests a trend for higher discontinuation (due to any reason or adverse events) with divalproex relative to placebo, however effects were not statistically significant.
- Very low to low quality single-RCT (N=202-232) evidence suggests non-significant effects of tiagabine relative to placebo on clinician-rated PTSD symptomatology, the rate of response or remission, depression symptoms, functional impairment, or discontinuation due

to adverse events, in adults with PTSD over 3 months after trauma. Low quality evidence from this same RCT (N=232) suggests there might be less discontinuation due to any reason associated with tiagabine relative to placebo, however this effect is not statistically significant.

- Moderate quality single-RCT (N=37) evidence suggests a moderate-to-large and statistically significant benefit of augmenting routine medications with pregbalin relative to placebo on improving self-rated PTSD symptomatology in adults with PTSD over 3 months after trauma. However, moderate to low quality evidence from this same RCT suggests non-significant effects of pregbalin augmentation on anxiety or depression symptoms, or quality of life. No participants discontinued from this trial.

Antipsychotics

- Very low quality evidence from 2-3 RCTs (N=108-355) suggests moderate-to-large and statistically significant benefits of antipsychotic monotherapy relative to placebo on improving PTSD symptomatology (self-rated and clinician-rated) and depression symptoms in adults with PTSD over 3 months after trauma. Very low to low quality evidence from 2 of these RCTs (N=327-376) also suggests a small and statistically significant benefit on improving sleeping difficulties, and clinically important but not statistically significant benefits on anxiety symptoms and discontinuation due to any reason. Very low to low quality single-RCT (N=28) evidence also suggests clinically important and statistically significant benefits of antipsychotic monotherapy on the rate of remission and response and on improving functional impairment. Low quality single-RCT (N=247) evidence suggests a non-significant effect on quality of life. Very low quality evidence from 2 RCTs (N=376) suggests higher discontinuation due to adverse events associated with antipsychotic monotherapy, however this effect is not statistically significant. Sub-analysis of the clinician-rated PTSD symptomatology outcome by CAPS subscale revealed no significant subgroup difference. Sub-analysis by multiplicity of trauma was only meaningful (>1 study per subgroup) for clinician-rated PTSD symptomatology and revealed no significant subgroup difference. Sub-analysis by specific drug was not meaningful as there was only 1 study in each subgroup.
- Very low quality evidence from 2 RCTs (N=66-72) suggests moderate and statistically significant benefits of augmenting routine medications with an antipsychotic, relative to placebo, on improving clinician-rated PTSD symptomatology and anxiety symptoms in adults with PTSD over 3 months after trauma. Very low quality evidence from 2 RCTs (N=95) also suggests a clinically important but not statistically significant benefit of antipsychotic augmentation on the rate of response. Very low quality evidence from 2 RCTs (N=66-95) suggests non-significant effects of antipsychotic augmentation on depression symptoms and discontinuation due to adverse events. Very low quality single-RCT (N=65) evidence suggests a trend for a higher rate of discontinuation due to any reason associated with antipsychotic augmentation, however this effect is not statistically significant. Sub-analysis of the clinician-rated PTSD symptomatology outcome by CAPS subscale revealed no significant subgroup difference. Sub-analyses by multiplicity of trauma or specific drug were not meaningful as there was only 1 study in each subgroup.

Benzodiazepines

- Moderate to low quality single-RCT (N=103) evidence suggests non-significant effects of augmenting virtual reality exposure therapy with alprazolam, relative to placebo, on self-rated PTSD symptomatology and remission (at endpoint, and 3-, 6- and 12-month follow-ups) and on discontinuation due to any reason, in adults with PTSD over 3 months after trauma. Low quality evidence from the same RCT suggests a moderate and statistically significant effect in favour of placebo relative to alprazolam augmentation on clinician-rated PTSD symptomatology at 3- and 6-month follow-ups, effects at endpoint and 1-year follow-up are non-significant. No evidence is available for discontinuation due to adverse events.
- Very low to moderate quality single-RCT (N=103) evidence suggests no significant difference between augmenting virtual reality exposure therapy with alprazolam relative to

d-cycloserine on PTSD symptomatology (self-rated or clinician-rated) or remission (at endpoint, and 3-, 6- and 12-month follow-ups) in adults with PTSD over 3 months after trauma. Moderate quality evidence from this same RCT suggests a higher rate of discontinuation for any reason may be associated with d-cycloserine relative to alprazolam, however this effect is not statistically significant. No evidence is available for discontinuation due to adverse events.

Other drugs

- Moderate quality single-RCT (N=34) evidence suggests a clinically important and statistically significant benefit of prazosin (in addition to TAU) relative to placebo (in addition to TAU) on the rate of response in adults with PTSD over 3 months after trauma. Very low quality evidence from 4 RCTs (N=480) also suggests a clinically important benefit that just misses statistical significance of prazosin (alone or in addition to TAU) on improving clinician-rated PTSD symptomatology. However, very low to moderate quality evidence from 1-4 of these RCTs (N=284-508) suggests neither clinically important nor statistically significant effects on self-rated PTSD symptomatology, depression symptoms, sleeping difficulties, quality of life, or discontinuation due to any reason. Moderate quality single-RCT (N=96) evidence suggests a clinically important but not statistically significant benefit of prazosin on the number of participants abstinent from alcohol during the trial, however, very low quality evidence from 2 RCTs (N=380) suggests a clinically important but not statistically significant harm on continuous measures of alcohol craving or consumption. Low quality evidence from all 4 RCTs (N=508) suggests a trend for a higher rate of discontinuation due to adverse events associated with prazosin, however this effect is not statistically significant.
- Moderate quality single-RCT (N=67) evidence suggests a large and statistically significant benefit of prazosin relative to hydroxyzine on improving sleeping difficulties in adults with PTSD over 3 months after trauma. However, low quality evidence from this same RCT suggests no significant difference between prazosin and hydroxyzine on clinician-rated PTSD symptomatology. Low quality evidence from this RCT (N=69) suggests a trend for a higher rate of discontinuation (due to any reason or adverse events) associated with prazosin relative to hydroxyzine, however these effects are not statistically significant.
- Low to moderate quality single-RCT (N=67) evidence suggests large and statistically significant benefits of hydroxyzine relative to placebo on improving clinician-rated PTSD symptomatology and sleeping difficulties in adults with PTSD over 3 months after trauma. No participants discontinued from this trial.
- Very low quality single-RCT (N=24) evidence suggests a large and statistically significant benefit of eszopiclone relative to placebo on improving clinician-rated PTSD symptomatology in adults with PTSD over 3 months after trauma. Very low quality evidence from this same RCT (N=27) also suggests less discontinuation due to any reason associated with eszopiclone relative to placebo, however this effect is not statistically significant.
- Low quality single-RCT (N=40) evidence suggests a non-significant effect of augmenting routine medications with propranolol relative to placebo on self-rated PTSD symptomatology in adults with PTSD over 3 months after trauma. No evidence was available for any other outcomes.
- Low quality single-RCT (N=24) evidence suggests a non-significant effect of augmenting routine medications with rivastigmine relative to placebo on self-rated PTSD symptomatology in adults with PTSD over 3 months after trauma. No evidence was available for any other outcomes.
- Low to moderate quality single-RCT (N=53) evidence suggests non-significant effects of augmenting routine medications with guanfacine relative to placebo on PTSD symptomatology (self-rated or clinician-rated), depression symptoms, quality of life or sleeping difficulties, in adults with PTSD over 3 months after trauma. Low quality evidence from this same RCT (N=63) suggests a trend for a higher rate of discontinuation (due to

any reason or adverse events) associated with guanfacine augmentation, however these effects are not statistically significant.

- Moderate quality single-RCT (N=67) evidence suggests clinically important and statistically significant benefits of augmenting exposure therapy with d-cycloserine, relative to placebo, on the rate of response and improving anxiety symptoms in adults with PTSD over 3 months after trauma. However, evidence from this same RCT suggests benefits are not maintained at 3-month follow-up, and effects on depression symptoms are non-significant at both endpoint and 3-month follow-up. Furthermore, moderate to very low quality evidence from 1-4 RCTs (N=67-224) suggests non-significant effects of d-cycloserine augmentation on self-rated and clinician-rated PTSD symptomatology, remission (at endpoint, and 3-, 6- and 12-month follow-ups) and discontinuation (due to any reason or adverse events).

Economic evidence statements

SSRIs

- Evidence from 1 Australian model-based economic study suggests that SSRIs are likely to be cost-effective for the treatment of PTSD in adults compared with pharmacological treatment as usual. This evidence is partially applicable to the UK context and is characterised by potentially serious limitations.
- Evidence from the guideline economic analysis suggests that SSRIs are likely to be cost-effective versus no treatment for the treatment of adults with clinically important PTSD symptoms 3 months after trauma. However, they appear to be less cost-effective than psychological interventions such as EMDR, brief individual trauma-focused CBT and self-help with support. The evidence is directly applicable to the UK context and is characterised by minor limitations.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Critical outcomes were measures of PTSD symptom improvement on validated scales, remission (as defined as a loss of diagnosis or scoring below threshold on a validated scale), and response (as measured by an agreed percentage improvement in symptoms and/or by a dichotomous rating of much or very much improved). Attrition from treatment (for any reason) was also considered an important outcome as a proxy for the acceptability of treatment, and discontinuation due to adverse events was considered as particularly important as an indicator of potential harm in terms of tolerability. The committee considered dissociative symptoms, personal/social/occupational functioning (including global functioning/functional impairment, sleeping or relationship difficulties, and quality of life), and symptoms of a coexisting condition (including anxiety and depression symptoms) as important but not critical outcomes. This distinction was based on the primacy of targeting the core PTSD symptoms, whilst acknowledging that broader symptom measures may be indicators of a general pattern of effect. Change scores were favoured over final scores as although in theory randomisation should balance out any differences at baseline, this assumption can be violated by small sample sizes. The committee also expressed a general preference for self-rated PTSD symptomatology, particularly for pharmacological interventions where the participant is likely to be blinded and may be less susceptible to bias than the study investigator(s). However, the committee discussed potential threats to blinding of the participant, for example in the context of side effects, and therefore triangulation with blinded clinician-rated outcome measures was also regarded as important.

The quality of the evidence

With the exception of a few outcomes of moderate quality, all the evidence reviewed was of very low or low quality, reflecting the high risk of bias associated with the studies (including for instance, lack of/unclear blinding of outcome assessment), the small numbers in many trials and the imprecision of many of the results (in terms of both the width of the confidence intervals and the failure to meet the optimal information size), and the risk of publication bias due to funding from pharmaceutical companies. Moreover, there is very little follow-up data available meaning that the evidence pertains only to short-term effects.

Consideration of clinical benefits and harms

When developing the recommendations, the committee considered a number of factors including the relative strength of the evidence, the preference that service users may have for medication (or psychological interventions) and the adverse effects of medication.

The committee considered the short term and long-term harms associated with the side effects of medication including for the SSRIs drowsiness, nausea, insomnia, agitation, restlessness and sexual problems, for venlafaxine discontinuation symptoms, and for the antipsychotics concerns with weight gain and hyperlipidaemia and raised blood glucose. The committee took these factors into account in developing the recommendations, but were also mindful of the negative consequences of prolonged PTSD and associated symptoms, the potential to ameliorate functional impairment, and the need to facilitate patient choice where there is a clear preference for medication over psychological interventions. The committee agreed that the benefits of pharmacological interventions for symptom management could be outweighed by the potential harms.

The committee discussed the strength of the evidence for SSRIs in terms of the number of RCTs and participants, the triangulation of effects on PTSD symptomatology across self-rated and clinician-rated measures, and benefits on other important outcomes (including depression symptoms, dissociative symptoms, functional impairment/global functioning, and quality of life). Conversely, the size of effects are small (in most cases falling below the threshold for clinical importance), there is no follow-up data, and there is evidence for harm as measured by discontinuation due to adverse events. Taken together, the committee regarded the consistency of the benefits to warrant a recommendation for those who have a preference for medication over psychological interventions, however, based on the effect sizes and limitations of the evidence a ‘consider’ rather than ‘offer’ recommendation was regarded as appropriate. The committee considered the evidence on the effectiveness of different SSRIs. There is no evidence for significant differential efficacy of specific SSRIs (sertraline, fluoxetine and paroxetine), so the committee decided not to recommend specific drugs and agreed that individual prescribers should be able to decide which SSRI to use. However, the committee agreed that it would be helpful to include sertraline as an example because it is one of two drugs licensed in the UK for this indication and the other drug, paroxetine, is likely to be associated with discontinuation symptoms. The committee felt it was important that SSRIs were not considered as a first-line treatment for PTSD (except where a person expresses a preference for drug treatment) due to concern about side effects of SSRIs, evidence from the guideline NMA that suggests relatively larger effect sizes for all psychological interventions recommended relative to SSRIs (trauma-focused CBT, EMDR, non-trauma-focused CBT and self-help with support), and evidence from the guideline economic modelling that suggests that SSRIs are less cost-effective than EMDR, brief individual trauma-focused CBT or self-help with support.

The evidence suggests benefits of venlafaxine on PTSD outcomes (both self-rated and clinician-rated) and on other important outcomes (including depression symptoms, functional impairment/global functioning, and quality of life). In discussing the relative merits of SSRIs and venlafaxine, the committee noted that the evidence was weaker for venlafaxine than for SSRIs in terms of the number of RCTs and no evidence is available for direct or indirect comparisons of venlafaxine relative to psychological interventions. Conversely, the effect sizes

are slightly larger for venlafaxine relative to SSRIs, there is no evidence for harm for venlafaxine (as measured by discontinuation due to adverse events), and there is limited evidence suggesting a small but statistically significant benefit of venlafaxine relative to sertraline. Taken together, the committee agreed that it was appropriate to offer a straight choice between SSRIs and venlafaxine, and given that the evidence for venlafaxine shares the same limitations as for SSRIs in terms of the lack of follow-up and modest effect sizes, a 'consider' recommendation was also appropriate here.

The committee discussed the evidence for antipsychotics that shows benefits (as monotherapy or augmentation of routine medications) on PTSD outcomes and associated symptoms (including anxiety and depression symptoms, functional impairment, and sleeping difficulties). The committee discussed whether benefits were limited to certain PTSD symptom domains, for instance effects on hyperarousal in the context of potentially sedative effects. However, examination of the sub-analysis of clinician-rated PTSD symptomatology by CAPS subscale did not reveal statistically significant differences between effects on re-experiencing, avoidance/numbing, or hyperarousal symptom domains. Based on limitations in the evidence, including a smaller number of RCTs than SSRIs or recommended psychological interventions, the restricted depth and breadth of evidence (for instance, no direct or indirect comparisons of antipsychotics relative to SSRIs or psychological interventions) and the lack of follow-up data, the committee agreed that a 'consider' rather than 'offer' recommendation was appropriate. The committee did not believe that antipsychotics should be considered as a first-line treatment for PTSD and recommended that they should only be considered as an adjunct to psychological therapies and only where symptoms have not responded to other drug or psychological treatments. The committee agreed that antipsychotics may be useful for symptom management where a person is experiencing significant functional impairment that may inhibit engagement with psychological treatment that targets core PTSD symptoms. The committee discussed whether people with PTSD who require symptom management with antipsychotics could be safely and effectively cared for within primary care services, and agreed that due to concerns about tolerability, antipsychotics should only be initiated in specialist services or after consultation with a specialist, and this treatment should be subject to regular specialist review.

Given the considerable evidence for psychological interventions and SSRIs, the committee considered it appropriate to set a relatively high bar for other interventions. There was limited evidence for neither significant benefits nor harms of mirtazapine (relative to SSRIs), SSRI augmentation of trauma-focused CBT (relative to trauma-focused CBT alone or with placebo), SSRIs as maintenance treatment for relapse prevention, nefazodone, bupropion, topiramate, divalproex, tiagabine, or augmentation of routine medications with propranolol, rivastigmine or guanfacine. For some interventions (such as TCAs, non-trauma-focused CBT augmentation with sertraline, trauma-focused CBT augmentation with d-cycloserine, augmentation of routine medications with pregbalin or prazosin, or treatment with phenelzine, eszopiclone or hydroxyzine alone), there is limited evidence for efficacy but the evidence base was considered too small to be confident that the benefits observed are true effects and thus a recommendation could not be supported. Finally, the committee discussed the evidence for alprazolam augmentation of virtual reality exposure therapy which shows non-significant benefit and potential harm in terms of less improvement in clinician-rated PTSD symptomatology. The committee discussed whether a negative recommendation should be made on the basis of this evidence and agreed that a negative recommendation was not appropriate given the weakness of the evidence base (a single RCT), and the fact that the negative effect is driven by greater improvement in the placebo arm but participants receiving alprazolam also showed improvement albeit to a lesser extent.

Cost effectiveness and resource use

Existing economic evidence suggested that SSRIs are cost-effective compared with pharmacological treatment as usual in adults with PTSD. The committee took this evidence into account but noted that this is only partially applicable to the UK and is characterised by

potentially serious limitations. The committee also considered the results of the guideline base-case economic analysis of psychological interventions for the treatment of adults with clinically important PTSD symptoms, which included SSRIs as a treatment option. The analysis was overall characterised by minor limitations and its results were directly applicable to the NICE decision-making context, so the committee was confident to use its findings to support recommendations. The committee noted that, according to the results, SSRIs were less cost-effective than psychological interventions such as EMDR, brief individual trauma-focused CBT and self-help with support, but more cost-effective than other interventions such as IPT, counselling, non-trauma-focused CBT, present-cantered therapy and no treatment. The committee therefore decided to recommend more cost-effective psychological interventions as first-line treatment options, but also make a 'consider' recommendation for SSRIs as an option for people who have a preference for pharmacological treatment.

The committee noted the lack of economic evidence on venlafaxine, but took into account that effect sizes for venlafaxine were a little larger than for SSRIs and also that both venlafaxine and SSRIs are available in generic form and therefore their acquisition costs are low and not very different. Consequently, the committee concluded that venlafaxine was likely to be similarly cost-effective to SSRIs, which supported a 'consider' recommendation for venlafaxine as another pharmacological option for people who have a preference for pharmacological treatment.

The committee noted the lack of economic evidence on antipsychotics. They considered the effectiveness of antipsychotics in improving PTSD symptoms and the fact that they are available in generic form, and therefore their acquisition cost is low. On the other hand, they noted that people taking antipsychotics need to be treated by specialists and to have regular reviews and they acknowledged that this increases total antipsychotic treatment costs. Moreover, use of antipsychotics is associated with the development of side effects such as extrapyramidal symptoms and metabolic syndrome, the management of which incurs extra costs. Nevertheless, the committee expressed the view that the overall benefits for people with PTSD who would be suitable to receive antipsychotics would overweigh the costs associated with treatment and decided to make a 'consider' recommendation for antipsychotics, adjunct to psychological therapies, for symptom management of adults with PTSD who have not responded to other pharmacological or psychological treatment and who have disabling symptoms and behaviours. This recommendation is expected to entail modest resource implications as it is relevant to a sub-group of adults with PTSD. The committee expressed the view that restricting the recommendation for initiation and regular review of antipsychotics only by specialists is likely to reduce variation in the way antipsychotics are used in current practice. As regular review of antipsychotics is essential but might not be happening currently, this should also improve consistency across settings.

Overall, the committee anticipated that the recommendations on pharmacological interventions for the treatment of PTSD in adults will result in a small change in practice, as in the previous guideline pharmacological treatment was recommended as an option to be considered only for adults who could not start psychological therapy, did not want to start trauma-focused psychological therapy or who had gained little or no benefit from a course of trauma-focused psychological therapy.

The committee noted that only paroxetine and sertraline are currently licensed for the treatment of PTSD in the UK so the recommendations involve off-licence use.

Other factors the committee took into account

The service user representatives on the committee drew attention to the importance of side effect profiles of different interventions, and commented that pharmacological interventions, and particularly polypharmacy, can be re-traumatising due to their sedating effect. The committee discussed the impact of this experience on the power dynamics within a patient-clinician relationship. They also noted that different groups, such as younger adults and ex-military may be more susceptible to coercion. The committee noted that there is a tendency to

use pharmacological interventions where the trauma is seen to be greater, or more complex, however in these instances they discussed the fact that it may be least helpful, and even counterproductive, to use these treatments at that point.

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Appendices

Appendix A – Review protocols

Review protocol for "For adults at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?

Review protocol for "For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

Both review questions are covered by a single protocol.

Topic	**Pharmacological interventions for the prevention and treatment of PTSD in adults**
Review question(s)	RQ. 4.1 For adults at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions? RQ. 4.2 For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?
Sub-question(s)	Where evidence exists, consideration will be given to the specific needs of:- women who have been exposed to sexual abuse or assault, or domestic violence lesbian, gay, bisexual, transsexual or transgender people people from black and minority ethnic groups people who are homeless or in insecure accommodation asylum seekers or refugees or other immigrants who are entitled to NHS treatment people who have been trafficked people who are socially isolated (and who are not captured by any other subgroup listed) people with complex PTSD people with neurodevelopmental disorders (including autism) people with coexisting conditions (drug and alcohol misuse, common mental health disorders, eating disorders, personality disorders, acquired brain injury, physical disabilities and sensory impairments) people who are critically ill or injured (for instance after a vehicle crash)

Topic	Pharmacological interventions for the prevention and treatment of PTSD in adults
Objectives	To identify the most effective pharmacological interventions for the prevention or treatment of PTSD in adults
Population	RQ 4.1: Adults at risk of PTSD At risk of PTSD is defined (in accordance with DSM) as: Exposure to actual or threatened death, serious injury or sexual violation. The exposure must result from one or more of the following scenarios, in which the individual: directly experiences the traumatic event; witnesses the traumatic event in person; learns that the traumatic event occurred to a close family member or close friend (with the actual or threatened death being either violent or accidental); or experiences first-hand repeated or extreme exposure to aversive details of the traumatic event (not through media, pictures, television or movies unless work-related) This population includes people with a diagnosis of acute stress disorder/acute stress reaction (according to DSM, ICD or similar criteria), people with clinically important PTSD symptoms within a month of the traumatic event, and people with sub-threshold symptoms The at-risk population for this review will also include the following groups that may not be captured by the DSM criteria: family members of people with PTSD family members or carers of people with a life-threatening illness or injury Adults with clinically important post-traumatic stress symptoms more than one month after the traumatic event will be excluded from RQ 4.1 as this question addresses prevention, this group are included in RQ 4.2 RQ 4.2: Adults with PTSD (as defined by a diagnosis of PTSD according to DSM, ICD or similar criteria, or clinically-significant PTSD symptoms as indicated by baseline scores above threshold on a validated scale more than one month after the traumatic event [see PTSD scales listed under outcomes])

Topic	Pharmacological interventions for the prevention and treatment of PTSD in adults
	For mixed adult and children populations, where possible disaggregated data will be obtained. If this is not possible then the study will be categorised according to the mean age of the population (<18 years as children and young people and ≥18 years as adult). If some, but not all, of a study's participants are eligible for the review, where possible disaggregated data will be obtained. If this is not possible then the study will be included if at least 80% of its participants are eligible for this review.
Exclude	Trials of people with adjustment disorders Trials of people with traumatic grief Trials of people with psychosis as a coexisting condition Trials of people with learning disabilities Trials of women with PTSD during pregnancy or in the first year following childbirth Trials of adults in contact with the criminal justice system (not solely as a result of being a witness or victim)
Intervention	Pharmacological interventions (pharmacological interventions listed below are examples of interventions which may be included either alone or in combination, for any duration at a dose at or above the minimum effective dose): SSRIs: fluoxetine paroxetine sertraline TCAs: amitriptyline imipramine MAOIs: brofaromine phenelzine SNRIs: venlafaxine Other antidepressant drugs: mirtazapine nefazodone

Topic	Pharmacological interventions for the prevention and treatment of PTSD in adults
	Anticonvulsants: carbamazepine divalproex lamotrigine tiagabine topiramate Antipsychotics: olanzapine risperidone Anxiolytics: buspirone Benzodiazepines: alprazolam clonazepam diazepam lorazepam Other drugs: clonidine cortisol d-cycloserine ketamine MDMA neuropeptide-Y oxytocin prazosin propranolol Combination interventions, such as combined pharmacological plus psychological versus psychological alone, will also be considered here.

Topic	Pharmacological interventions for the prevention and treatment of PTSD in adults
	A distinction will be made between early interventions (delivered within 3 months of the traumatic event) and delayed interventions (delivered more than 3 months after the traumatic event) Exclude: Inoculation interventions for people who may be at risk of experiencing but have not experienced, a traumatic event Interventions that are not targeted at PTSD symptoms
Comparison	Any other intervention Placebo
Critical outcomes	Efficacy PTSD symptomology (mean endpoint score or change in PTSD score from baseline) Diagnosis of PTSD (number of people meeting diagnostic criteria for PTSD according to DSM, ICD or similar criteria) Recovery from PTSD/Remission (number of people no longer meeting diagnostic criteria for PTSD according to DSM, ICD or similar criteria at endpoint, or endpoint scores below threshold on a validated scale) Response (as measured by an agreed percentage improvement in symptoms and/or by a dichotomous rating of much or very much improved on Clinical Global Impressions [CGI] scale) Relapse (number of people who remitted at endpoint but at follow-up either met diagnostic criteria for PTSD according to DSM, ICD or similar criteria, or whose follow-up scores were above threshold on a validated scale) The following PTSD scales will be included: Assessor-rated PTSD symptom scales: Clinician-Administered PTSD Scale for DSM–IV (CAPS) or DSM-V (CAPS-5) Anxiety Disorders Interview Schedule for DSM-IV: Lifetime version (ADIS-IV-L) or DSM-5 (ADIS-5) - Adult and Lifetime Version PTSD Symptom Scale – Interview Version (PSS-I) Number of symptoms on the Structured Clinical Interview for DSM-IV (SCID) Symptoms of Trauma Scale (SOTS) Self-report instruments of PTSD symptoms: PTSD Checklist (PCL), including all versions (PCL-5, PCL-M, PCL-C and PCL-S) PTSD Symptom Scale – Self Report (PSS-SR)

Topic	Pharmacological interventions for the prevention and treatment of PTSD in adults
	Life Events Checklist for DSM-5 (LEC-5) Trauma Screening Questionnaire (TSQ) Primary Care PTSD Screen (PC-PTSD) Davidson Trauma Scale (DTS) Post-Traumatic Diagnostic Scale (PDS) Impact of Event Scale (IES)/Impact of Event Scale Revised (IES-R) Acceptability/tolerability Acceptability of the intervention Discontinuation due to adverse effects Discontinuation due to any reason (including adverse effects)
Important, but not critical outcomes	Dissociative symptoms as assessed by: Assessor-rated scales: Dissociation symptom cluster score on CAPS Self-report scales: Dissociative Experiences Scale (DES) Multiscale Dissociation Inventory (MDI) Traumatic Dissociation Scale Personal, social and occupational functioning Sleeping difficulties (as assessed with a validated scale including the Pittsburgh Sleep Quality Index Addendum for PTSD [PSQI-A] and Insomnia Severity Index [ISI]) Employment (for instance, number in paid employment) Housing (for instance, number homeless or in insecure accommodation) Functional impairment (as assessed with a validated scale including the Work and Social Adjustment Scale [WSAS]) Relationship difficulties (with spouse and/or children) Quality of life (as assessed with a validated scale including the 36-item Short-Form Survey [SF-36] and Warwick-Edinburgh Mental Well-being Scale [WEMWBS])

Topic	Pharmacological interventions for the prevention and treatment of PTSD in adults
	Coexisting conditions (note that target of intervention should be PTSD symptoms): Symptoms of and recovery from a coexisting condition Self-harm Suicide
Study design	Systematic reviews of RCTs RCTs
Include unpublished data?	Clinical trial registries (ISRCTN and ClinicalTrials.gov) will be searched to identify any relevant unpublished trials and authors will be contacted to request study reports (where these are not available online). Unpublished data will only be included where a full study report is available with sufficient detail to properly assess the risk of bias. Authors of unpublished evidence will be asked for permission to use such data, and will be informed that summary data from the study and the study's characteristics will be published in the full guideline. Conference abstracts and dissertations will not be included.
Restriction by date?	All relevant studies from existing reviews from the 2005 guideline will be carried forward. No restriction on date for the updated search.
Minimum sample size	N = 10 in each arm
Study setting	Primary, secondary, tertiary, social care and community settings. Treatment provided to troops on operational deployment or exercise will not be covered.
The review strategy	Reviews If existing systematic reviews are found, the committee will assess their quality, completeness, and applicability to the NHS and to the scope of the guideline. If the committee agrees that a systematic review appropriately addresses a review question, a search for studies published since the review will be conducted. Data Extraction (selection and coding) Citations from each search will be downloaded into EndNote and duplicates removed. Titles and abstracts of identified studies will be screened by two reviewers for inclusion against criteria, until a good inter-rater reliability has been observed (percentage agreement =>90% or Kappa statistics, K>0.60). Initially 10% of references will be double-screened. If inter-rater agreement is good then the remaining references will be screened by one reviewer.

Topic	Pharmacological interventions for the prevention and treatment of PTSD in adults
	All primary-level studies included after the first scan of citations will be acquired in full and re-evaluated for eligibility at the time they are being entered into a study database (standardised template created in Microsoft Excel). At least 10% of data extraction will be double-coded. Discrepancies or difficulties with coding will be resolved through discussion between reviewers or the opinion of a third reviewer will be sought. Non-English-language papers will be excluded (unless data can be obtained from an existing review). Data Analysis Where data is available, meta-analysis using a fixed-effects model will be used to combine results from similar studies. Heterogeneity will be considered and if a random-effects model is considered more appropriate it will be conducted. For risk of bias, outcomes will be downgraded if the randomisation and/or allocation concealment methods are unclear or inadequate. Outcomes will also be downgraded if no attempts are made to blind the assessors or participants in some way, i.e. by either not knowing the aim of the study or the result from other tests. Outcomes will also be downgraded if there is considerable missing data (see below). Handling missing data: Where possible an intention to treat approach will be used. Outcomes will be downgraded if there is a dropout of more than 20%, or if there was a difference of >20% between the groups. For heterogeneity: outcomes will be downgraded once if I2>50%, twice if I2 >80% For imprecision: outcomes will be downgraded if: Step 1: If the 95% CI is imprecise i.e. crosses 0.8 or 1.25 (dichotomous) or -0.5 or 0.5 (for continuous). Outcomes will be downgraded one or two levels depending on how many lines it crosses. Step 2: If the clinical decision threshold is not crossed, we will consider whether the criterion for Optimal Information Size is met, if not we will downgrade one level for the following. for dichotomous outcomes: <300 events for continuous outcomes: <400 participants For clinical effectiveness, if studies report outcomes using the same scale mean differences will be considered, if not standardized mean differences (SMDs) will be considered and the following criteria will be used:

Topic	Pharmacological interventions for the prevention and treatment of PTSD in adults
	SMD <0.2 too small to likely show an effect SMD 0.2 small effect SMD 0.5 moderate effect SMD 0.8 large effect RR <0.8 or >1.25 clinical benefit Anything less (RR >0.8 and <1.25), the absolute numbers will be looked at to make a decision on whether there may be a clinical effect.
Heterogeneity (sensitivity analysis and subgroups)	Where substantial heterogeneity exists, sensitivity analyses will be considered, for instance: Studies with <50% completion data (drop out of >50%) will be excluded. Where possible, the influence of subgroups will be considered, including subgroup analyses giving specific consideration to the groups outlined in the sub-question section and to the following groups: People working in trauma-exposed (or trauma-prone) occupations (including child social workers, emergency services and the military) Trauma type (including single incident relative to chronic exposure) Duration of intervention (for instance, short-term [≤12 weeks] relative to long-term [>12 weeks]) Intensity of intervention (for instance, low dose relative to high dose)First-line treatment relative to second-line treatment and treatment-resistant PTSD (≥2 inadequate treatments) Acute PTSD symptoms (clinically important PTSD symptoms for less than 3 months) relative to chronic PTSD symptoms (clinically important PTSD symptoms for 3 months or more)
Notes	

Appendix B – Literature search strategies

Literature search strategy for "For adults at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Literature search strategy for "For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

One search strategy covered both evidence review questions

Clinical evidence

Database: Medline

Last searched on: **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R), Embase, PsycINFO**

Date of last search: 29 January 2018

#	Searches
1	*acute stress/ or *behavioural stress/ or *emotional stress/ or *critical incident stress/ or *mental stress/ or *posttraumatic stress disorder/ or *psychotrauma/
1	*acute stress/ or *behavioural stress/ or *emotional stress/ or *critical incident stress/ or *mental stress/ or *posttraumatic stress disorder/ or *psychotrauma/
2	1 use emez
3	stress disorders, traumatic/ or combat disorders/ or psychological trauma/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or stress, psychological/
4	3 use mesz
5	exp posttraumatic stress disorder/ or acute stress disorder/ or combat experience/ or "debriefing (psychological)"/ or emotional trauma/ or post-traumatic stress/ or traumatic neurosis/ or trauma/ or stress reactions/ or psychological stress/ or chronic stress/
6	5 use psyh
7	(railway spine or (rape adj2 trauma*) or reexperienc* or re experienc* or torture syndrome or traumatic neuros* or traumatic stress).ti,ab.
8	(trauma* and (avoidance or grief or horror or death* or nightmare* or night mare* or emotion*)).ti,ab.
9	(posttraumatic* or post traumatic* or stress disorder* or acute stress or ptsd or asd or desnos or (combat neuros* or combat syndrome or concentration camp syndrome or extreme stress or flashback* or flash back* or hypervigilan* or hypervigilen* or psych* stress or psych* trauma* or psycho?trauma* or psychotrauma*)).ti,ab.
10	or/2,4,6-9
11	exp *antidepressant agent/
12	11 use emez
13	antidepressive agents/ or serotonin uptake inhibitors/ or monoamine oxidase inhibitors/
14	13 use mesz
15	antidepressant drugs/ or serotonin reuptake inhibitors/ or serotonin reuptake inhibitors/ or monoamine oxidase inhibitors/
16	15 use psyh
17	(tricyclic* or tca*1).tw.
18	(ssri* or ((serotonin or 5 ht or 5 hydroxytryptamine) adj (uptake or reuptake or re uptake) adj inhibit*)).tw.

#	Searches
19	(antidepress* or anti depress* or maoi* or ((adrenaline or amine or mao or mono amin* or monoamin* or tyramin*) adj2 inhibit*)).tw.
20	(snri* or ssnri* or ((noradrenalin or norepinephrine) adj serotonin adj (uptake or reuptake or re uptake) adj inhibitor*) or (serotonin adj (noradrenalin or norepinephrine) adj (uptake or reuptake or re uptake) adj inhibitor*)).tw.
21	or/12,14,16,17-20
22	fluoxetine/ use emez,mesz,psyh
23	paroxetine/ use emez,mesz,psyh
24	sertaline/ use emez,mesz,psyh
25	(fluoxetin* or fluctin*1 or flunirin* or fluoxifar or lovan or prosac or prozac or prozamin* or sarafem or symbyax).tw.
26	(paroxetin* or aropax or deroxat or motivan or paxil* or pexeva or seroxat or tagonis).tw.
27	(sertralin* or altrulin* or aremis or besitran* or gladem or lustral* or naphthylamin* or sealdin* or serad or serlain* or tresleen or zoloft).tw.
28	or/22-27
29	*amitriptyline/ use emez or amitriptyline/ use mesz,psyh
30	(amitriptyl* or amitryptil* or amitryptin* or amitryptylin* or amytriptil* or amytriptyl* or amytryptil* or adepress or adepril* or ambivalon* or amineurin* or amitid* or amitril* or amitrip or amitrol* or anapsique or anp 3548 or antitriptylin* or apoamitriptylin* or damilen* or damylen* or domical* or elatrol* or elavil* or endep or enovil* or etafon* or etafron* or euplit* or lantron* or laroxal* or laroxyl* or lentizol* or novoprotect or proheptadien* or redomex or sarboten retard 75 or saroten* or sarotex or stelminal* or sylvemid* or syneudon* or teperin* or terepin* or triptafen* or triptanol* or triptizol* or triptyl or triptylin* or tryptanol* or tryptin* or tryptizol*).tw.
31	*imipramine/ use emez or imipramine/ use mesz,psyh
32	(imipramin* or antideprin* or berkomin* or chrytemin* or deprinol* or ia pram or imavate or imidobenzyl* or imidol* or imipramid* or imiprex or imiprin* or imizin* or janimin* or melipramin* or norchlorimipramin* or norpramin* tablets or novopramin* or presamin* or pryleugan* or psychoforin* or psychoforin* or servipramin* or sk pramin* or tofranil* or trofanil*).tw.
33	or/29-32
34	brofaromin*.sh.
35	(brofaremin* or brofaromin* or brofarominum or consonar).ti,ab.
36	phenelzin*.sh.
37	(phenelzin* or 2 phenethylhydrazin* or 2 phenylethylhydrazin* or benzylmethylhydrazin* or beta phenethylhydrazin* or beta phenylethylhydrazine or fenelzin or fenizin* or mao rem or nardelzin* or nardil* or phenalzin* or phenethylhydrazin* or phenylethylhydrazin* or stinerval*).tw.
38	or/34-37
39	*venlafaxine/ use emez
40	venlafaxine hydrochloride/ use mesz or venlafaxine/ use psyh
41	(venlafaxin* or efexor or effexor or trevilor).tw.
42	or/39-41
43	*mirtazapine/ use emez or mirtazapine/ use mesz,psyh or (mirtazapin* or 6 azamianserin* or lerivon* or remergil* or remergon* or remeron* or tolvon* or zispin).tw.
44	neuroleptic agent/ use emez or antipsychotic agents/ use mesz or neuroleptic drugs/ use psyh
45	(antipsychotic* or anti psychotic* or (major adj2 (butyrophenon* or phenothiazin* or tranquil*)) or neuroleptic*).tw.
46	45
47	*olanzapine/ use emez or olanzapine/ use mesz,psyh

#	Searches
48	(olanzapin* or lanzac or ly 170053 or ly170053 or midax or olansek or zydis or zyprex*).tw.
49	*risperidone/ use emez or risperidone/ use mesz,psyh
50	(risperidon* or belivon* or risolept or risperdal*).tw.
51	or/47-50
52	or/43,44,46-51
53	carbamazepin*.sh. or (amizepin or amizepine or atretol or biston or calepsin or camapine or carbadac or carbamazepin or carbategral or carbatol or carbatrol or carbazene or carbazep or carbazin* or carmaz or carpaz or carzepin or carzepine or clostedal or convuline or epileptol or epimax or epitol or eposal retard or equetro or espa-lepsin or finlepsin or foxalepsin or hermolepsin or karbamazepin or kodapan or lexin or mazepine or mazetol or neugeron or neurotol or neurotop or nordotol or panitol or servimazepin or sirtal or tardotol or taver or tegol or tegral or tegretal or tegretol or tegrital or telesmin or temporal or temporol or teril or timonil).ti,ab.
54	clonidine/ use emez,mesz or (adesipress or arkamin or atensina or caprysin or catapres or catapresan or catapressant or catasan or chlofazolin or chlophazolin or chlophelin or chlophazolin or clinidine or clofelin or clofeline or clomidine or clondine or clonicel or clonidin* or clonipresan or clonistada or clonnirit or clophelin* or daipres or dixarit or duraclon or gemiton or haemiton or hemiton or hypodine or isoglaucon or jenloga or kapvay or klofelin or klofenil or melzin or normopresan or normopresin or paracefan or sulmidine or taitecin or tenso timelets).ti,ab.
55	propranolol/ use emez,mesz or (acifol or adrexan or alperol or anaprilin * or anaprilinium or anaprylin* or angilol or apsolol or arcablock or artensol or authus or avlocardyl or becardin or bedranol or beprane or bercolol or berkolol or beta neg or beta tablinen or beta timelets or betabloc or betadipresan or betaneg or betaprol or betares or betraden or betaryl or blocard or blocaryl or cardinol or ciplar or corbeta or deralin or dexpropranolol or dibudinate or dideral or dociton * or durabeton or duranol or efektolol or elbrol or emforal or farmadral or farprolol or frekven or frina or hemangeol or hemangiol or hopranolol or ikopal or impral or inderal or inderalici or inderex or indicardin or indobloc or innopran or inpanol or ipran or lederpronol or levopropranolol or napriline or noloten or obsidan or obsin or obzidan or oposim or phanerol or prandol or prano puren or pranopuren or prestoral or prolol or pronovan or propabloc or propal or propalong or propanolol or propayerst or propercuten or prophylux or propra ratiopharm or propral or propranur or proprasylyt* or reducor or rexigen or sagittol or slow deralin or stapranolol or sumial or tenomal or tensiflex or waucoton).ti,ab.
56	or/53-55
57	*carbamazepine/ use emez or carbamazepine/ use mesz,psyh or (amizepin * or carbamazepin* or atretol or biston or carbamazepin or carbategral or carbatol or carbatrol or carzepin or carzepine or epimax or epitol or equetro or finlepsin or lexin or neurotop or sirtal or tegral or tegretal or tegretol or tegrital or timonil).ti,ab.
58	*valproate semisodium/ use emez or valproic acid/ use mesz,psyh or (delepsine or depakote or divalproex or epilim chrono or valproate or valproic acid).ti,ab.
59	*lamotrigine/ use emez or lamotrigine/ use mesz,psyh or (labileno or lamotrigin* or lamepil or lamictal or lamictin or lamodex).ti,ab.
60	*tiagabine/ use emez or tiagabine/ use mesz,psyh or (gabitril or tiabex or tiagabin*).ti,ab.
61	*topiramate/ use emez or topiramate/ use mesz,psyh or (epitomax or qudexy or topamax or topimax or topiramat* or trokendi).ti,ab.
62	*nefazodone/ use emez or nefazodone/ use mesz,psyh or (nefazodon* or nefadar or nefazadone or reseril or serzone).ti,ab.
63	*buspirone/ use emez or buspirone/ use mesz,psyh or (axoren or bespar or buspar or buspin or buspiron*).ti,ab.
64	*lorazepam/ use emez or lorazepam/ use mesz,psyh or (almazine or alzapam or ativan or bonatranquan or kendol or laubeel or lorabenz or loram or loranase or loranaze or lorans or lorax or lorazepam or lorazin or loridem or lorivan or mesmerin or nervistop or orifadal or pro dorm or quait or securit or tavor or temesta or tolid or upan or wypax).ti,ab.

#	Searches
65	*diazepam/ use emez or diazepam/ use mesz,psyh or (antenex or assival or calmpose or cercin or cercine or diapam or diastat or diazemuls or diazepam or diazidem or ducene or eurosan or fanstan or faustan or neocalme or novazam or paceum or pacitran or plidan or psychopax or relanium or seduxen or serendin or sonacon or stesolid or valaxona or valiquid or valium or valpam or valrelease or vatran or zetran).ti,ab.
66	*clonazepam/ use emez or clonazepam/ use mesz,psyh or (aklonil or antelepsin or clonazepam or clonex or clonopin or clonotril or iktorivil or klonopin or rivatril or rivotril).ti,ab.
67	*alprazolam/ use emez or alprazolam/ use mesz,psyh or (aceprax or alprazolam or anax or constan or frontal or helex or neupax or niravam or solanax or tafil or trankimazin or valeans or xanax or xanor).ti,ab.
68	*cycloserine/ use emez or cycloserine/ use mesz,psyh or (cycloserin* or seromicina or seromycin or terizidon or 4-amino-3-isoxazolidinone).ti,ab.
69	*ketamine/ use emez or ketamine/ use mesz,psyh or (ketamin* or ketalar or calipsol or calypsol or imalgene or kalipsol or ketaject or ketalar or ketaminol or ketanest or ketased or ketaset or ketaved or ketavet or ketoject or ketolar or narkamon or narketan or velonarcon or vetalar).ti,ab.
70	*3,4 methylenedioxymethamphetamine/ use emez or n-methyl-3,4-methylenedioxyamphetamine/ use mesz or methylenedioxymethamphetamine/ use psyh or (ecstasy or mdma or methylenedioxy-methamphetamine or methylenedioxymethamphetamine).ti,ab.
71	*neuropeptide y/ use emez or neuropeptide/ use mesz,psyh or (neuropeptide y or neuropeptide tyrosine).ti,ab.
72	*oxytocin/ use emez or oxytocin/ use mesz,psyh or (atonin or di sipidin or disipidin or endopituitrin or mipareton or orasthin or orastina or oxystin or oxytan or pareton or partacon or partocon or partolact or partoxin or physormon or pitocin or piton or pituilobine or pitupartin or synpitan or syntocinon or utedrin or uteracon or uterason).ti,ab.
73	prazosin.sh. or (prazosin or adversuten or alpress or deprazolin or hypovase or lentopres or minipress or peripress or pratsiol or prazac or prazosin diffutab or vasoflex).ti,ab.
74	*propranolol/ use emez or propranolol/ use mesz,psyh or (propranolol or anaprilin or anapriline or arcablock or authus or avlocardyl or avlocardyl retard or bedranol or beprane or beta timelets or betadipresan or cardinol or ciplar or corbeta or deralin or dociton or duranol or efektolol or elbrol or frekven or hemangeol or hemangiol or inderal or inderalici or inderex or innopran or ipran or obsidan or prandol or prolol plus or propabloc or propal or propercuten or prophylux or propra ratiopharm or propral or propranur or sagittol or sumial).ti,ab.
75	*hydrocortisone/ use emez or hydrocortisone/ use mesz,psyh or (alfacort or cort dome or cortef or cortenema or cortisol* or dioderm or ef cortelan or efcortelan or egocort or eksalb or epicort or ficortril or hycor or hycort or hydracort or hydrocort or hydrocortison* or hydrocortone or hydrokortison or hydrotopic or hysone or hytisone or hytone or mildison or munitren or novohydrocort or plenadren or proctocort or proctosone or rectocort or schericur or scherosone or synacort or texacort).ti,ab.
76	or/57-75
77	anticonvulsant agent/ use emez or benzodiazepine derivative/ use emez or tranquilizer/ use emez or anticonvulsants/ use mesz or anti anxiety agents/ use mesz or benzodiazepines/ use mesz or anticonvulsant drugs/ use psyh or benzodiazepines/ use psyh or tranquilizing drugs/ use psyh or (anticonvuls* or anti convuls*).ti,ab.
78	(anxiolytic* or antianxiety or anti anxiety).ti,ab.
79	benzodiaz*.ti,ab.
80	or/77-79
81	or/21,28,33,38,42,52,56,76,80
82	meta analysis/ or "meta analysis (topic)"/ or systematic review/
83	82 use emez
84	meta analysis.sh,pt. or "meta-analysis as topic"/ or "review literature as topic"/
85	84 use mesz

#	Searches
86	(literature review or meta analysis).sh,id,md. or systematic review.id,md.
87	86 use psyh
88	(exp bibliographic database/ or (((electronic or computer* or online) adj database*) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review*.ti,ab,sh,pt. or systematic*.ti,ab.)
89	88 use emez
90	(exp databases, bibliographic/ or (((electronic or computer* or online) adj database*) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review*.ti,ab,sh,pt. or systematic*.ti,ab.)
91	90 use mesz
92	(computer searching.sh,id. or (((electronic or computer* or online) adj database*) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review*.ti,ab,pt. or systematic*.ti,ab.)
93	92 use psyh
94	((analy* or assessment* or evidence* or methodol* or quantativ* or systematic*) adj2 (overview* or review*)).tw. or ((analy* or assessment* or evidence* or methodol* or quantativ* or systematic*).ti. and review*.ti,pt.) or (systematic* adj2 search*).ti,ab.
95	(metaanal* or meta anal*).ti,ab.
96	(research adj (review* or integration)).ti,ab.
97	reference list*.ab.
98	bibliograph*.ab.
99	published studies.ab.
100	relevant journals.ab.
101	selection criteria.ab.
102	(data adj (extraction or synthesis)).ab.
103	(handsearch* or ((hand or manual) adj search*)).ti,ab.
104	(mantel haenszel or peto or dersimonian or der simonian).ti,ab.
105	(fixed effect* or random effect*).ti,ab.
106	((pool* or combined or combining) adj2 (data or trials or studies or results)).ti,ab.
107	or/83,85,87,89,91,93-106
108	exp "clinical trial (topic)"/ or exp clinical trial/ or crossover procedure/ or double blind procedure/ or placebo/ or randomization/ or random sample/ or single blind procedure/
109	108 use emez
110	exp clinical trial/ or exp "clinical trials as topic"/ or cross-over studies/ or double-blind method/ or placebos/ or random allocation/ or single-blind method/
111	110 use mesz
112	(clinical trials or placebo or random sampling).sh,id.
113	112 use psyh
114	(clinical adj2 trial*).ti,ab.
115	(crossover or cross over).ti,ab.
116	(((single* or doubl* or trebl* or tripl*) adj2 blind*) or mask* or dummy or doubleblind* or singleblind* or trebleblind* or tripleblind*).ti,ab.
117	(placebo* or random*).ti,ab.
118	treatment outcome*.md. use psyh
119	animals/ not human*.mp. use emez
120	animal*/ not human*/ use mesz

#	Searches
121	(animal not human).po. use psyh
122	or/109,111,113-118
123	122 not (or/119-121)
124	or/107,123
125	10 and 81 and 124

Database: **CDSR, DARE, HTA, CENTRAL**

Date of last search: 29 January 2018

#	Searches
#1	MeSH descriptor: Stress Disorders, Traumatic this term only
#2	MeSH descriptor: Combat Disorders this term only
#3	MeSH descriptor: Psychological Trauma this term only
#4	MeSH descriptor: Stress Disorders, Post-Traumatic this term only
#5	MeSH descriptor: Stress Disorders, Traumatic, Acute this term only
#6	MeSH descriptor: Stress, Psychological this term only
#7	("railway spine" or (rape near/2 trauma*) or reexperienc* or "re experienc*" or "torture syndrome" or "traumatic neuros*" or "traumatic stress"):ti (Word variations have been searched)
#8	("railway spine" or (rape near/2 trauma*) or reexperienc* or "re experienc*" or "torture syndrome" or "traumatic neuros*" or "traumatic stress"):ab (Word variations have been searched)
#9	(trauma* and (avoidance or grief or horror or death* or nightmare* or "night mare*" or emotion*)):ti (Word variations have been searched)
#10	(trauma* and (avoidance or grief or horror or death* or nightmare* or "night mare*" or emotion*)):ab (Word variations have been searched)
#11	(posttraumatic* or "post traumatic*" or "stress disorder*" or "acute stress" or ptsd or asd or desnos or ("combat neuros*" or "combat syndrome" or "concentration camp syndrome" or "extreme stress" or flashback* or "flash back*" or hypervigilan* or hypervigilen* or "psych* stress" or "psych* trauma*" or psychotrauma* or psychotrauma*) or (posttrauma* or traumagenic* or "traumatic stress*")):ti (Word variations have been searched)
#12	(posttraumatic* or "post traumatic*" or "stress disorder*" or "acute stress" or ptsd or asd or desnos or ("combat neuros*" or "combat syndrome" or "concentration camp syndrome" or "extreme stress" or flashback* or "flash back*" or hypervigilan* or hypervigilen* or "psych* stress" or "psych* trauma*" or psychotrauma* or psychotrauma*) or (posttrauma* or traumagenic* or "traumatic stress*")):ab (Word variations have been searched)
#13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

Database: **CINAHL PLUS**

Date of last search: 29 January 2018

#	Searches
s52	s6 and s51
s51	s40 or s50
s50	s48 not s49
s49	(mh "animals") not (mh "human")
s48	s41 or s42 or s43 or s44 or s45 or s46 or s47
s47	ti (placebo* or random*) or ab (placebo* or random*)

#	Searches
s46	ti (single blind* or double blind* or treble blind* or mask* or dummy* or singleblind* or doubleblind* or trebleblind* or tripleblind*) or ab (single blind* or double blind* or treble blind* or mask* or dummy* or singleblind* or doubleblind* or trebleblind* or tripleblind*)
s45	ti (crossover or cross over) or ab (crossover or cross over)
s44	ti clinical n2 trial* or ab clinical n2 trial*
s43	(mh "crossover design") or (mh "placebos") or (mh "random assignment") or (mh "random sample")
s42	mw double blind* or single blind* or triple blind*
s41	(mh "clinical trials+")
s40	s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17 or s18 or s19 or s20 or s21 or s22 or s23 or s29 or s30 or s31 or s34 or s35 or s36 or s37 or s38 or s39
s39	ti (analy* n5 review* or evidence* n5 review* or methodol* n5 review* or quantativ* n5 review* or systematic* n5 review*) or ab (analy* n5 review* or assessment* n5 review* or evidence* n5 review* or methodol* n5 review* or qualitativ* n5 review* or quantativ* n5 review* or systematic* n5 review*)
s38	ti (pool* n2 results or combined n2 results or combining n2 results) or ab (pool* n2 results or combined n2 results or combining n2 results)
s37	ti (pool* n2 studies or combined n2 studies or combining n2 studies) or ab (pool* n2 studies or combined n2 studies or combining n2 studies)
s36	ti (pool* n2 trials or combined n2 trials or combining n2 trials) or ab (pool* n2 trials or combined n2 trials or combining n2 trials)
s35	ti (pool* n2 data or combined n2 data or combining n2 data) or ab (pool* n2 data or combined n2 data or combining n2 data)
s34	s32 and s33
s33	ti review* or pt review*
s32	ti analy* or assessment* or evidence* or methodol* or quantativ* or qualitativ* or systematic*
s31	ti “systematic* n5 search*” or ab “systematic* n5 search*”
s30	ti “systematic* n5 review*” or ab “systematic* n5 review*”
s29	(s24 or s25 or s26) and (s27 or s28)
s28	ti systematic* or ab systematic*
s27	tx review* or mw review* or pt review*
s26	(mh "cochrane library")
s25	ti (bids or cochrane or embase or “index medicus” or “isi citation” or medline or psyclit or psychlit or scisearch or “science citation” or web n2 science) or ab (bids or cochrane or “index medicus” or “isi citation” or psyclit or psychlit or scisearch or “science citation” or web n2 science)
s24	ti (“electronic database*” or “bibliographic database*” or “computeri?ed database*” or “online database*”) or ab (“electronic database*” or “bibliographic database*” or “computeri?ed database*” or “online database*”)
s23	(mh "literature review")
s22	pt systematic* or pt meta*
s21	ti (“fixed effect*” or “random effect*”) or ab (“fixed effect*” or “random effect*”)
s20	ti (“mantel haenszel” or peto or dersimonian or “der simonian”) or ab (“mantel haenszel” or peto or dersimonian or “der simonian”)
s19	ti (handsearch* or "hand search*" or "manual search*") or ab (handsearch* or "hand search*" or "manual search*")
s18	ab "data extraction" or "data synthesis"
s17	ab "selection criteria"
s16	ab "relevant journals"
s15	ab "published studies"

#	Searches
s14	ab bibliograph*
s13	ti "reference list*"
s12	ab "reference list*"
s11	ti (“research review*” or “research integration”) or ab (“research review*” or “research integration”)
s10	ti (metaanal* or “meta anal*” or metasynthes* or “meta synethes*”) or ab (metaanal* or “meta anal*” or metasynthes* or “meta synethes*”)
s9	(mh "meta analysis")
s8	(mh "systematic review")
s7	(mh "literature searching+")
s6	s1 or s2 or s3 or s4 or s5
s5	ti ((posttraumatic* or "post traumatic*" or "stress disorder*" or "acute stress" or ptsd or asd or desnos or ("combat neuros*" or "combat syndrome" or "concentration camp syndrome" or "extreme stress" or flashback* or "flash back*" or hypervigilan* or hypervigilen* or "psych* stress" or "psych* trauma*" or psychotrauma* or psychotrauma*) or (posttrauma* or traumagenic* or "traumatic stress*"))) or ab ((posttraumatic* or "post traumatic*" or "stress disorder*" or "acute stress" or ptsd or asd or desnos or ("combat neuros*" or "combat syndrome" or "concentration camp syndrome" or "extreme stress" or flashback* or "flash back*" or hypervigilan* or hypervigilen* or "psych* stress" or "psych* trauma*" or psychotrauma* or psychotrauma*) or (posttrauma* or traumagenic* or "traumatic stress*")))
s4	ti ((trauma* and (avoidance or grief or horror or death* or nightmare* or "night mare*" or emotion*))) or ab ((trauma* and (avoidance or grief or horror or death* or nightmare* or "night mare*" or emotion*)))
s3	ti (("railway spine" or (rape near/2 trauma*) or reexperienc* or "re experienc*" or "torture syndrome" or "traumatic neuros*" or "traumatic stress")) or ab (("railway spine" or (rape near/2 trauma*) or reexperienc* or "re experienc*" or "torture syndrome" or "traumatic neuros*" or "traumatic stress"))
s2	(mh "stress, psychological")
s1	(mh "stress disorders, post-traumatic")

Health Economic evidence

Note: evidence resulting from the health economic search update was screened to reflect the final dates of the searches that were undertaken for the clinical reviews (see review protocols).

Database: Medline

Last searched on: **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R), Embase, PsycINFO**

Date of last search: 1 March 2018

#	Searches
1	*acute stress/ or *behavioural stress/ or *emotional stress/ or *critical incident stress/ or *mental stress/ or *posttraumatic stress disorder/ or *psychotrauma/
1	*acute stress/ or *behavioural stress/ or *emotional stress/ or *critical incident stress/ or *mental stress/ or *posttraumatic stress disorder/ or *psychotrauma/
2	1 use emez
3	stress disorders, traumatic/ or combat disorders/ or psychological trauma/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or stress, psychological/
4	3 use mesz, prem

#	Searches
5	exp posttraumatic stress disorder/ or acute stress disorder/ or combat experience/ or "debriefing (psychological)"/ or emotional trauma/ or post-traumatic stress/ or traumatic neurosis/ or "trauma"/ or stress reactions/ or psychological stress/ or chronic stress/
6	5 use psyh
7	(railway spine or (rape adj2 trauma*) or reexperienc* or re experienc* or torture syndrome or traumatic neuros* or traumatic stress).ti,ab.
8	(trauma* and (avoidance or grief or horror or death* or nightmare* or night mare* or emotion*)).ti,ab.
9	(posttraumatic* or post traumatic* or stress disorder* or acute stress or ptsd or asd or desnos or (combat neuros* or combat syndrome or concentration camp syndrome or extreme stress or flashback* or flash back* or hypervigilan* or hypervigilen* or psych* stress or psych* trauma* or psycho?trauma* or psychotrauma*)).ti,ab.
10	or/2,4,6-9
11	budget/ or exp economic evaluation/ or exp fee/ or funding/ or exp health care cost/ or health economics/ or exp pharmacoeconomics/ or resource allocation/
12	151 use emez
13	exp budgets/ or exp "costs and cost analysis"/ or economics/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or exp "fees and charges"/ or value of life/
14	153 use mesz, prem
15	exp "costs and cost analysis"/ or cost containment/ or economics/ or finance/ or funding/ or "health care economics"/ or pharmacoeconomics/ or exp professional fees/ or resource allocation/
16	155 use psyh
17	(cost* or economic* or pharmacoeconomic* or pharmaco economic*).ti. or (cost* adj2 (effective* or utilit* or benefit* or minimi*)).ab. or (budget* or fee or fees or financ* or price or prices or pricing or resource* allocat* or (value adj2 (monetary or money))).ti,ab.
18	or/12,14,16-17
19	decision theory/ or decision tree/ or monte carlo method/ or nonbiological model/ or (statistical model/ and exp economic aspect/) or stochastic model/ or theoretical model/
20	159 use emez
21	exp decision theory/ or markov chains/ or exp models, economic/ or models, organizational/ or models, theoretical/ or monte carlo method/
22	161 use mesz, prem
23	exp decision theory/ or exp stochastic modeling/
24	163 use psyh
25	((decision adj (analy* or model* or tree*)) or economic model* or markov).ti,ab.
26	or/20,22,24-25
27	quality adjusted life year/ or "quality of life index"/ or short form 12/ or short form 20/ or short form 36/ or short form 8/ or sickness impact profile/
28	167 use emez
29	quality-adjusted life years/ or sickness impact profile/
30	169 use mesz, prem
31	(((disability or quality) adj adjusted) or (adjusted adj2 life)).ti,ab.
32	(disutili* or dis utili* or (utilit* adj1 (health or score* or value* or weigh*))).ti,ab.
33	(health year equivalent* or hye or hyes).ti,ab.
34	(daly or qal or qald or qale or qaly or qtime* or qwb*).ti,ab.
35	discrete choice.ti,ab.
36	(euroqol* or euro qol* or eq5d* or eq 5d*).ti,ab.

#	Searches
37	(hui or hui1 or hui2 or hui3).ti,ab.
38	(((general or quality) adj2 (wellbeing or well being)) or quality adjusted life or qwb or (value adj2 (money or monetary))).ti,ab.
39	(qol or hql* or hqol* or hrqol or hr ql or hrql).ti,ab.
40	rosser.ti,ab.
41	sickness impact profile.ti,ab.
42	(standard gamble or time trade* or tto or willingness to pay or wtp).ti,ab.
43	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
44	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
45	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
46	(sf16 or sf 16 or short form 16 or shortform 16 or shortform16).ti,ab.
47	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
48	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
49	or/28,30-48
50	or/18,26,49

Database: **HTA, NHS EED**

Date of last search: 1 March 2018

#	Searches
#1	MeSH descriptor: Stress Disorders, Traumatic this term only
#2	MeSH descriptor: Combat Disorders this term only
#3	MeSH descriptor: Psychological Trauma this term only
#4	MeSH descriptor: Stress Disorders, Post-Traumatic this term only
#5	MeSH descriptor: Stress Disorders, Traumatic, Acute this term only
#6	MeSH descriptor: Stress, Psychological this term only
#7	("railway spine" or (rape near/2 trauma*) or reexperienc* or "re experienc*" or "torture syndrome" or "traumatic neuros*" or "traumatic stress"):ti (Word variations have been searched)
#8	("railway spine" or (rape near/2 trauma*) or reexperienc* or "re experienc*" or "torture syndrome" or "traumatic neuros*" or "traumatic stress"):ab (Word variations have been searched)
#9	(trauma* and (avoidance or grief or horror or death* or nightmare* or "night mare*" or emotion*)):ti (Word variations have been searched)
#10	(trauma* and (avoidance or grief or horror or death* or nightmare* or "night mare*" or emotion*)):ab (Word variations have been searched)
#11	(posttraumatic* or "post traumatic*" or "stress disorder*" or "acute stress" or ptsd or asd or desnos or ("combat neuros*" or "combat syndrome" or "concentration camp syndrome" or "extreme stress" or flashback* or "flash back*" or hypervigilan* or hypervigilen* or "psych* stress" or "psych* trauma*" or psychotrauma* or psychotrauma*) or (posttrauma* or traumagenic* or "traumatic stress*")):ti (Word variations have been searched)
#12	(posttraumatic* or "post traumatic*" or "stress disorder*" or "acute stress" or ptsd or asd or desnos or ("combat neuros*" or "combat syndrome" or "concentration camp syndrome" or "extreme stress" or flashback* or "flash back*" or hypervigilan* or hypervigilen* or "psych* stress" or "psych* trauma*" or psychotrauma* or psychotrauma*) or (posttrauma* or traumagenic* or "traumatic stress*")):ab (Word variations have been searched)
#13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

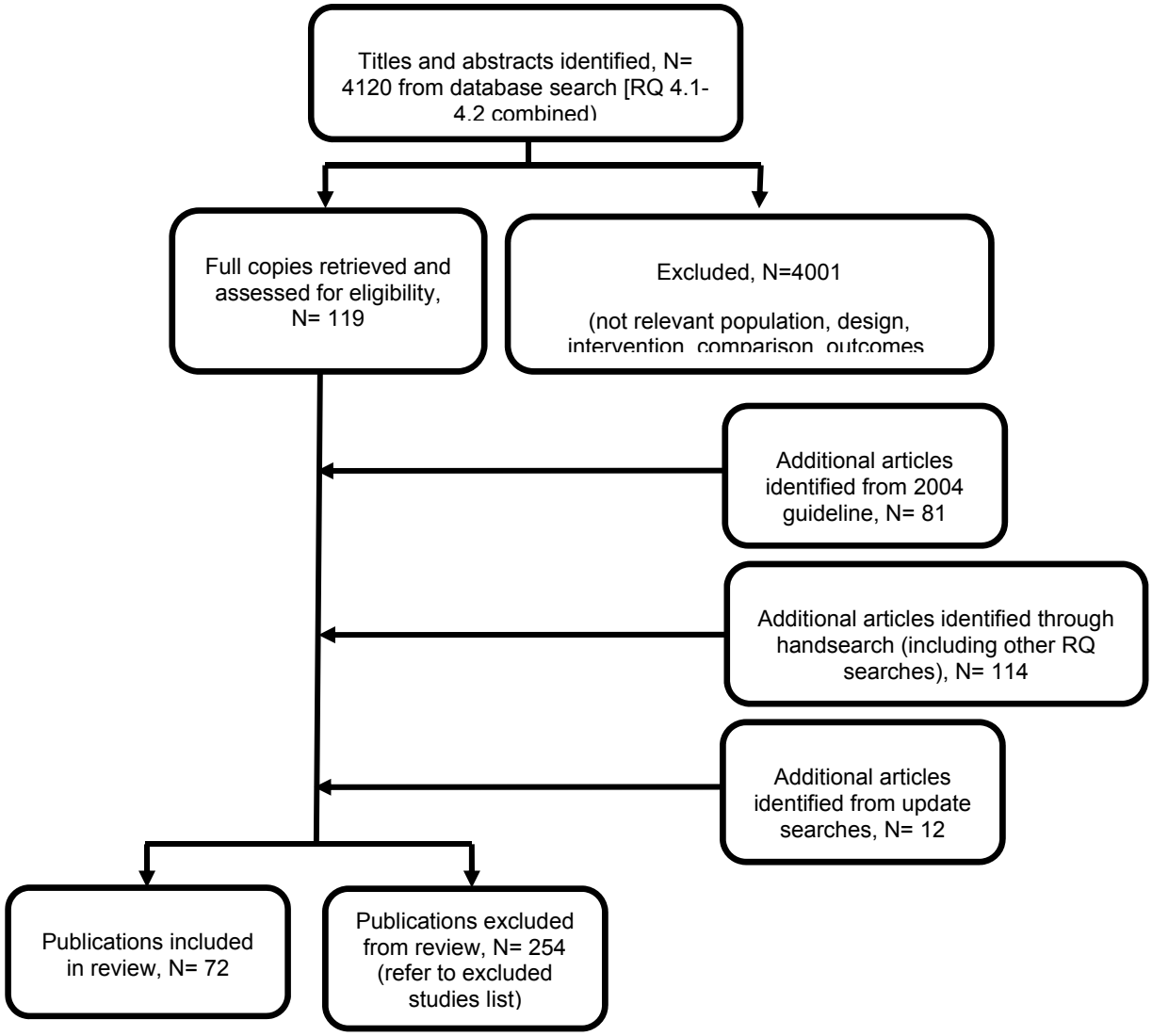
Appendix C – Clinical evidence study selection

Clinical evidence study selection for "For adults at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Clinical evidence study selection for "For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

One flow diagram covers both evidence review questions

Figure 1: Flow diagram of clinical article selection for review



Appendix D – Clinical evidence tables

Clinical evidence tables for "For adults at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
Delahanty 2013	Symptom severity at baseline: Unclear	Motor Vehicle Collision: Motor vehicle accident (58%); fall (19%); assault (17%); other (6%) Mean months since trauma: 0.016 (within 12 hours)	68	Age: 30.6 (18-56) Gender (% female): 34 BME (% non-white): 16 Country: US Coexisting conditions: Not reported	Inclusion criteria: injury victims admitted as trauma inpatients at a Midwestern Level-1 trauma unit; non-amnestic participants who met criterion A for exposure to a traumatic event; score ≥27 on the Peritraumatic Dissociative Experiences Questionnaire Self-Report Version (PDEQ) scale. Exclusion criteria: Glasgow Coma Scale (GCS) score <14; exposure to a traumatic event that occurred more than 12 hours before initial medication dose could be given or inability to initiate first medication dose within 12 hours of event; allergy to cortisol or medical/medicinal contraindications to cortisol administration; pregnant or breastfeeding; exposure to a trauma of a potentially ongoing nature (e.g., domestic violence); presence of injuries requiring delayed operative procedures; patient reported corticosteroid use in the previous 6 months; and/or patient had injuries that required treatment with steroids.
Germain 2012	Non-significant symptoms at baseline (below threshold and <50% maximum score on scale)	Military combat: Combat Theatre: 48% Operations Iraqi/Enduring Freedom; 18% Persian Gulf War; 12% Vietnam; 6% Other theatre of operations; 15% No conflict	34	Age: 41.3 (range not reported) Gender (% female): 6 BME (% non-white): 12 Country: US Coexisting conditions:	Inclusion criteria: had served or were serving in the US military; had current sleep complaints (defined by a score≥3 of the nightmare item of the Clinician-Administered PTSD Scale and a score>5 on the Pittsburgh Sleep Quality Index and at least one daytime functional impairment or sleep disruption, and persistence for more than 1 month).

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
		Mean months since trauma: Not reported		All participants had sleep complaints. SCID primary diagnosis: 3% Generalized anxiety disorder; 24% Primary insomnia or insomnia related to another disorder; 6% no diagnosis on axis I	Exclusion criteria: unstable medical conditions; resting blood pressure of less than 90/60 during the physical examination; history of bipolar or psychotic disorder; current (within the last 3 months) substance/alcohol abuse or dependence; positive drug screen; diagnosis of obstructive sleep apnea; using a beta-blocker or another alpha-1 antagonist
Hoge 2012	Symptom severity at baseline: Unclear	Motor Vehicle Collision: Motor vehicle accident (63%); work injury (10%); burn/electric shock (10%); falls (7%); physical assault (5%); hit by bicycle (2%); fire (2%) Mean months since trauma: 0.006 (mean 4.44 hours)	43	Age: 33.5 (range NR) Gender (% female): 56 BME (% non-white): Not reported Country: US Coexisting conditions: Not reported	Inclusion criteria: adults aged 18-65 years; attending emergency department at the Massachusetts General Hospital; experienced an event that met the DSM-IV PTSD A.1 (stressor) and A.2 (response) criteria; occurrence of the traumatic event no earlier than 12 hours prior to the first dose of study medication. Exclusion criteria: physical injury that would complicate participation; hospital stay longer than overnight; head injury with loss of consciousness; a medical condition that contraindicated the administration of propranolol (e.g. asthma); use of medications with potentially dangerous interactions with propranolol; previous adverse reaction to a β-blocker; blood alcohol concentration above 0.02% or presence of substances of abuse on saliva testing; pregnancy; traumatic event reflecting ongoing victimization; contraindicating psychiatric condition such as psychotic, bipolar, major depressive, or posttraumatic stress disorder from another event; suicidality or homicidality; unwillingness or inability to come to Boston for the research visits; treating physician did not concur with enrolment in the study

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
Mellman 2002	Clinically important PTSD symptoms (scoring above a threshold on validated scale) at baseline	Motor Vehicle Collision: Motor vehicle accident (68%); industrial accidents (9%); impersonal assaults (23%) Mean months since trauma: 0.47 (mean 14.3 days)	22	Age: 36.1 (range NR) Gender (% female): 36 BME (% non-white): 91 Country: US Coexisting conditions: All participants had sleep disturbance	Inclusion criteria: participants admitted to a level I trauma centre following life-threatening incidents; had recall of the incident; endorsed at least moderate impairment of sleep initiation or maintenance; met full criteria for at least 2 PTSD symptom clusters (DSM-IV criteria) during a structured interview assessment; able and willing to provide informed consent. Exclusion criteria: having been intoxicated at the time of the incident; brain injury; pre-existing active psychiatric disorders
Pitman 2002	Unclear symptom severity at baseline	Motor Vehicle Collision: Motor vehicle accident (71%) Mean months since trauma: 0.008 (within 6 hours)	41	Age: 34.3 (range NR) Gender (% female): 51 BME (% non-white): Not reported Country: US Coexisting conditions: Not reported	Inclusion criteria: Emergency Department (ED) patients who had just experienced a traumatic event that met the DSM-IV PTSD A.1 (stressor) and A.2 (response) criteria; had a heart rate (HR) of 80 beats per minute (BPM) or greater at the time of ED presentation; upon mental status examination were found competent to understand the purpose of the study and the nature of the procedures; gave written informed consent after the procedures had been fully explained. Exclusion criteria: serious physical injury; systolic blood pressure under 100 mm Hg; substance intoxication; pregnancy; lifetime history of congestive heart failure; heart block or bronchial asthma
Stein 2007	Non-significant symptoms (below threshold and <50% maximum score on scale) at baseline	Motor Vehicle Collision: Motor vehicle collisions (58%); falls (21%); burns (6%); pedestrian versus automobile (4%); assault (4%); other (6%)	48	Age: Median 29 (18-61) Gender (% female): 46 BME (% non-white): 65 Country: US	Inclusion criteria: adults aged 18-65 years; admitted to the University of California San Diego (UCSD) Level 1 Surgical Trauma Centre for a severe physical injury requiring specialized, emergent trauma care

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
		Mean months since trauma: 0.066 (within 48 hours)		Coexisting conditions: Not reported	
Suliman 2015	Clinically important PTSD symptoms (scoring above a threshold on validated scale) at baseline	Mixed: Physical or sexual assault (69%); other, including motor vehicle accident or witnessing event (31%) Mean months since trauma: NR (≤1 month)	31	Age: Median 29.5 (range NR) Gender (% female): 34 BME (% non-white): 100 Country: South Africa Coexisting conditions: Depression (34%); other anxiety disorders (21%); alcohol dependence or abuse (17%); antisocial personality disorder (3%)	Inclusion criteria: experience of a traumatic event, such as a vehicle collision or other accident, physical or sexual assault within the previous 4 weeks; aged 18-65 years; sufficient knowledge of English in order to read, understand and sign the Informed consent form as well as study procedures and assessment instruments; met criteria for either full DSM-IV criteria or intrusion and hyper-arousal criteria for acute stress disorder (ASD). Exclusion criteria: refusal of any medication therapy; serious physical injury at inclusion (Abbreviated Injury Scale [AIS] score ≥ 3); concomitant medications not allowed in the study (monoamine oxidase inhibitors [MAOIs], reversible inhibitors of monoamine oxidase A [RIMAs], mood stabilisers, antipsychotics or psychoactive herbal remedies within the 3 weeks prior to screening, anxiolytics or serotonergic agonists within the 2 weeks prior to screening, treatment with any anticonvulsant drug); lifetime DSM-IV-TR criteria for mania or bipolar disorder, schizophrenia, any personality disorder, mental retardation or pervasive developmental disorder, or cognitive disorder; significant suicide risk and/or a score of ≥5 on item 10 of the Montgomery Asberg Depression Rating Scale (MADRS) scale; history of severe suicide attempt; electroconvulsive therapy within the last year; currently serving in the South African security forces.; history of drug allergy or hypersensitivity to escitalopram or citalopram; illness severe enough to prevent participation in the study (including liver or renal insufficiency;

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
					cardiovascular, pulmonary, gastrointestinal, endocrine (including uncontrolled thyroid), neurological (including epilepsy), infectious, neoplastic, or metabolic disturbances; pregnant or breast-feeding; refusal of adequate contraceptive use (if female)
van Zuiden 2017	Subthreshold symptoms (below threshold but ≥50% maximum score on scale) at baseline	Unintentional injury: 80% accidental; 20% assault Mean months since trauma: 0.29 (mean 8.9 days, inclusion criterion within 12 days)	120	Age: Median 35.5 (range NR) Gender (% female): 50 BME (% non-white): Not reported Country: Netherlands Coexisting conditions: Not reported	Inclusion criteria: patients attending one of three emergency departments after experiencing a traumatic event (DSM-IV PTSD A1 criterion); aged 18–65 years; had moderate to severe acute distress (defined as Trauma Screening Questionnaire [TSQ] score ≥5 and Peritraumatic Distress Inventory [PDI] score ≥17). Exclusion criteria: current PTSD or depression; psychotic, bipolar, substance-related, and personality disorder; severe/chronic systemic disease; mental retardation; neurological/endocrine disorder; ongoing traumatization; medications potentially interfering with oxytocin administration (e.g., systemic glucocorticoids or psychotropic medications); oxytocin allergy; persistent impaired consciousness or amnesia; pregnancy; breastfeeding

Clinical evidence tables for "For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
Ahmadpanah 2014	Diagnosis (ICD/DSM) Chronic (symptoms for 3 months or more) Mean months since	Mixed (51% Persian gulf war, 37% Car accident, 4% Disaster, 7% Other) Mean months since traumatic event: Not reported	102	Age: 35.4 (18-45) Gender (% female): 29 BME (% non-white): NR Country: Iran	Participants were included if they: (1) had a diagnosis of PTSD according to the diagnostic criteria of the DSM-IV TR; (2) had severe sleep disorders; (3) were aged 18-45 years. Participants were excluded if they: (1) had further

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
	onset of PTSD: 94.2			Coexisting conditions: Not reported	psychiatric comorbidities such as major depressive disorder, anxiety disorders, substance abuse (alcohol, drugs), psychosis and personality disorders; (2) were women who were pregnant or intending to get pregnant or who were breast-feeding; (3) had a known physical illness such as heart disease; (4) had adverse experience with prazosin (hypotension caused by prazosin injection) or hydroxyzine; (5) showed a sudden dramatic drop of the repeatedly and routinely measured blood pressure
Akuchekian 2004	Diagnosis (ICD/DSM) Chronic (symptoms for ≥3 months) Mean months since onset of PTSD: 214.8	Military combat (58.2% explosion wave; 10.4% chemical weapons exposure; 7.5% captivity and torture; 20.9% injury; 3% witnessing the death of their fellow soldiers) Mean months since traumatic event: Not reported	67	Age: 30-50 (39.5) Gender (% female): 0 BME (% non-white): Not reported Country: Iran Coexisting conditions: Not reported	Participants were included if they: (1) had chronic PTSD; (2) were being treated with psychotropic drugs for at least 6 months, having no response to other medications; (3) had no kidney disease or stone. Participants were excluded if they: (1) were highly sensitive to medication, and not tolerating the drug side effects
Baker 1995	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Military combat (15% sexual assault; 7% physical assault; 8% accident; 1% natural disaster; 60% combat-related; 8% other)	118	Age: 23-73 (44.4) Gender (% female): 19.4 BME (% non-white): NR Country: US Coexisting conditions: NR	Participants were included if they: (1) met DSM-III-R criteria for PTSD; (2) had a minimum Clinician Administered PTSD Scale (CAPS) score of 45; (3) had a maximum Montgomery- Asberg Depression Scale (MADRS) score of 22; (4) had been symptomatic for at least 6 months. Participants were excluded if they: (1) were women of child-bearing potential; (2) had comorbid medical or psychiatric conditions; (3) were at immediate risk of suicide; (4) were in active pursuit of compensation; (5) were receiving other forms of active treatment such as psychotherapy; (6) had a known sensitivity to MAOIs; (6) were receiving psychotropic medication (with the exception of low-

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
					dose choral hydrate, diphenhydramine, hydroxyzine, and benzodiazepines under specified conditions); (7) responded to placebo, i.e., patients who showed a 30% or more improvement in the CAPS score between the screening and baseline visits
Banisadi 2014	Diagnosis (ICD/DSM) Chronic (symptoms for ≥3 months [all participants had PTSD≥5 years]) Mean months since onset of PTSD: 210 Treatment-resistant population (all of the patients had previously received periods of pharmacotherapy with one or more of the following types of agents: SSRIs, SNRIs, benzodiazepines, tricyclic antidepressants, and anticonvulsants. The patients had also all had at least one and at most seven prior hospital admissions. Although no universally	Military combat (Iran-Iraq war)	37	Age: 48.2 (40-60) Gender (% female): 0 BME (% non-white): NR Country: Iran Coexisting conditions: NR	Participants were included if they: (1) were male and aged 40-60 years; (2) had been diagnosed with chronic PTSD based on DSM-IV-TR criteria; (3) had been admitted to the combat veterans ward of Ibn-E-Sina Psychiatric Hospital; (4) had previously received periods of pharmacotherapy with one or more of the following types of agents: SSRIs, SNRIs, benzodiazepines, tricyclic antidepressants, and anticonvulsants and had shown an incomplete response. Participants were excluded if they: (1) were unwilling to continue in the trial; (2) had a history of serious side effects with pregabalin or sensitivity to pregabalin; (3) had an active medical disease; (4) had a primary diagnosis of an Axis I disorder other than PTSD (e.g., primary diagnosis of major depressive disorder), and diagnosis of an Axis II disorder (i.e., mental retardation, personality disorder)

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
	accepted clinical criteria for defining treatment-resistant PTSD exist, all of the patients enrolled in this study had chronic PTSD and had not shown a complete response to previous treatments)				
Bartzokis 2005	Diagnosis (ICD/DSM) Chronic (symptoms for ≥3 months) Mean months since onset of PTSD: Not reported	Military combat (97% Vietnam veterans; 3% Persian Gulf War Veterans) Mean months since traumatic event: Not reported	65	Age: 38-63 (51.6) Gender (% female): 0 BME (% non-white): 32 Country: US Coexisting conditions: Not reported	Participants were included if they: (1) met DSM-IV criteria for a principal diagnosis of PTSD as determined by psychiatric interview conducted by experienced clinicians; (2) had a score of 65 or higher on the Clinician Administered PTSD Scale (CAPS); (3) had proof of military service (form DD-214 service record). Participants were excluded if they: (1) were receiving current treatment with antipsychotic medications; (2) had a psychotropic antidepressant regimen that had been changed within 6 weeks prior to admission to the program; (3) had significant medical illness, physical impairment, or cognitive impairment that would adversely affect validity of clinical ratings or capacity to participate in study; (4) had a history of seizure disorder that required treatment; (5) had alcohol or substance abuse or dependence in the past 6 months; (6) had a high risk of suicide or directed violence (as determined by experienced clinicians based on past history and admission evaluation).
Batki 2014	Diagnosis (ICD/DSM) Chronicity not	Military combat (73% combat-exposed [participants were	30	Age: Range not reported (50) Gender (% female): 7	Participants were included if they: (1) met DSM-IV-TR (American Psychiatric Association, 2000) diagnostic criteria for both current alcohol

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
	reported Mean months since onset of PTSD: Not reported	veterans of Vietnam, the Gulf Wars, or Iraq and Afghanistan with war-zone and/or civilian related trauma exposure]) Mean months since traumatic event: Not reported		BME (% non-white): 53 Country: US Coexisting conditions: 100% alcohol use disorder	dependence and PTSD; (2) reported “at-risk” or “heavy” drinking in accordance with National Institutes of Health/National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria (at least 15 standard drinks per week on average over the 4 weeks prior to study entry for men and at least 8 standard drinks per week on average for women; Willenbring et al., 2009); (3) expressed a desire to reduce alcohol consumption with the possible long-term goal of abstinence. Participants were excluded if they: (1) met diagnostic criteria for psychotic disorders, bipolar disorder, and dementia; (2) were known to have any clinically significant unstable psychiatric or medical conditions; (3) had a suicide attempt or suicidal ideation in the 6 months prior to enrolment; (4) had acute alcohol withdrawal; (5) had a history of either nephrolithiasis, narrow angle glaucoma or seizure disorder; (5) were currently using other anticonvulsant medications; (5) had used topiramate within the past 4 weeks; (6) were concurrently participating in other treatment studies.
Becker 2007	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Military combat (Index trauma: 50% war trauma; 7% domestic violence; 4% rape; 7% motor vehicle accident; 7% homicide; 11% medical illness; 7% death/suicide of a loved one; 7% childhood sexual or physical abuse)	30	Age: Range NR (50.39) Gender (% female): 21 BME (% non-white): 71 Country: US Coexisting conditions: NR	Participants were included if they: (1) were outpatients of the Durham Veteran’s Administration Medical Centre and aged 34 to 62 years; (2) were medically stable; (3) fulfilled the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for PTSD; (4) spoke English; (5) completed written informed consent. Participants were excluded if they: (1) were already prescribed other psychiatric medications and were not considered medically stable on the dosage; (2) had ulcers, seizure disorder, psychosis, bipolar

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
					disorder, or eating disorders; (3) were pregnant or lactating; (4) had current drug/alcohol abuse or dependence.
Brady 2000	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed (9% serious unintentional injury or fire; 61% physical or sexual assault; 9% seeing someone hurt or die; 6% being in war or combat; 15% miscellaneous other events)	187	Age: 18-69 (39.9) Gender (% female): 73 BME (% non-white): 15 Country: US Coexisting conditions: Current major depression (33%) and current anxiety disorder (16%)	Participants were included if they: (1) were male and female outpatients aged 18 years and older who met Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) criteria for a principal diagnosis of PTSD as determined by part 1 of the Clinician Administered PTSD scale (CAPS); (2) had a minimum 6-month duration of PTSD illness; (3) a total severity score of at least 50 on the CAPS part 2 at the end of a 2-week placebo run-in period; (4) were free of psychotropic medication for at least 2 weeks prior to beginning treatment; (5) had negative results on a beta-human chorionic gonadotropin pregnancy test and stable use of a medically accepted form of contraception (for females). Participants were excluded if they: (1) had current or past history of bipolar, schizophrenic, or other psychotic disorder; (2) had current organic mental disorder, factitious disorder or malingering, or primary diagnosis of major depression, OCD, or other anxiety disorders; (3) had alcohol or substance dependence or abuse in the past 6 months; (4) showed evidence of clinically significant hepatic or renal disease or any other acute or unstable medical condition that might interfere with the safe conduct of the study; (5) had an intolerance or hypersensitivity to sertraline or nonresponse to previous adequate trial; (6) were currently using any medication (except chloral hydrate, taken as needed) with clinically significant psychotropic activity (within 2 weeks of randomization (or 5 weeks for fluoxetine); (7) had

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
					received any cognitive-behavioural therapy during the trial; (8) received any psychotherapy that initiated or ended during the trial
Brady 2005	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed (Civilian trauma: 39% Sexual; 53% Physical; 51% Childhood)	94	Age: 18-65 (36.7) Gender (% female): 46 BME (% non-white): NR Country: US Coexisting conditions: Co-occurring alcohol dependence and PTSD	Participants were included if they: (1) met DSM-IV (American Psychiatric Association, 1994) criteria for current alcohol dependence (within the past 3 months) and current PTSD (within the past 6 months) in response to civilian (e.g., sexual assault, physical assault, serious accident) trauma
Buhmann 2016	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed (Trauma history: 39% torture; 22% refugee camp; 57% Danish asylum centre; 27% ex-combatant)	141	Age: Range NR (45.5) Gender (% female): 45 BME (% non-white): NR Country: Denmark Coexisting conditions: Patients were not excluded solely based on psychotic symptoms (12% psychotic during treatment). 94% depression according to ICD-10. 27% Personality change after catastrophic events (ICD-10 code F62.0). 23% report traumatic brain injury.	Participants were included if they: (1) were aged 18 years or older; (2) were refugees and persons based in Denmark because of family reunification with a refugee; (3) had PTSD according to the ICD-10 diagnostic criteria; (4) had a history of war-related psychological trauma such as imprisonment, torture, inhuman and degrading treatment or punishment, organised violence, prolonged political persecution and harassment or war; (5) were motivated to receive treatment; (6) gave written, voluntary informed consent. Participants were excluded if they: (1) had a severe personality disorder (ICD-10 diagnosis F2x and F30.1-F31.9); (2) were addicted to psychoactive substances (ICD-10 F1x.24-F1x.26); (3) had a need for somatic or psychiatric hospitalisation; (4) were pregnant or lactating.
Carey 2012	Diagnosis (ICD/DSM) Chronic (symptoms for ≥3 months)	Mixed (Non-combat PTSD) Mean months since	34	Age: Range not reported (40.8) Gender (% female): 61 BME (% non-white):	Participants were included if they: (1) were male or female and aged at least 18 years; (2) had DSM-IV, non-combat, chronic PTSD (PTSD symptoms of at least 3months); (3) had a minimum score of 50 on

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
	Mean months since onset of PTSD: Not reported	traumatic event: Not reported		Not reported Country: South Africa Coexisting conditions: Not reported	the Clinician Administered PTSD Scale (CAPS); (4) were willing to provide written informed consent to their participation; (5) were free of disallowed psychotropic medication for a washout period of 5 days for all except fluoxetine (5 weeks) prior to randomization. Participants were excluded if they: (1) had current major depressive disorder and a Montgomery Äsberg Depression Rating Scale (MADRS) score≥20 at baseline; (2) had a significant suicide risk according to the clinical judgement of the investigator; (3) had a substance use disorder within 6 months of randomization; (4) had a positive urine drug screen for illicit substances; (5) had a history of severe personality disorder (based on clinician judgement); (6) had a lifetime history of schizophrenia or other psychotic disorder; (7) were pregnant or breastfeeding women; (8) were women of child-bearing potential not willing to use contraception; (9) had an unstable medical condition, and unresolved clinically significant laboratory or electrocardiogram findings; (10) had previously failed to respond to or shown an intolerance of a second generation antipsychotic (SGA); (11) had failed to respond to two or more trials of an SSRI or an SNRI given in adequate doses for an adequate duration; (12) they started or changed psychotherapy within 8 weeks of screening; (13) had received electroconvulsive therapy in the 3 months before screening; (14) had participated in a clinical trial in the 6 months before screening; (15) showed an improvement of 2 or more points on the Clinical Global Impressions (CGI) severity score from screening to randomization

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
Celik 2011	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Military combat	50	Age: Range NR (30.8) Gender (% female): NR BME (% non-white): NR Country: Turkey Coexisting conditions: NR	Participants were included if they: (1) were diagnosed as chronic PTSD with Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I). Participants were excluded if they: (1) had a concurrent affective and anxiety disorder and PTSD was not considered to be the principal diagnosis (i.e. the main focus of attention or need for treatment) and that the onset of PTSD did not precede that of concurrent disorders; (2) had another axis I disorder as a principal diagnosis within 6 months of screening; (3) had previous treatment with an SSRI at antidepressant doses for 4 or more weeks; (4) had manifested psychotic symptoms or serious suicidal ideation or met criteria for schizophrenia, schizoaffective, organic or bipolar disorders; (5) exhibited behaviour strongly suggestive of inability to comply with a research protocol; (6) had substance abuse diagnosis during last 6 months; (7) had an unstable medical illness or abnormal laboratory or electrocardiographic examinations; (8) were receiving concomitant pharmacotherapy or psychotherapy
Chung 2004/2005	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Military combat (veterans of the Korean or Vietnam war)	113	Age: Range NR (59.8) Gender (% female): 0 BME (% non-white): NR Country: Korea Coexisting conditions: 17% major depressive disorder, 79% dysthymia and 4% dysthymia and major depressive disorder	Participants were included if they: (1) were male veterans of the Korean or Vietnam war; (2) had PTSD as a primary diagnosis according to DSM-IV (American Psychiatric Association, 1994) and CAPS-1 criteria (Blake et al., 1990) and possible co-morbid major depression or dysthymia if symptoms of depression had been present for more than 3 months. Participants were excluded if they: (1) had schizophrenia, bipolar disorder, organic mental disorder, factitious disorder, malingering, obsessive

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
					compulsive disorder, or other mental disorders; (2) had alcohol or other substance dependency or abuse within previous 6 months; (3) had used neuroleptic drugs within previous 2 weeks; (4) had shown a non-response to previous treatment with mirtazapine for at least 8 weeks; (5) had received electroshock therapy in the past; (6) had clinically significant laboratory or EKG abnormalities; (7) had a history of convulsive disorder or treatment with anticonvulsants because of such symptoms; (8) had a baseline score below 50 on the CAPS-2.
Connor 1999b	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed (civilian trauma)	54	Age: NR Gender (% female): 91 BME (% non-white): 7 Country: US Coexisting conditions: NR	Participants were included if they: (1) met DSM-III-R and DSM-IV criteria for PTSD according to the SCID; (2) were civilians. Participants were excluded if they: (1) had a history of psychosis, bipolar disorder, antisocial personality disorder, current or recurrent or recent risk of suicide, homicide; (2) had drug or alcohol abuse disorder within past 6 months.
Davidson (unpublished)	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Unclear (trauma population NR)	538	Age: Range NR (32) Gender (% female): 65 BME (% non-white): NR Country: NR Coexisting conditions: NR	NR
Davidson 1990	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Military combat	46	Age: NR Gender (% female): NR BME (% non-white): NR Country: US Coexisting conditions: 67% common mental health disorder and	Patients were included if they: (1) were inpatients or outpatients of the Veterans Administration Medical centre; (2) met DSM-III criteria for PTSD Participants were excluded if they: (1) had schizophrenia or bipolar disorder; (2) had a history of serious violence over the past 5 years; (3) had

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
				15% substance misuse	any medical condition that would preclude the use of amitriptyline.
Davidson 2001a	Responders (in relapse prevention study)	Mixed (Index traumatic events: 6% serious accident, injury, or fire; 55% physical or sexual assault; 13% seeing someone hurt or die; 9% being in a war or combat; 17% miscellaneous other events)	96	Age: 21-69 (43.4) Gender (% female): 70 BME (% non-white): NR Country: US Coexisting conditions: 40% currently met criteria for a secondary depressive disorder and 20% met criteria for a secondary anxiety disorder	Participants were included if they: (1) were male and female outpatients at least 18 years of age who had completed the previous 24 weeks of open-label continuation treatment with sertraline [Londberg 2001] and who met responder criteria at the final two visits. The responder criteria were a Clinical Global Impression improvement score ≤2 (much or very much improved) and ≥30% improvement in the total severity score in part 2 of the Clinician-Administered PTSD Scale, both indexed against the pre-treatment baseline of the original double-blind acute treatment study [Brady 2000 or Davidson 2001b]; (2) did not have any clinically significant abnormalities identified in a physical examination and laboratory testing conducted at the end of week 24 of continuation treatment study; (3) were using medically acceptable birth control throughout the study (for females). Participants were excluded [from the original acute treatment studies] if they: (1) had a current or past history of bipolar disorder, schizophrenia, or organic mental disorder; (2) had a primary diagnosis of major depression, OCD, or other anxiety disorders; (3) they had alcohol or other substance dependence or abuse in the past 6 months
Davidson 2001b	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed (Type of traumatic event: 62% physical or sexual assault; 12% seeing someone hurt or die; 12% serious accident/fire/injury; 5%	208	Age: 18-69 (37.1) Gender (% female): 78 BME (% non-white): 16 Country: US Coexisting conditions:	Participants were included if they: (1) male and female outpatients aged 18 years and older who met Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) criteria for a principal diagnosis of PTSD as determined by part 1 of the Clinician Administered

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
		being in a war or combat; 9% other event)		Current major depression (40%) and current anxiety disorder (20%)	PTSD scale (CAPS); (2) had a minimum 6-month duration of PTSD illness; (3) a total severity score of at least 50 on the CAPS part 2 at the end of a 1-week placebo run-in period; (4) were free of psychotropic medication for at least 2 weeks prior to beginning treatment or 5 weeks for fluoxetine; (5) had negative results on a beta-human chorionic gonadotropin pregnancy test and stable use of a medically accepted form of contraception (for females). Participants were excluded if they: (1) had current or past history of bipolar, schizophrenic, or other psychotic disorder; (2) had current organic mental disorder, factitious disorder or malingering, or primary diagnosis of major depression; (3) had alcohol or substance dependence or abuse in the past 6 months; (4) showed evidence of clinically significant hepatic or renal disease or any other acute or unstable medical condition that might interfere with the safe conduct of the study; (5) had an intolerance or hypersensitivity to sertraline or nonresponse to previous adequate trial; (6) were currently using any medication (except occasional use of chloral hydrate) with clinically significant psychotropic properties; (7) had received any cognitive-behavioural therapy during the trial; (8) received new psychotherapy or counselling that was initiated within 3 months before randomization
Davidson 2004a (Secondary analysis of pooled data from Brady 2000 and Davidson 2001b)	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed	NR	Age: Range NR (38.4) Gender (% female): 76 BME (% non-white): NR Country: US Coexisting conditions: NR	Participants were included if they: (1) were a participant in one of two double-blind, placebo-controlled, 12-week trials of sertraline and PTSD (Brady et al., 2000; Davidson et al., 2001b); (2) were least 18 years of age; (3) fulfilled DSM-III-R (American Psychiatric Association, 1987) criteria for PTSD, along with a CAPS-I score of at least 50.

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
Davidson 2005a	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed (Principal trauma: 32% combat; 16% sexual trauma; 16% other violence; 19% death [bereavement]; 18% other)	62	Age: Range NR (44.1) Gender (% female): 50 BME (% non-white): 28 Country: US Coexisting conditions: NR	Participants were included if they: (1) were male or female aged 18-70 years; (2) were free of psychotropic medication for at least 2 weeks before entering open-label treatment; (3) were of nonpregnant status (for females). Patients were excluded if they: (1) had a history of schizophrenia, bipolar disorder, organic brain disease, alcohol or drug abuse/dependence (within the previous 6 months), mental retardation; (2) they had a need for ongoing psychotropic medication; (3) had a significant risk of suicide or history of suicide attempt within in the previous 6 months; (4) had a history of significant violence within the previous year; (5) were in a medically unstable state; (6) had prior nonresponse to adequate treatment with fluoxetine (i.e., 40 mg/d or greater for at least 8 weeks); (7) needed trauma-focused psychotherapy; (8) had a positive urine drug screen for illicit substances; (9) had clinically significant abnormal laboratory tests.
Davidson 2006a/2008/2012	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed (12% combat; 1% sexual abuse [childhood]; 12% sexual assault [adulthood]; 29% nonsexual abuse; 18% accidental injury; 2% natural disaster; 7% witnessing; 13% unexpected death; 5% other; 1% unknown)	329	Age: Range NR (41.3) Gender (% female): 54 BME (% non-white): NR Country: Argentina, Chile, Colombia, Denmark, Finland, Mexico, Norway, Portugal, South Africa, Spain, Sweden, UK Coexisting conditions: NR	Patients were included if they: (1) were at least 18 years of age; (2) could provide legal consent; (3) were not currently hospitalized; (4) met the DSM-IV criteria for a primary diagnosis of PTSD; (5) had a score of at least 60 on the Clinician-Administered PTSD Scale, abbreviated 1-Week Symptom Status Version (CAPS-SX17); (6) had PTSD symptoms for at least the previous 6 months; (7) had a negative serum pregnancy test at screening (for women of childbearing potential); (8) were generally in good health as determined by the investigator on the basis of medical history, physical examination, and screening laboratory results; (8) were willing and able to return for all protocol-defined visits; (9) were fluent in written and spoken forms of English,

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
					Spanish, or Portuguese; (10) were willing and able to provide written informed consent prior to admission. Participants were excluded if they: (1) had intolerance, hypersensitivity, or nonresponse to a previous adequate trial of venlafaxine; (2) were unable to tolerate or respond to adequate trials of 3 antidepressants; (3) had current primary major depression or panic disorder; (4) had a current mental disorder due to a general medical condition or history of bipolar disorder, schizophrenia, or other psychotic disorder; (5) had abused or were dependent on alcohol or other drugs within 6 months of randomization or had a positive urine drug screen; (6) showed a high risk of suicide or violence; (7) used any investigational drug, antipsychotic, or monoamine oxidase inhibitor within 30 days of randomization; (8) had electroconvulsive therapy within 3 months of randomization or likelihood of requiring electroconvulsive therapy during the study; (9) used triptans or any other psychoactive drug, including fluoxetine, or herbal preparation within 7 days of randomization; (10) had current involvement in criminal proceedings or compensation claims related to trauma; (11) were nursing, pregnant, or sexually active without acceptable birth control (for females); (12) had initiated or changed psychotherapy of any kind within 3 months of study enrolment
Davidson 2006b	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed (Most common types of primary trauma were: nonsexual abuse [26.2%]; adult sexual abuse [15.8%]; childhood	538	Age: NR Gender (% female): NR BME (% non-white): NR	Participants were included if they: (1) were male or female outpatients aged 18 years or older; (2) met DSM-IV criteria for a primary diagnosis of PTSD based on the Structured Clinical Interview for DSM-IV; (3) had a score of at least 40 on the Davidson

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
		sexual abuse [14.9%]; unexpected death [12.6%]; accidental injury [11.9%];and combat [9.0%])		Country: US Coexisting conditions: NR	Trauma Scale (DTS); (4) had a score of at least 60 on the 17-item Clinician-administered PTSD Scale (CAPS-SX), 1-week symptom status version; (5) had PTSD symptoms for at least the previous 6 months; (6) had a negative serum pregnancy test at screening (for women of childbearing potential); (7) were generally in good health based on medical history, physical examination, and screening laboratory results; (8) were judged to have high likelihood of complying with protocol. Participants were excluded if they: (1) showed a decrease of more than 25% on the DTS between screening and baseline; (2) had shown intolerance, hypersensitivity, or nonresponse to a previous adequate trial of venlafaxine or sertraline; (3) were unable to tolerate or respond to adequate trials of 3 or more antidepressants; (4) had current primary major depression or panic disorder (determined using the structured Mini-International Neuropsychiatric Interview); (5) had a current mental disorder due to a general medical condition or history of bipolar disorder, schizophrenia, or other psychotic disorder; (6) had alcohol or drug abuse or dependence within 6 months of randomization or a positive urine drug screen; (7) had a high risk of suicide or violence; (8) used any investigational drug, antipsychotic, or monoamine oxidase inhibitor within 30 days of randomization; (9) received electroconvulsive therapy within 3 months of randomization or likelihood of requiring electroconvulsive therapy during the study; (10) received triptans or any other psychoactive drug (including SSRIs or tricyclic antidepressants) or herbal preparation within 7 days of randomization; (11) initiated or changed psychotherapy within 3 months of randomization; (12) were currently

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
					involved in criminal proceedings or compensation claims related to trauma; (13) were women and were nursing, pregnant, or engaging in sexual activity without acceptable birth control
Davidson 2007	Diagnosis (ICD/DSM) Chronic (symptoms for ≥3 months) Mean months since onset of PTSD: 157.2	Mixed (53% physical and sexual assault/violence; 15% witnessing harm or death; 9% serious accident/fire/injury; 9% combat; 2% natural or technological disaster; 11% other) Mean months since traumatic event: Not reported	232	Age: 18-64 (42.6) Gender (% female): 66 BME (% non-white): Not reported Country: US Coexisting conditions: 38% major depressive disorder	Participants were included if they: (1) met the DSM-IV criteria for PTSD, as determined by the Clinician-Administered PTSD Scale (CAPS); (2) had both CAPS and Davidson Trauma Scale (DTS) scores of 50 or more at screening and baseline visits. Participants were excluded if they: (1) had other psychiatric Axis I disorders (DSM-IV) as a principal diagnosis (except PTSD), an eating disorder within 6 months of screening, or any history of obsessive-compulsive disorder, psychotic disorder, bipolar disorder, mental retardation, or antisocial personality disorder; (2) showed a decrease of 50% or more in CAPS or DTS score between the screening and baseline visits; (3) had a medical condition that could affect the pharmacokinetics of tiagabine; (4) had a history of unresponsiveness to 2 or more previously documented pharmacological treatments of PTSD; (5) had drug or alcohol abuse (within the last 3 months) or dependence (within the last 6 months, except nicotine and caffeine dependence); (6) had previously used tiagabine; (7) had a history of seizures; or (8) were involved in PTSD-related litigation or disability payments.
Davis 2004	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Military combat (98% combat; 2% sexual)	41	Age: 32-73 (46.9) Gender (% female): 2 BME (% non-white): 40 Country: US Coexisting conditions: 39% major	Participants were included if they: (1) had a diagnosis of chronic PTSD; (2) were aged 19 to 75 years; (3) had stable physical health; (4) had negative urine drugs-of-abuse screen; (5) were able to take oral medication; (6) were free of all psychotropic medication in the previous 2 weeks (6 weeks for fluoxetine); (7) provided a signed

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
				depression; 27% dysthymia; 2% panic with agoraphobia; 5% panic without agoraphobia; 29% lifetime alcohol use disorder; 12% lifetime polysubstance use disorder	informed consent form. Participants were excluded if they: (1) women of childbearing potential and were not using at least one medically approved method of birth control; (2) had a lifetime history of bipolar, psychotic, or cognitive disorder; (3) had acute suicidality or homicidality; (4) had active substance abuse/dependence within the previous 4 months (except nicotine and caffeine); (5) had an unstable medical condition; (6) had a history of sensitivity to nefazodone; (7) were unable to attend follow-up visits; (8) were women who were pregnant, planning to become pregnant, or breastfeeding.
Davis 2008a	Diagnosis (ICD/DSM) Chronic (symptoms for ≥3 months) Mean months since onset of PTSD: 292.8	Military combat (95% combat-related trauma) Mean months since traumatic event: Not reported	85	Age: Range not reported (55.2) Gender (% female): 2 BME (% non-white): Not reported Country: US Coexisting conditions: Not reported	Participants were included if they: (1) had diagnosis of PTSD confirmed by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and Clinician-Administered PTSD Scale (CAPS), using the "rule-of-fours" and a total CAPS score of at least 45; (2) were aged 19 to 70 years; (3) had a stable medical condition. Participants were excluded if they: (1) had a substance use disorder (other than caffeine and nicotine) in the previous 2 months; (2) had used psychotropic medications for the previous 2 weeks (6 weeks for fluoxetine); (3) had a lifetime history of bipolar, psychotic, or cognitive disorders; (4) had a history of seizure disorder; (5) had a history of sensitivity to divalproex; (6) had current suicidal ideation, homicidal ideation, or psychotic symptoms that might interfere with the patient's ability to give informed consent or preclude safe maintenance on divalproex monotherapy for the duration of the study; (7) were a woman of childbearing potential

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
					and were not using a medically approved method of contraception; (8) were pregnant or breastfeeding during the course of the study
de Kleine 2012/2014/2015	Diagnosis (ICD/DSM) Chronicity not reported Mean months since onset of PTSD: Not reported	Mixed (52% sexual assault including childhood sexual abuse; 30% violent nonsexual assault; 4% a road traffic or other accident; 3% war-zone experiences; 10% other) Mean months since traumatic event: Not reported	75	Age: 38.3 (Range NR) Gender (% female): 81 BME (% non-white): NR Country: Netherlands Coexisting conditions: The most common current coexisting Axis I disorders were depressive disorder (53.7%) and anxiety disorders (41.8%)	Participants were included if they: (1) were aged 18-65 years; (2) had current PTSD DSM-IV diagnosis confirmed by a structured diagnostic interview. Participants were excluded if they: (1) had (current or past) psychosis or delusional disorders; (2) had acute suicidal tendency; (3) had mental retardation; (4) had substance abuse or dependence; (5) were pregnant or lactating; (6) had a serious and unstable medical condition (e.g., pacemaker, renal disease, porphyria); (7) had a history of epileptic seizures; (8) were taking medication that might interfere with DCS (e.g., anticoagulants); (9) were unable to speak or write Dutch
Difede 2008/2014	Diagnosis (ICD/DSM) Chronicity not reported Mean months since onset of PTSD: Not reported	World Trade Centre attacks (44% from occupations-at-risk for PTSD [16% firefighters, 24% police, and 4% EMT/paramedic] and 56% were civilians) Mean months since traumatic event: Not reported	25	Age: 45.8 (25-70) Gender (% female): 24 BME (% non-white): 16 Country: US Coexisting conditions: 40% comorbid major depression	Participants were included if they: (1) were English-speaking adults aged 18–70 years; (2) were in good health; (3) had PTSD following exposure to the World Trade Centre attacks. Participants were excluded if they: (1) had substance dependence, active suicidal or homicidal ideation; (2) significant health impairment; (3) were currently using oral anticoagulant medication or anti-tuberculosis medications; (4) had a history of seizures; (5) had hypersensitivity to d-cycloserine
Friedman 2007	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Military combat (Frequency of trauma by category: 2% serious accident, injury or fire; 15% physical or sexual assault; 8% seeing someone hurt or die; 71%	169	Age: Range NR (45.3) Gender (% female): NR BME (% non-white): 31 Country: US Coexisting conditions:	Participants were included if they: (1) were a literate male or female aged 18 or over; (2) had a DSM-III-R diagnosis of PTSD determined by trained raters who administered Part 1 of the Clinician-Administered PTSD Scale (CAPS-1); (3) had a minimum duration of 6 months of PTSD; (4) had a total score of at least 50 on Part 2 of the

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
		being in war or combat; 4% miscellaneous other events)		47% current major depression and 19% current DSM-III-R anxiety disorder	CAPS (CAPS-2) at the end of a 1-week placebo run-in period; (5) had a negative urine drug screen on day 1 of the placebo run-in; (6) had a complete medical and psychiatric history at study entry; (7) had no significant medical problems as determined through physical examination; (8) had discontinued all other psychotropic medication (except chloral hydrate for sleep) prior to entry into the study; (9) were judged reliable for medication compliance; (10) were practicing a medically acceptable method of contraception and had a negative serum ß-human chorionic gonadotropin pregnancy test (for females). Participants were excluded from the study if they: (1) had an organic mental disorder; (2) had a primary current diagnosis meeting DSM-III-R criteria for major depression single episode, dysthymic disorder, personality disorder from clusters other than cluster C, OCD, GAD, panic disorder, simple or social phobia, agoraphobia, anxiety disorder or bipolar disorder; (3) had any current psychotic features or had a history of schizophrenia, delusional disorder, or psychotic disorder; (4) met criteria for any substance use disorder in the past 6 months; (5) were receiving any concomitant psychotropic therapy of any type; (6) had therapy with any depot neuroleptic within 6 months; (7) would be receiving behaviour therapy during the study; (8) had a history of nonresponse to adequate treatment; (9) were taking drugs with a psychotropic component, neuroleptics, MAOIs, antidepressants, or hypnotics or anxiolytics in the previous 2 weeks (5 weeks for fluoxetine); (10) had history or evidence of malignancy or significant hematologic, endocrine, cardiovascular, renal, hepatic, neurologic, or gastrointestinal disease;

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
					(11) had a liver function test result greater than twice the upper limit of the normal range at screening; (12) had current impulse control problems; (13) were currently involved in litigation for disability benefits or for damages related to the subject's disorder
Germain 2012	Clinically important PTSD symptoms (scoring above a threshold on validated scale) Chronic (symptoms for 3 months or more) Mean months since onset of PTSD: Not reported	Military combat (Combat Theatre: 48% Operations Iraqi/Enduring Freedom; 18% Persian Gulf War; 12% Vietnam; 6% Other theatre of operations; 15% No conflict) Mean months since traumatic event: Not reported	34	Age: 41.3 (Range NR) Gender (% female): 6 BME (% non-white): 12 Country: US Coexisting conditions: SCID primary diagnosis: 67% Current posttraumatic stress disorder; 3% Generalized anxiety disorder; 24% Primary insomnia or insomnia related to another disorder; 6% no diagnosis on axis I	Participants were included if they: (1) had served or were serving in the US military; (2) had current sleep complaints (defined by a score≥3 of the nightmare item of the Clinician-Administered PTSD Scale and a score>5 on the Pittsburgh Sleep Quality Index and at least one daytime functional impairment or sleep disruption, and persistence for more than 1 month). Participants were excluded if they: (1) had an unstable medical conditions; (2) had resting blood pressure of less than 90/60 during the physical examination; (3) had a history of bipolar or psychotic disorder; (4) had current (within the last 3 months) substance/alcohol abuse or dependence; (5) had a positive drug screen; (6) had a diagnosis of obstructive sleep apnea; (7) were using a beta-blocker or another alpha-1 antagonist
Hien 2015/Ruglass 2015	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed (Lifetime traumatic experiences: 46% child physical; 46% adult physical; 39% child sexual; 36% adult sexual; 67% transportation accident; 22% life-threatening illness; 35% exposed to violent death)	69	Age: Range NR (42.4) Gender (% female): 81 BME (% non-white): 77 Country: US Coexisting conditions: Alcohol dependence: 88% alcohol dependence; 4% alcohol abuse; 42% early-onset AUD. Drug dependence: 12%	Participants were included if they: (1) were aged 18-65 years; (2) met Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM-IV-TR; American Psychiatric Association, 2000) criteria for full PTSD or subthreshold PTSD; (3) met DSM-IV-TR criteria for current alcohol dependence or alcohol abuse with at least 2 heavy drinking days (more than 3 drinks for women and more than 4 drinks for men) in the past 90 days or at least 14 drinks over 30 consecutive days or less than 22 consecutive abstinent days. Individuals who did not meet criteria for alcohol abuse or

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
				cannabis dependence; 30% cocaine dependence; 55% comorbid AUD and SUD; 61% current major depression	dependence were eligible if they reported at least one episode of alcohol misuse during the prior 90 days. Alcohol misuse was defined as either hazardous drinking (for women, more than 7 drinks per week; for men, more than 14 drinks per week) or binge drinking (4 or more drinks over a 2 hour time frame for women and 5 or more drinks over a 2 hour time frame for men; NIAAA, 2013). Participants were excluded if: (1) they had an advanced stage medical disease as indicated by global physical deterioration and incapacitation; (2) had an organic mental syndrome; (3) had a diagnosis of bipolar I or psychotic-spectrum disorders; (4) had any disorder which might have made antidepressant treatment hazardous; (5) were currently pregnant or lactating; (6) had a history of seizures (not related to alcohol withdrawal); (7) were currently using or prescribed psychotropic medications by another physician; (8) had a history of allergic reaction to sertraline; (9) had current active suicidal or homicidal ideation, intent, or behaviour; (10) refused to be audio and videotaped.
Kosten 1991	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Military combat (Vietnam combat veterans)	60	Age: Range NR (39) Gender (% female): 0 BME (% non-white): 13 Country: US Coexisting conditions: 47% dysthymia	Participants were included if they: (1) met DSM-III criteria for PTSD. Participants were excluded if they: (1) had schizophrenia or bipolar disorder; (2) had misused substance(s) within the month prior to the study starting.
Krystal 2011/2016	Diagnosis (ICD/DSM) Chronic (symptoms for ≥3 months) Mean months since	Military combat (72% veterans of Vietnam war or earlier; 24% veterans of wars in Iraq and Afghanistan)	296	Age: Range not reported (54.4) Gender (% female): 3 BME (% non-white): 34	Participants were included if they: (1) were aged at least 18 years; (2) participated in a military combat theatre; (3) met diagnostic criteria for military service–related chronic PTSD on the basis of a structured interview for making psychiatric

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
	onset of PTSD: Not reported	Mean months since traumatic event: Not reported		Country: US Coexisting conditions: 70% above threshold for major depressive disorder, 10% above threshold for dysthymia and 10% above threshold for generalized anxiety disorder. 6% over threshold for antisocial personality disorder	diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV); (4) had a Clinician-Administered PTSD Scale (CAPS) score greater than 50; (5) had a clinical history of intolerance of or nonresponse to 2 or more antidepressants, and had an inadequate response to 2 adequate SRI treatments (minimum of 4 weeks of pharmacotherapy each); (6) had a fixed address within 50 miles of the research site or confirmed transportation for all visits; (7) were using an acceptable method of birth control (female patients); (8) gave written informed consent. Participants were excluded if they: (1) met lifetime diagnostic criteria for bipolar disorder or schizophrenia; (2) required antipsychotic medication for the treatment of psychosis; (3) met diagnostic criteria for dependence on a substance other than nicotine in the 30 days prior to screening; (4) had clinical or laboratory evidence (levels of aspartate aminotransferase, alanine aminotransferase, bilirubin, blood urea nitrogen, or creatinine) of hepatic or renal compromise; (5) had a medical disorder that might increase the risks of risperidone treatment (insulin-dependent diabetes) or complicate interpretation of study results (epilepsy, dementia); (6) had a history of intolerance of antipsychotics; (7) had attempted suicide or assaulted someone in the prior year; (8) had an impending legal incarceration; (9) received SGAs, serotonergic (5HT2) receptor antagonists (cyproheptadine, methysergide, trazodone), α1 receptor antagonists (prazosin), and α2 receptor agonists/antagonists (clonidine, guanfacine, mirtazapine)

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
Lindley 2007	Diagnosis (ICD/DSM) Chronic (symptoms for ≥3 months) Mean months since onset of PTSD: Not reported	Military combat (Vietnam combat veterans) Mean months since traumatic event: Not reported	40	Age: 49-59 (53.4) Gender (% female): 0 BME (% non-white): 38 Country: US Coexisting conditions: Not reported	Participants were included if they: (1) were free from alcohol or other substances of abuse for at least the past month; (2) had a primary diagnosis of PTSD for at least 1 year as determined by a thorough review of psychiatric records, complete psychiatric interview, and the Clinician-Administered PTSD Scale (CAPS). Participants were excluded if they: (1) had any clinically unstable medical disorder; (2) had liver enzymes greater than 2 times the upper limit of normal; (3) had a history of nephrolithiasis; (4) were taking a carbonic anhydrase inhibitor
Litz 2012	Diagnosis (ICD/DSM) Chronicity not reported Mean months since onset of PTSD: Not reported	Military combat (veterans of the Iraq and Afghanistan wars) Mean months since traumatic event: Not reported	26	Age: 32.2 (Range NR) Gender (% female): NR BME (% non-white): 23 Country: US Coexisting conditions: 27% comorbid major depressive disorder, 8% comorbid social anxiety, 19% current alcohol use	Participants were included if they: (1) were veterans of the Iraq and Afghanistan wars who had a primary diagnosis of PTSD (designated by the patient as the most important source of distress). Participants were excluded if they: (1) had a lifetime history of bipolar disorder, schizophrenia, psychosis, delusional disorders or obsessive-compulsive disorder; (2) had organic brain syndrome; (3) had past history of reported seizures; (4) were using Isoniazid; (5) had cognitive dysfunction that could interfere with capacity to engage in therapy; (6) had significant medical conditions, including renal insufficiency, that would increase risks of drug toxicity; (7) had a history of substance or alcohol dependence (other than nicotine) in the last 6 months (or otherwise unable to commit to refraining from alcohol use during the acute period of study participation); (8) had suicidal ideation or suicidal behaviours within 6 months prior to intake; (9) were participating in ongoing exposure-based psychotherapy for PTSD.

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
Mahabir 2016	Clinically important PTSD symptoms (scoring above a threshold on validated scale) Chronic (symptoms for 3 months or more) Mean months since onset of PTSD: Mean NR (36-144)	Mixed (6% physical and sexual assaults; 20% accidents; 10% violent or unexpected deaths of close ones; 2% combat exposure; 2% other stressors) Mean months since traumatic event: Not reported	41	Age: 43.4 (Range NR) Gender (% female): 73 BME (% non-white): NR Country: Canada Coexisting conditions: 29% co-morbid Major Depressive Disorder and 51% other anxiety disorders (assessed with MINI)	Participants were included if they: (1) were males or females who experienced traumatic events; (2) had a Clinician Administered PTSD Scale (CAPS) score≥50 at initial assessment; (3) were free of illicit substances (assessed with urinalyses). Participants were excluded if they: (1) were at risk of cardiac complications (assessed in participants>40 years with electrocardiograms); (2) were pregnant; (3) had bipolar disorder; (4) had a head injury; (5) had a medical condition that contraindicated propranolol use
Manteghi 2014	Diagnosis (ICD/DSM) Chronicity not reported Mean months since onset of PTSD: Not reported	Military combat (Iran-Iraq war Iranian combat veterans) Mean months since traumatic event: Not reported	40	Age: 44.8 (Range NR) Gender (% female): 0 BME (% non-white): NR Country: Iran Coexisting conditions: NR	Participants were included if they: (1) were Iran-Iraq war Iranian combat veterans with PTSD (diagnosis of PTSD was established by 2 independent psychiatrists based on DSM-IV-TR criteria; (2) aged 25-65 years. Participants were excluded if they: (1) had an altered mental status (Mini-Mental Status Examination was administered to rule out cognitive deficits); (2) had unstable medical conditions; (3) had a history of seizure; (4) had active psychosis; (5) had a history of a suicide or homicide attempt; (6) had substance abuse or dependence; (7) had used long-acting psychotropic medications in the past 2 weeks; (8) had a known history of allergy to baclofen; (9) had a lack of interest in follow-up
Marshall 2001	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed (The most common trauma types in the three treatment groups were physical or sexual assault [48%–54%], witnessing injury or death [17%–18%], serious accident or	563	Age: Range NR (41.8) Gender (% female): NR BME (% non-white): NR Country: US Coexisting conditions: 45% met DSM-IV	Participants were included if they: (1) were male and female outpatients 18 years or older; (2) met DSM-IV criteria for chronic PTSD as determined by the diagnostic version of the Clinician-Administered PTSD Scale, part 1, and the Mini International Neuropsychiatric Interview; (3) had a total score of 50 points or higher on Clinician- Administered PTSD Scale, part 2; (4) had a negative serum

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
		injury [6%–12%], and combat [5%–8%])		criteria for major depressive disorder. Other comorbid diagnoses included generalized anxiety disorder (28%–32%), agoraphobia (21%–25%), panic disorder (14%–17%), and dysthymia (9%–12%)	pregnancy test and a medically accepted method of contraception (for females of childbearing potential) Participants were excluded if they: (1) had a concurrent affective and anxiety disorder and PTSD was not considered to be the principal diagnosis (i.e. the main focus of attention or need for treatment) and that the onset of PTSD did not precede that of concurrent disorders; (2) had another axis I disorder as a principal diagnosis within 6 months of screening; (3) were receiving disability payments or were involved in litigation related to PTSD or any other psychiatric illness; (4) had alcohol or substance abuse or dependence within 6 months of screening; (5) were taking psychotropic medications within 2 weeks of the first dose of study medication (or 4 weeks for fluoxetine); (6) had received psychotherapy or ECT within 12 weeks of screening; (7) presented a homicidal or suicidal risk; (7) had an intolerance to paroxetine or any other SSRI; (8) had a serious medical condition.
Martenyi 2002a	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed	301	Age: Range NR (37.9) Gender (% female): 19 BME (% non-white): 9 Country: Belgium, Bosnia, Croatia, Israel, South Africa, Yugoslavia Coexisting conditions: NR	Participants were included if they: (1) were male or female aged 18-65 years; (2) met DSM-IV criteria for PTSD according to the structured clinical interview for DSM-IV Axis I Disorders, Investigator version (SCID-I) and the CAPS, Current Diagnostic Version (CAPS-DX); (3) had a total score =>50 on the CAPS, and a score =>4 on the CGI-S at baseline. Participants were excluded if they: (1) had a MADRS score >20 at baseline; (2) had a serious comorbid illness, serious suicidal risk or hetero-aggressivity or a diagnosis of Axis I psychiatric disorder as defined by DSM-IV criteria within the 5

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
					years prior to the traumatic episode with the exception of GAD, depression, panic disorder or social phobia; (3) had substance misuse where the abuse had not resolved at least 6 months prior to study entry.
Martenyi 2002b	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed	131	Age: Range NR (38.2) Gender (% female): 19 BME (% non-white): 10 Country: Belgium, Bosnia, Croatia, Israel, South Africa, Yugoslavia Coexisting conditions: NR	Participants were included if they: (1) were participants in Martenyi 2002a and after 12 weeks of acute treatment with fluoxetine or placebo, they had responded to treatment by a 50% decrease in the eight-item Treatment Outcome PTSD (TOP–8) score (Davidson & Colket, 1997) from baseline, a CGI–S score ≤2, and did not meet DSM–IV diagnostic criteria for PTSD in a 24-week relapse prevention phase
Martenyi 2007	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed (Traumatic events reported: 5% Combat-related; 27% Sexual assault; 16% Domestic violence; 12% Accident; 11% Incest; 10% Witnessed another person's death)	411	Age: Range NR (40.7) Gender (% female): 72 BME (% non-white): 23 Country: US Coexisting conditions: NR	Participants were included if they: (1) were male or female aged 18-75 years; (2) met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for PTSD according to the Structured Clinical Interview for DSM-IV Axis I Disorders, Investigator Version and CAPS Current Diagnostic Version; (3) had a score of 50 or more on the CAPS Current Diagnostic Version and a score of 4 or more on the Clinical Global Impression of Severity (CGI-S) scale at baseline. Participants were excluded if they: (1) had severe (comorbid) depression as defined by Montgomery-Asberg Depression Rating Scale (MADRS) score greater than 20 at baseline
McRae 2004	Clinically important PTSD symptoms (scoring above a threshold on validated scale)	Mixed (Trauma type: 15% Childhood physical or sexual abuse; 19% Physical assault; 31%	37	Age: 18-65 (40.3) Gender (% female): 77 BME (% non-white): NR Country: US	Participants were included if they: (1) had a minimum 3-month duration of PTSD symptoms and a total severity score of at least 50 on the Clinician Administered PTSD Scale, Part 2 (CAPS-2) at the end of a 1-week placebo wash-out period.

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
		Sexual assault; 15% Accident; 19% Other)		Coexisting conditions: NR	Participants were excluded if they: (1) had any clinically significant medical condition or laboratory abnormality that could be expected to progress, recur, or change such that it might bias the assessment of the clinical and mental status of the subject; (2) had a history of seizure disorder or organic brain disease; (3) were pregnant or breast-feeding; (4) had a current diagnosis of a psychotic disorder, bulimia or anorexia, bipolar disorder, or obsessive compulsive disorder; (5) had current substance abuse or dependence (defined as not having a documented recovery of at least 3 months duration); (6) had a current diagnosis of major depression, panic disorder, or agoraphobia if these conditions were not deemed secondary to PTSD; (7) were currently using any psychotropic medication or other medication that would interfere with assessment of effectiveness or compromise safety of study participants, including medications that are substrates of the cytochrome P450 system; (8) had a hypersensitivity to nefazodone or sertraline; (9) had a history of non-response to nefazodone or sertraline; (10) were treatment-refractory patients (defined as patients who had three trials of psychotropic treatment of adequate dose and duration for treatment of PTSD); (11) were receiving PTSD-specific psychotherapy; (12) they had a decrease of over 30% in CAPS score between the screening visit and the end of the placebo wash-out
Neylan 2006	Diagnosis (ICD/DSM) 'Chronic PTSD' (no further details on chronicity reported) Mean months since	Military combat ('veterans', no further detail reported) Mean months since traumatic event: Not reported	63	Age: NR Gender (% female): NR BME (% non-white): NR Country: US	Participants were included if they: (1) were medically healthy male and female veterans aged 20-60 years; (2) met DSM-IV criteria for current (and chronic) PTSD; (3) were medication-free or receiving a stable regimen of pharmacotherapy for 2 months.

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
	onset of PTSD: Not reported			Coexisting conditions: NR	Participants were excluded if they: (1) met criteria for alcohol or substance abuse within the past 6 months; (2) met lifetime criteria for organic mental disorder, schizophrenia, schizoaffective disorder, or bipolar disorder; (3) had a history of brain disease; (4) had a current systemic illness affecting CNS function; (5) had myocardial infarction in the past year; (6) had recently used guanfacine or clonidine; (7) showed 30% or greater improvement on the Impact of Event Scale-Revised (IES-R) at the end of the 1-week single-blind placebo lead in
Onder 2006	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Natural disasters (such as severe floods, earthquakes or tsunamis)	103	Age: Range NR (31.4) Gender (% female): 50 BME (% non-white): NR Country: Turkey Coexisting conditions: NR	Participants were included if they: (1) were male and female outpatients 18 years and older; (2) met DSM-IV criteria for a primary diagnosis of PTSD as determined by SCID; (3) had PTSD due to the earthquake. Participants were excluded if they: (1) had clinically significant medical illness, including diabetes mellitus; (2) had any cardiac condition causing documented hemodynamic compromise; (3) had epilepsy; (4) were pregnant; (5) had a current or past history of bipolar disorder, schizophrenic, or other psychotic disorder; (6) had alcohol or substance abuse or dependence in the past 6 months; (7) had a primary diagnosis of major depression assessed with SCID or a score of 12 points or higher on 17-item Hamilton Depression Scale
Panahi 2011	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Military combat (Iranian Iran–Iraq war veterans)	70	Age: Range NR (45.6) Gender (% female): 0 BME (% non-white): NR Country: Iran	Participants were included if they: (1) were male Iranian Iran–Iraq war veteran outpatients who had been referred to the neuropsychiatric clinic of Baqiyatallah Hospital (Tehran, Iran); (2) met DSM-IV-TR criteria for a primary diagnosis of PTSD; (3) had a duration of at least 6 months of illness; (4)

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
				Coexisting conditions: NR	had a Clinical Global Impression scale – Severity (CGI-S) score of at least 4 at baseline. Participants were excluded if they: (1) had any axis I disorder other than PTSD (subjects with concurrent depression were included provided that their depression was secondary to PTSD and initiated after PTSD); (2) showed evidence of clinically significant hepatic or renal disorder or any other medical condition (in acute or unstable form) that might confound the procedure or the results of the trial ; (3) had alcohol or substance abuse or dependency within the preceding 6 months; (4) had an intolerance or hypersensitivity to sertraline ; (5) were currently using any psychotropic medication (except for chloral hydrate or diazepam, taken as needed) with clinically significant psychotropic activity within 2 weeks of randomization (or 5 weeks for fluoxetine); (6) were receiving any cognitive-behavioural therapy during the trial ; (7) received any psychotherapy that was initiated or ended during the trial
Petrakis 2016	Diagnosis (ICD/DSM) Chronicity not reported Mean months since onset of PTSD: Not reported	Military combat ('Veterans', no further detail reported) Mean months since traumatic event: Not reported	96	Age: 44 (Range NR) Gender (% female): 6 BME (% non-white): 19 Country: US Coexisting conditions: 100% comorbid alcohol dependence, 39% current major depression, 19% had another anxiety disorder, 11% had current marijuana abuse/dependence,	Participants were included if they: (1) were men or women aged 21-65 years; (2) met DSM-IV criteria for current PTSD and alcohol dependence (determined by structured clinical interview), and reported at least 1 episode of heavy drinking (defined as >5 for men and >4 for women on 1 occasion) over the past 14 days; (3) were medically healthy by physical and laboratory examination; (4) were not pregnant, and using adequate birth control (for females). Participants were excluded if they: (1) had unstable or current serious psychotic symptoms, suicidal or homicidal ideation; (2) had medical problems that

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
				and 18% had current cocaine abuse/dependence	would contraindicate the use of prazosin; (3) were taking medication thought to influence alcohol consumption (such as naltrexone, disulfiram, or acamprosate); (4) were not abstinent for 2 days prior to randomization (abstinence was determined by self-report and a negative breathalyzer reading)
Pfizer 588	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed (Physical/sexual assault)	193	Age: Range NR (37) Gender (% female): 75 BME (% non-white): NR Country: US Coexisting conditions: NR	Participants were included if they: (1) had a diagnosis of PTSD by DSM-III-R; (2) were otherwise healthy. Participants were excluded if: (1) they had a score of <50 on CAPS-2 at baseline (one exception to this)
Pfizer 589	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Military combat (Most common trauma = war/combat 71%)	169	Age: Range NR (45) Gender (% female): 20 BME (% non-white): NR Country: US Coexisting conditions: NR	Participants were included if they: (1) had a diagnosis of PTSD by DSM-III-R; (2) were outpatients at Veterans Administration Medical Centres. No exclusion criteria reported
Popiel 2015	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Motor Vehicle Collisions	228	Age: Range NR (37.7) Gender (% female): NR BME (% non-white): NR Country: Poland Coexisting conditions: 46% Comorbid Axis I disorder; 40% Comorbid personality disorder; 22% traumatic brain injury	Participants were included if they: (1) were adults who presented PTSD symptoms and were diagnosed with PTSD (according to DSM IV-TR) following a motor vehicle collision. Participants were excluded if they: (1) had elevated suicide risk; (2) had an unstable medical condition with contraindications for SSRI; (3) were pregnant; (4) had co-occurring medical conditions requiring psychotropic medication other than the study medication; (5) had a lack of commitment to maintaining the study regime such as refusal of random allocation, terminating existing treatments before beginning the treatment within the study or participation in weekly therapy sessions; (6) had

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
					received previous treatment for PTSD with paroxetine or prolonged exposure.
Ramaswamy 2016	Diagnosis (ICD/DSM) Chronic (symptoms for ≥3 months) Mean months since onset of PTSD: Not reported	Trauma type not reported Mean months since traumatic event: Not reported	30	Age: Range not reported (38.9) Gender (% female): 87 BME (% non-white): Not reported Country: US Coexisting conditions: Not reported	Participants were included if they were: (1) male or female patients aged 19-64 years meeting DSM-IV criteria for PTSD; (2) competent to provide informed consent; (3) able to attend weekly clinic appointments; (4) using an approved contraceptive if of childbearing potential (for females). Participants were excluded if they: (1) had a history of prior treatment with ziprasidone; (2) had a medical condition that may prevent safe administration of ziprasidone, such as clinically significant/severe hepatic, cardiac, kidney, or pulmonary disease and seizure disorders, with the exception of childhood seizure disorders; (3) had a primary major psychotic disorder (i.e., schizophrenia, schizoaffective disorder, or bipolar disorder); (4) had suicidal or homicidal ideation or other clinically significant dangerousness; (5) had changed their psychotropic medication within 90 days of study entry
Raskind 2007	Diagnosis (ICD/DSM) Chronic (symptoms for 3 months or more) Mean months since onset of PTSD: Not reported ('chronic', no further detail)	Military combat (80% veterans of the Vietnam War, 5% veterans of World War II, 8% of the Korean War, 3% of the Panama invasion, and 5% of the first Gulf War) Mean months since traumatic event: Not reported	40	Age: 56 (Range NR) Gender (% female): 5 BME (% non-white): 35 Country: US Coexisting conditions: Not reported	Participants were included if they: (1) met DSM-IV criteria (diagnosis made by consensus of senior investigators based on results of CAPS interview) for PTSD related to combat exposure or other life-threatening war zone trauma; (2) had a score≥5 (of a maximum score of 8) on both the CAPS “recurrent distressing dreams” item and the CAPS “difficulty falling asleep or staying asleep” item; (3) had been free of alcohol or other substance abuse for at least three months. Participants were excluded if they had: (1) a history of schizophrenia, bipolar disorder, other psychotic disorder or depression with active suicidal ideation

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
Rothbaum 2014/ Norrholm 2016	Diagnosis (ICD/DSM) Chronicity not reported Mean months since onset of PTSD: Not reported	Military combat (Iraq/Afghanistan veterans) Mean months since traumatic event: Not reported	156	Age: 35.1 (32-38) Gender (% female): 5 BME (% non-white): 58 Country: US Coexisting conditions: 28% comorbid mood disorder	Participants were included if they were: (1) aged 22-55 years and were medically stable Iraq/Afghanistan veterans; (2) met DSM-IV criteria for PTSD due to military trauma (verified via the participant's discharge papers). Participants were excluded if they: (1) had a lifetime history of psychosis or bipolar disorder; (2) posed a current suicidal risk; (3) had current alcohol or drug dependence; (4) were pregnant (for females); (5) were currently using medications that could confound data (glucocorticoids, benzodiazepines, chronic opioid use); (6) had been off long-acting benzodiazepines for 1 month and short-acting benzodiazepines for 2 weeks before screening
Saygin 2002	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Natural disasters (such as severe floods, earthquakes or tsunamis) - Marmara Earthquake (1999)	60	Age: Range NR (41.5) Gender (% female): 76 BME (% non-white): NR Country: Turkey Coexisting conditions: Comorbidity was high, 40% of sertraline group and 25% of nefazodone group had another psychiatric diagnosis: 9% OCD; 9% MDD; 6% GAD; 2% Panic Disorder; 2% Social Phobia; 2% Specific Phobia; 4% Conversion Disorder	Participants were included if they: (1) Had a Diagnosis of PTSD (made by non-structured clinical interview by a psychiatrist and then independently by a psychologist using SCID-1). Participants were excluded if they: (1) had a history of alcohol or drug abuse; (2) had a neurological disorder; (3) had a current organic mental disorder; (4) were taking psychiatric medication less than 2 weeks before the study
Schneier 2012	PTSD diagnosis according to ICD/DSM criteria	Terrorist attacks (World Trade Centre attack)	37	Age: Range NR (50.2) Gender (% female): 54 BME (% non-white): 32	Participants were included if they: (1) were aged 18–70 years; (2) had a principal DSM-IV diagnosis of PTSD that was related to the World Trade Centre attack; (3) had a symptom duration ≥3

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
	(including self-report of diagnosis)			Country: US Coexisting conditions: 70% Current Axis I Comorbid Diagnosis; 16% Current Axis II Diagnosis	months of at least moderate severity (CAPS score ≥45). Participants were excluded if they: (1) had prominent suicidal ideation; (2) had current psychotic disorder; (3) had an unstable medical illness; (4) were pregnant or nursing; (5) had alcohol or substance use disorder in the past 3 months; (6) had a history of seizure disorder; (7) were unwilling to use contraception (for women of childbearing potential); (8) had conditions that contraindicated study treatments (such as an unsuccessful trial or intolerance of paroxetine, three unsuccessful SSRI trials, or an unsuccessful trial of prolonged exposure therapy); (9) had received psychotropic medication during the 2 weeks (4 weeks for fluoxetine or monoamine oxidase inhibitors) before randomization, except zolpidem for insomnia.
Seo 2010	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed	40	Age: Range NR (37.3) Gender (% female): 70 BME (% non-white): NR Country: Korea Coexisting conditions: Exclusion criteria prohibited people with a current diagnosis of any other DSM-IV axis I disorder or a history of substance abuse or dependence (within the previous 6 months) from entering the trial	Participants were included if they were: (1) aged 18-65 years; (2) had PTSD according to SCID-CV. Participants were excluded if they: (1) had a current diagnosis of any other DSM-IV axis I disorder; (2) had a history of substance abuse or dependence within the previous 6 months; (3) had used psychotropic medication within the past 2 weeks; (4) had a history of unresponsiveness to treatment with mirtazapine or paroxetine for a minimum of 6 months; (5) had a clinically significant medical condition or lab abnormality; (6) had a history of organic brain disease; (7) were pregnant or breast feeding.

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
Simon 2006/Davidson 2006c	Awaiting paper				
Simpson 2012/2015	Diagnosis (ICD/DSM) Chronicity not reported Mean months since onset of PTSD: Not reported	Mixed (Trauma type: 97% physical assault; 70% weapon assault; 57% natural disaster; 67% transportation accident; 63% sexual assault; 50% witnessing sudden violent death; 43% serious work accident; 27% fire or explosion; 20% combat exposure; 63% 3 or more Criterion A; 80% 1 or more childhood trauma) Mean months since traumatic event: Not reported	30	Age: 43.3 (21-59) Gender (% female): 37 BME (% non-white): 60 Country: US Coexisting conditions: 100% comorbid alcohol dependence	Participants were included if they: (1) had current DSM-IV diagnoses of alcohol dependence and PTSD; (2) had recent alcohol consumption at or above 14 (women) or 21 (men) drinks per week; (3) had at least 2 days of heavy drinking (>4 drinks per occasion for women and >5 drinks for men) over a 30 day period in the last 90 days. Participants were excluded if they: (1) had uncontrolled psychosis or mania; (2) had current opioid dependence or abuse or positive urine screen (UDAS) for opioids, methamphetamines, benzodiazepines or sedative hypnotics; (3) had systolic blood pressure <110mmHg or pre-existing orthostatic hypotension; (4) had health conditions including unstable angina, Meniere's disease, narcolepsy, benign positional vertigo, chronic renal or hepatic failure, pancreatitis or insulin-dependent diabetes mellitus; (5) were using any anti-alcohol medication (e.g., naltrexone, acamprosate, or disulfiram); (6) had an unstable psychiatric medication regimen in the past month; (9) were engaged in trauma-focused PTSD treatment or behaviourally focused addiction treatment; (10) had concomitant use of trazodone, tadalafil, or vardenafil (for males only) due to increased risk of priapism; (11) were female and of child-bearing age and not using a birth control method judged by the study clinician to be effective.
SKB627	PTSD diagnosis according to ICD/DSM criteria	Unclear	322	Age: 18-75 (mean NR) Gender (% female): 54 BME (% non-white): NR	Participants were excluded if they: (1) showed a placebo run-in compliance of <80% at baseline; (2) had unresolved clinical abnormalities in laboratory or ECG findings; (3) had a history of non-

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
	(including self-report of diagnosis)			Country: Unclear Coexisting conditions: NR	discontinuation of psychotropic drugs; (4) had used paroxetine within 1 month of screening; (5) had undergone ECT; (6) had a known intolerance to paroxetine; (7) had received psychotherapy in past 12 months; (8) had substance misuse; (9) presented a suicide/homicide risk; (10) were of child-bearing potential without adequate use of contraception, pregnancy, medical disorder preventing use of paroxetine; (11) had a major depressive disorder episode preceding PTSD diagnosis
SKB650	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Unclear	176	Age: 18-82 (43) Gender (% female): 66 BME (% non-white): NR Country: Unclear Coexisting conditions: Exclusion criteria prohibited people with Axis I disorder diagnosis or with a depressive episode preceding PTSD diagnosis from entering the trial	Participants were excluded if they: (1) had a score <50 on CAPS at baseline; (2) had an Axis I disorder diagnosis; (3) had a depressive episode preceding PTSD diagnosis; (4) had a CGI score decreasing by 2+ points during screening; (5) were deemed likely to exaggerate symptoms; (6) showed a placebo run-in compliance of <80% or >120% at baseline visit; (7) had abnormal ECG; (8) had continuing use of psychotropic drugs; (9) received herbal treatments; (10) received investigational drug within 3 months of screening; (11) received ECT within past 3 months; (12) had a known intolerance to an SSRI; (13) had received psychotherapy within past 12 weeks; (14) had substance misuse or dependence within past 6 months; (15) presented a suicide risk; (16) were pregnant; (17) were not using contraception (for females); (18) had a serious medical illness; (19) had previously participated in similar studies; (20 were judged as unable to comply with instructions
Spivak 2006	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Motor Vehicle Collisions	40	Age: Range NR (40.08) Gender (% female): 48 BME (% non-white): NR	Participants were included if they: (1) had a primary current diagnosis of PTSD according to the Structured Clinical Interview for Axis I DSM-IV Disorders–Patient Version and the Clinician Administered PTSD Scale for DSM-IV (CAPS), Part

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
				Country: Israel Coexisting conditions: NR	1; (2) had experienced PTSD symptoms for at least 1 month before study recruitment and had a total score of at least 60 on the first 17 items of the CAPS, Part 2 (CAPS-2) at baseline. Participants were excluded if they: (1) had a diagnosis of any DSM-IV Axis I psychiatric disorder (except any mood or anxiety disorder considered to be comorbid with the primary diagnosis of PTSD); (2) had past or current traumatic brain injury and loss of consciousness; (3) had past or current medical or neurological illness; (4) had past or current alcohol or any other substance abuse; (5) had current major routine laboratory abnormality; (6) were involved in any current litigation; (7) had been treated with any psychotropic medication for a period of 2 months before study enrolment.
Tucker 2001	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed	323	Age: Range NR (40.8) Gender (% female): 66 BME (% non-white): 28 Country: USA and Canada Coexisting conditions: NR	Participants were included if they: (1) were male or female patients at least 18 years of age; (2) met DSM-IV criteria for chronic PTSD as determined by the MINI and the CAPS-1 Participants were excluded if they: (1) had comorbid bipolar disorder, dissociative disorder or any psychotic disorder; (2) had a comorbid mood or anxiety disorder that was considered the primary diagnosis; (3) scored less than 50 on the first 17 items of the CAPS-2 following a 1-week placebo run-in phase; (4) were involved in litigation or were receiving disability payments because of any psychiatric disorder; (5) had received formal psychotherapy or ECT in the 12 weeks prior to the initial assessment; (6) met DSM-IV criteria for alcohol/drug dependence or abuse within the preceding 6 months.; (7) were women of childbearing potential and were not practicing a

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
					clinically accepted method of contraception; (8) had a positive pregnancy test at screening or who were lactating; (9) had received psychoactive herbal medications (e.g. St John's Wort)
Tucker 2003/2004	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed	59	Age: Range NR (38.1) Gender (% female): 73 BME (% non-white): 14 Country: US Coexisting conditions: 92% common mental health disorder	Participants were included if they: (1) were aged 18-64 years; (2) had a PTSD diagnosis according to DSM criteria; (3) were able to give informed consent; (4) had a CAPS score >=50 (moderate to severe PTSD). Participants were excluded if they: (1) had a medical condition that precluded the use of an SSRI; (2) had previously failed to tolerate citalopram or sertraline; (3) were judged to find the trauma script procedure too stressful; (4) their psychiatric condition was such that placebo treatment would be unsafe or psychotherapy was indicated; (5) had another primary Axis I condition (with the exception of depression, panic or dysthymia if secondary to the PTSD); (6) had any significant medical illness; (7) were on medication affecting autonomic functioning; (8) had received any other psychotropic medications for at least 2 weeks at baseline, and not on fluoxetine for at least 4 weeks; (9) had alcohol or substance abuse; (10) were actively suicidal; (11) were deemed unlikely to comply with protocol requirements.
Tucker 2007	Diagnosis (ICD/DSM) Chronic (symptoms for ≥3 months) Mean months since onset of PTSD: Not reported	Mixed (24% childhood sexual abuse; 8% childhood physical abuse; 18% domestic/other violence; 11% rape; 11% motor vehicle accident; 16% death/injury of loved one; 5% witness death; 8% tornado; 16% other)	40	Age: 18-64 (41.5) Gender (% female): 79 BME (% non-white): 11 Country: US Coexisting conditions: 61% major depression	Participants were included if they: (1) were aged 18-64 years; (2) were men or non-pregnant women; (3) had a diagnosis of civilian, non-combat-related Axis I PTSD for greater than 6 months according to DSM-IV criteria as measured by Structured Clinical Interview for DSM-IV (SCID-IV) and with a Clinician-Administered PTSD Scale (CAPS) score of 50 or over.

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
		Mean months since traumatic event: Not reported			Participants were excluded if they: (1) were women and not postmenopausal or practicing reliable contraception; (2) had major organic psychiatric disease, current substance dependence or abuse (excluding nicotine or caffeine), serious or unstable concurrent illness, medical conditions potentially affecting drug absorption; (3) had a history of nephrolithiasis or seizures; (4) had reduced renal clearance; (5) had elevated serum liver enzyme levels; (6) were currently enrolled in a cognitive-behavioural therapy programme; (7) had a history of primary major depressive disorder or primary major anxiety disorder; (8) had known hypersensitivity to, or a prior adverse event with, topiramate
van der Kolk 1994	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed	64	Age: 22-44 (38.9) Gender (% female): 20 BME (% non-white): NR Country: US Coexisting conditions: 55% common mental health disorder	Participants were included if they: (1) were outpatients who met a DSM-III-R primary Axis I diagnosis of PTSD; (2) had a score of 45 or above on the CAPS. Participants were excluded if they: (1) reported diagnoses of schizophrenia, bipolar I disorder, organic mental disorder or drug and alcohol addiction within 6 months of the initial interview or met criteria for any of these disorders in the psychiatric evaluation; (2) had a clinically significant cardiovascular, renal, hepatic, endocrine or neurologic disease; (3) were pregnant or nursing mothers.
van der Kolk 2007	PTSD diagnosis according to ICD/DSM criteria (including self-report of diagnosis)	Mixed	88	Age: Range NR (36.1) Gender (% female): 83 BME (% non-white): 33 Country: US Coexisting conditions: NR	Participants were included if they: (1) were 18-65 years; (2) had current PTSD and mixed trauma exposure at least 1 year prior to intake Participants were excluded if they: (1) had an unstable medical condition; (2) had contraindications to treatment (i.e. pregnancy,

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
					glaucoma or detached retine, or history of severe allergies or multiple adverse drug reactions); (3) were unable to be weaned off current psychotropic medications; (4) had psychotic or bipolar disorder; (5) had current alcohol or substance abuse/dependence; (6) had severe dissociation, active suicidality or life threatening mutilation; (7) had previously received active study interventions; (8) were concurrently receiving trauma focused treatment; (9) had an unstable living situation; (10) had a GAF score <40; (11) had received disability compensation for PTSD or pending trauma-related lawsuit.
Yeh 2011	Diagnosis (ICD/DSM) Chronic (symptoms for ≥3 months) Mean months since onset of PTSD: 43.8	Unclear ('Civilian sample' but no details of trauma type reported) Mean months since traumatic event: Not reported	35	Age: 18-62 (40.5) Gender (% female): 68 BME (% non-white): Country: Brazil Coexisting conditions: Not reported	Participants were included if they: (1) were aged 18–62 years with a diagnosis of PTSD according to Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV), confirmed by the use of the Structured Clinical Interview for DSM-IV Axis I and Axis II (SCID-I and SCID II, respectively). Participants were excluded if they: (1) were women of childbearing potential and were not practicing reliable contraception or were pregnant or breastfeeding during the study; (2) had a lifetime history of bipolar, psychotic, borderline personality disorder, substance dependence or abuse (excluding nicotine and caffeine) in the previous 6 months; (3) had serious or unstable concurrent illness; (4) had a history of nephrolithiasis; (5) had used psychotropic medications for the previous 2 weeks (6 weeks for fluoxetine); (6) had a body mass index below 20; (7) had current suicidal ideation or psychotic symptoms
Zohar 2002	PTSD diagnosis according to	Military combat (Israeli military veterans; The	51	Age: Range NR (39.6) Gender (% female): 12	Participants were included if they: (1) were male or female outpatients aged 18 years and older who

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
	ICD/DSM criteria (including self-report of diagnosis)	index traumatic event, defined as the event that was currently most distressing to the patient, consisted of combat-related violence [76%], motor vehicle accident [19%], and captivity [5%])		BME (% non-white): NR Country: Israel Coexisting conditions: NR	met DSM-III-R criteria for a primary diagnosis of PTSD as determined by part 1 of the Clinician-Administered PTSD Scale (CAPS-1); (2) had a minimum 6-month duration of PTSD illness; (3) had a Clinical Global Impression Scale-Severity (CGI-S) score of 4 or higher and a total severity score of 50 or higher on the CAPS-2 at baseline; (4) had a negative beta human chorionic gonadotropin pregnancy test and use of a medically accepted form of contraception for at least 3 months (for females). Participants were excluded if they: (1) had any other primary axis I disorder (concurrent depression was permitted only if its onset was judged to be secondary to PTSD and with a later onset of illness); (2) had alcohol or substance abuse or dependence in the past 6 months; (3) showed evidence of clinically significant hepatic or renal disease or any other acute or unstable medical condition that might interfere with the safe conduct of the study; (4) had an intolerance or hypersensitivity to sertraline; (5) had showed nonresponse to a previous adequate trial of any SSRI in the treatment of any axis I disorder; (6) were currently using psychotropic medication (except infrequent chloral hydrate or temazepam on an as-needed basis); (7) 20% or greater reduction in the CAPS-2 total severity score during the placebo lead-in period

Appendix E – Forest plots

Forest plots for "For adults at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Antidepressants: Selective serotonin reuptake inhibitors (SSRIs)

Escitalopram versus placebo for the early prevention (<1 month) of PTSD in adults

Figure 2: PTSD symptomatology clinician-rated (CAPS change score)

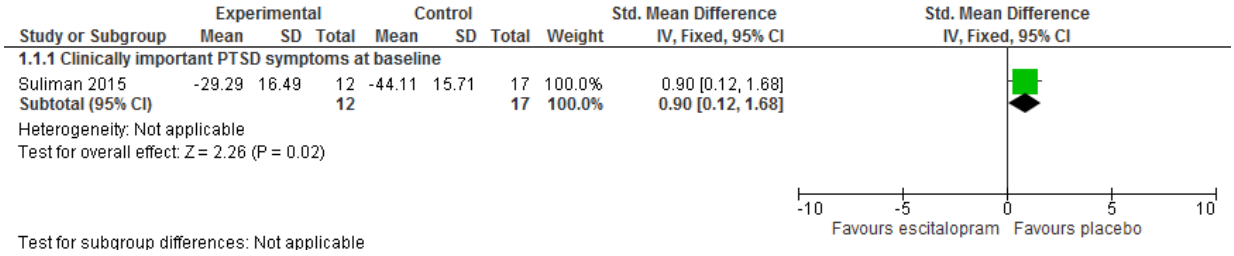


Figure 3: Depression symptoms (MADRS change score)

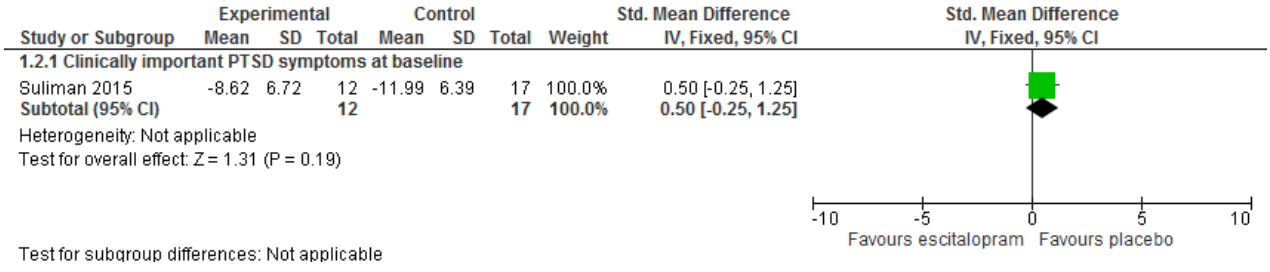


Figure 4: Functional impairment (SDS change score)

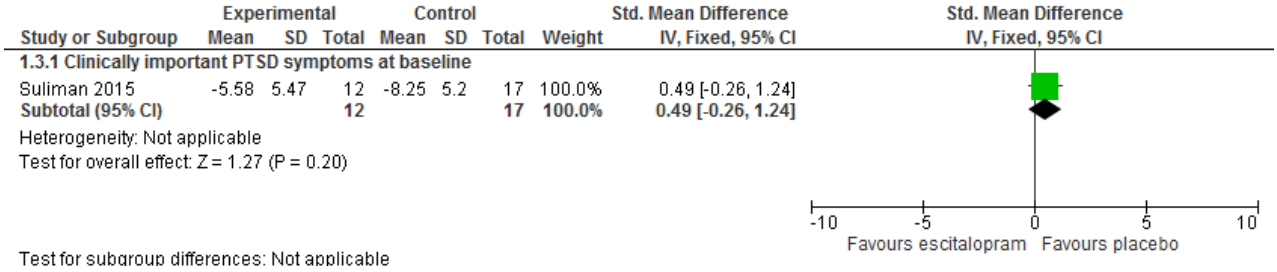
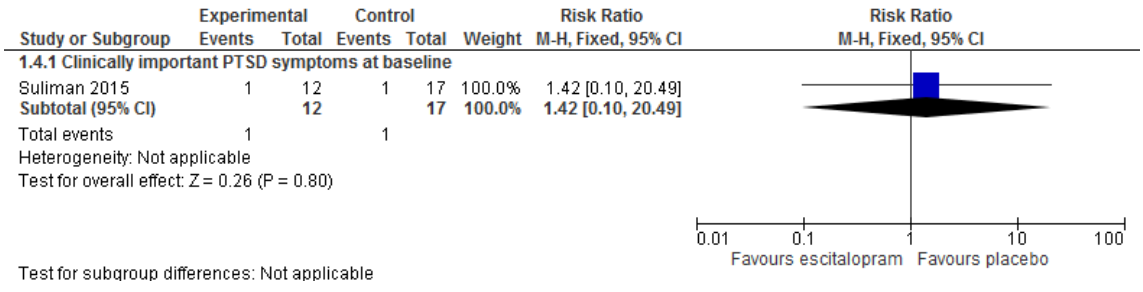


Figure 5: Discontinuation due to any reason (including adverse events)



Anticonvulsants

Gabapentin versus placebo for the early prevention (<1 month) of PTSD in adults

Figure 6: PTSD/ASD symptomatology (ASDS endpoint score)

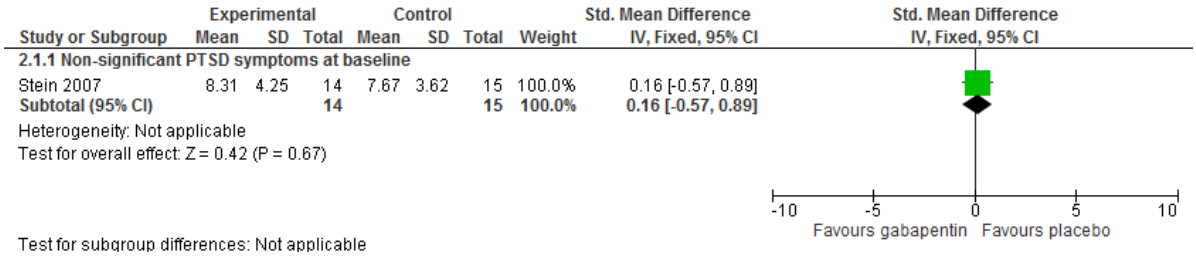


Figure 7: Diagnosis of PTSD at 3-month follow-up

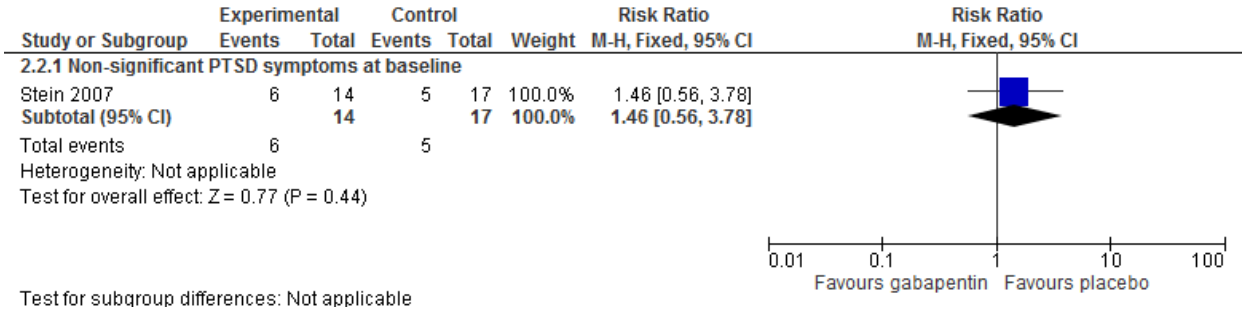
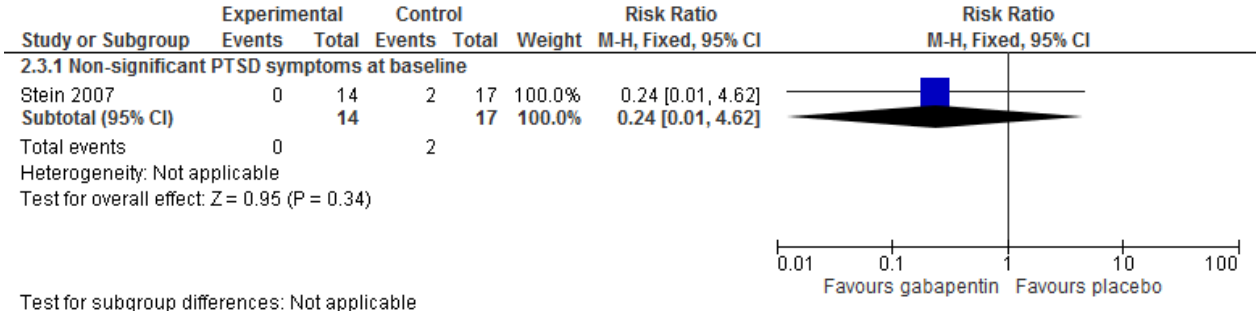


Figure 8: Discontinuation due to any reason (including adverse events)



Benzodiazepines

Temazepam versus placebo for the early prevention (<1 month) of PTSD in adults

Figure 9: PTSD symptomatology clinician-rated (CAPS change score); Clinically important PTSD symptoms at baseline

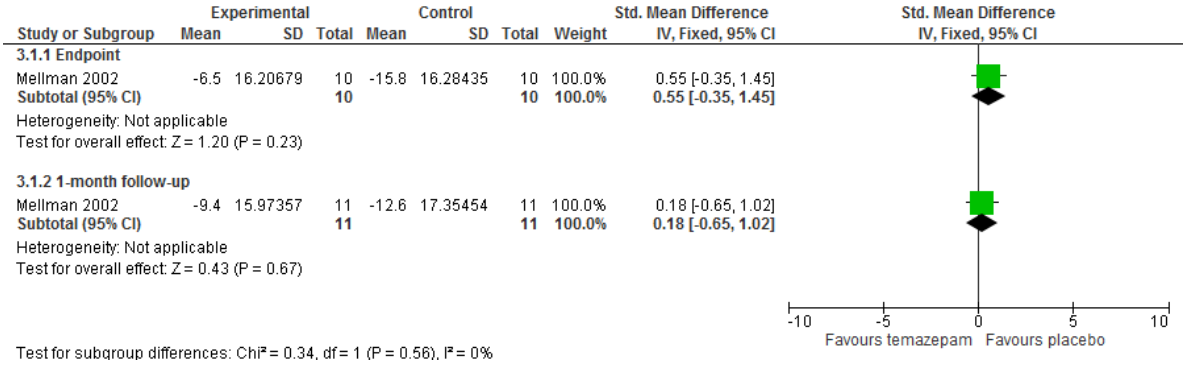
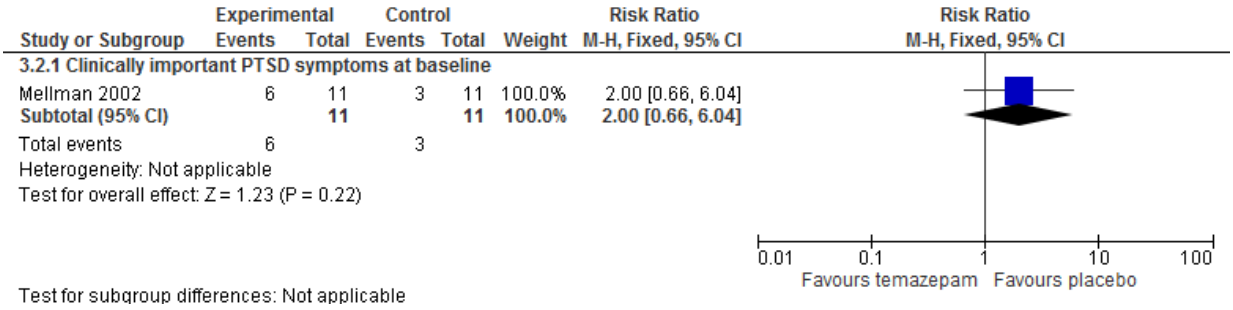


Figure 10: Diagnosis of PTSD at 1-month follow-up



Other drugs

Hydrocortisone versus placebo for the early prevention (<1 month) of PTSD in adults

Figure 11: PTSD symptomatology clinician-rated (CAPS endpoint score); Unclear severity of PTSD symptoms at baseline

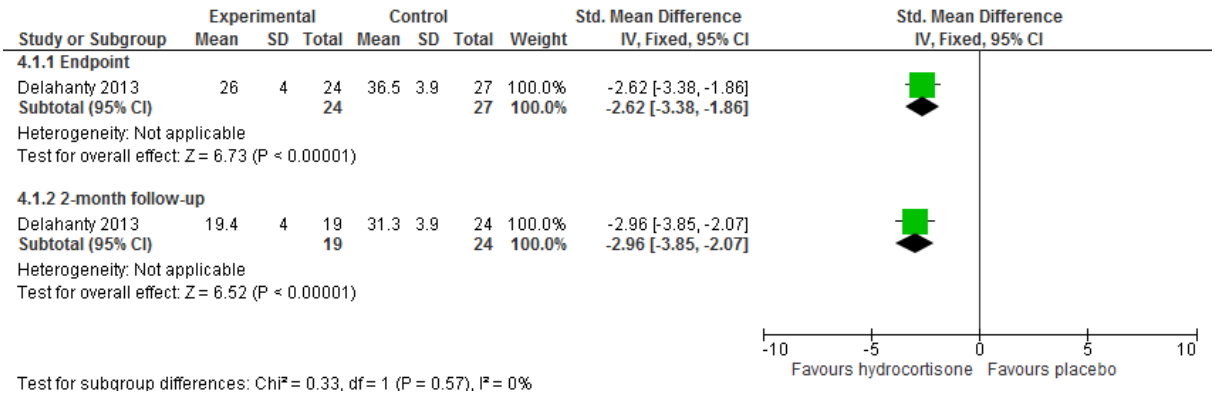


Figure 12: Diagnosis of PTSD; Unclear severity of PTSD symptoms at baseline

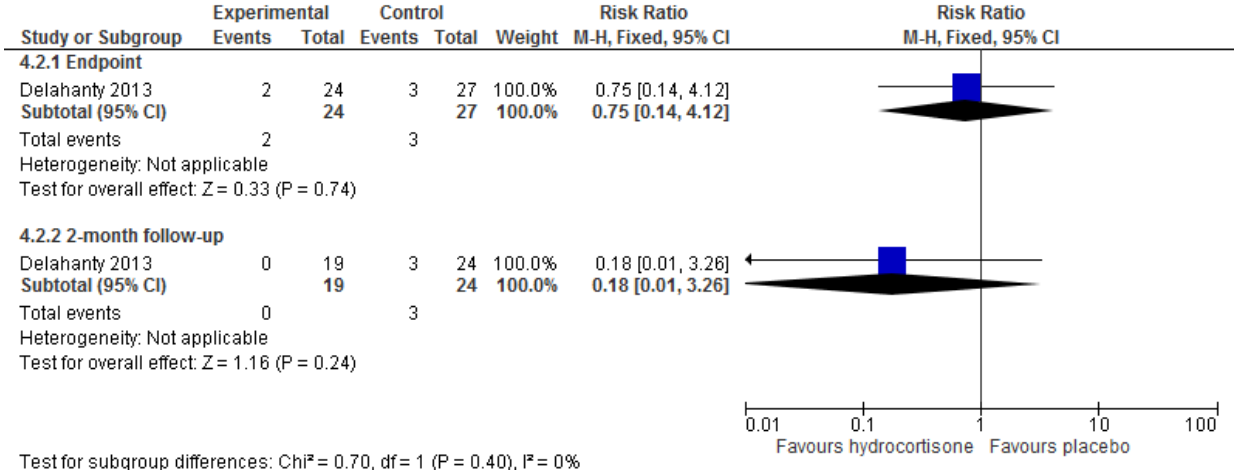


Figure 13: Depression symptoms (CES-D endpoint score); Unclear severity of PTSD symptoms at baseline

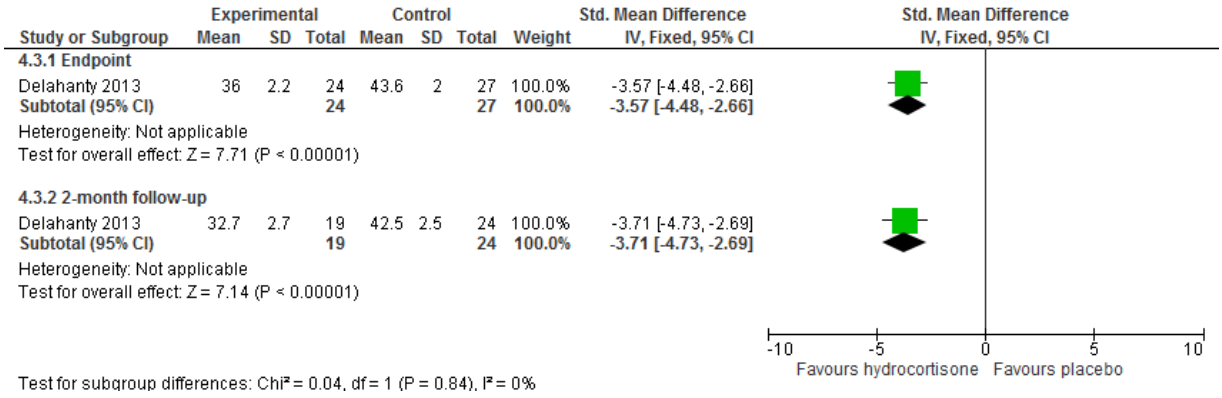


Figure 14: Quality of life (SF-36 General health change score)

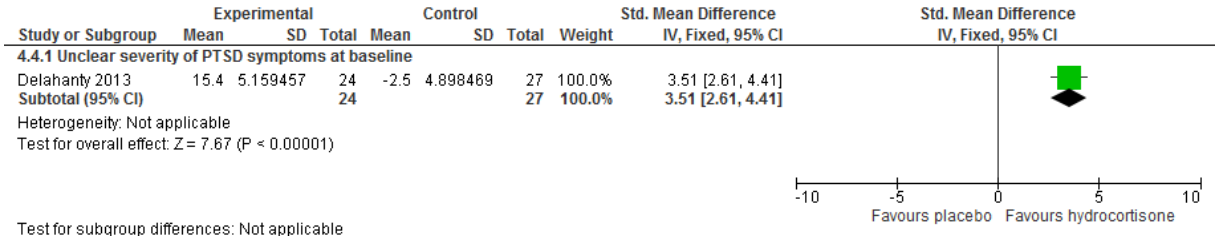
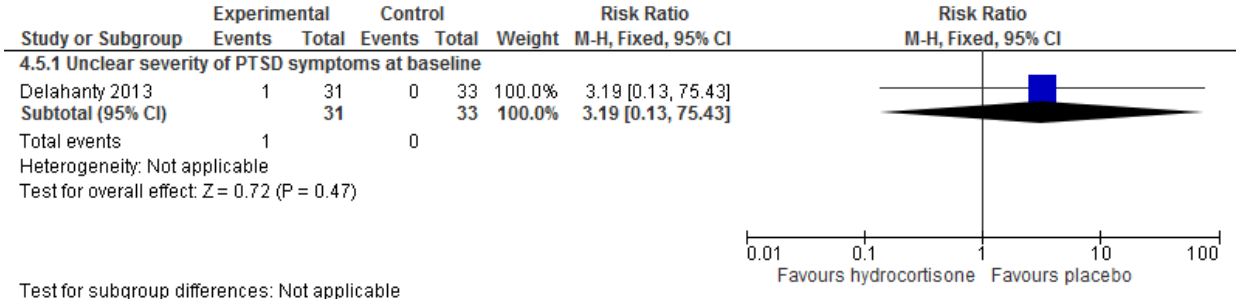


Figure 15: Discontinuation due to adverse events



Oxytocin versus placebo for the early prevention (<1 month) of PTSD in adults

Figure 16: PTSD symptomatology self-rated (IES-R change score); Subthreshold symptoms (below threshold but ≥50% maximum score on scale) at baseline

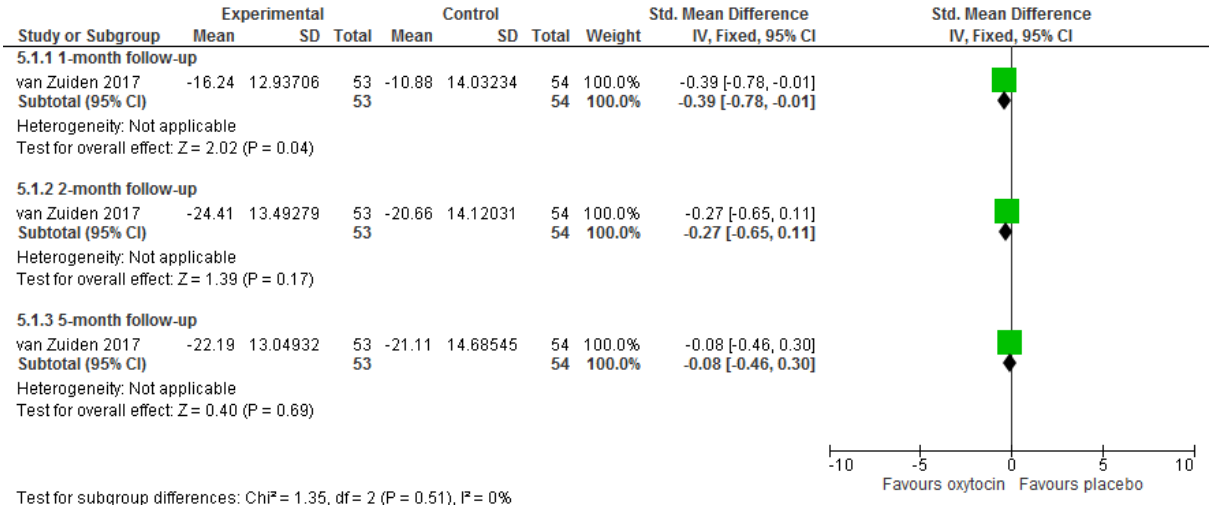


Figure 17: PTSD symptomatology clinician-rated (CAPS change score); Subthreshold symptoms (below threshold but ≥50% maximum score on scale) at baseline

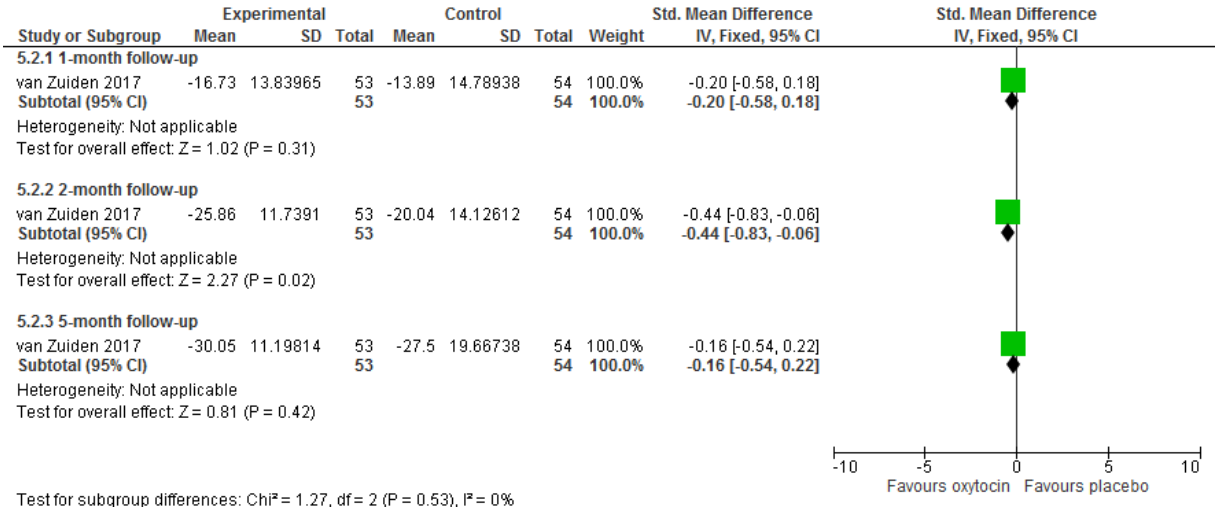


Figure 18: Anxiety symptoms (HADS-A change score); Subthreshold symptoms (below threshold but ≥50% maximum score on scale) at baseline

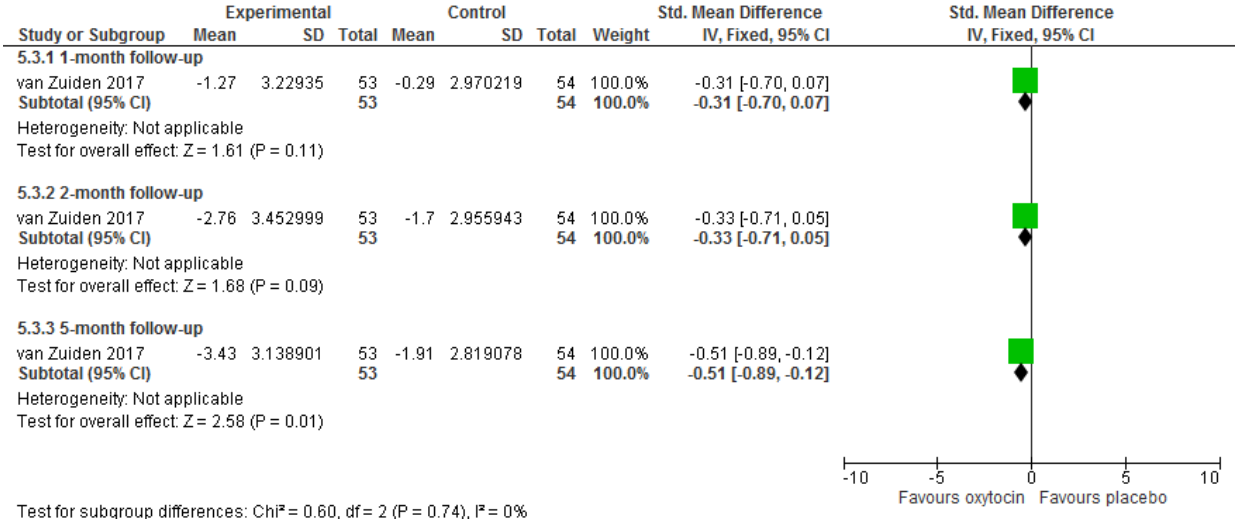


Figure 19: Depression symptoms (HADS-D change score); Subthreshold symptoms (below threshold but ≥50% maximum score on scale) at baseline

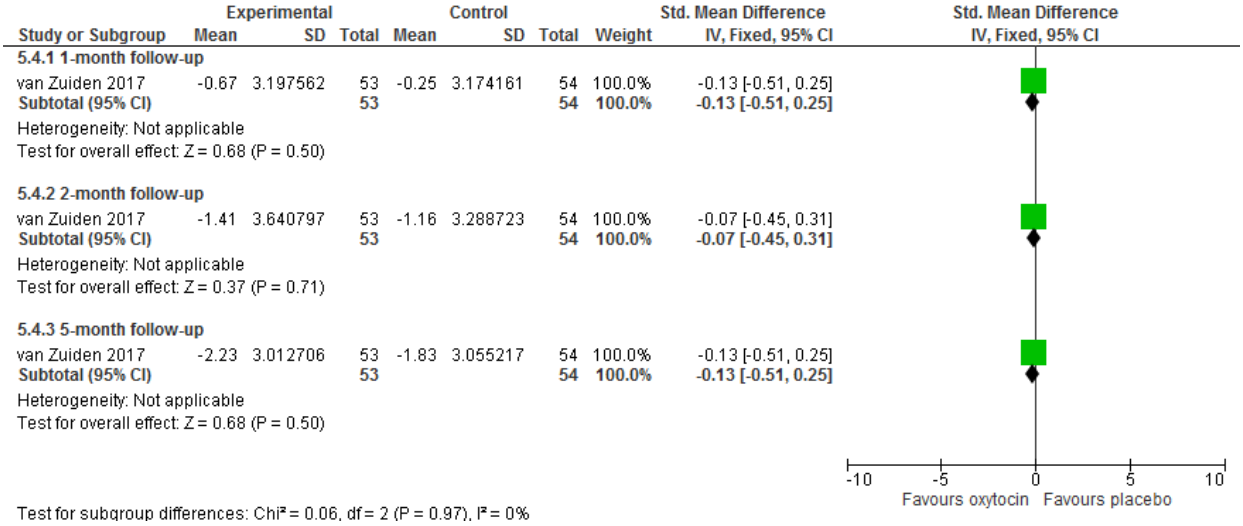
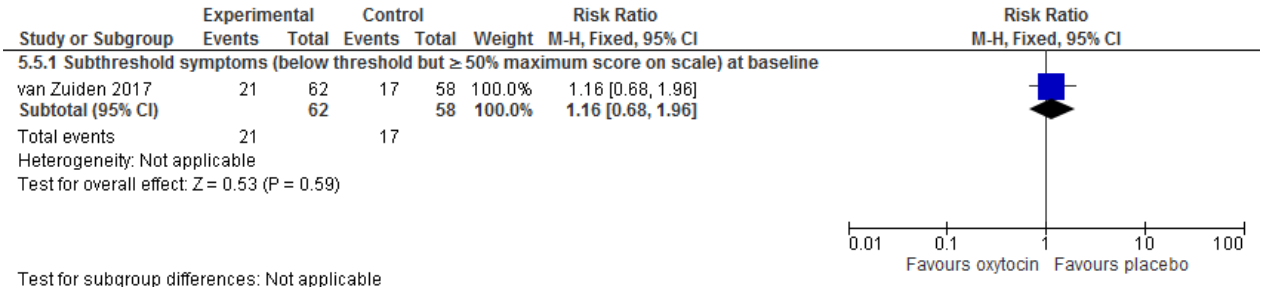


Figure 20: Discontinuation due to any reason (including adverse events)



Propranolol versus placebo for the early prevention (<1 month) of PTSD in adults

Figure 21: PTSD/ASD symptomatology self-rated (ASDS endpoint score)

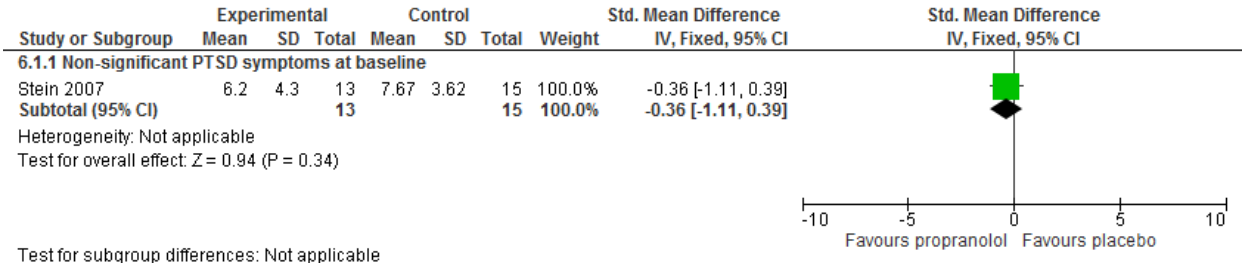


Figure 22: PTSD symptomatology clinician-rated at endpoint (CAPS endpoint score)

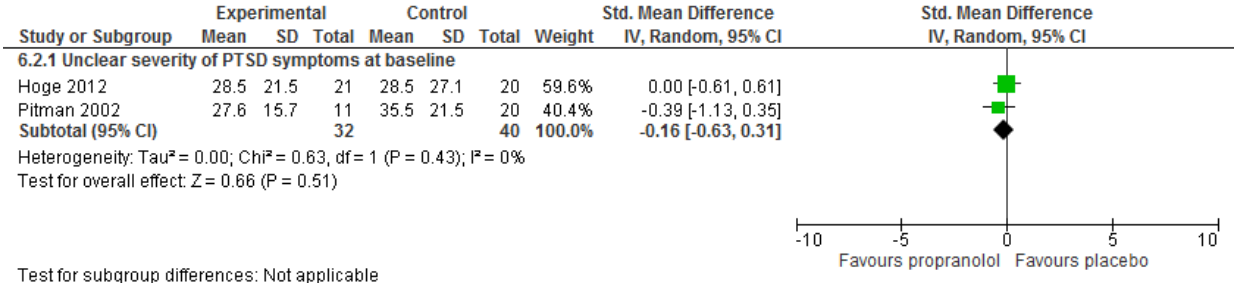


Figure 23: PTSD symptomatology clinician-rated at endpoint (CAPS endpoint score)

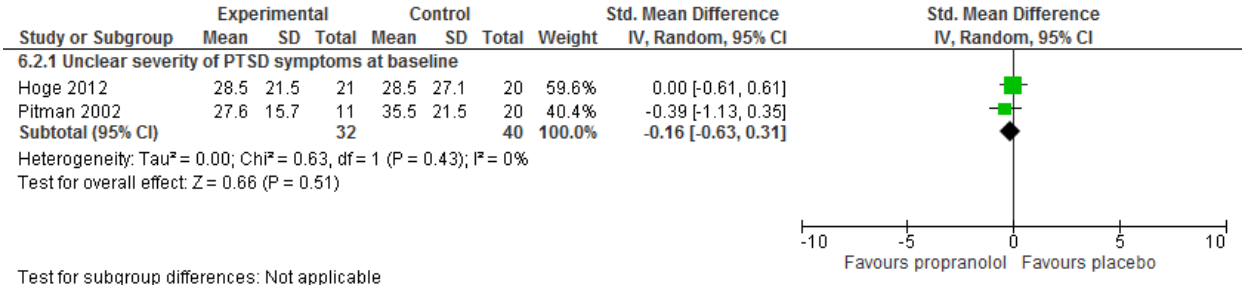


Figure 24: PTSD symptomatology clinician-rated at 2-month follow-up (CAPS endpoint score)

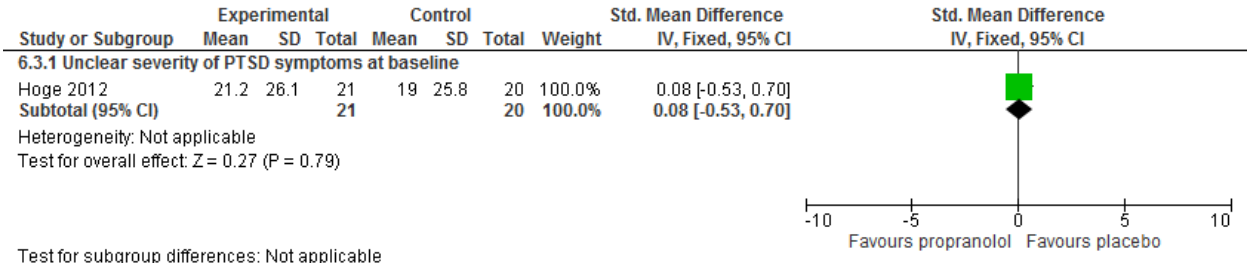


Figure 25: Diagnosis of PTSD at endpoint

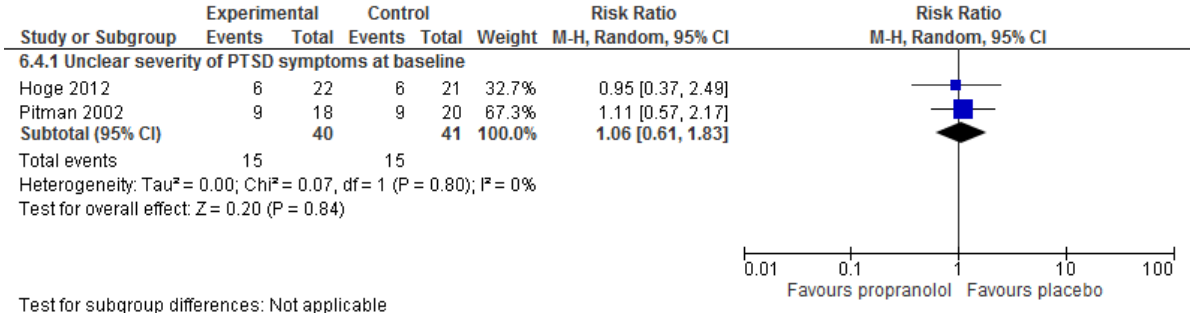


Figure 26: Diagnosis of PTSD at 2-3 month follow-up

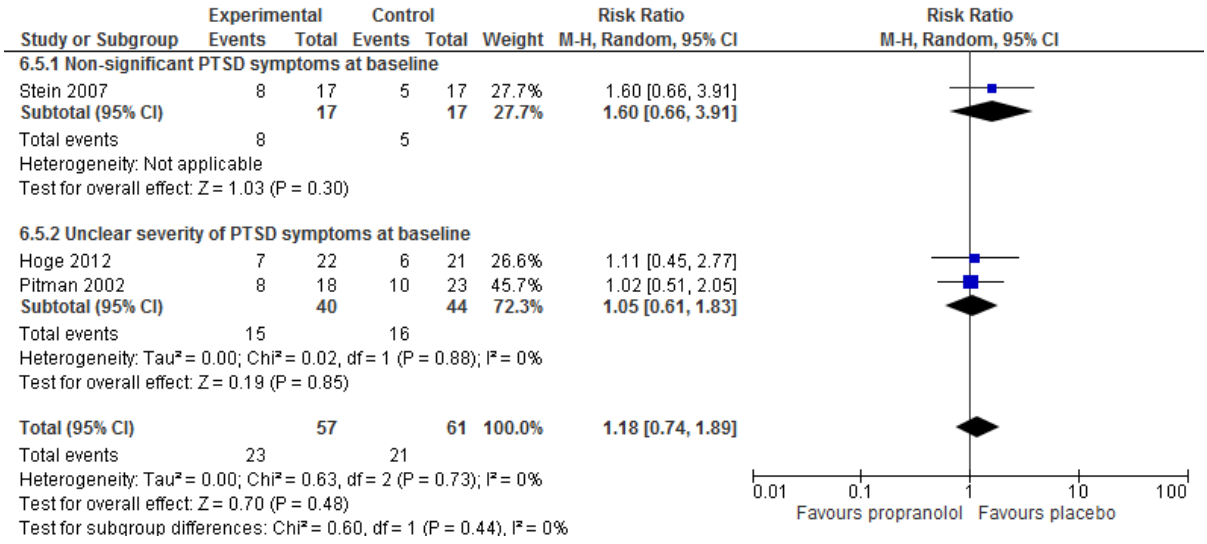
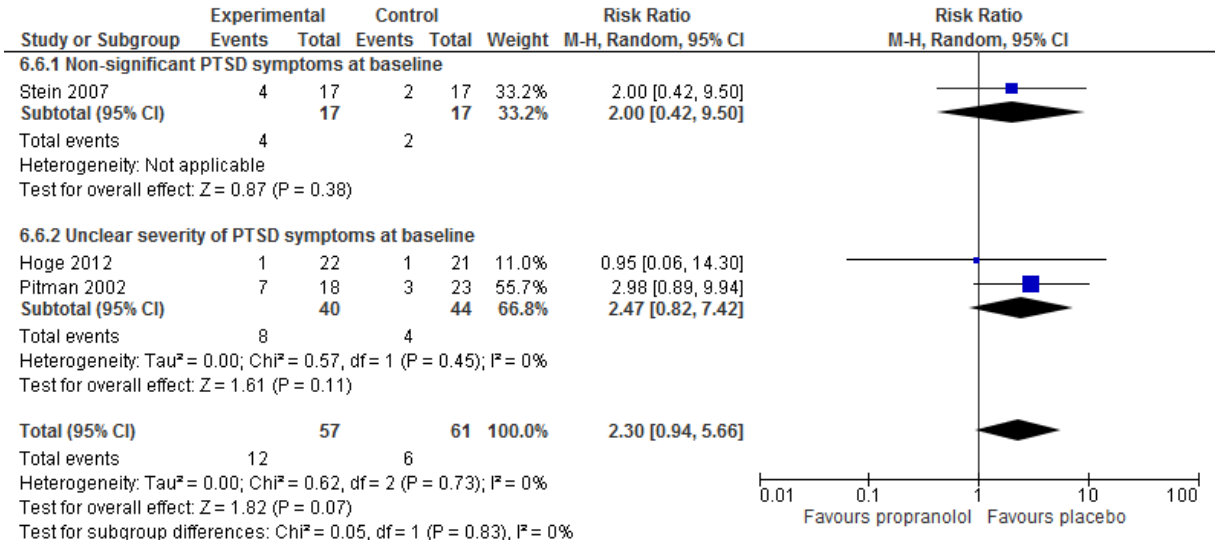


Figure 27: Discontinuation due to any reason



Propranolol versus gabapentin for the early prevention (<1 month) of PTSD in adults

Figure 28: PTSD/ASD symptomatology self-rated (ASDS endpoint score)

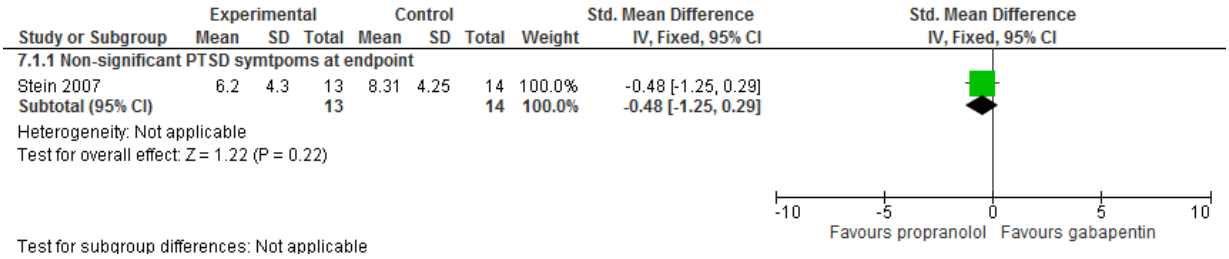


Figure 29: Diagnosis of PTSD at 3-month follow-up

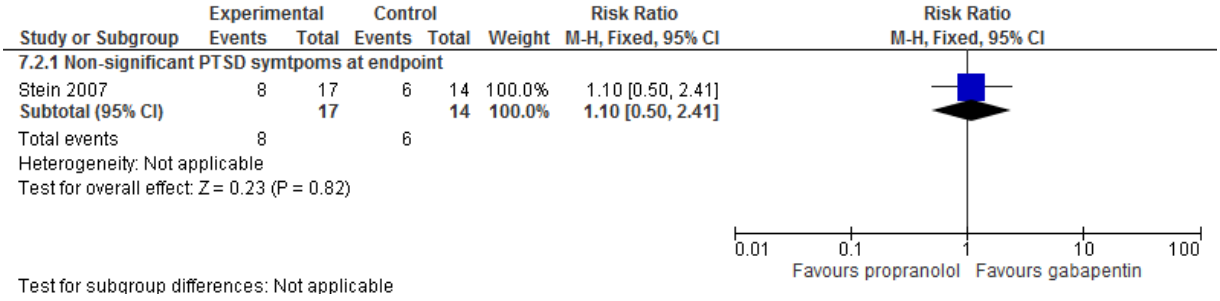
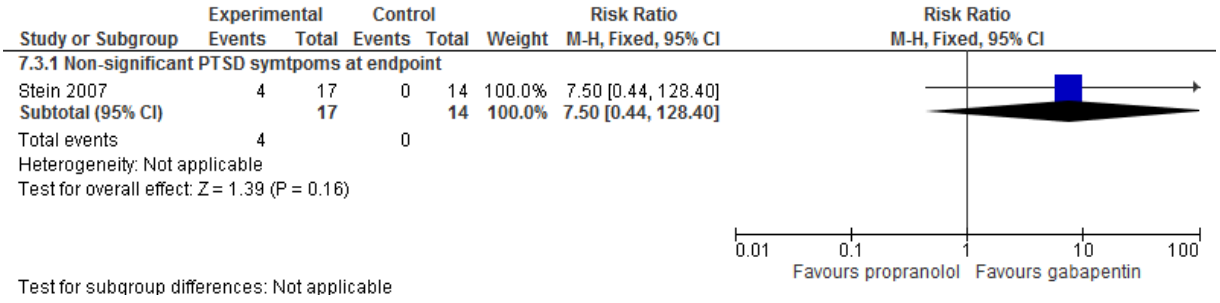


Figure 30: Discontinuation for any reason (including adverse events)



Prazosin versus placebo for the delayed treatment (>3 months) of non-significant PTSD symptoms in adults

Figure 31: PTSD symptomatology self-rated (PCL change score); Non-significant PTSD symptoms at baseline

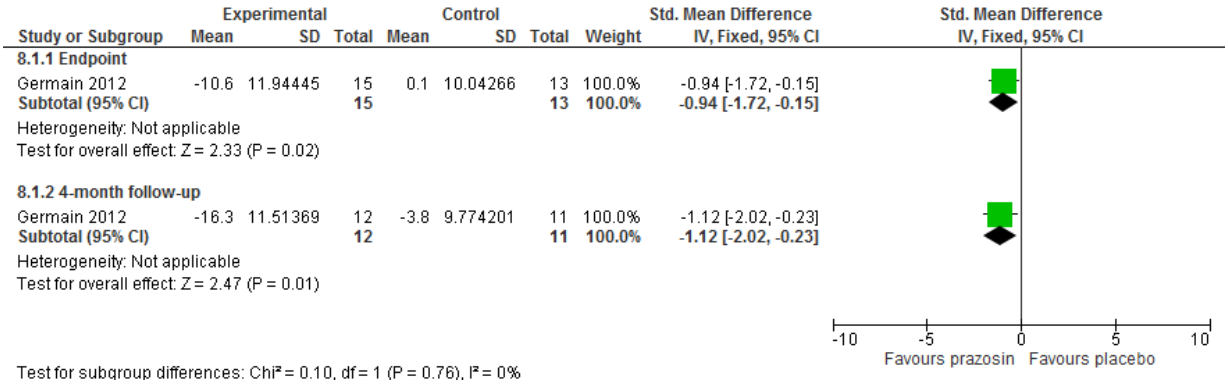


Figure 32: Anxiety symptoms (BAI change score); Non-significant PTSD symptoms at baseline

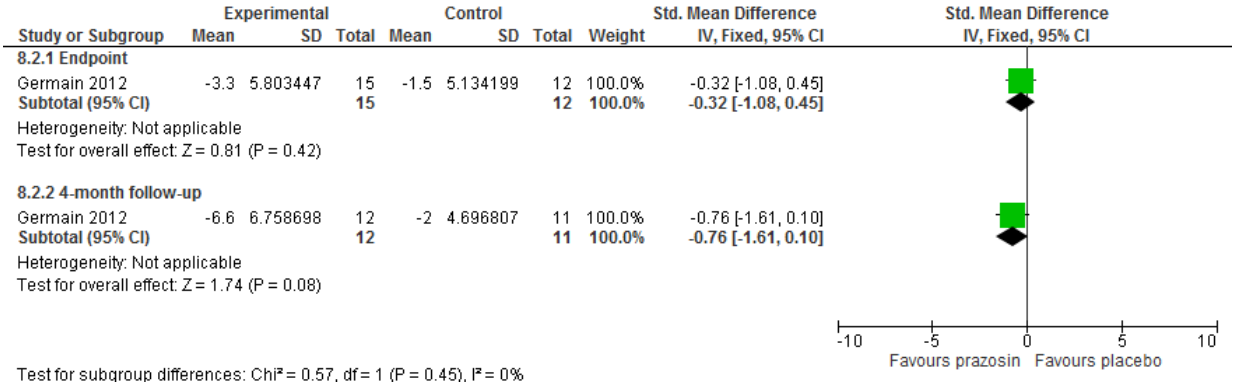


Figure 33: Depression symptoms (BDI change score); Non-significant PTSD symptoms at baseline

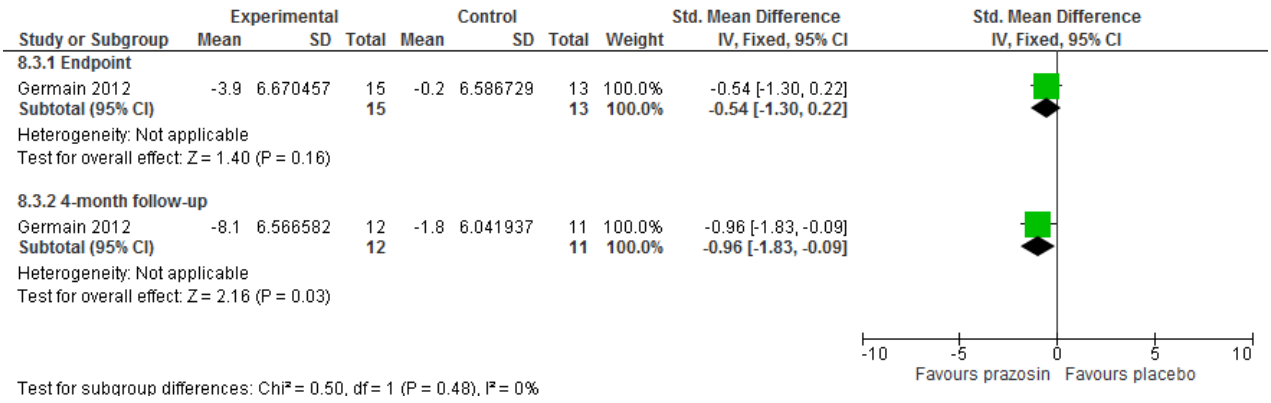


Figure 34: Functional impairment (SDS change score); Non-significant PTSD symptoms at baseline

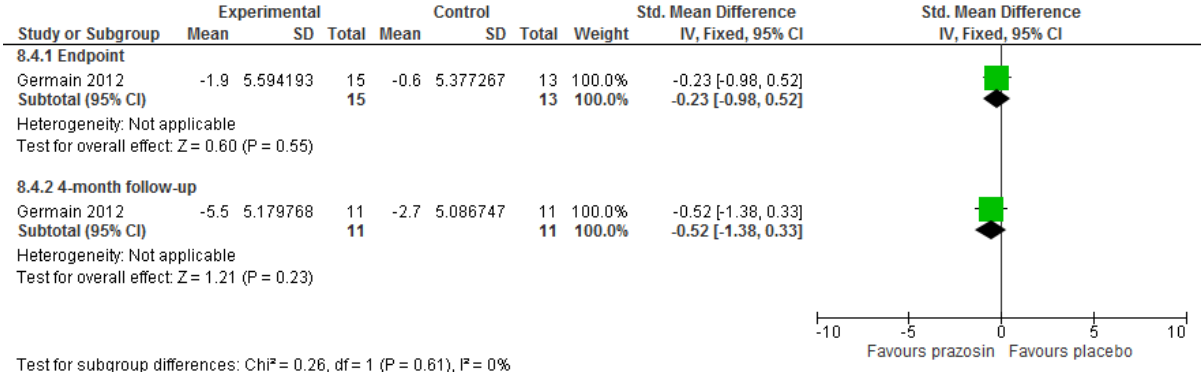


Figure 35: Sleeping difficulties (PSQI change score); Non-significant PTSD symptoms at baseline

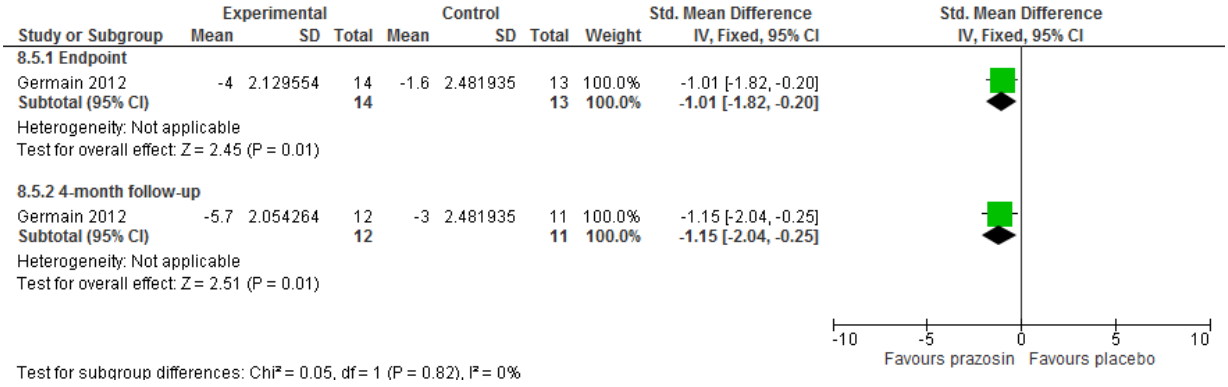


Figure 36: Discontinuation due to any reason (including adverse events)

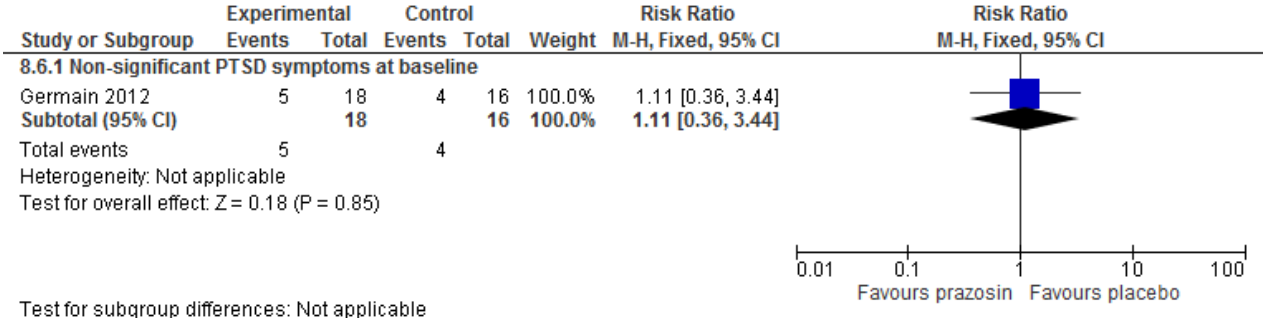
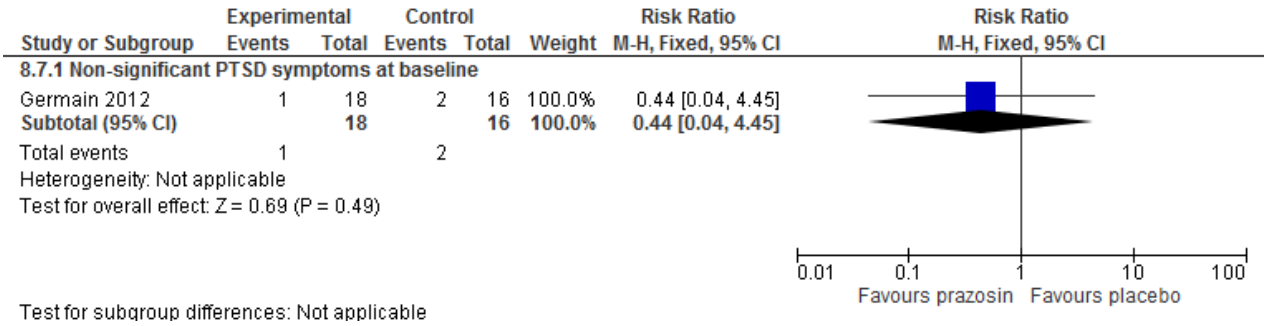


Figure 37: Discontinuation due to adverse events

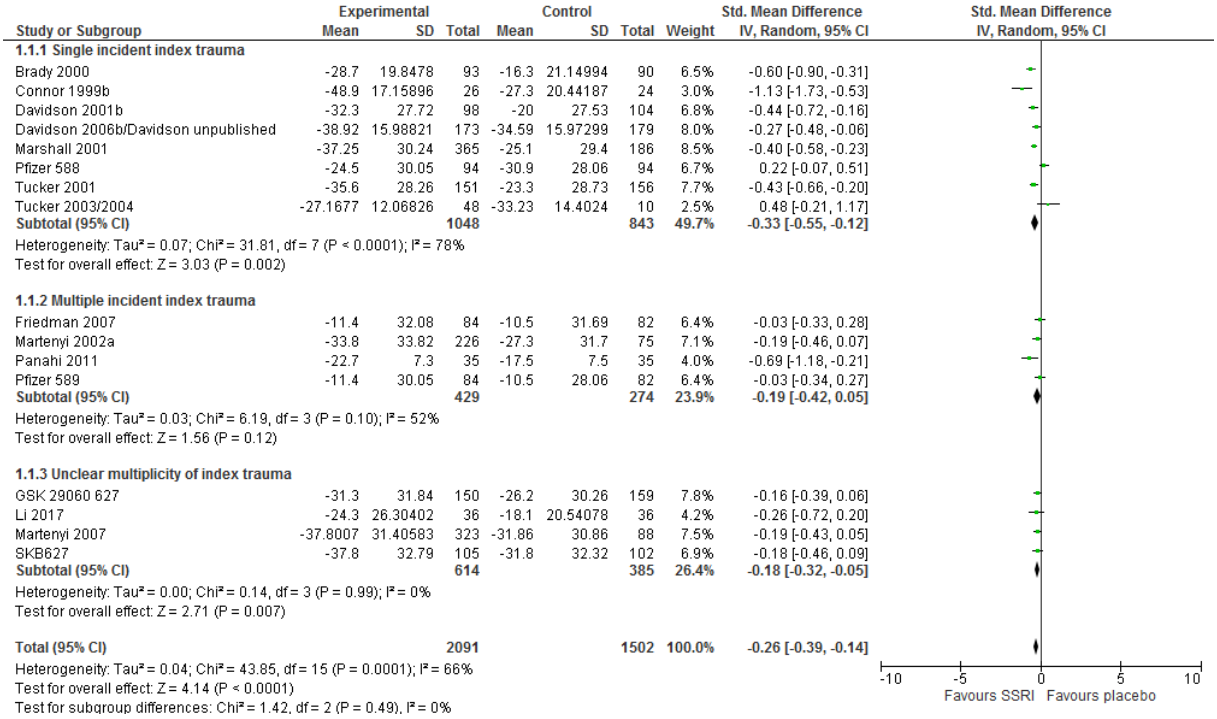


Forest plots for "For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

Antidepressants: Selective serotonin reuptake inhibitors (SSRIs)

SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 38: SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (DTS/IES-R change score)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Single incident index trauma								
Brady 2000	-28.7	19.8478	93	-16.3	21.14994	90	6.5%	-0.60 [-0.90, -0.31]
Connor 1999b	-48.9	17.15896	26	-27.3	20.44187	24	3.0%	-1.13 [-1.73, -0.53]
Davidson 2001b	-32.3	27.72	98	-20	27.53	104	6.8%	-0.44 [-0.72, -0.16]
Davidson 2006b/Davidson unpublished	-38.92	15.98821	173	-34.59	15.97299	179	8.0%	-0.27 [-0.48, -0.06]
Marshall 2001	-37.25	30.24	365	-25.1	29.4	186	8.5%	-0.40 [-0.58, -0.23]
Pfizer 588	-24.5	30.05	94	-30.9	28.06	94	6.7%	0.22 [-0.07, 0.51]
Tucker 2001	-35.6	28.26	151	-23.3	28.73	156	7.7%	-0.43 [-0.66, -0.20]
Tucker 2003/2004	-27.1677	12.06826	48	-33.23	14.4024	10	2.5%	0.48 [-0.21, 1.17]
Subtotal (95% CI)			**1048**			**843**	**49.7%**	**-0.33 [-0.55, -0.12]**
Heterogeneity: Tau² = 0.07; Chi² = 31.81, df = 7 (P < 0.0001); I² = 78%								
Test for overall effect: Z = 3.03 (P = 0.002)								
1.1.2 Multiple incident index trauma								
Friedman 2007	-11.4	32.08	84	-10.5	31.69	82	6.4%	-0.03 [-0.33, 0.28]
Martenyi 2002a	-33.8	33.82	226	-27.3	31.7	75	7.1%	-0.19 [-0.46, 0.07]
Panahi 2011	-22.7	7.3	35	-17.5	7.5	35	4.0%	-0.69 [-1.18, -0.21]
Pfizer 589	-11.4	30.05	84	-10.5	28.06	82	6.4%	-0.03 [-0.34, 0.27]
Subtotal (95% CI)			**429**			**274**	**23.9%**	**-0.19 [-0.42, 0.05]**
Heterogeneity: Tau² = 0.03; Chi² = 6.19, df = 3 (P = 0.10); I² = 52%								
Test for overall effect: Z = 1.56 (P = 0.12)								
1.1.3 Unclear multiplicity of index trauma								
GSK 29060 627	-31.3	31.84	150	-26.2	30.26	159	7.8%	-0.16 [-0.39, 0.06]
Li 2017	-24.3	26.30402	36	-18.1	20.54078	36	4.2%	-0.26 [-0.72, 0.20]
Martenyi 2007	-37.8007	31.40583	323	-31.86	30.86	88	7.5%	-0.19 [-0.43, 0.05]
SKB627	-37.8	32.79	105	-31.8	32.32	102	6.9%	-0.18 [-0.46, 0.09]
Subtotal (95% CI)			**614**			**385**	**26.4%**	**-0.18 [-0.32, -0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 3 (P = 0.99); I² = 0%								
Test for overall effect: Z = 2.71 (P = 0.007)								
Total (95% CI)			**2091**			**1502**	**100.0%**	**-0.26 [-0.39, -0.14]**
Heterogeneity: Tau² = 0.04; Chi² = 43.85, df = 15 (P = 0.0001); I² = 66%								
Test for overall effect: Z = 4.14 (P < 0.0001)								
Test for subgroup differences: Chi² = 1.42, df = 2 (P = 0.49), I² = 0%								

Figure 39: SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS/SI–PTSD change score)

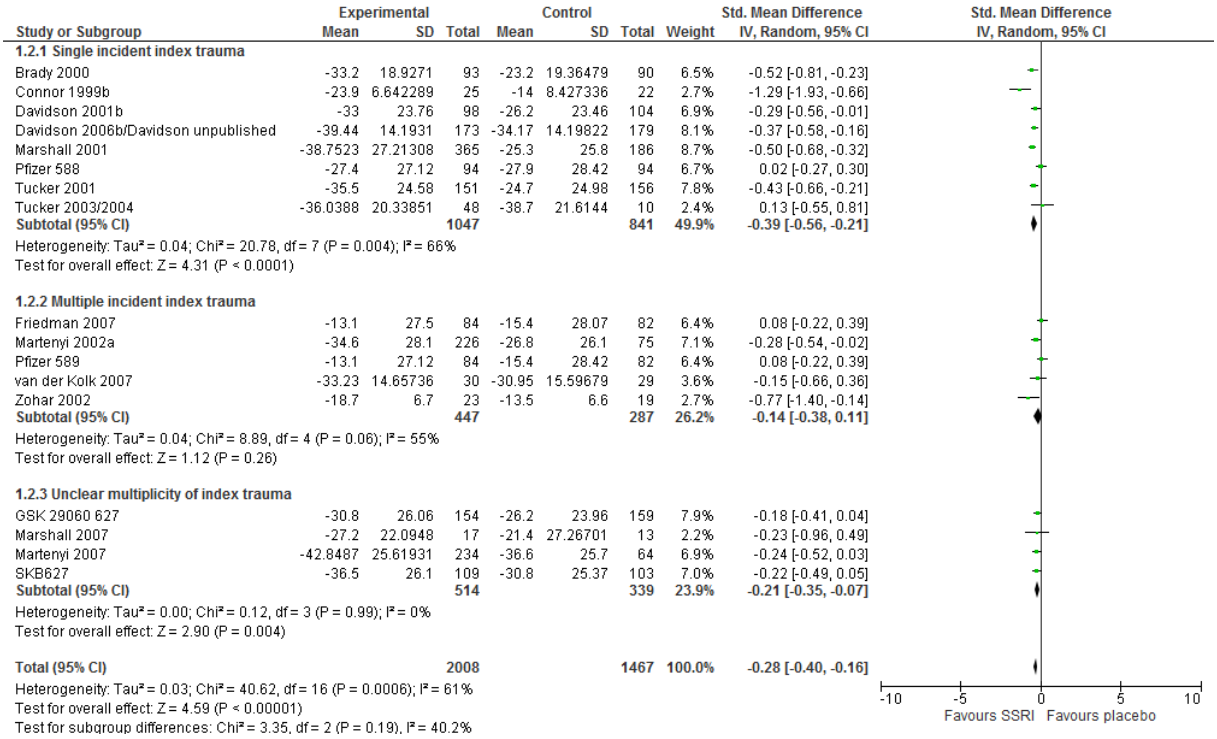


Figure 40: SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Remission clinician-rated (number of people scoring <20 on CAPS/no longer meeting diagnostic criteria for PTSD)

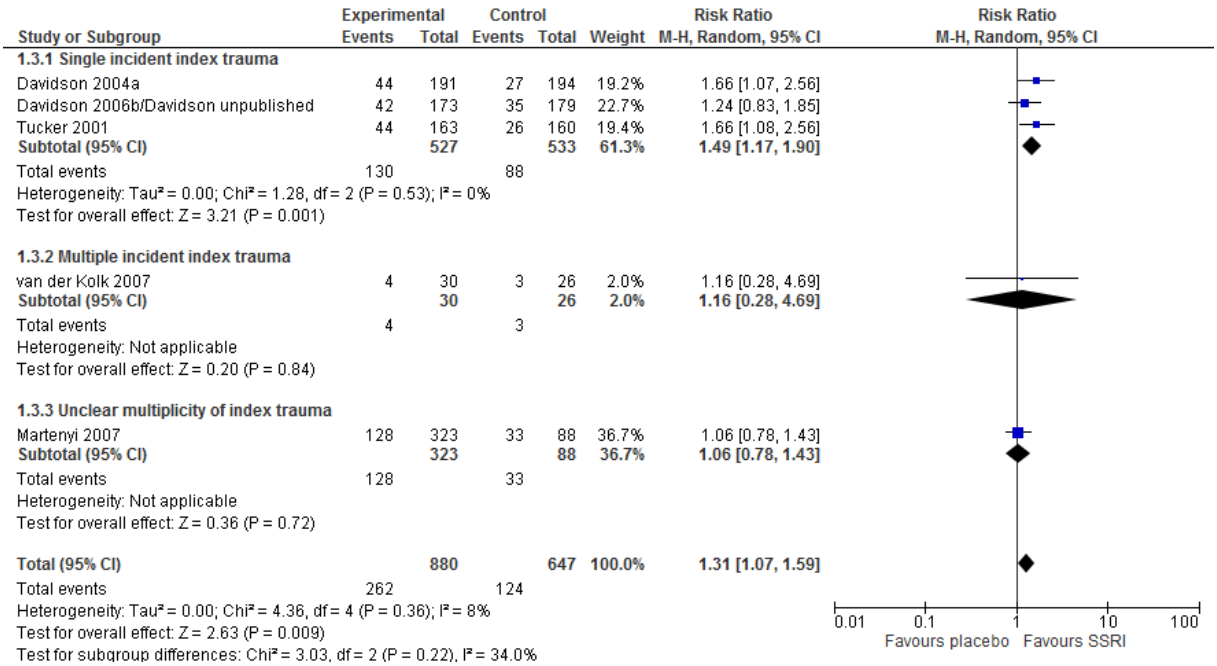


Figure 41: SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Remission self-rated (number of people scoring <18 on DTS)

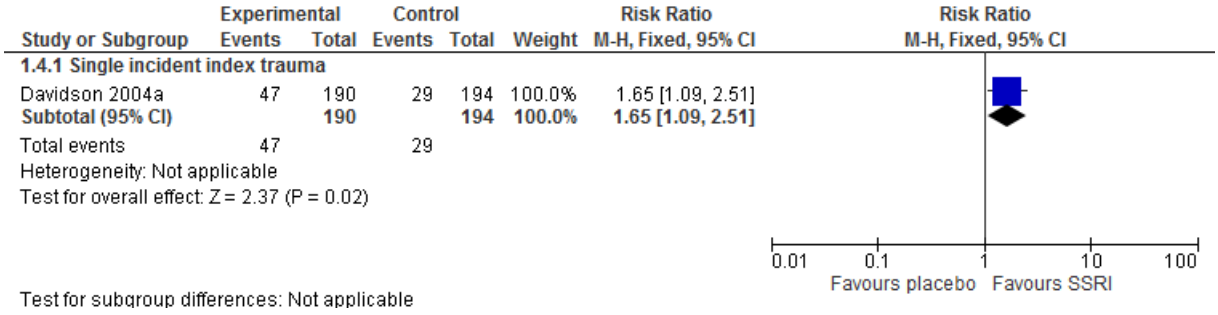


Figure 42: SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people showing ≥30% improvement on CAPS or IES-R/≥50% improvement on TOP-8 and/or CGI-I much or very much improved)

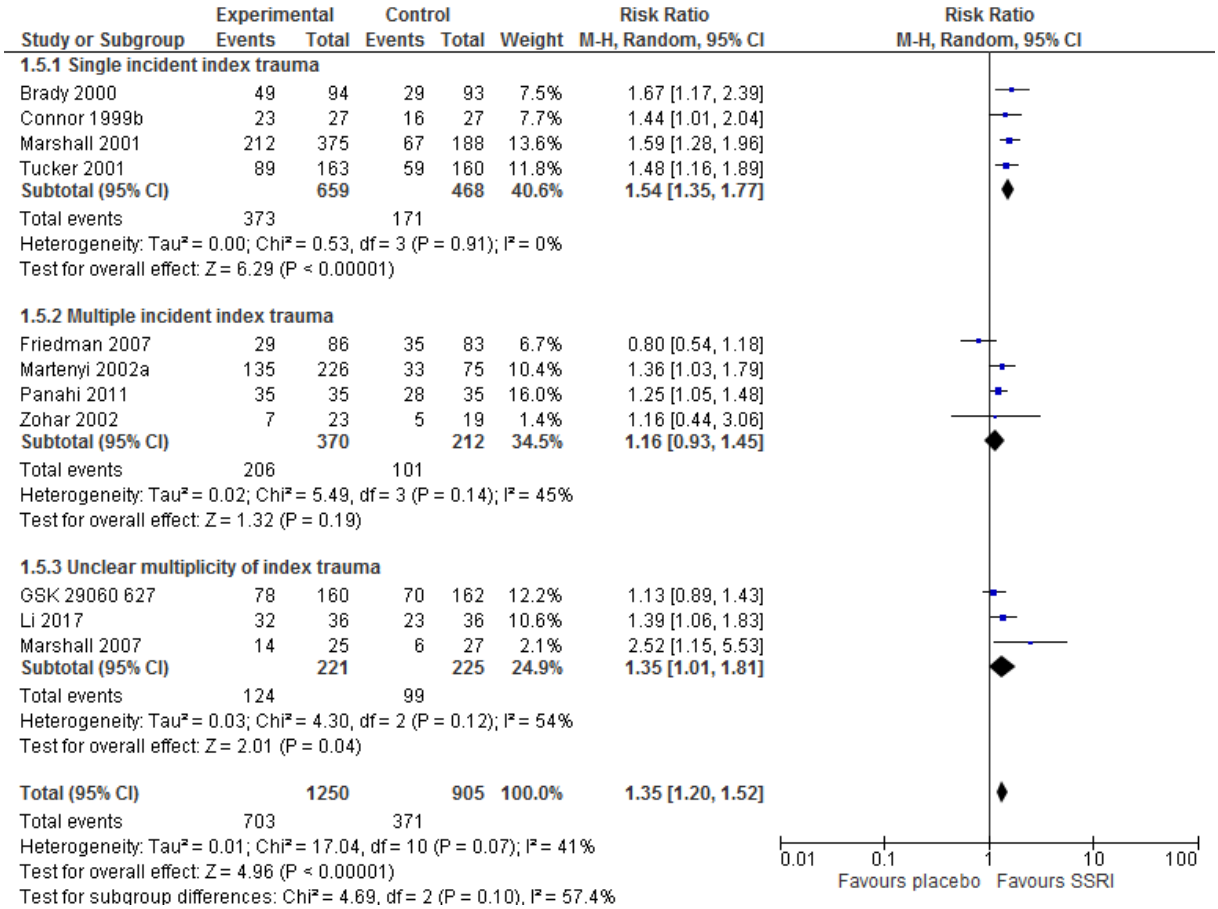


Figure 43: SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms (HAM-A change score)

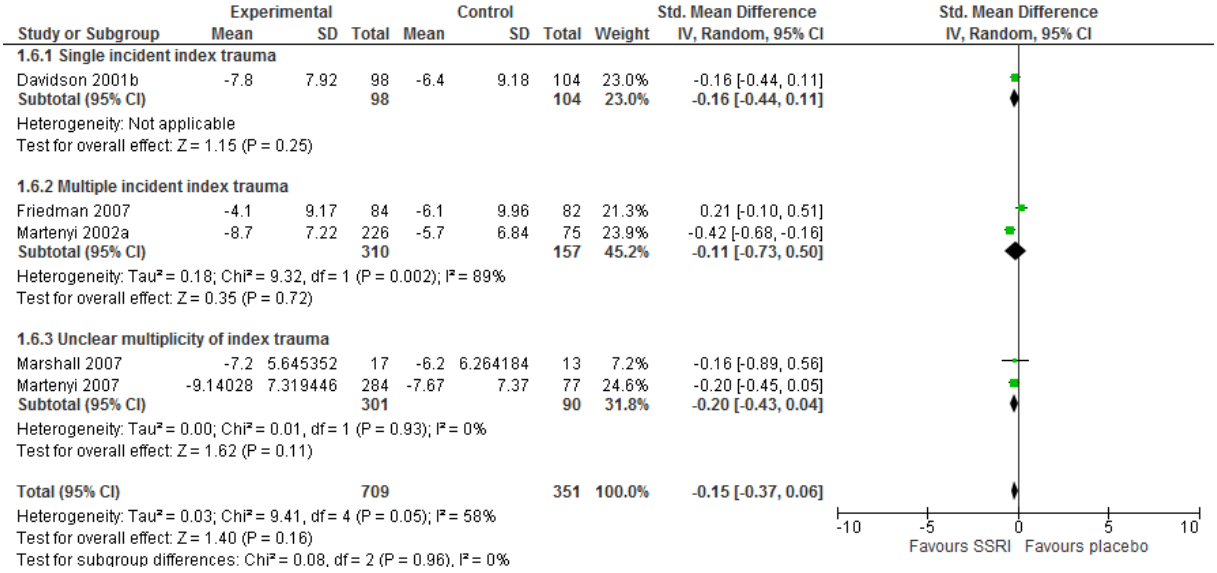


Figure 44: SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (HAM-D/MADRS/BDI/BDI-II change score)

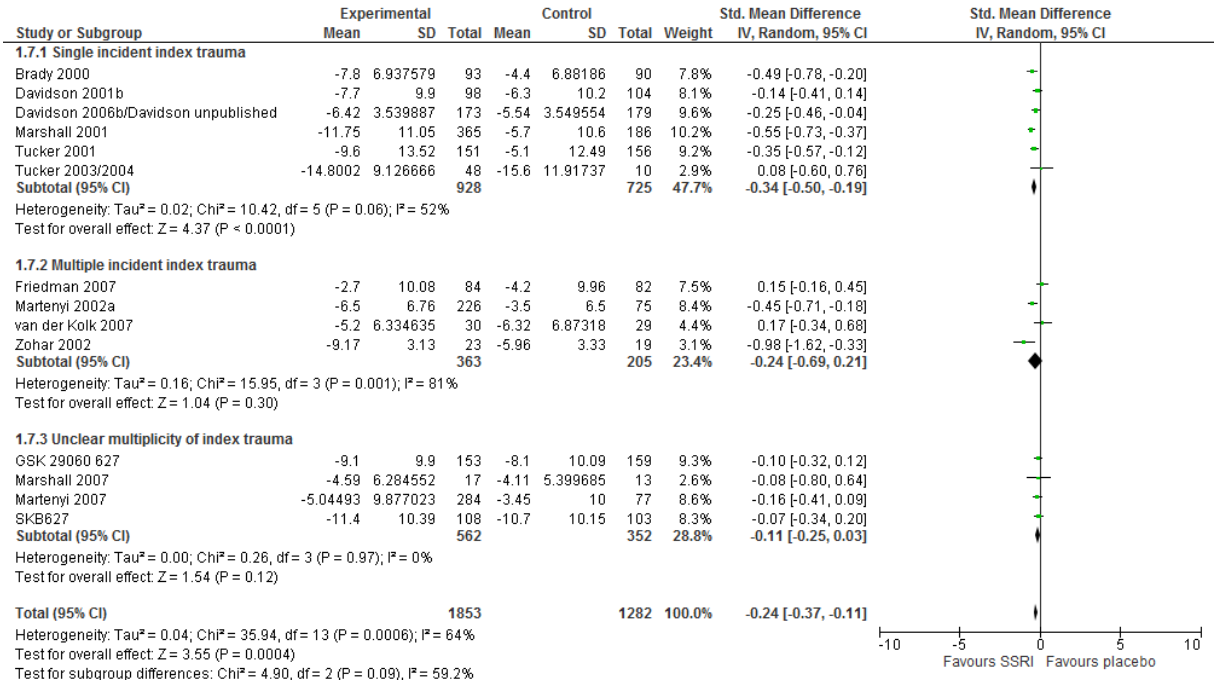


Figure 45: SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Dissociative symptoms (DES change score)

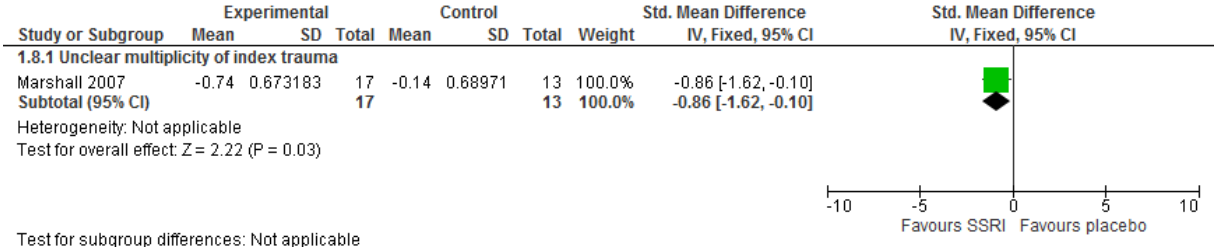


Figure 46: SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Functional impairment (SDS change score)

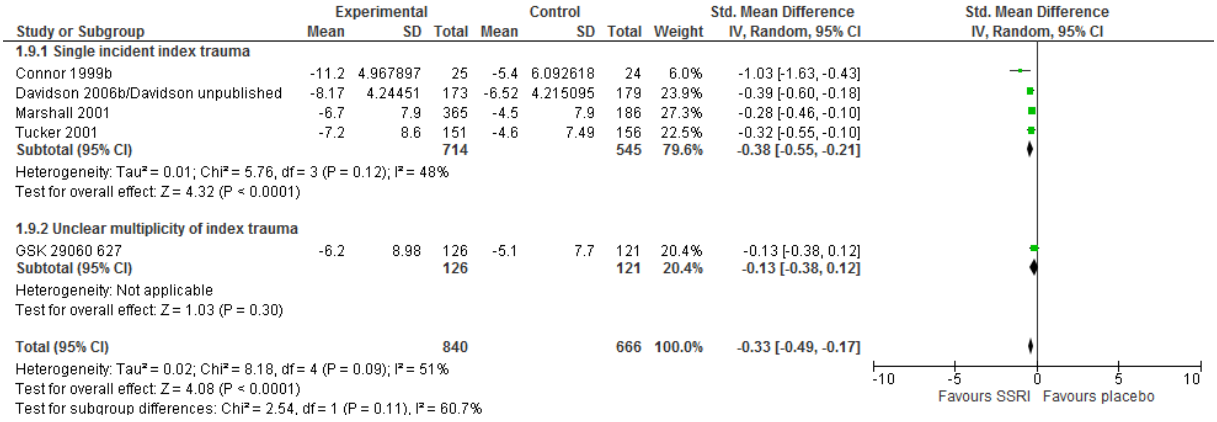


Figure 47: SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Global functioning (GAF change score)

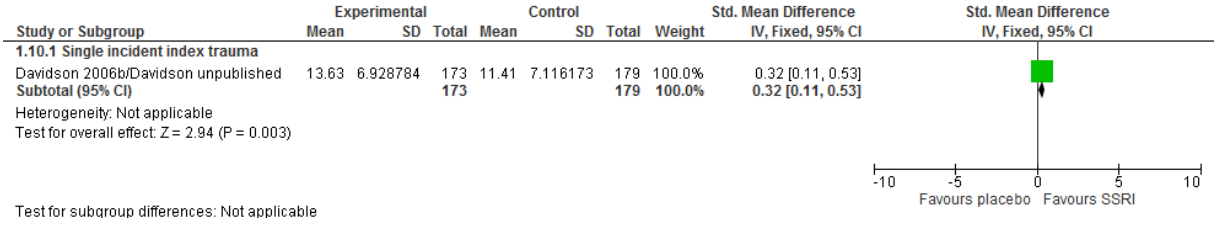


Figure 48: SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Quality of life (Q-LES-Q-SF change score)

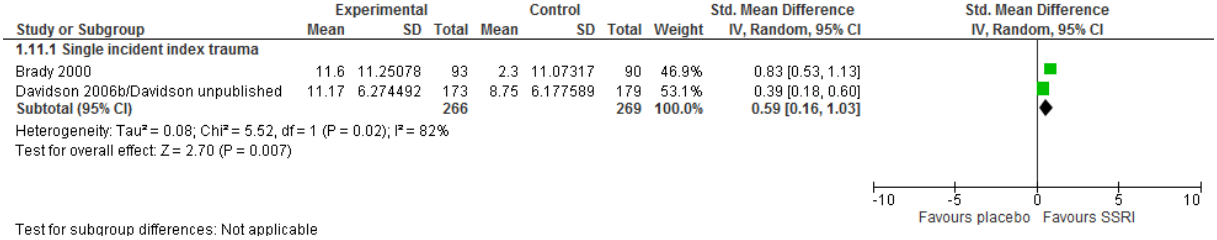


Figure 49: SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Sleeping difficulties (PSQI change score)

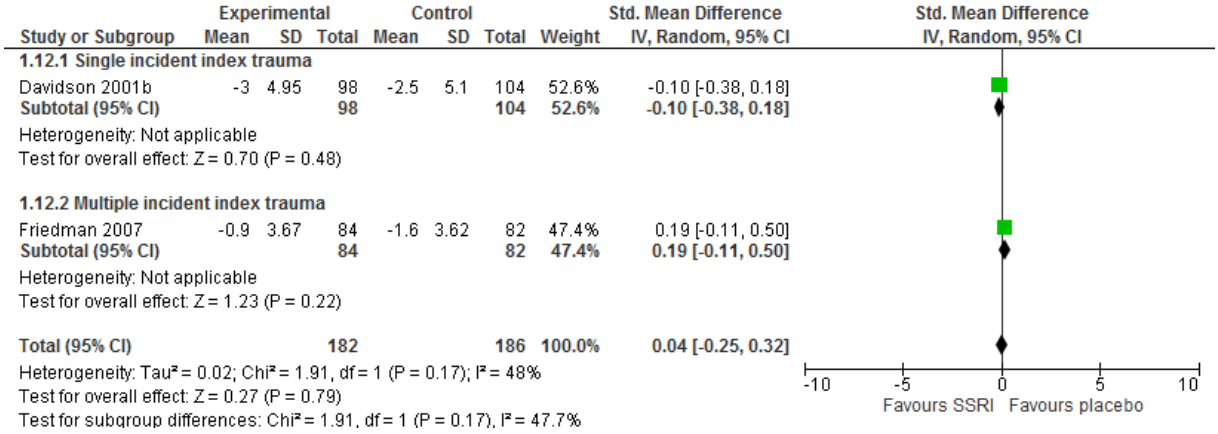


Figure 50: SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Relationship difficulties (IIP change score)

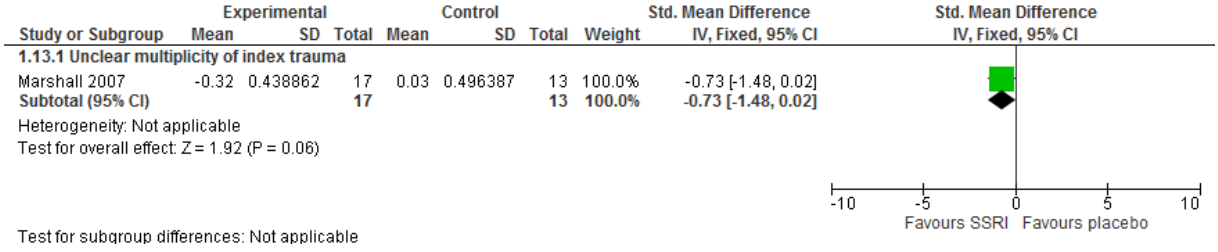


Figure 51: SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

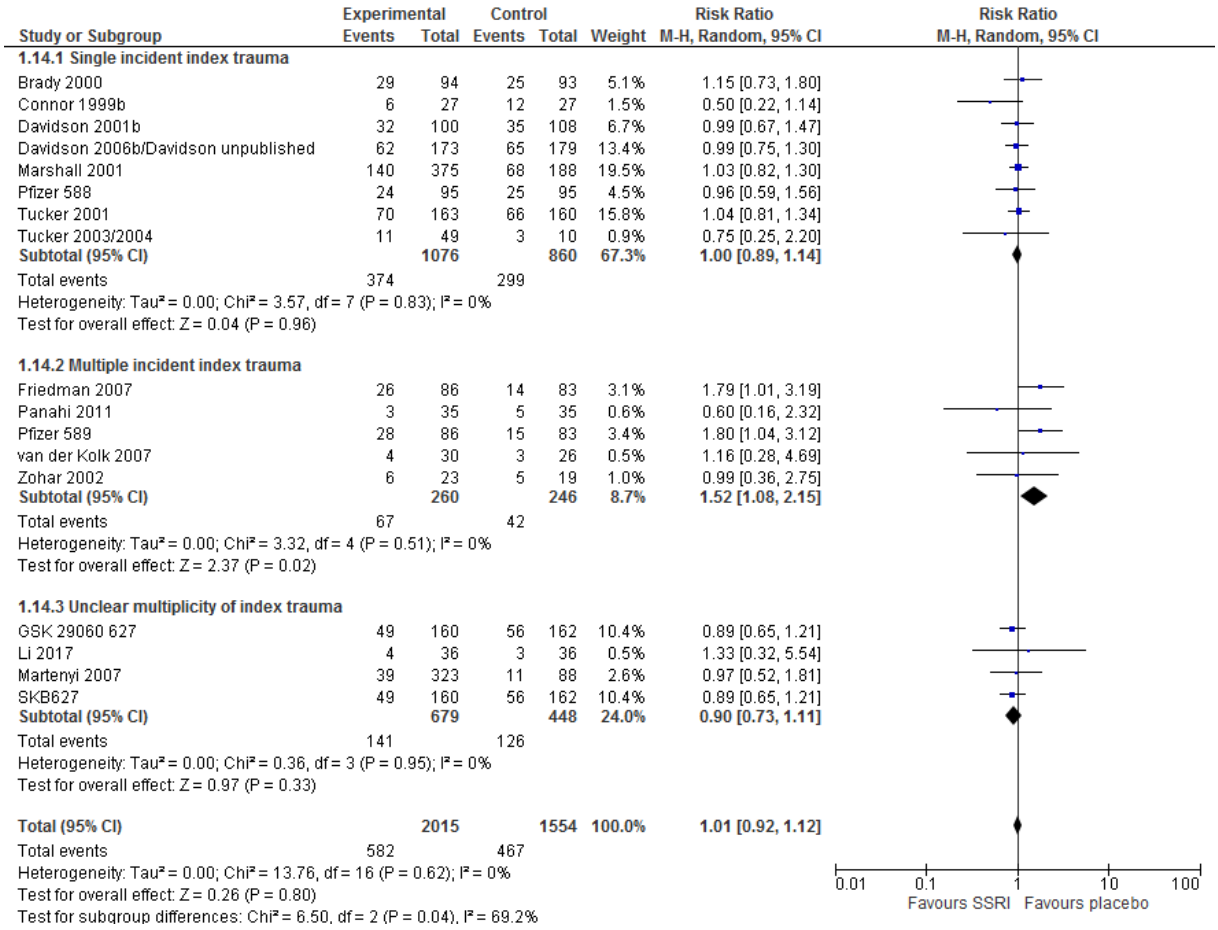
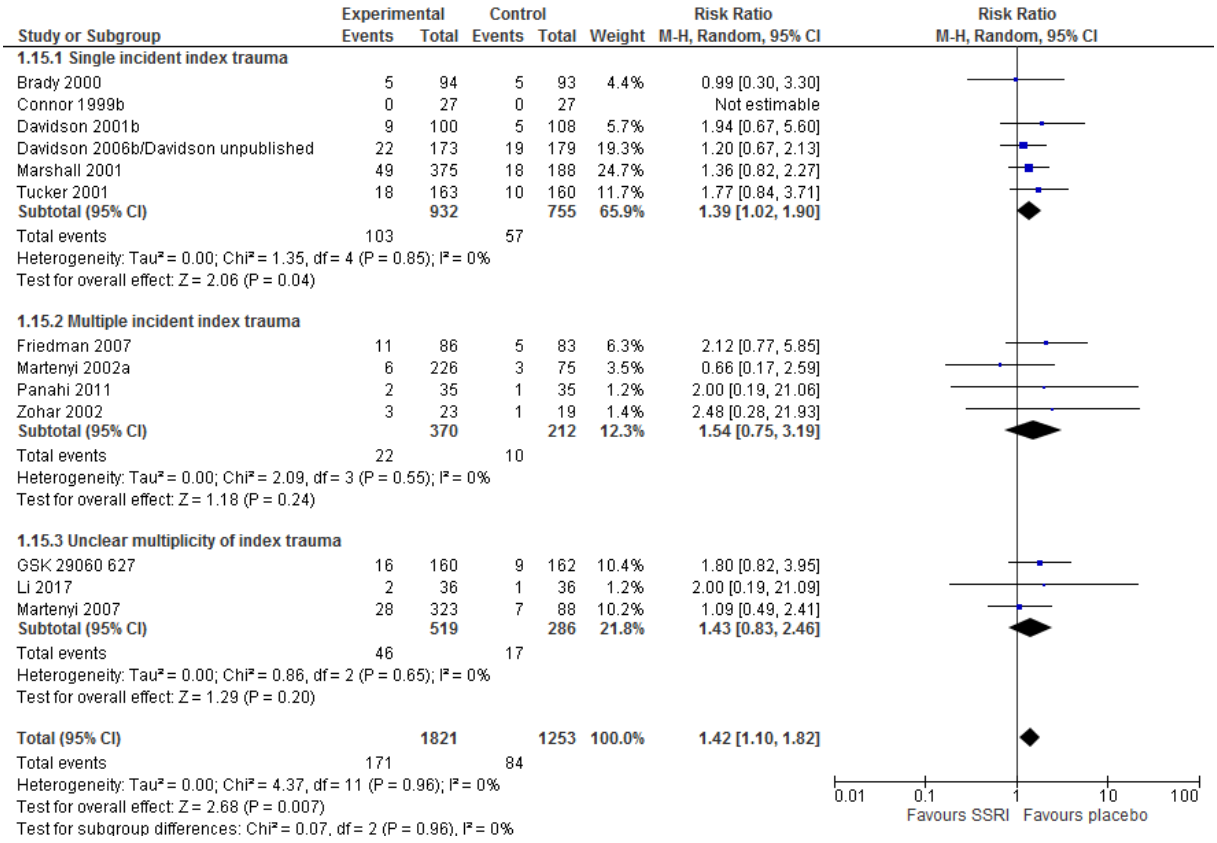


Figure 52: SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Sub-analysis by specific intervention: SSRI versus Placebo

Figure 53: Sub-analysis by specific intervention: SSRI versus Placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (DTS/IES-R change score)

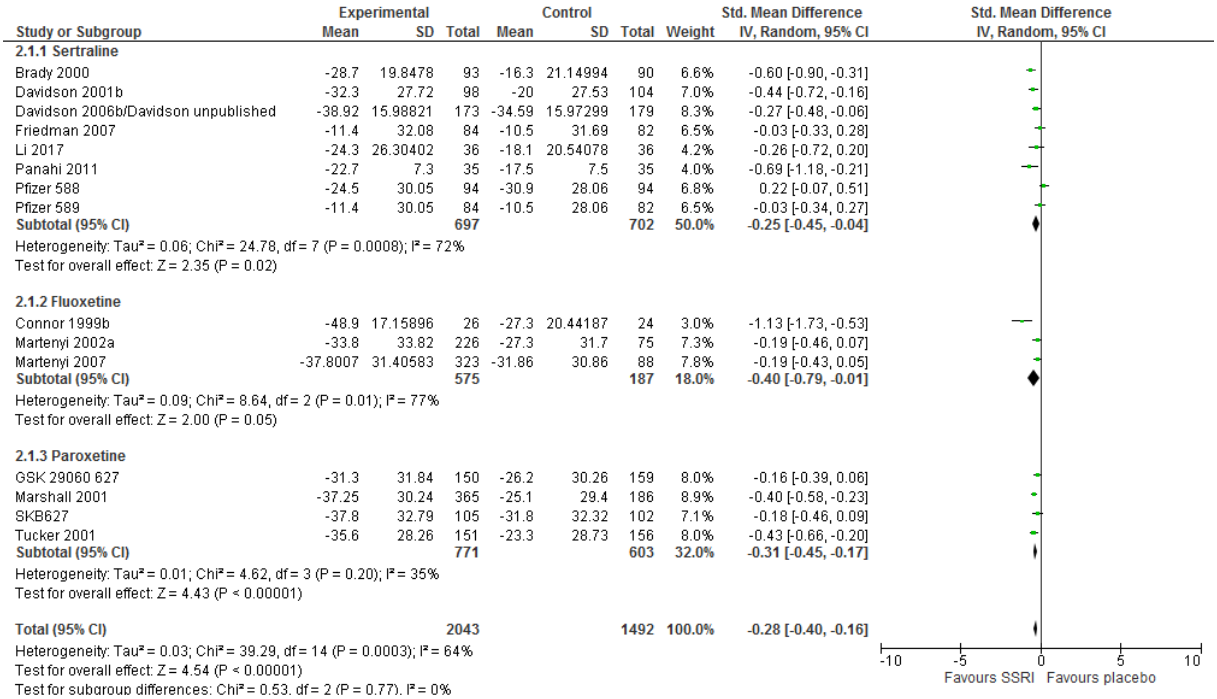


Figure 54: Sub-analysis by specific intervention: SSRI versus Placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS/SI–PTSD change score)

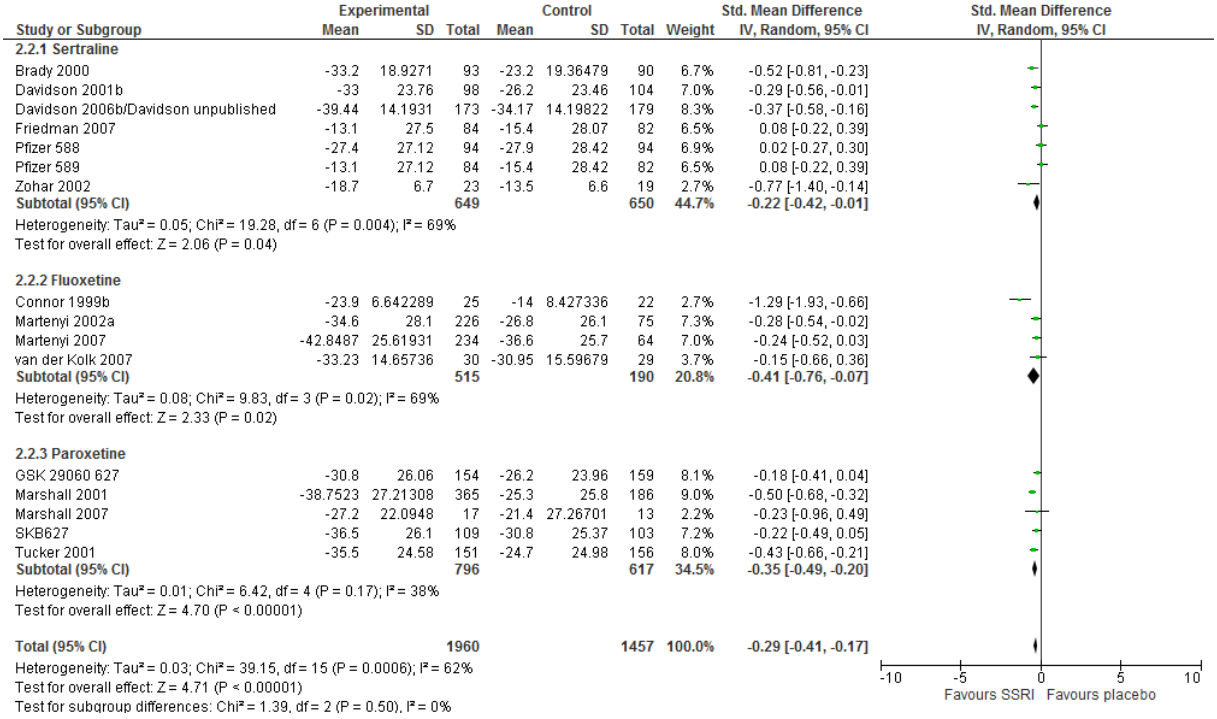


Figure 55: Sub-analysis by specific intervention: SSRI versus Placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Remission clinician-rated (number of people scoring <20 on CAPS/no longer meeting diagnostic criteria for PTSD)

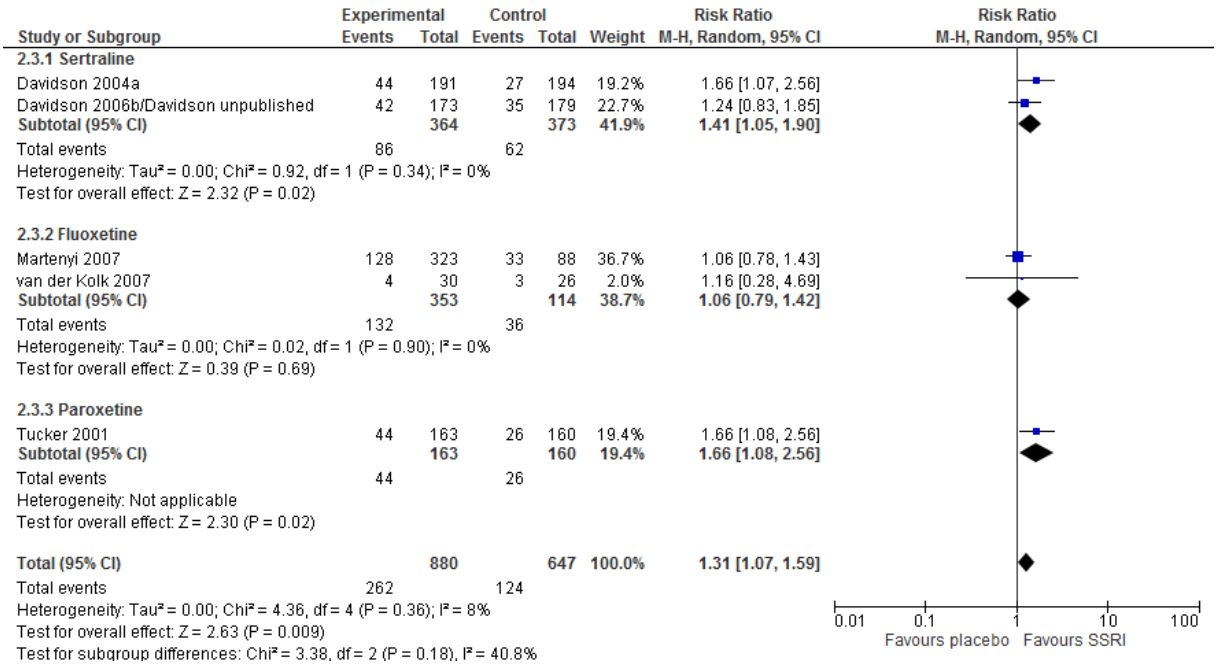


Figure 56: Sub-analysis by specific intervention: SSRI versus Placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Remission self-rated (number of people scoring <18 on DTS)

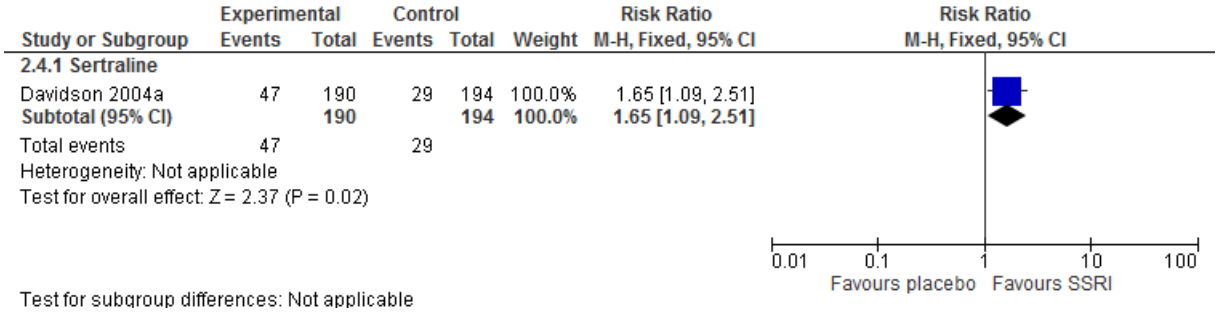


Figure 57: Sub-analysis by specific intervention: SSRI versus Placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people showing ≥30% improvement on CAPS or IES-R/≥50% improvement

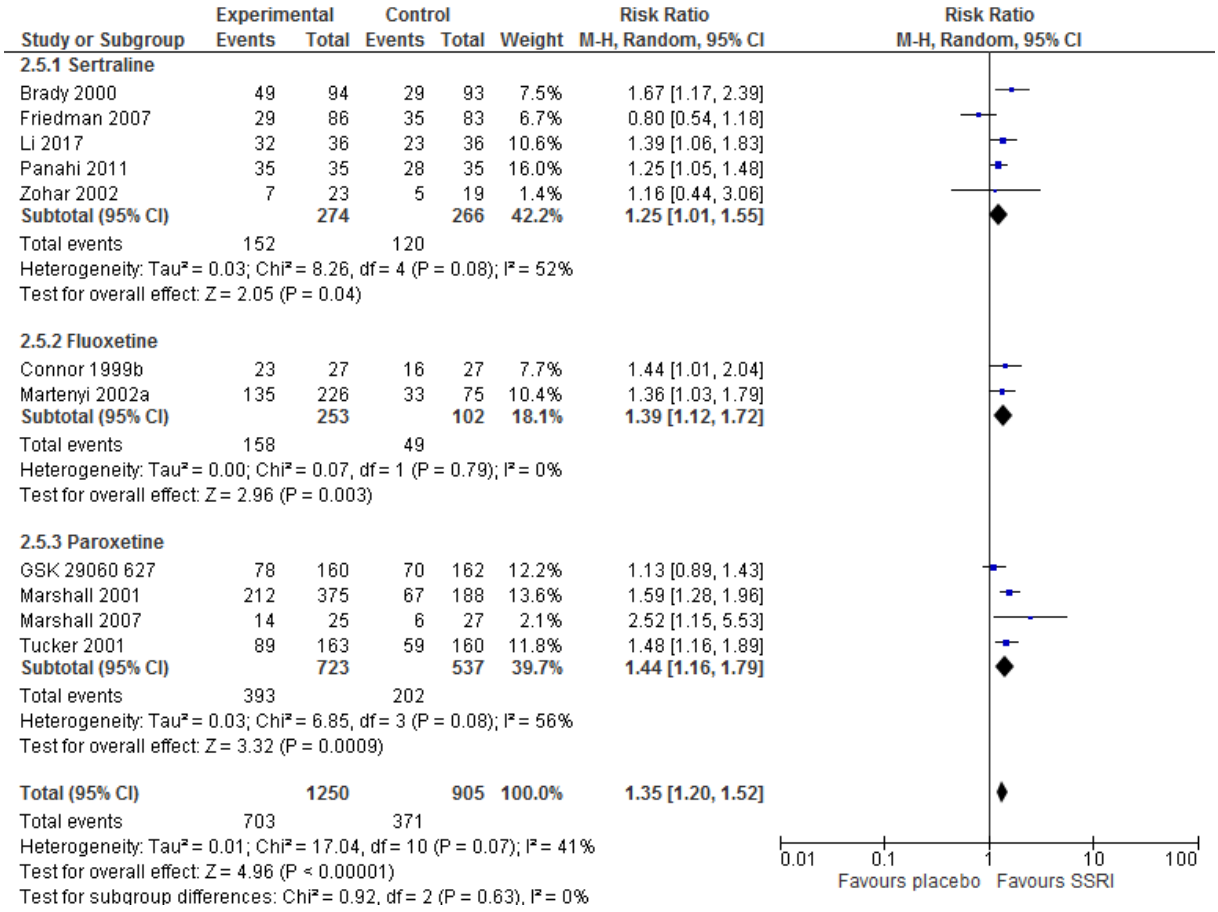


Figure 58: Sub-analysis by specific intervention: SSRI versus Placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms (HAM-A change score)

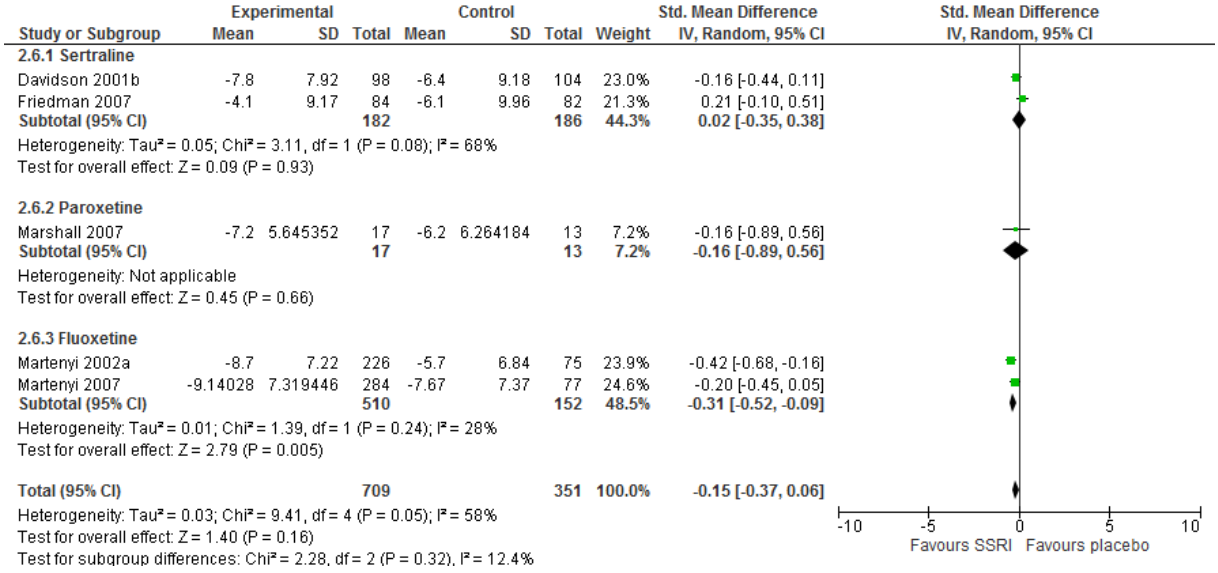


Figure 59: Sub-analysis by specific intervention: SSRI versus Placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (HAM-D/MADRS/BDI-II change score)

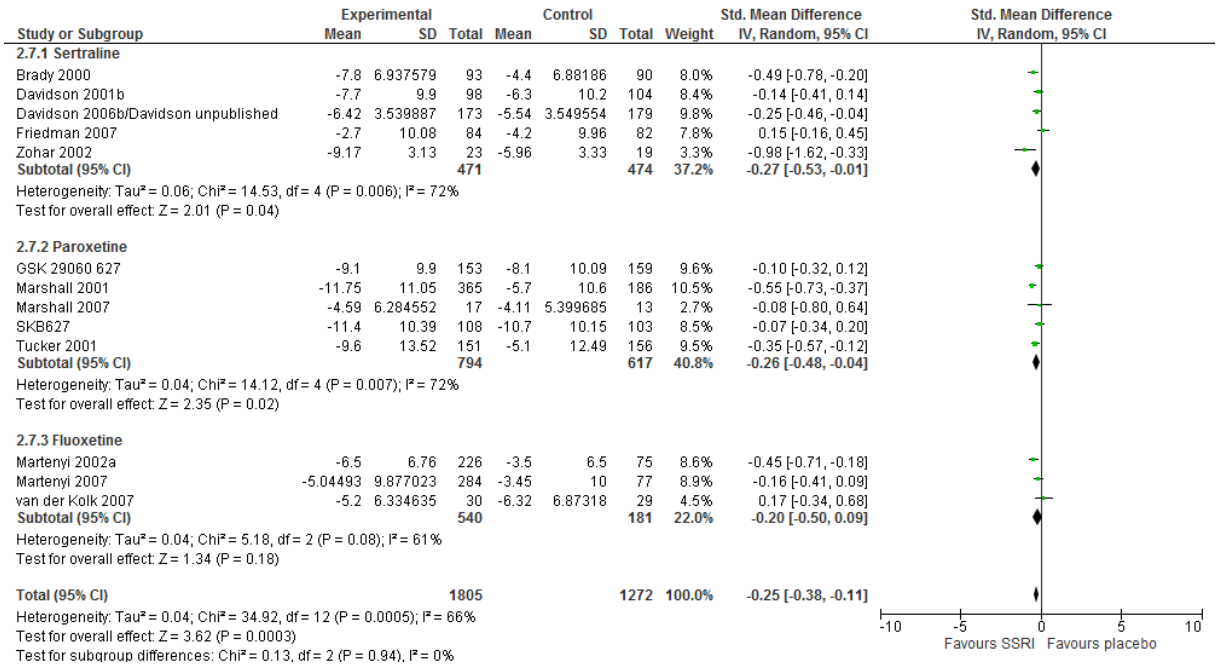


Figure 60: Sub-analysis by specific intervention: SSRI versus Placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Dissociative symptoms (DES change score)

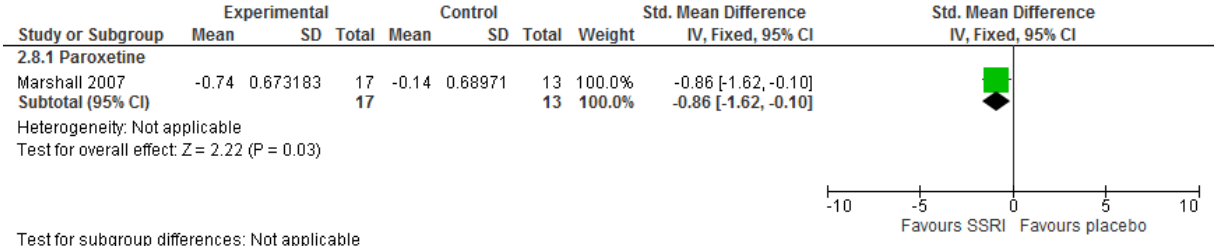


Figure 61: Sub-analysis by specific intervention: SSRI versus Placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Functional impairment (SDS change score)

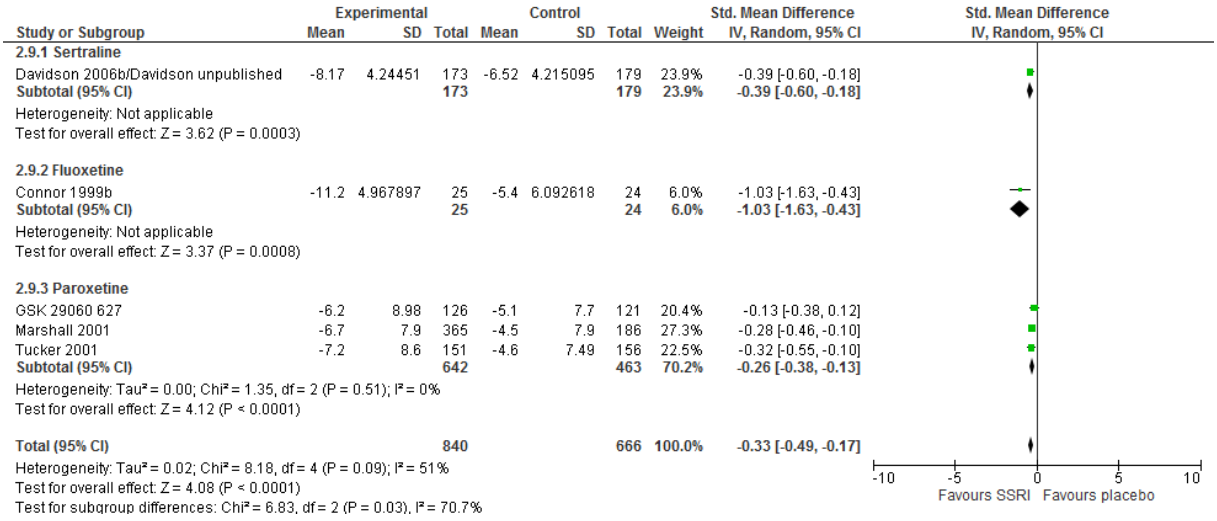


Figure 62: Sub-analysis by specific intervention: SSRI versus Placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Global functioning (GAF endpoint score)

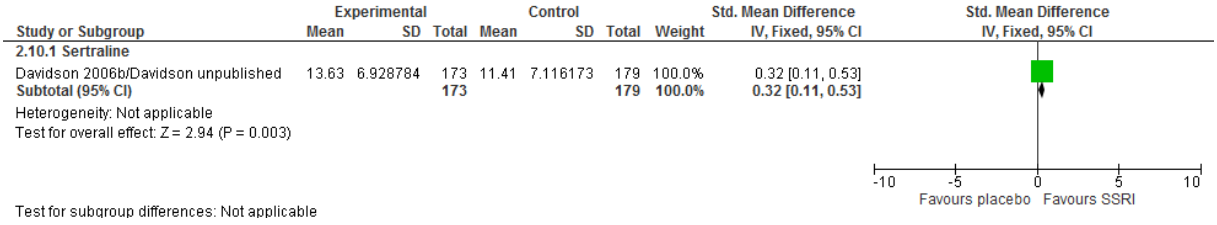


Figure 63: Sub-analysis by specific intervention: SSRI versus Placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Quality of life (Q-LES-Q-SF change/endpoint score)

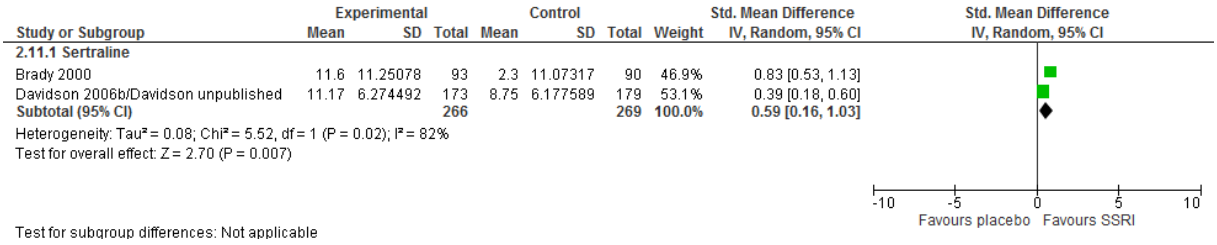


Figure 64: Sub-analysis by specific intervention: SSRI versus Placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Sleeping difficulties (PSQI change score)

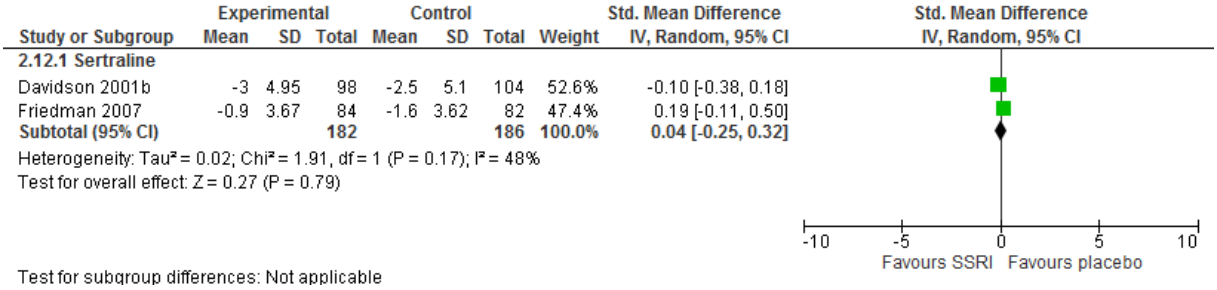


Figure 65: Sub-analysis by specific intervention: SSRI versus Placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Relationship difficulties (IIP change score)

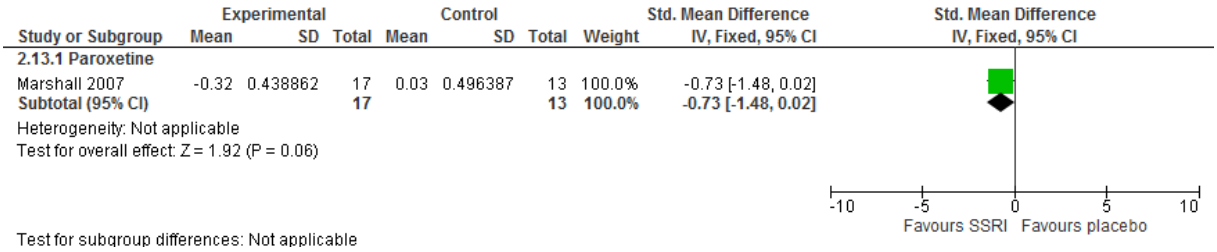


Figure 66: Sub-analysis by specific intervention: SSRI versus Placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

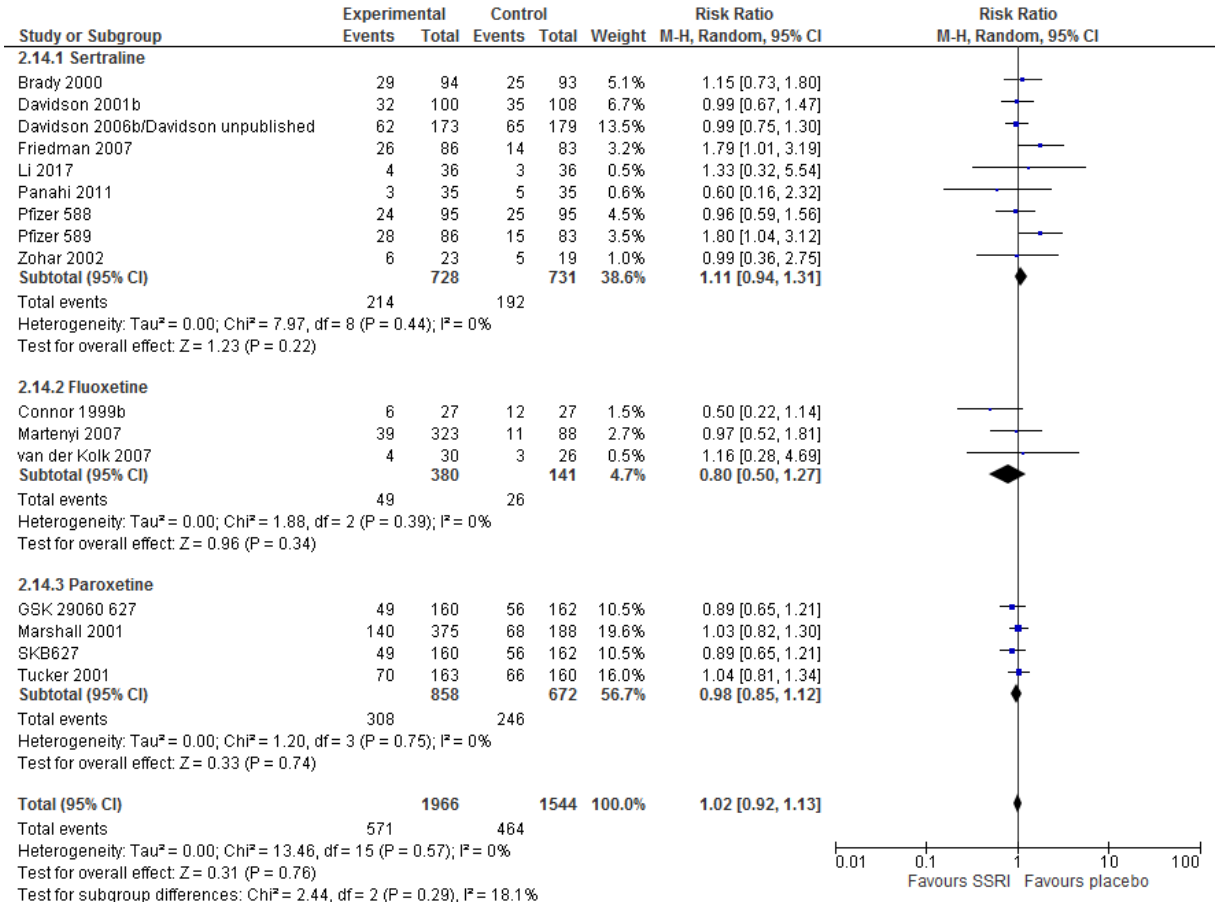
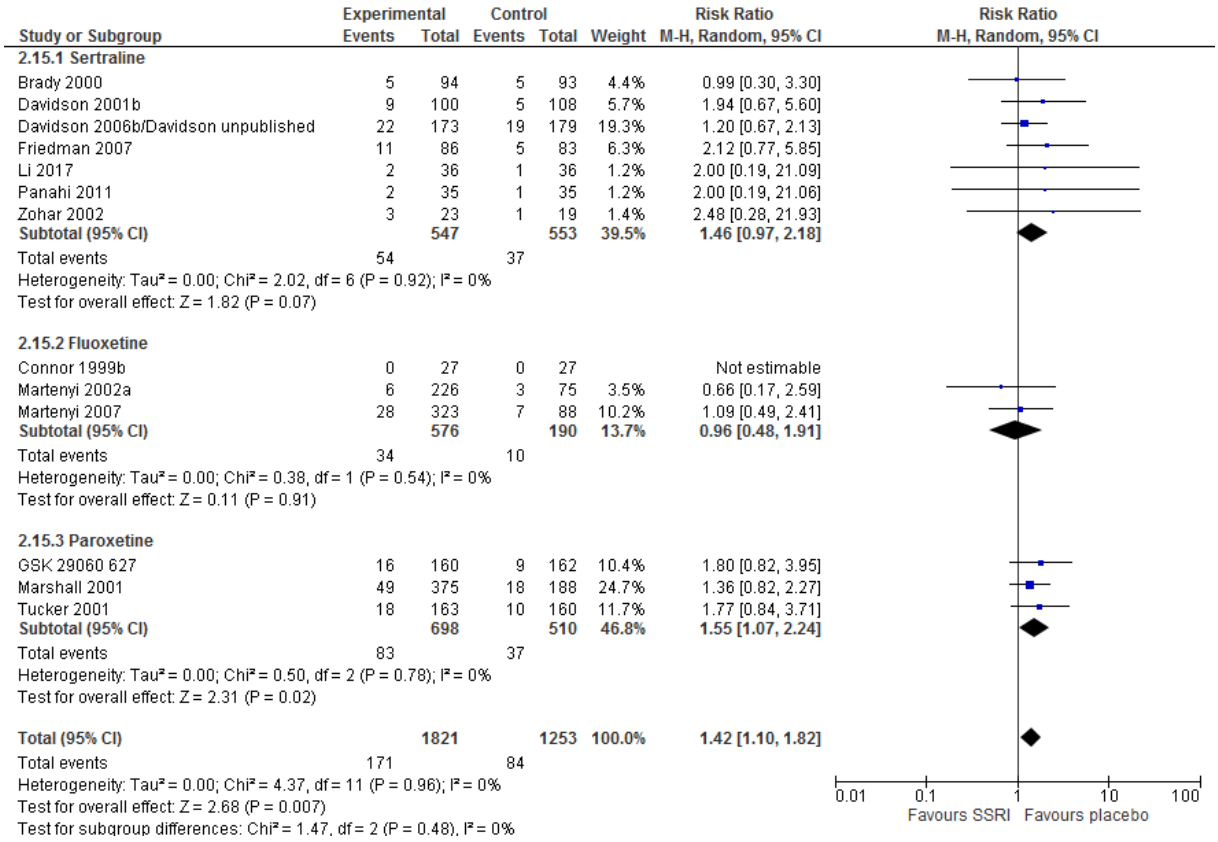


Figure 67: Sub-analysis by specific intervention: SSRI versus Placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Sertraline (+ non-trauma-focused cognitive therapy) versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 68: Sertraline (+non-trauma-focused cognitive therapy) versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score); Unclear multiplicity of index trauma

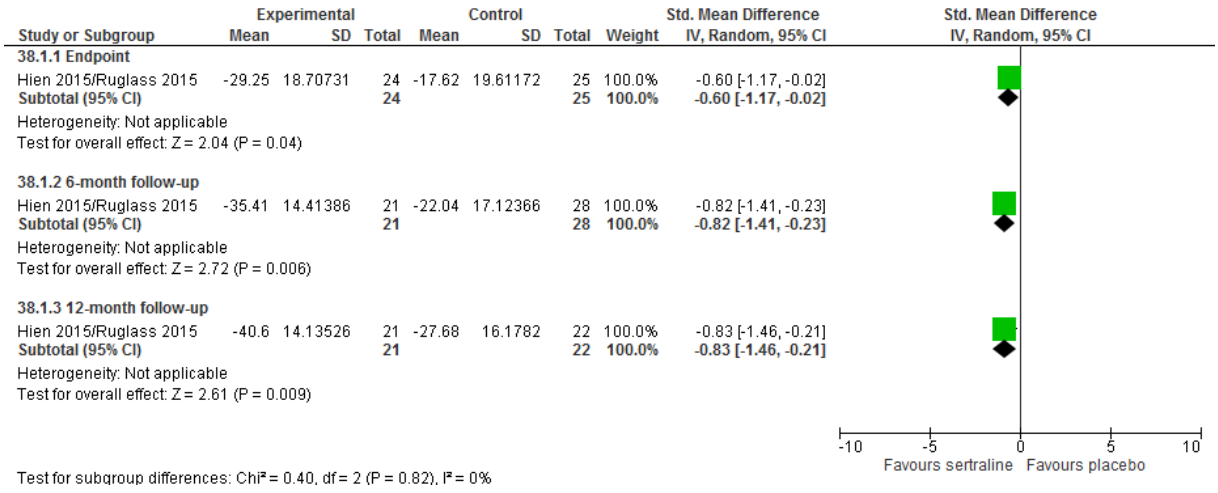


Figure 69: Sertraline (+non-trauma-focused cognitive therapy) versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people showing improvement of at least 15 points on CAPS); Unclear multiplicity of index trauma

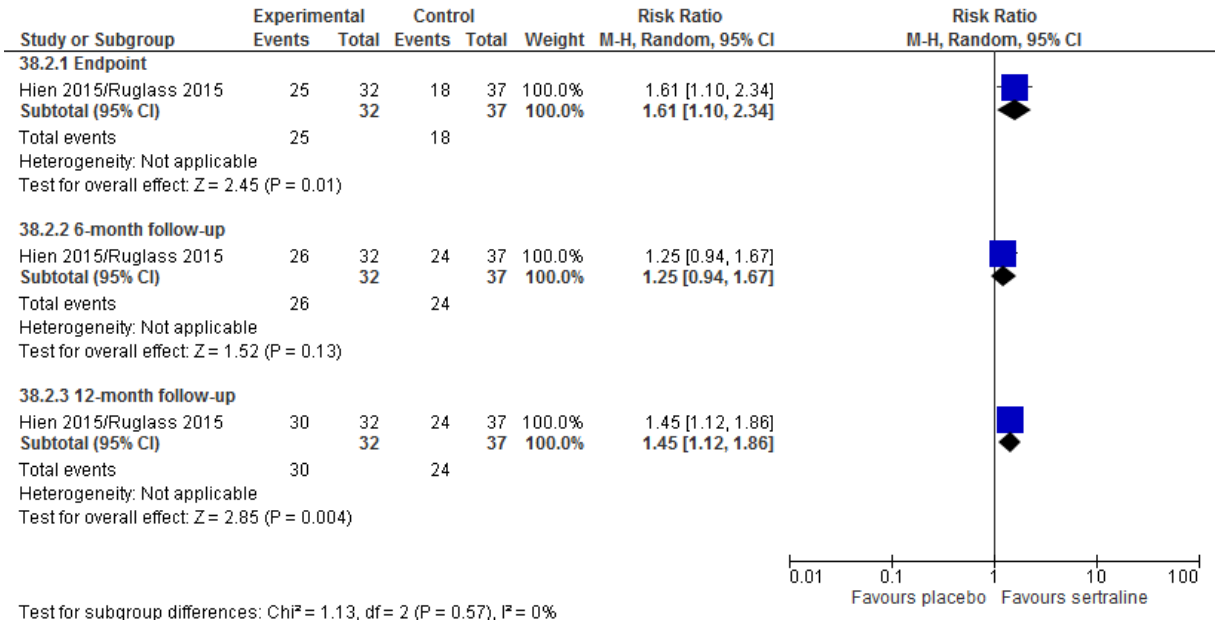


Figure 70: Sertraline (+non-trauma-focused cognitive therapy) versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Alcohol use: Number of heavy drinking days in the past 7 days (TLFB HDD; ≥5 drinks/day for men and ≥4 drinks/day for women; Change score); Unclear multiplicity of index trauma

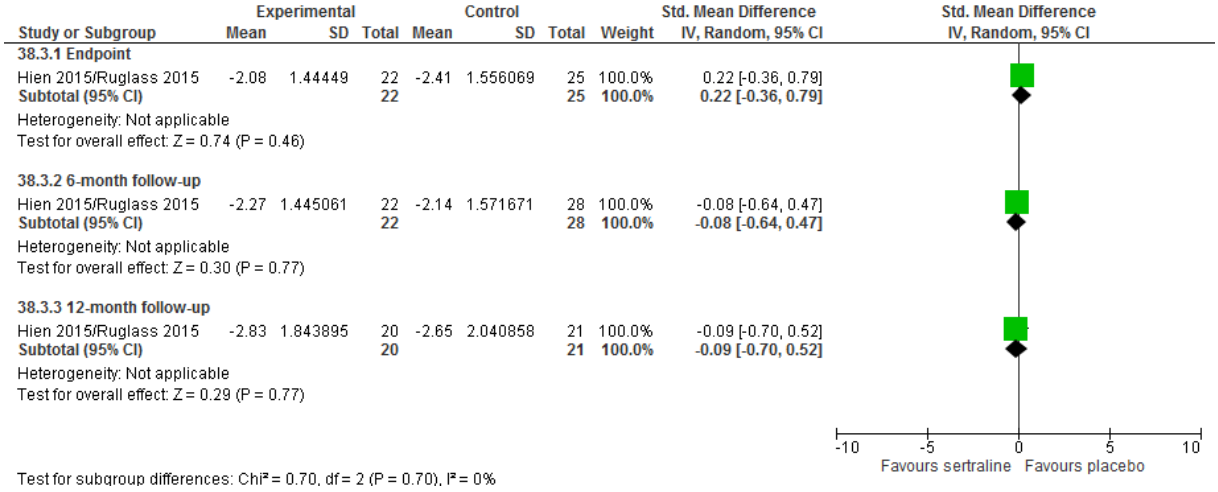


Figure 71: Sertraline (+non-trauma-focused cognitive therapy) versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Alcohol use: Drinks per drinking day (TLFB DDD; change score); Unclear multiplicity of index trauma

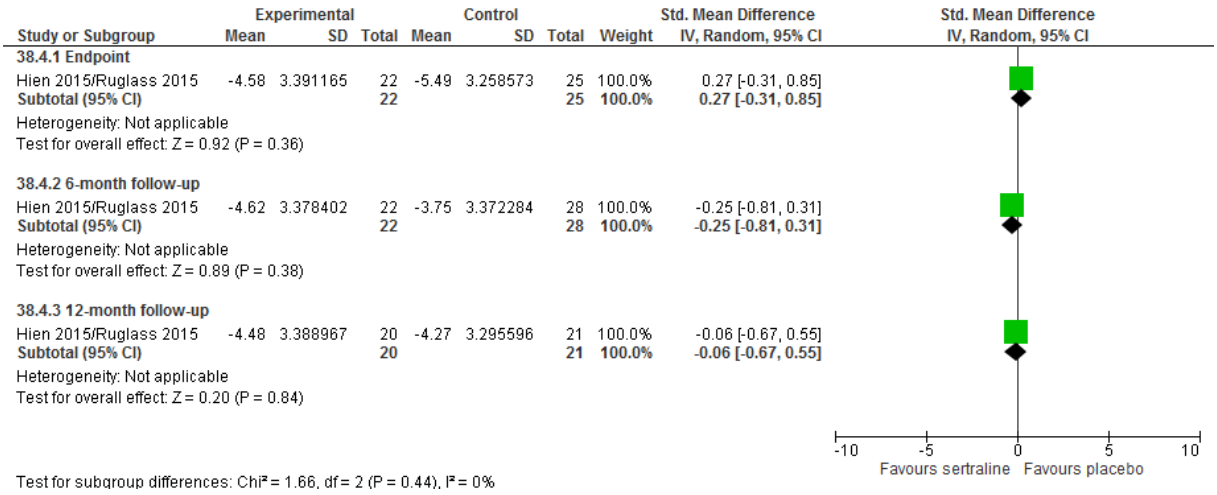


Figure 72: Sertraline (+non-trauma-focused cognitive therapy) versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Alcohol use: Number of participants abstinent from alcohol (in the prior 7 days; TLFB); Unclear multiplicity of index trauma

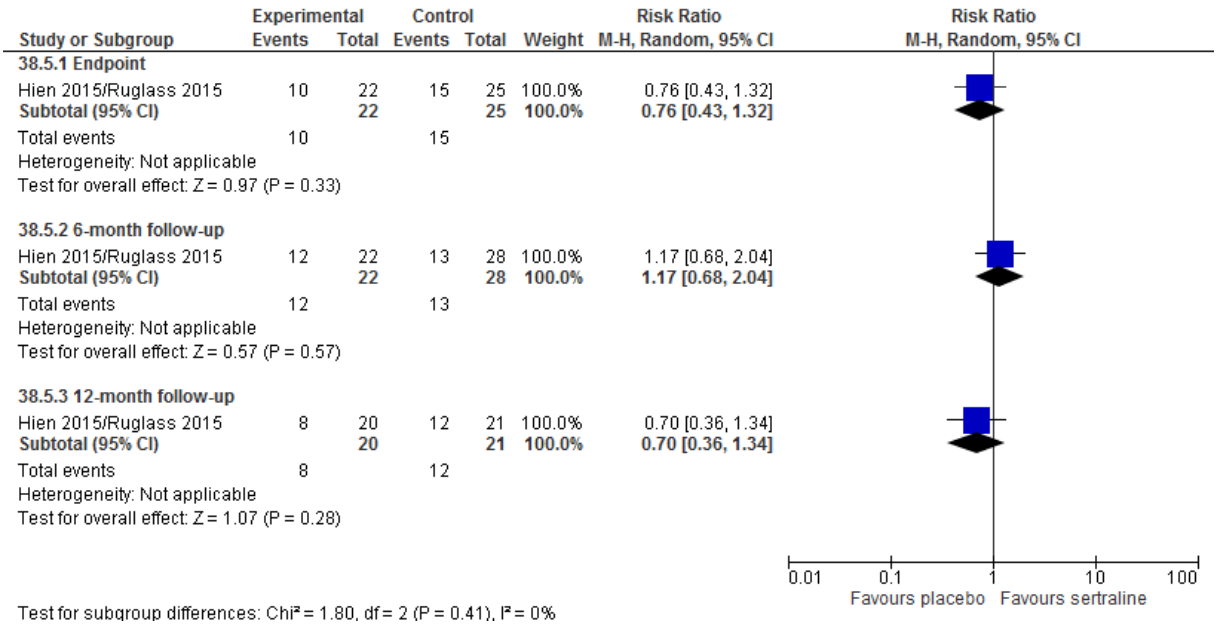


Figure 73: Sertraline (+non-trauma-focused cognitive therapy) versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

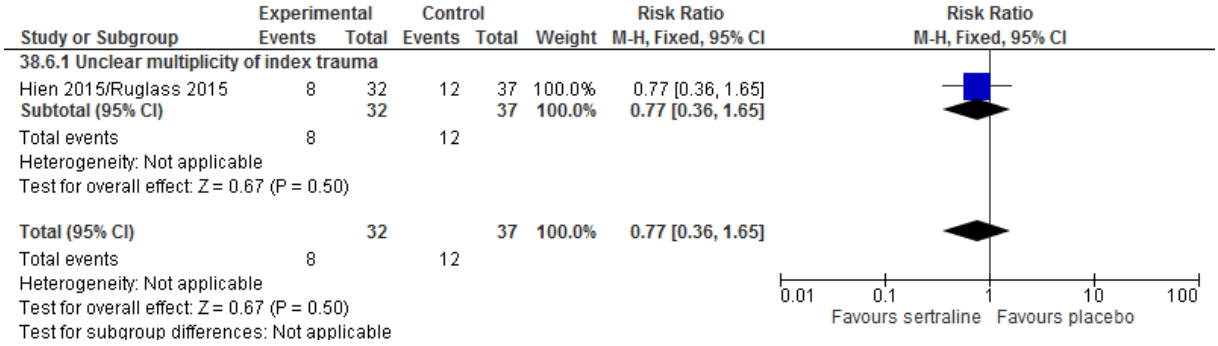
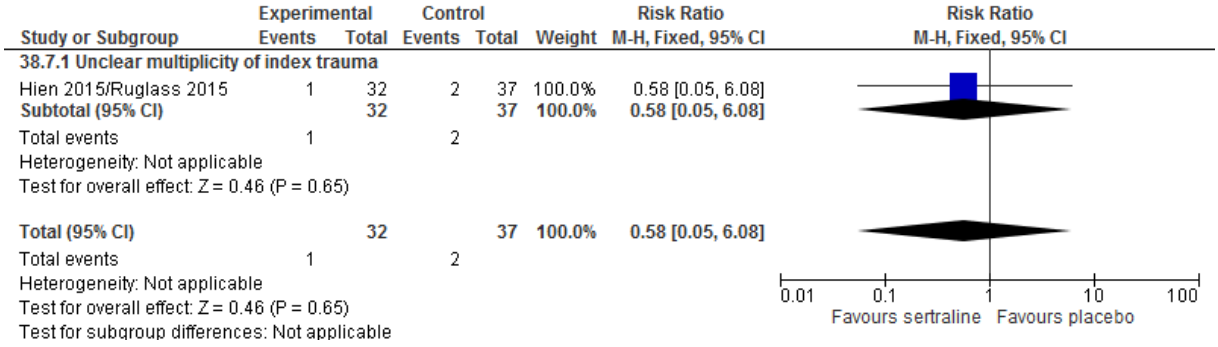


Figure 74: Sertraline (+non-trauma-focused cognitive therapy) versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



SSRI versus mirtazapine for the delayed treatment (>3 months) of clinically important PTSD symptoms

Figure 75: SSRI versus mirtazapine for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

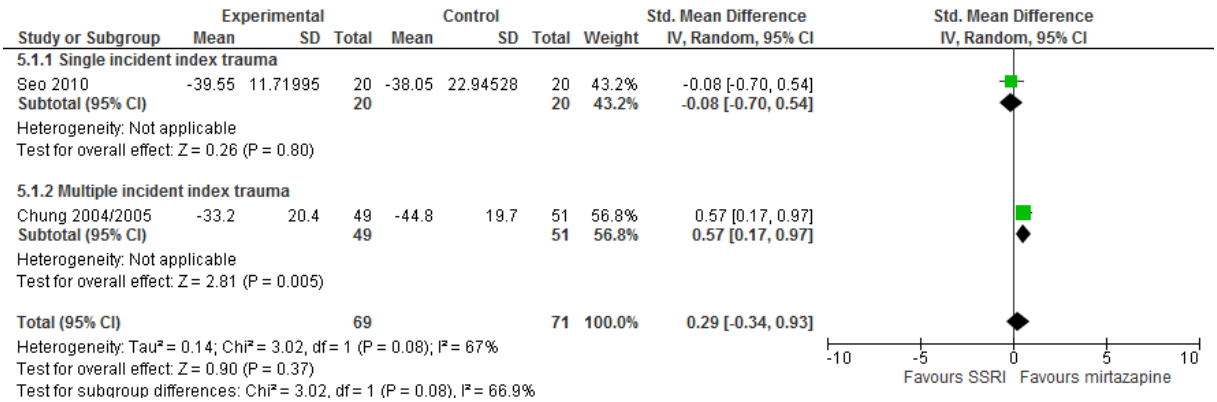


Figure 76: SSRI versus mirtazapine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people showing ≥30% improvement on CAPS)

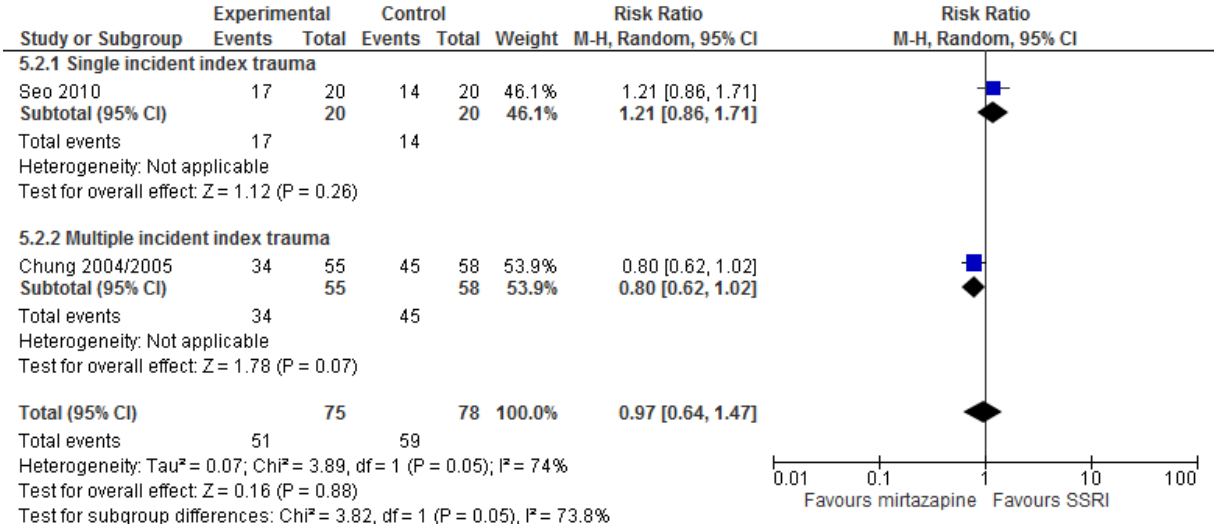


Figure 77: SSRI versus mirtazapine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (HAM-D/BDI-II change score)

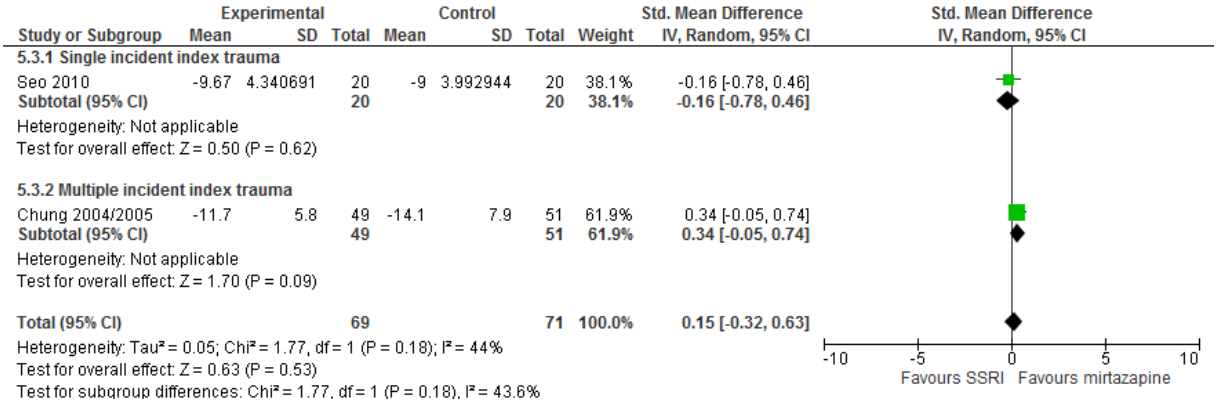


Figure 78: SSRI versus mirtazapine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

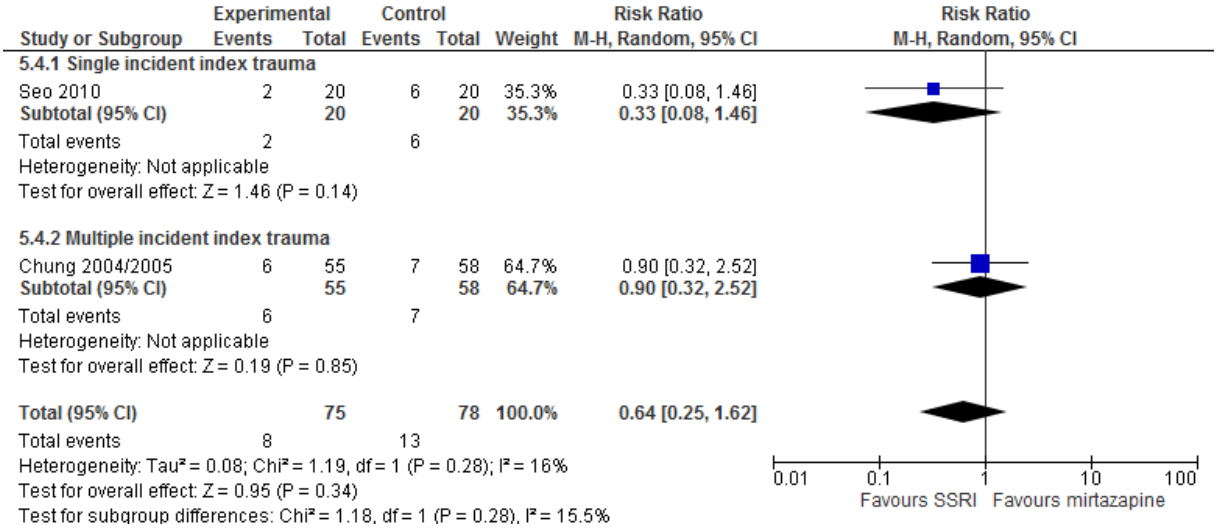
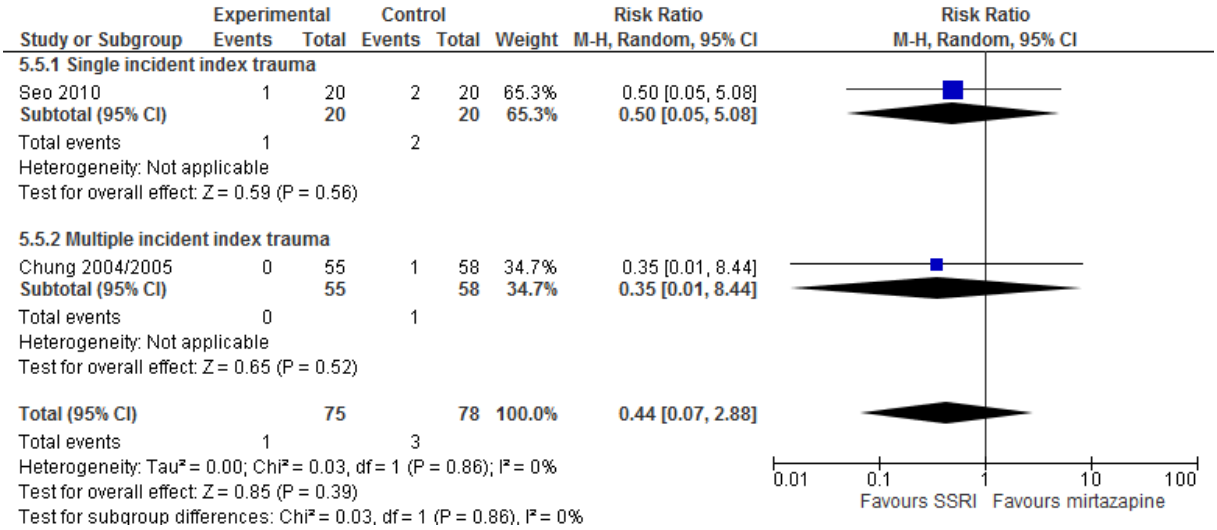


Figure 79: SSRI versus mirtazapine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Sertraline versus nefazodone for the delayed treatment (>3 months) of clinically important PTSD symptoms

Figure 80: Sertraline versus nefazodone for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (DTS change score)

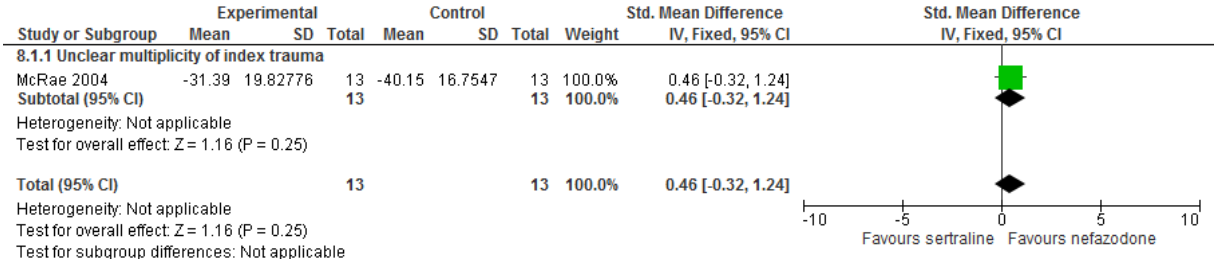


Figure 81: Sertraline versus nefazodone for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS/TOP-8 change score)

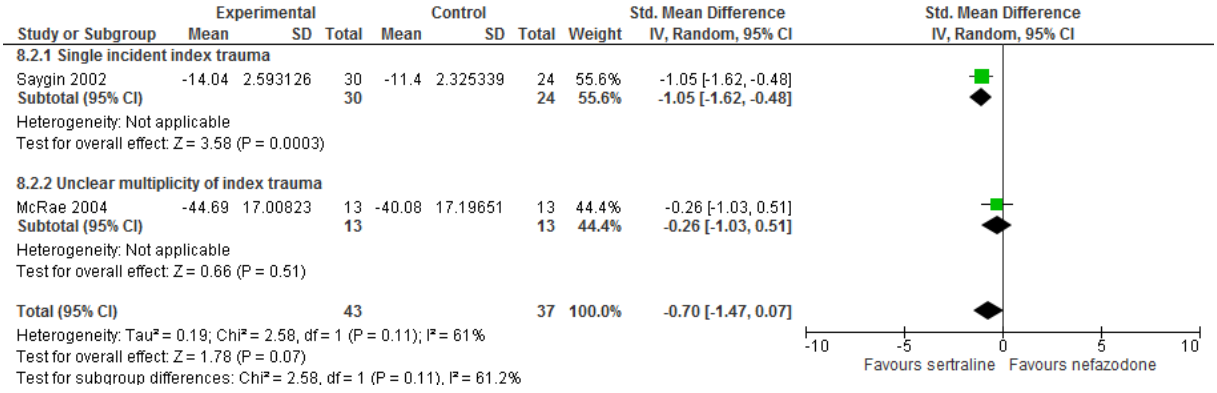


Figure 82: Sertraline versus nefazodone for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms (HAM-A change score)

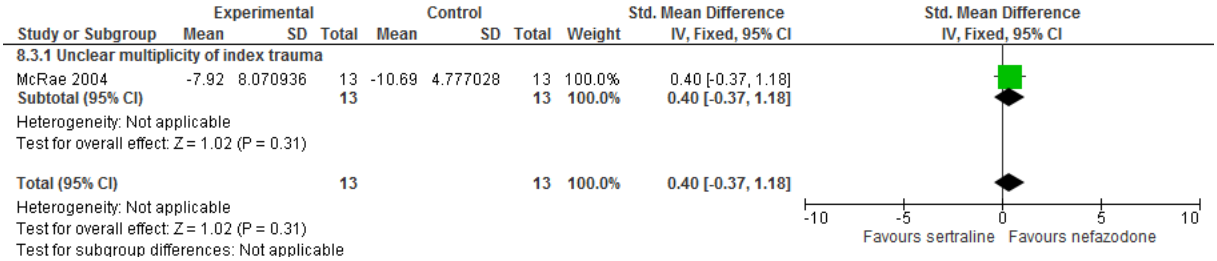


Figure 83: Sertraline versus nefazodone for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (MADRS change score)

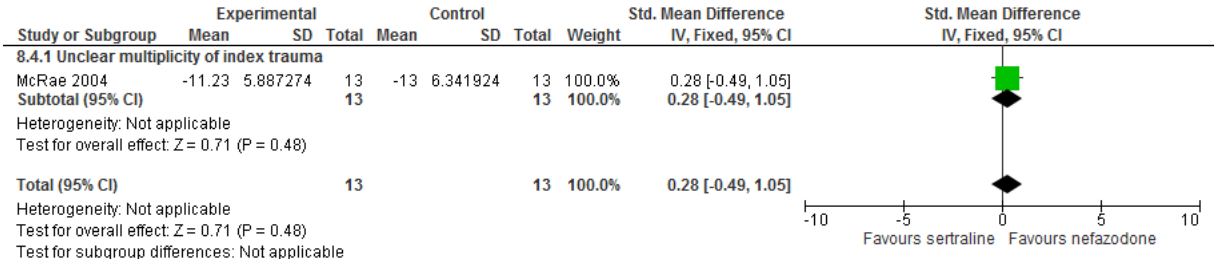


Figure 84: Sertraline versus nefazodone for the delayed treatment (>3 months) of clinically important PTSD symptoms: Functional impairment (SDS change score)

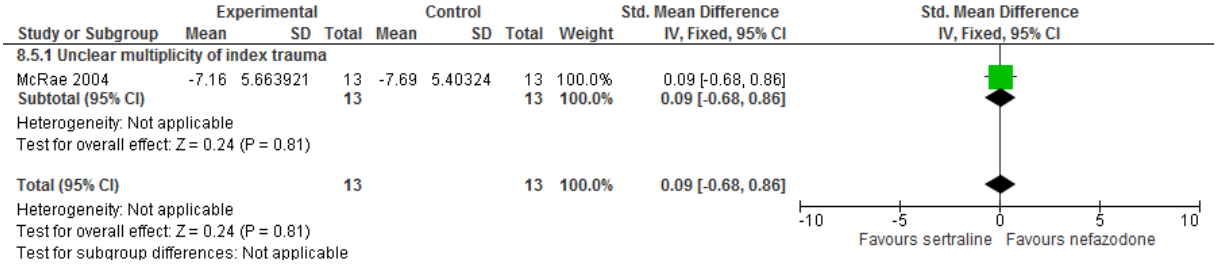


Figure 85: Sertraline versus nefazodone for the delayed treatment (>3 months) of clinically important PTSD symptoms: Sleeping difficulties (PSQI change score)

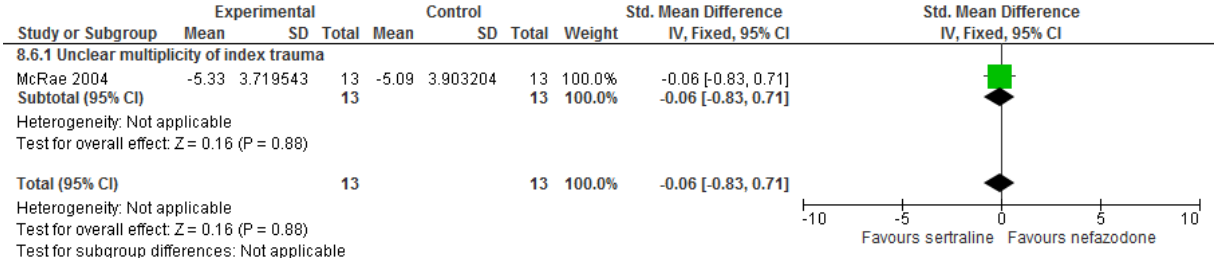


Figure 86: Sertraline versus nefazodone for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

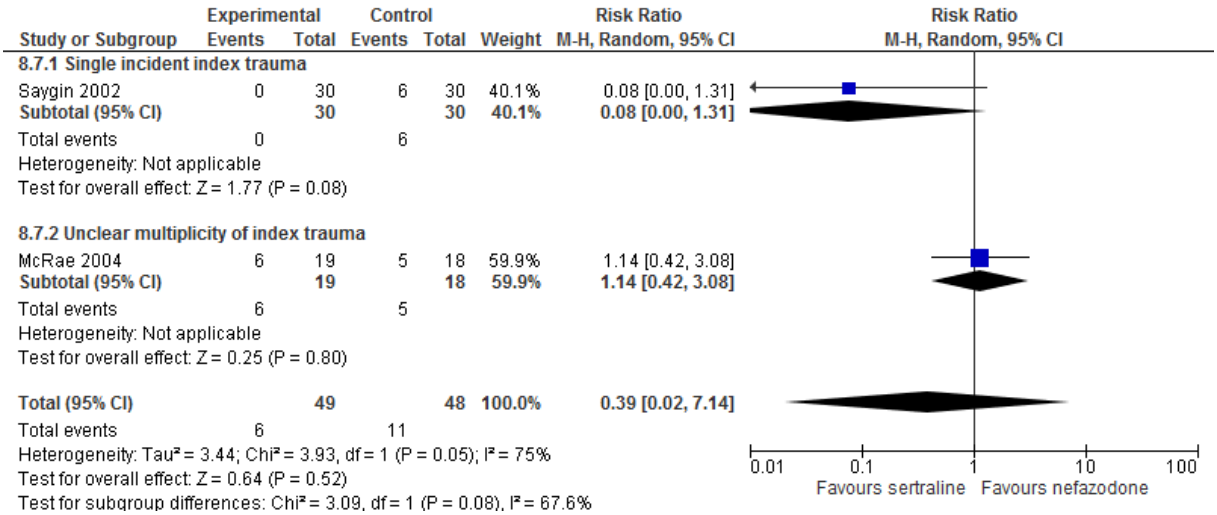
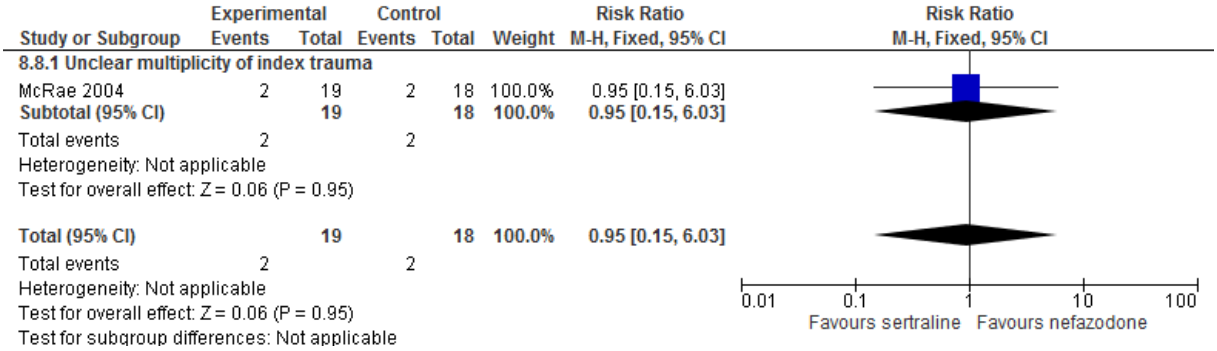


Figure 87: Sertraline versus nefazodone for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Fluoxetine versus moclobemide for the delayed treatment (>3 months) of clinically important PTSD symptoms

Figure 88: Fluoxetine versus moclobemide for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

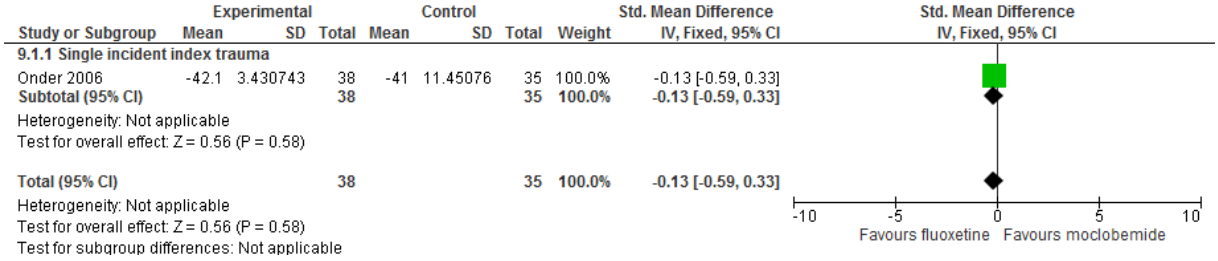


Figure 89: Fluoxetine versus moclobemide for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people showing >50% improvement on CAPS)

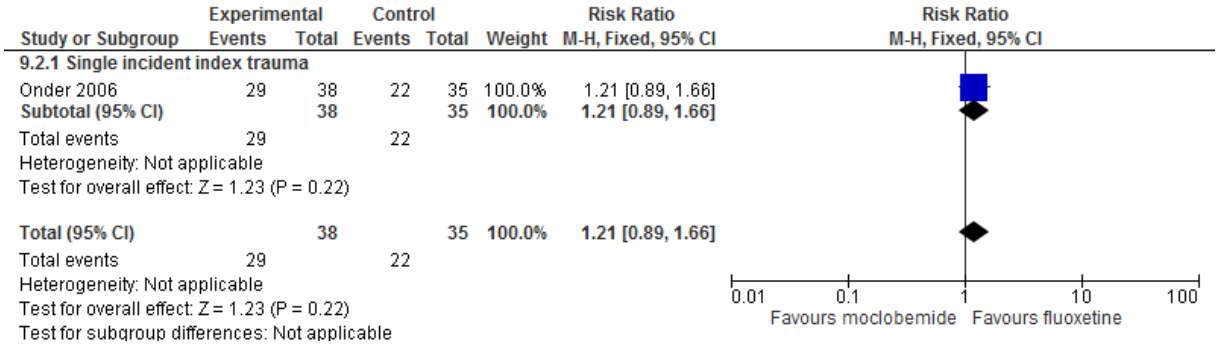


Figure 90: Fluoxetine versus moclobemide for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

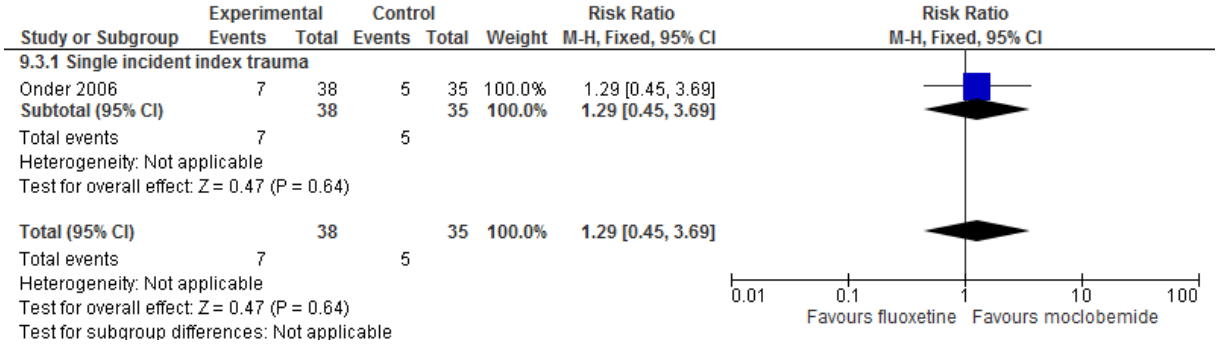
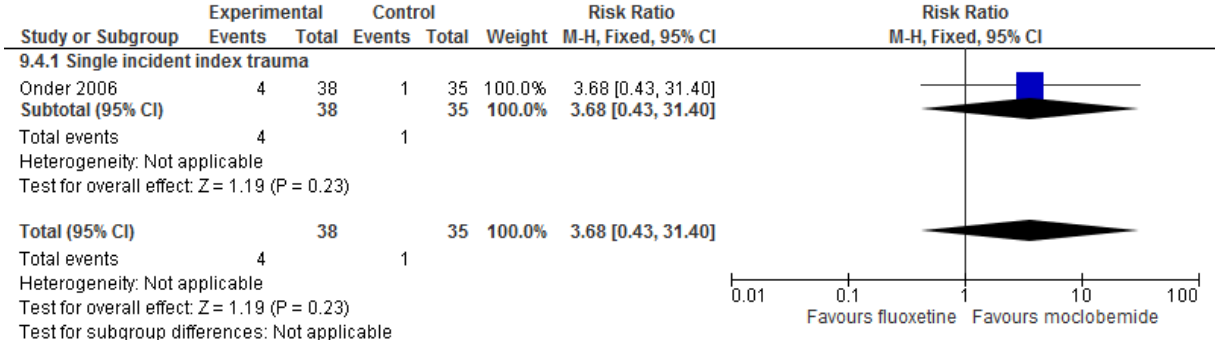


Figure 91: Fluoxetine versus moclobemide for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Fluoxetine versus tianeptine for the delayed treatment (>3 months) of clinically important PTSD symptoms

Figure 92: Fluoxetine versus tianeptine for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

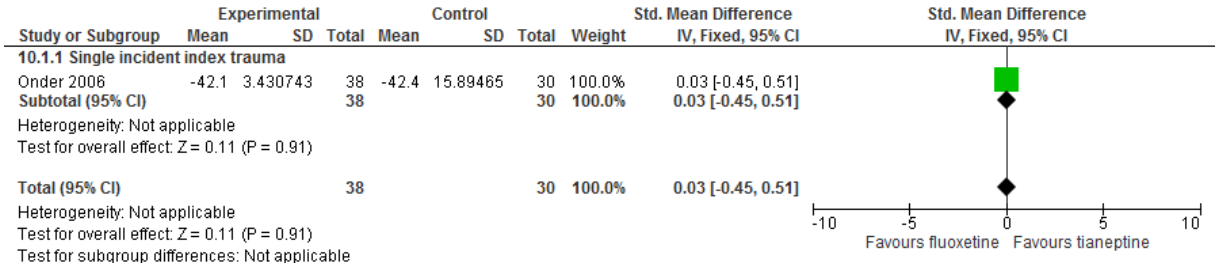


Figure 93: Fluoxetine versus tianeptine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people showing >50% improvement on CAPS)

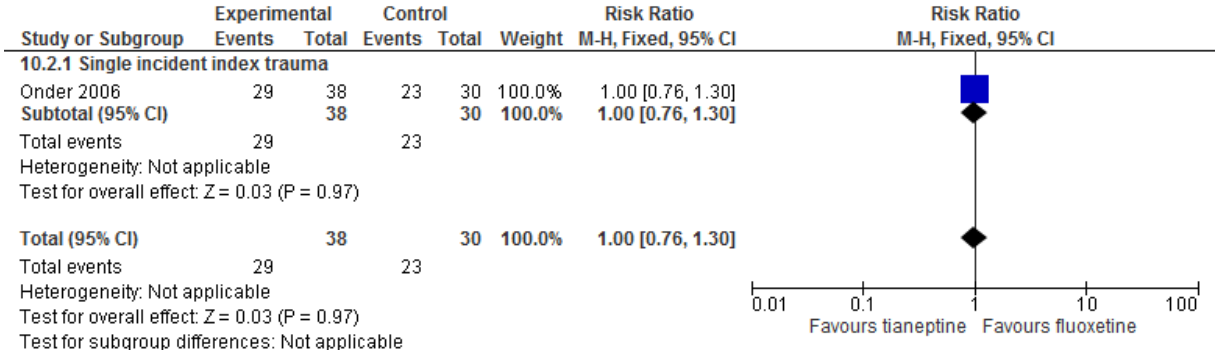


Figure 94: Fluoxetine versus tianeptine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

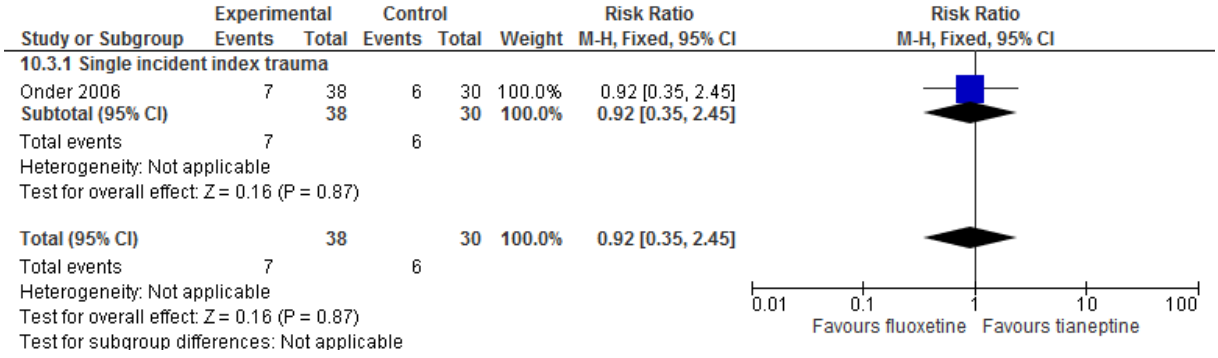
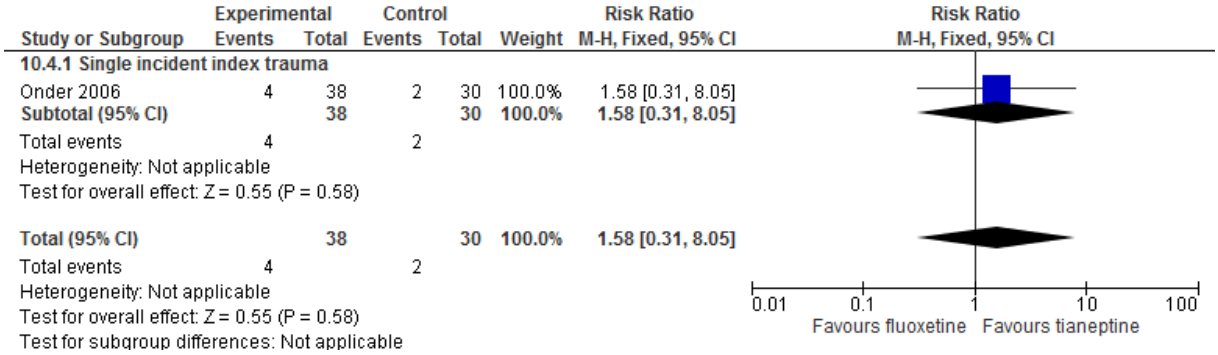


Figure 95: Fluoxetine versus tianeptine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Fluoxetine versus reboxetine for the delayed treatment (>3 months) of clinically important PTSD symptoms

Figure 96: Fluoxetine versus reboxetine for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

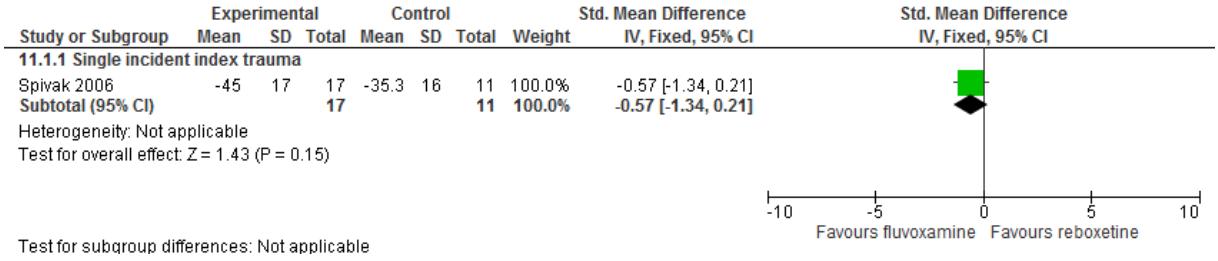


Figure 97: Fluoxetine versus reboxetine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms (HAM-A change score)

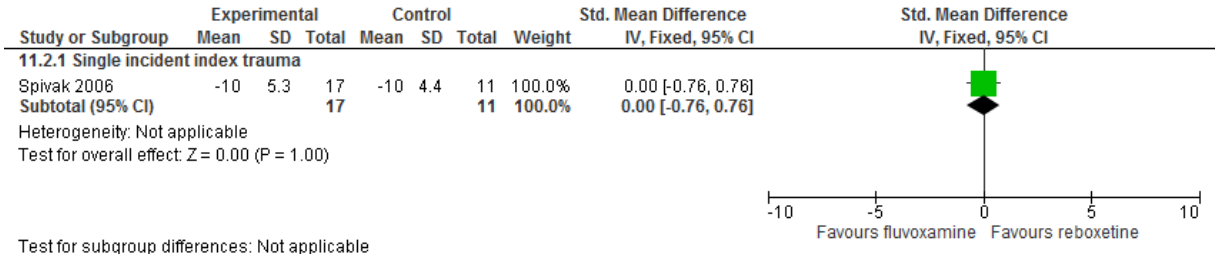


Figure 98: Fluoxetine versus reboxetine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (HAM-D change score)

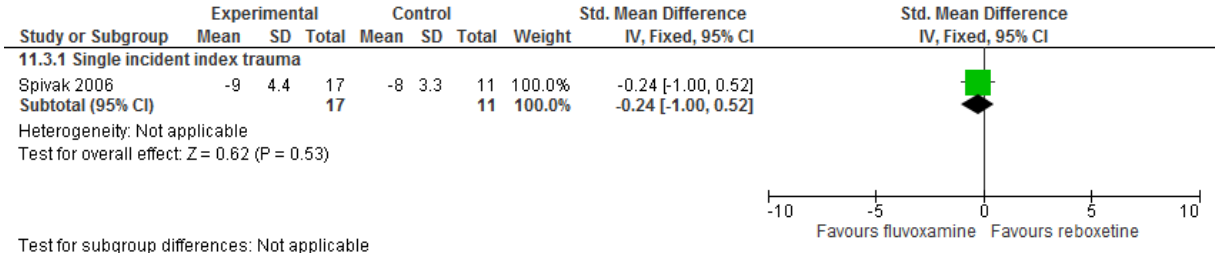
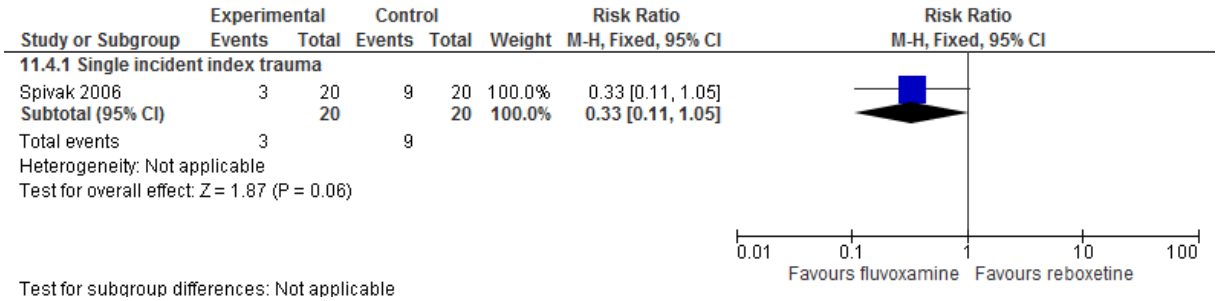


Figure 99: Fluoxetine versus reboxetine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)



Sertraline versus venlafaxine for treatment of PTSD for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 100: Sertraline versus venlafaxine for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (DTS change score)

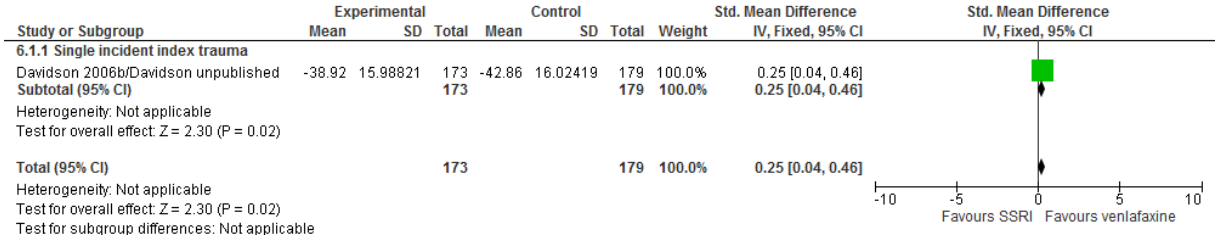


Figure 101: Sertraline versus venlafaxine for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

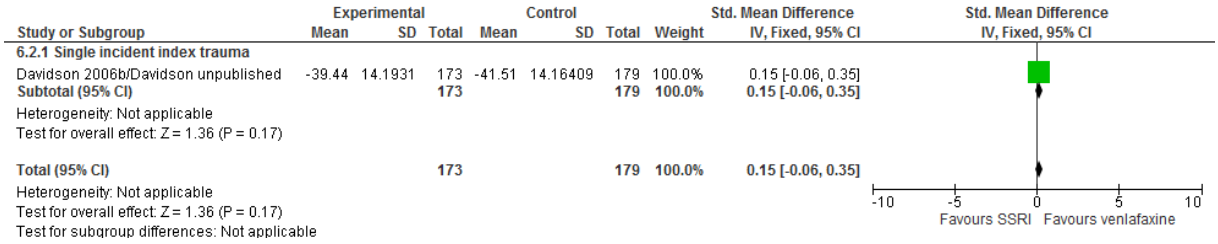


Figure 102: Sertraline versus venlafaxine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Remission (number of people scoring <20 on CAPS)

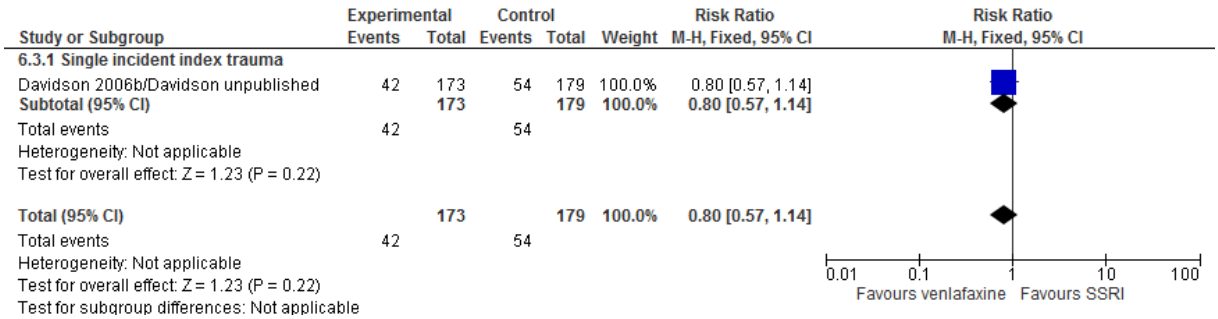


Figure 103: Sertraline versus venlafaxine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (HAM-D change score)

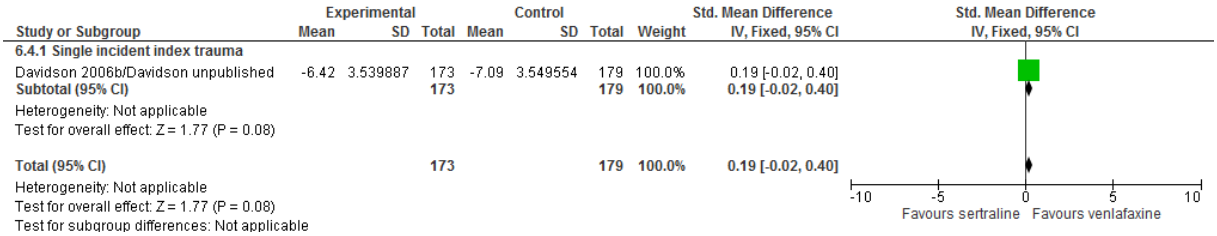


Figure 104: Sertraline versus venlafaxine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Functional impairment (SDS change score)

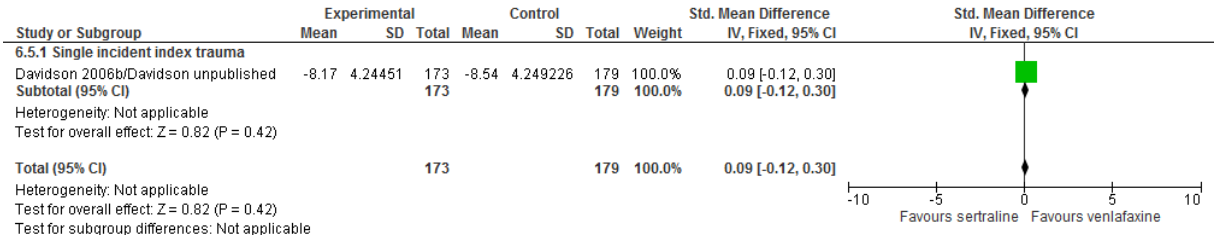


Figure 105: Sertraline versus venlafaxine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Global functioning (GAF change score)

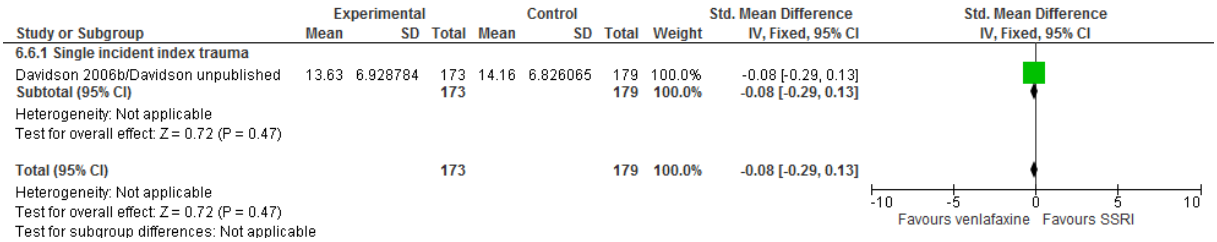


Figure 106: Sertraline versus venlafaxine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Quality of life (Q-LES-Q-SF change score)

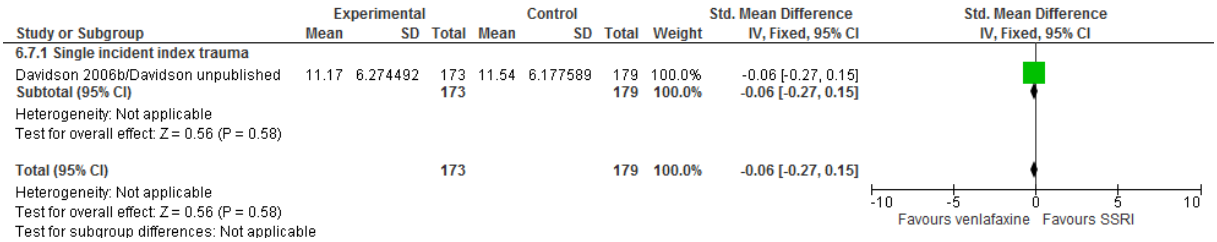


Figure 107: Sertraline versus venlafaxine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

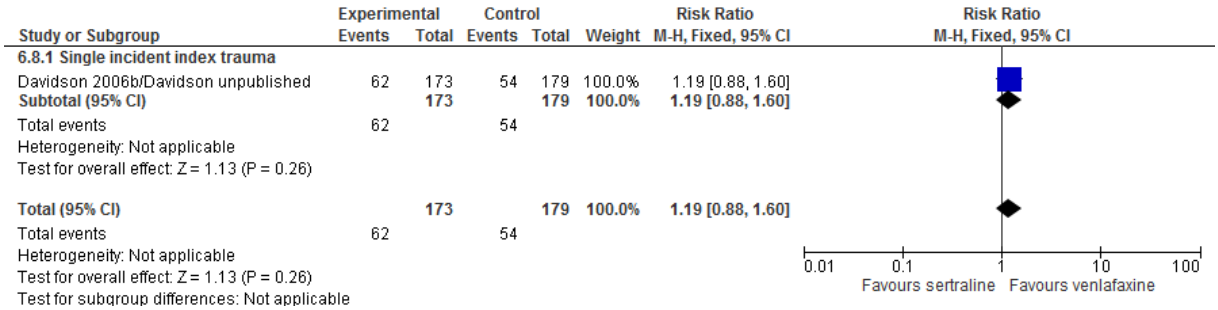
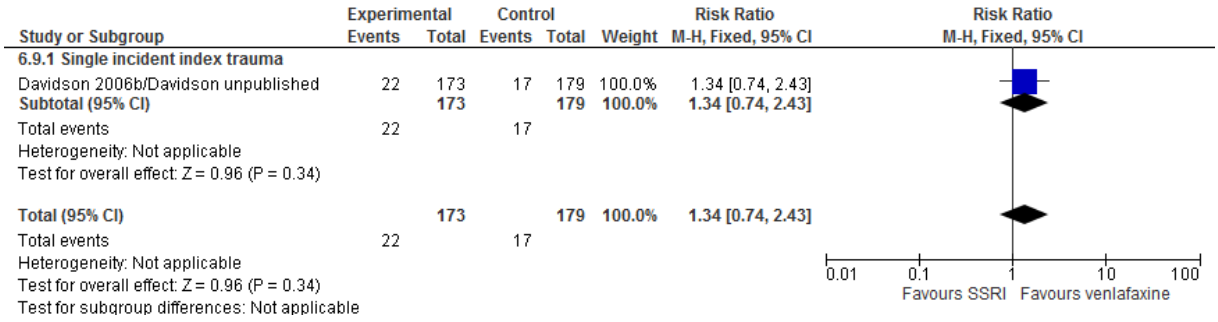


Figure 108: Sertraline versus venlafaxine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Sertraline (+ trauma-focused CBT) versus venlafaxine (+ trauma-focused CBT) for the delayed treatment (>3 months) of clinically important PTSD symptoms

Figure 109: Sertraline (+trauma-focused CBT) versus venlafaxine (+trauma-focused CBT) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (HTQ change score)

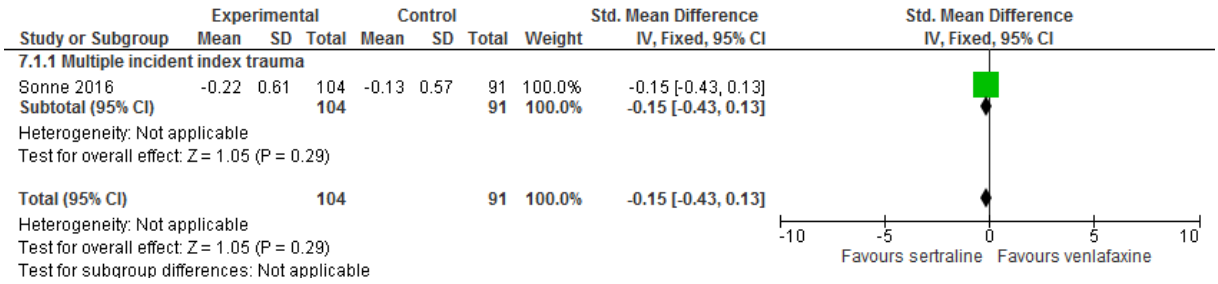


Figure 110: Sertraline (+trauma-focused CBT) versus venlafaxine (+trauma-focused CBT) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms (HAM-A change score)

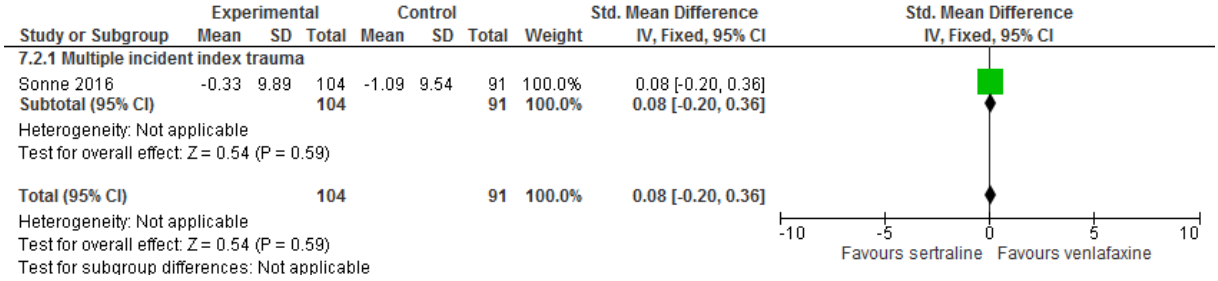


Figure 111: Sertraline (+trauma-focused CBT) versus venlafaxine (+trauma-focused CBT) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (HAM-D change score)

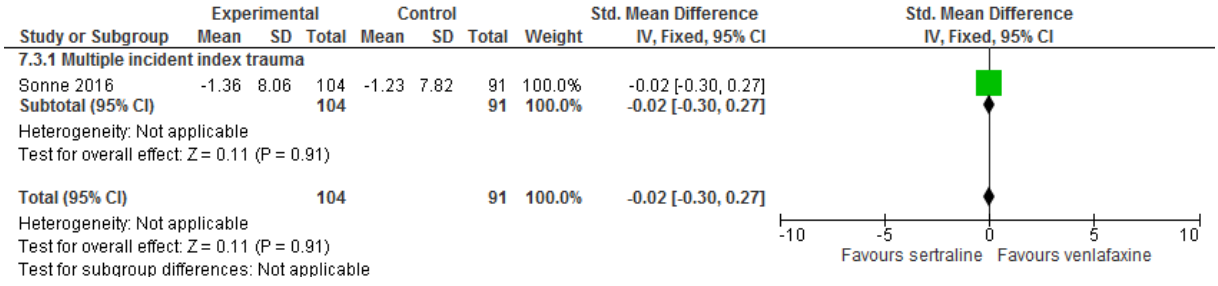


Figure 112: Sertraline (+trauma-focused CBT) versus venlafaxine (+trauma-focused CBT) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Functional impairment (SDS change score)

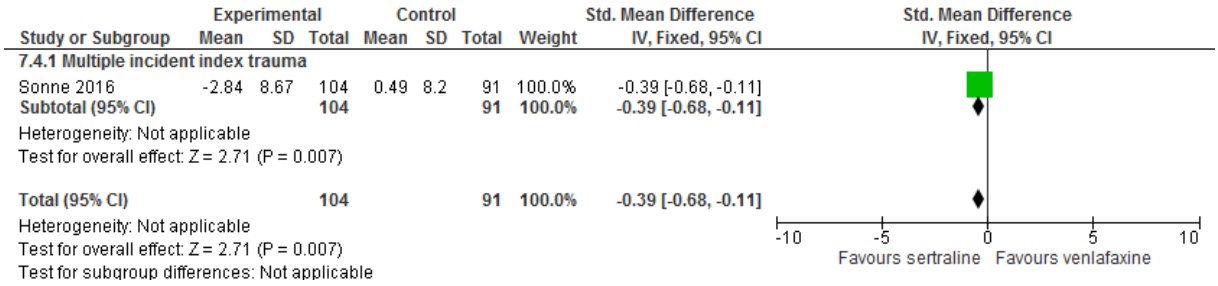


Figure 113: Sertraline (+trauma-focused CBT) versus venlafaxine (+trauma-focused CBT) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Quality of life (WHO-5 change score)

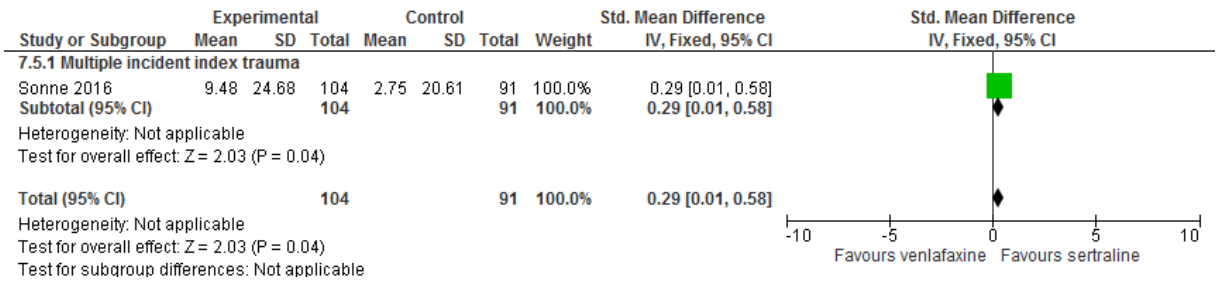
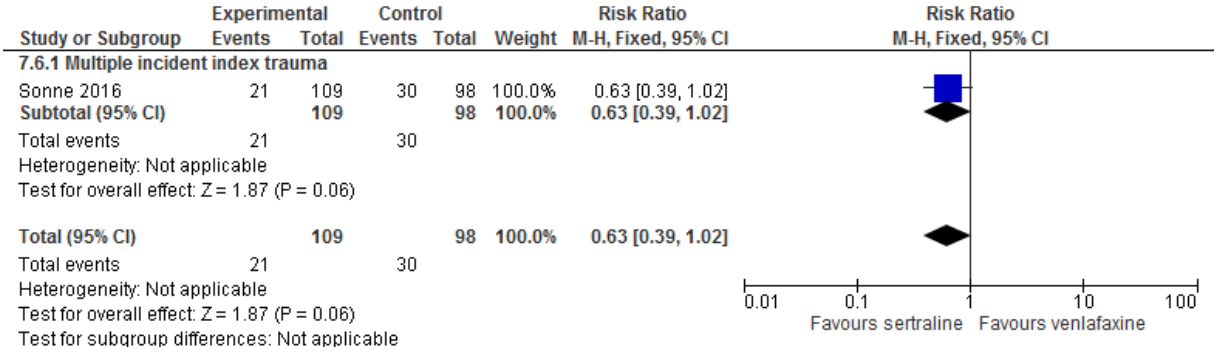


Figure 114: Sertraline (+trauma-focused CBT) versus venlafaxine (+trauma-focused CBT) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)



Paroxetine versus amitriptyline for the delayed treatment (>3 months) of clinically important PTSD symptoms

Figure 115: Paroxetine versus amitriptyline for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

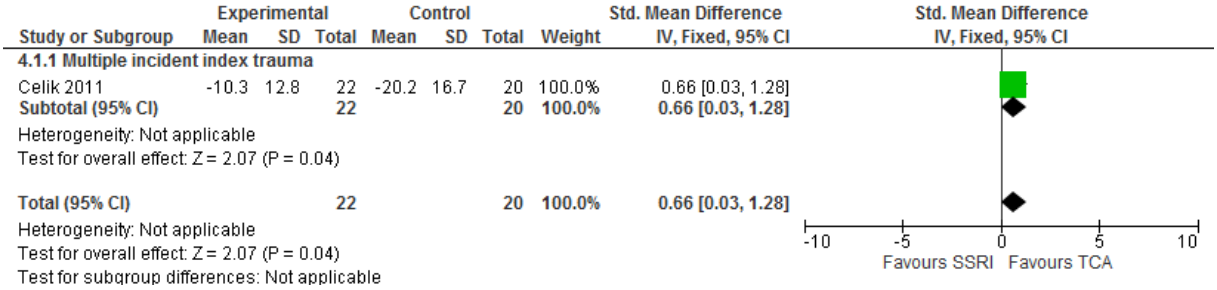


Figure 116: Paroxetine versus amitriptyline for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people showing ≥30% improvement on CAPS & CGI-I much or very much improved)

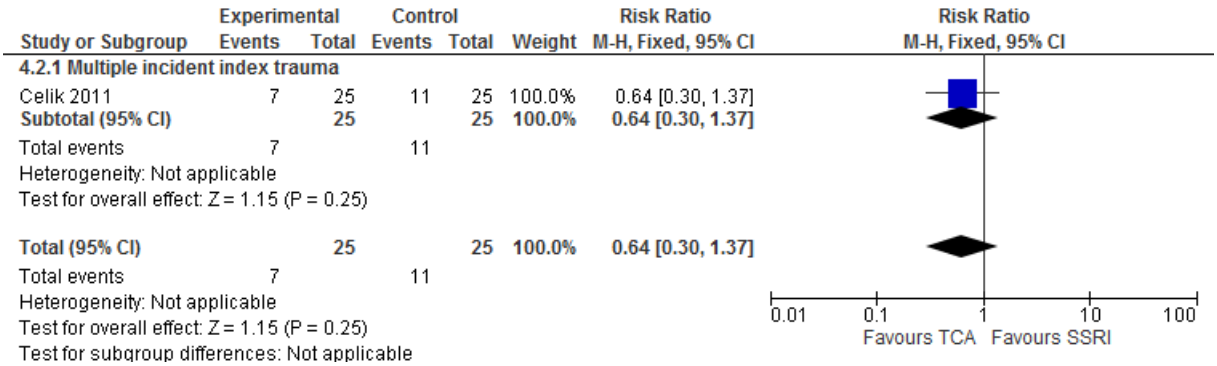


Figure 117: Paroxetine versus amitriptyline for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms (BAI change score)

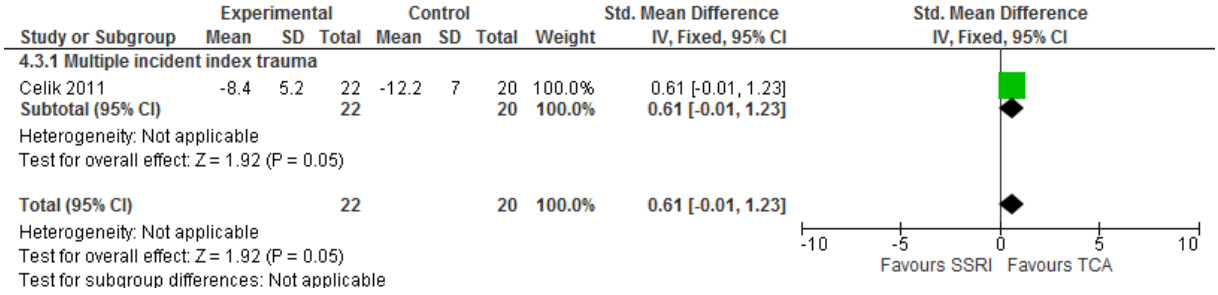


Figure 118: Paroxetine versus amitriptyline for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (BDI change score)

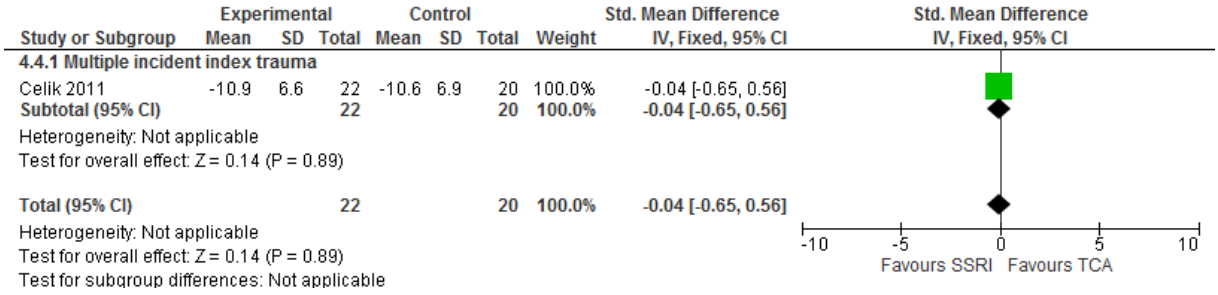


Figure 119: Paroxetine versus amitriptyline for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

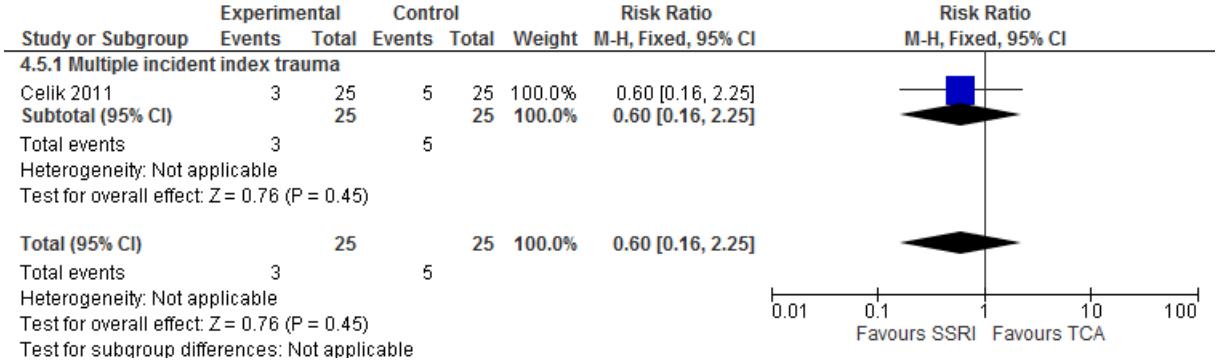
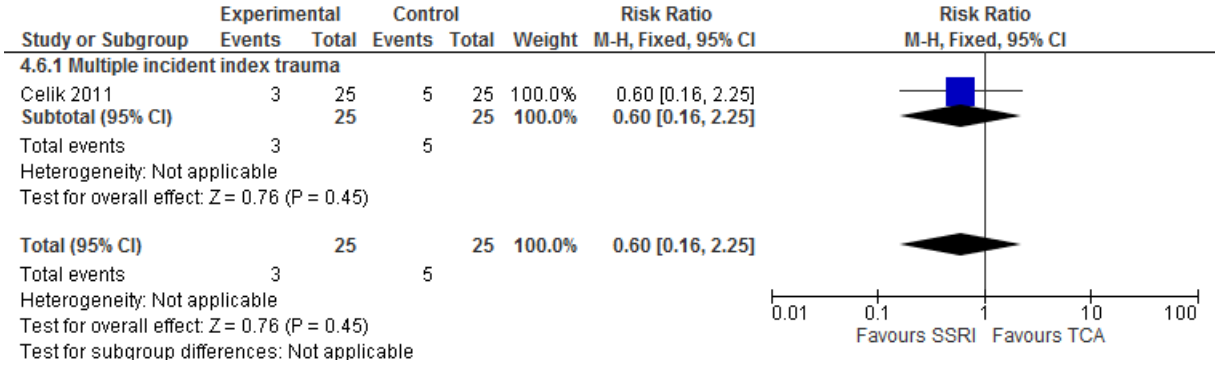


Figure 120: Paroxetine versus amitriptyline for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



SSRI versus placebo for maintenance treatment of PTSD symptoms

Figure 121: SSRI versus placebo for maintenance treatment of PTSD symptoms: Relapse

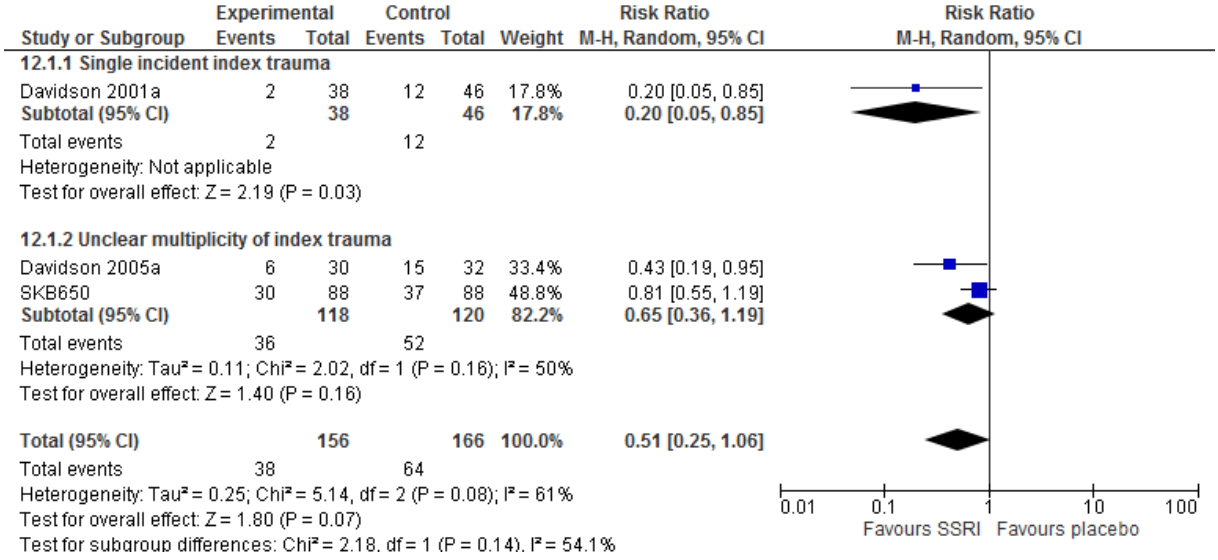


Figure 122: SSRI versus placebo for maintenance treatment of PTSD symptoms: PTSD symptomatology self-rated (DTS change score)

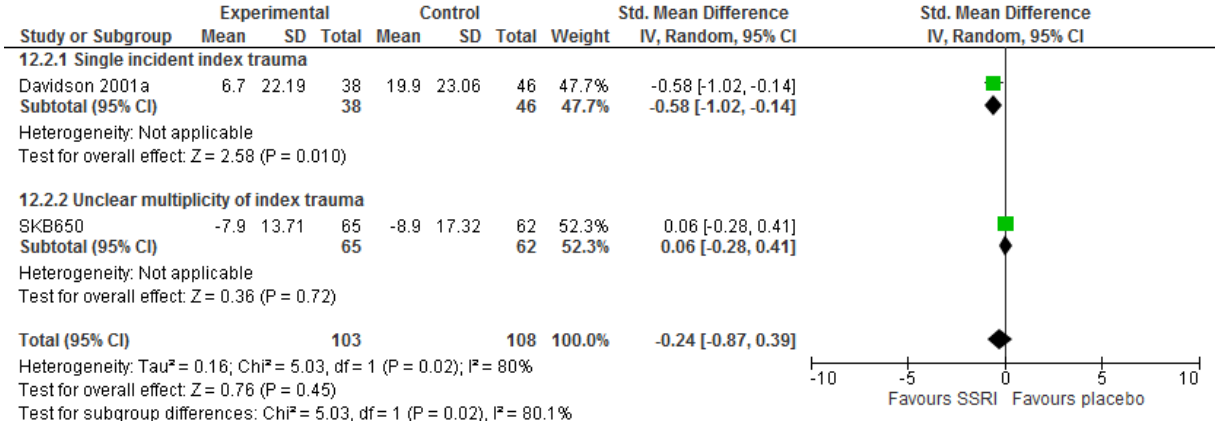


Figure 123: SSRI versus placebo for maintenance treatment of PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

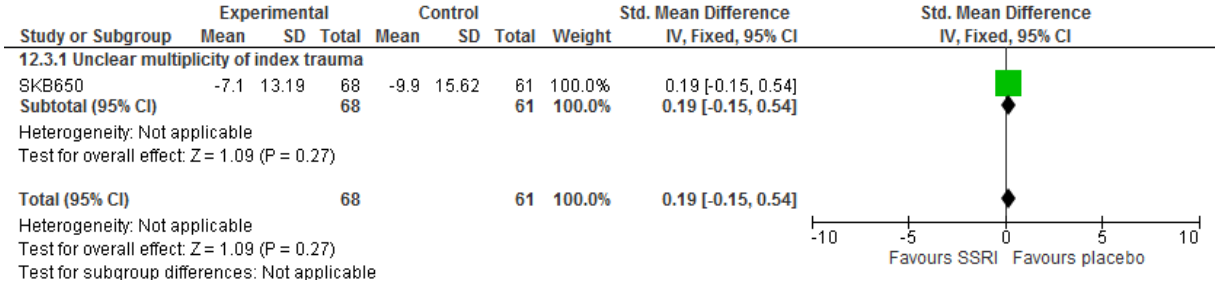


Figure 124: SSRI versus placebo for maintenance treatment of PTSD symptoms: Depression symptoms (HAM-D change score)

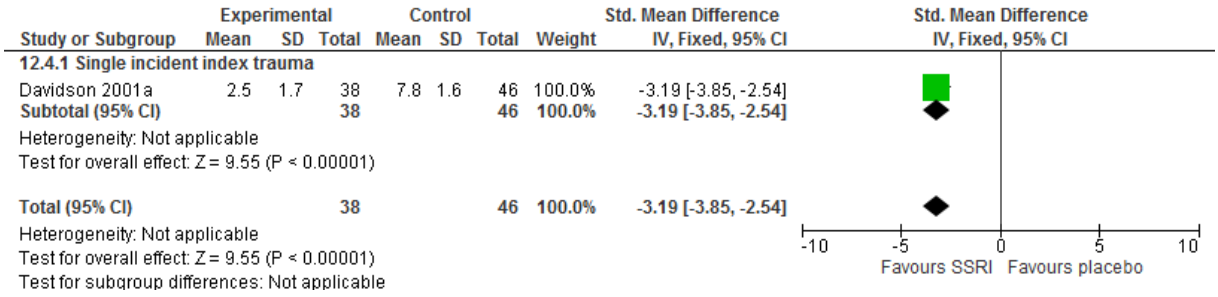


Figure 125: SSRI versus placebo for maintenance treatment of PTSD symptoms: Quality of life (Q-LES-Q-SF change score)

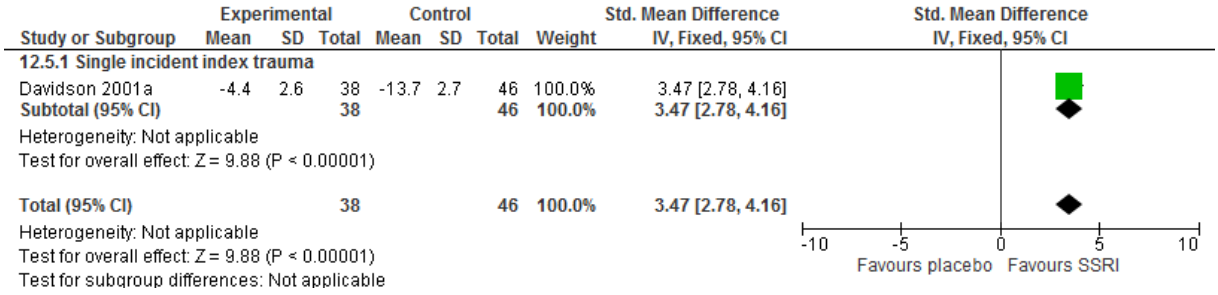


Figure 126: SSRI versus placebo for maintenance treatment of PTSD symptoms: Discontinuation due to any reason (including adverse events)

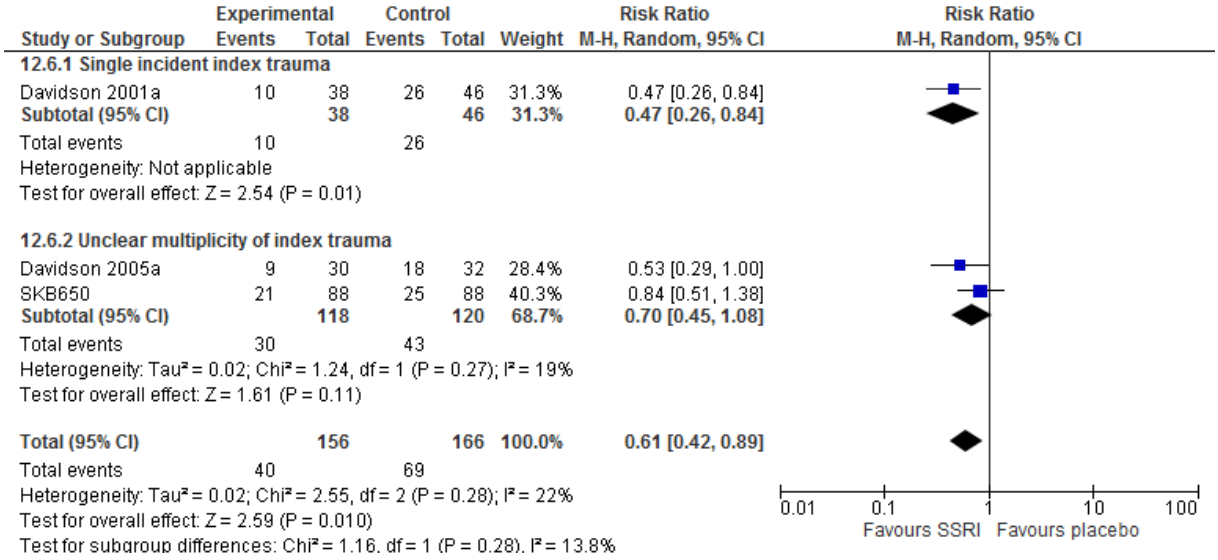
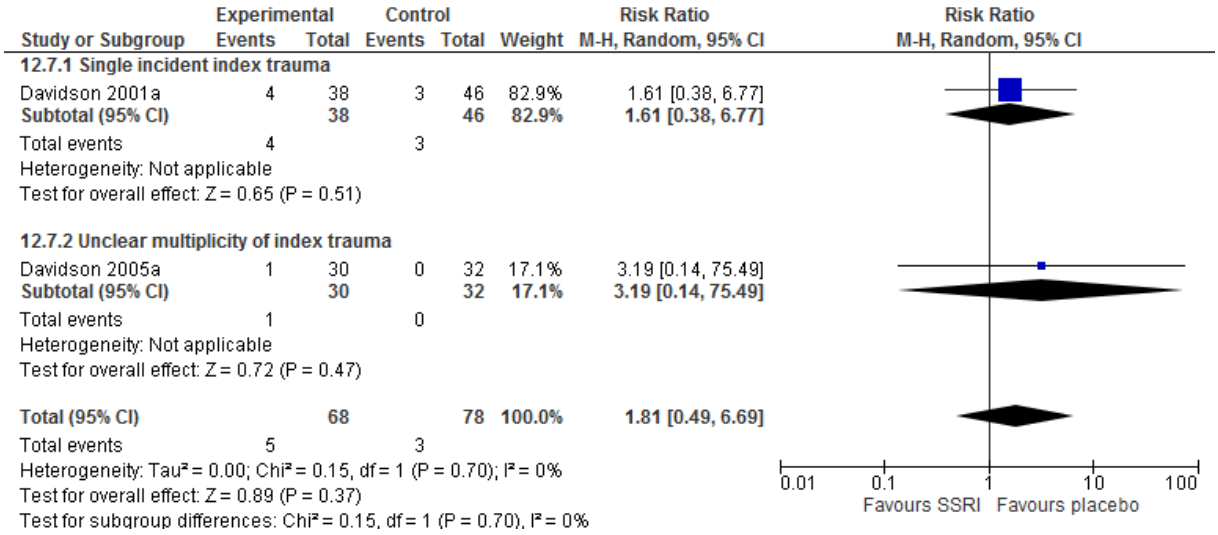


Figure 127: SSRI versus placebo for maintenance treatment of PTSD symptoms: Discontinuation due to adverse events



SSRI + trauma-focused CBT versus trauma-focused CBT (±placebo) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 128: SSRI + trauma-focused CBT versus trauma-focused CBT (±placebo) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated at endpoint (HTQ/PDS change score)

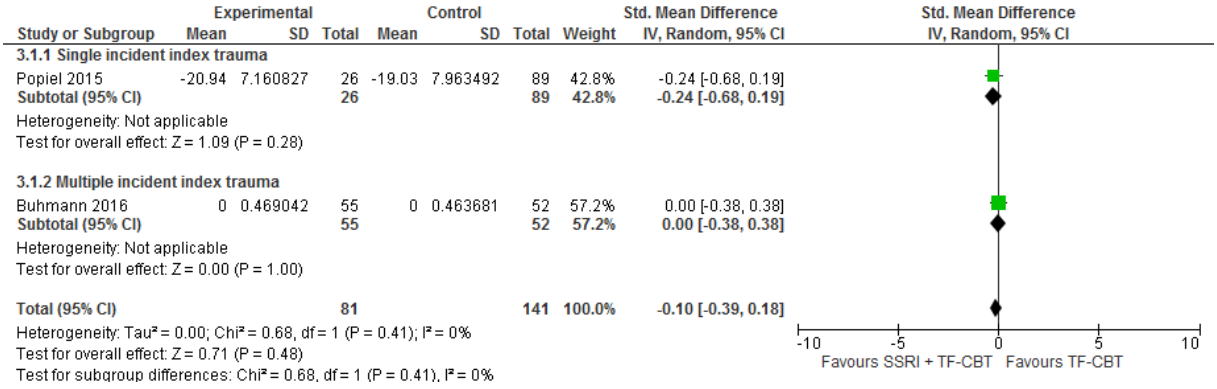


Figure 129: SSRI + trauma-focused CBT versus trauma-focused CBT (±placebo) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated at 1-year follow-up (PDS change score)

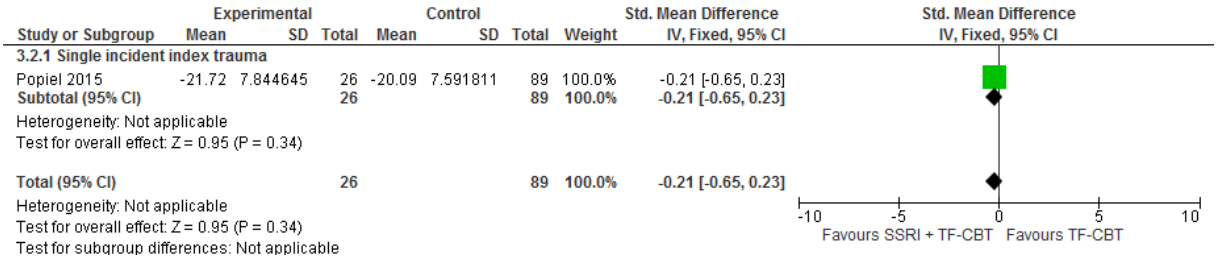


Figure 130: SSRI + trauma-focused CBT versus trauma-focused CBT (±placebo) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS/SI–PTSD change score)

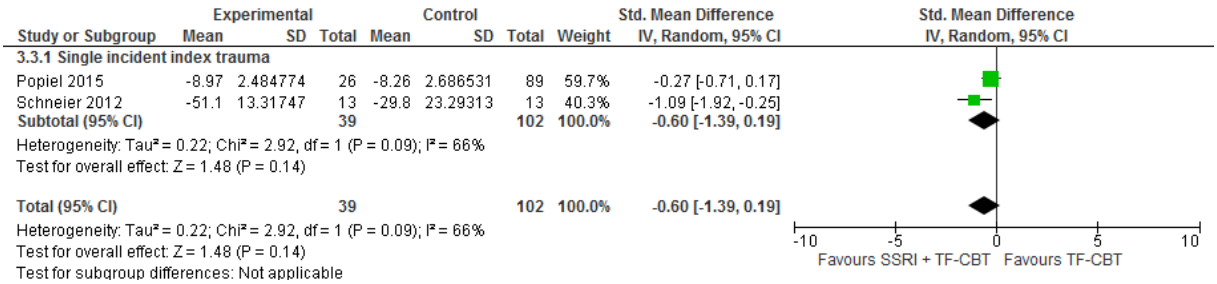


Figure 131: SSRI + trauma-focused CBT versus trauma-focused CBT (±placebo) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Remission (number of people no longer meeting diagnostic criteria for PTSD/scoring ≤20 on CAPS & CGI-I score=1)

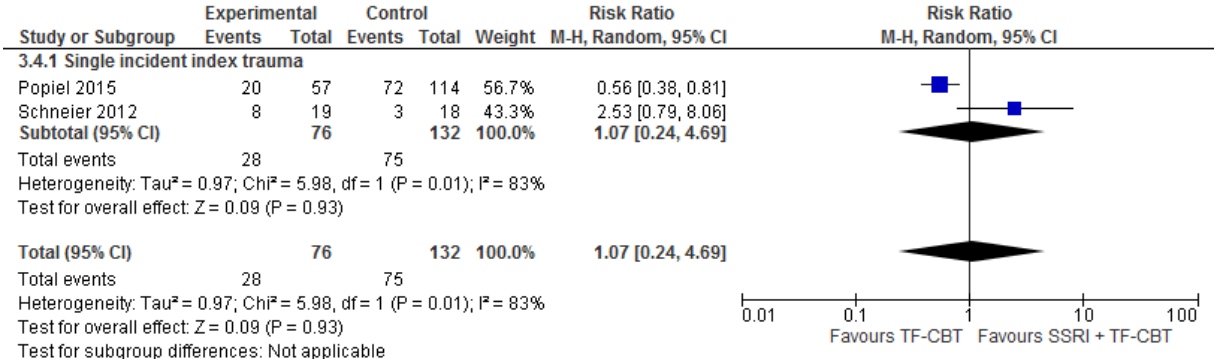


Figure 132: SSRI + trauma-focused CBT versus trauma-focused CBT (±placebo) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people rated as 'much' or 'very much' improved on CGI-I)

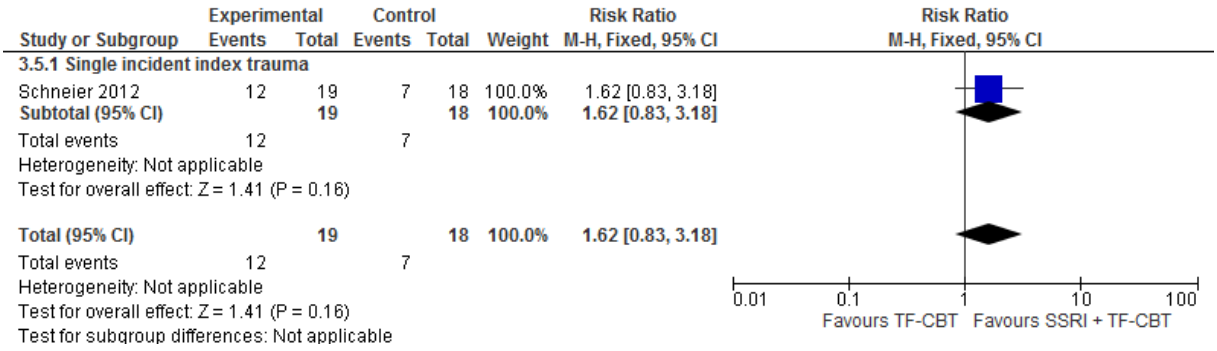


Figure 133: SSRI + trauma-focused CBT versus trauma-focused CBT (±placebo) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms at endpoint (HAM-A/STAI State change score)

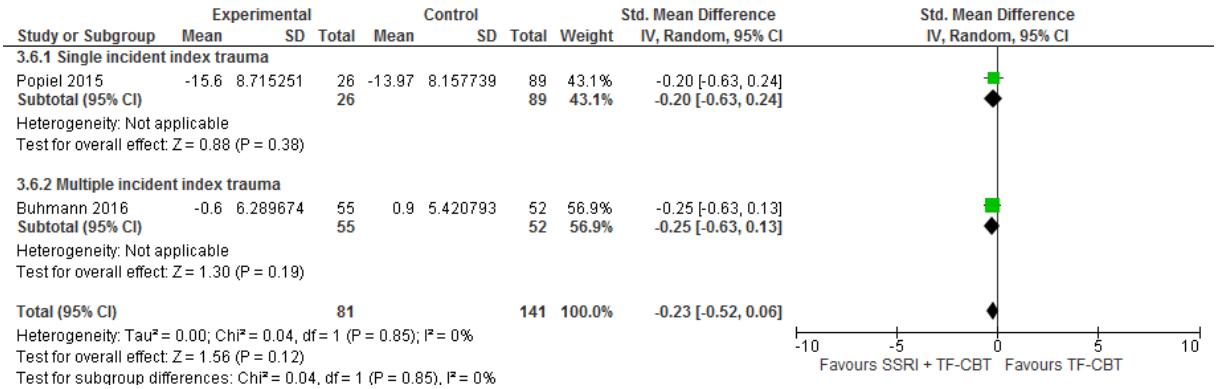


Figure 134: SSRI + trauma-focused CBT versus trauma-focused CBT (±placebo) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms at 1-year follow-up (STAI State change score)

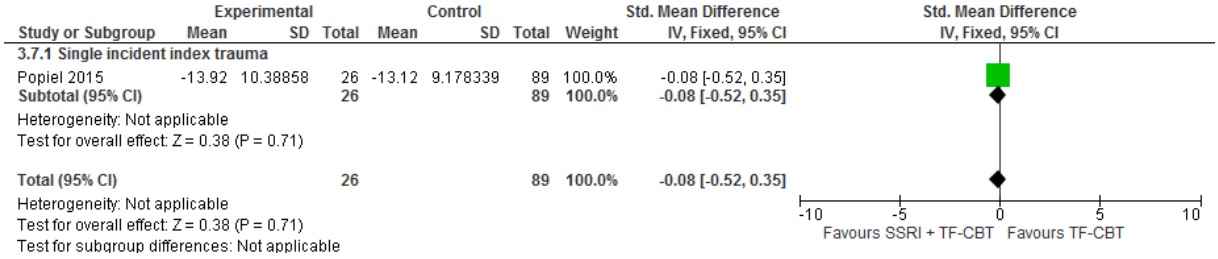


Figure 135: SSRI + trauma-focused CBT versus trauma-focused CBT (±placebo) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms at endpoint (HAM-D/BDI-II change score)

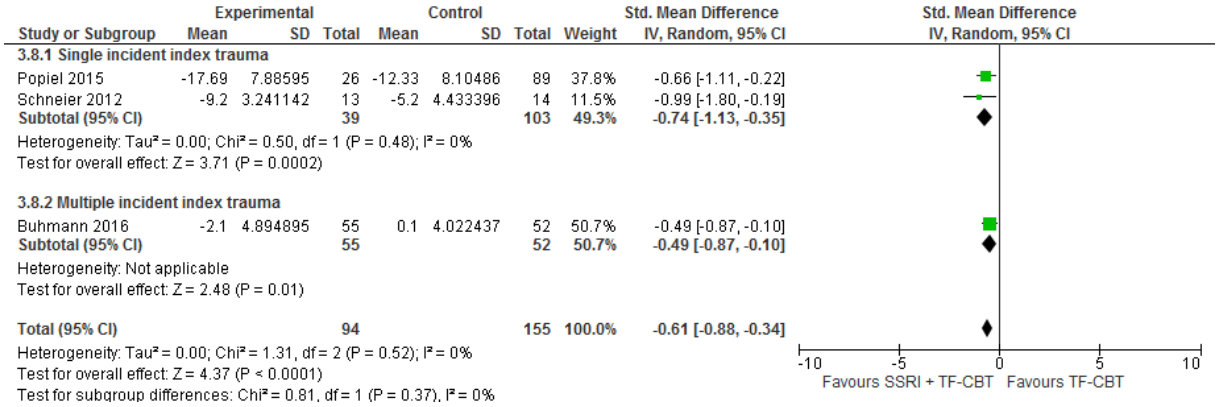


Figure 136: SSRI + trauma-focused CBT versus trauma-focused CBT (±placebo) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms at 1-year follow-up (BDI-II change score)

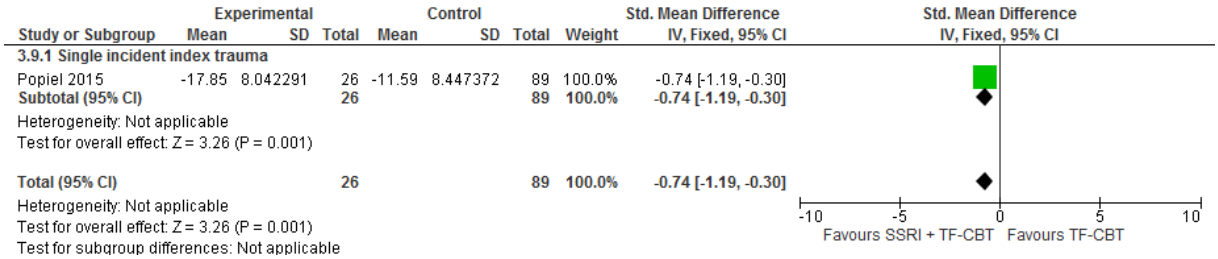


Figure 137: SSRI + trauma-focused CBT versus trauma-focused CBT (±placebo) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Functional impairment (SDS change score)

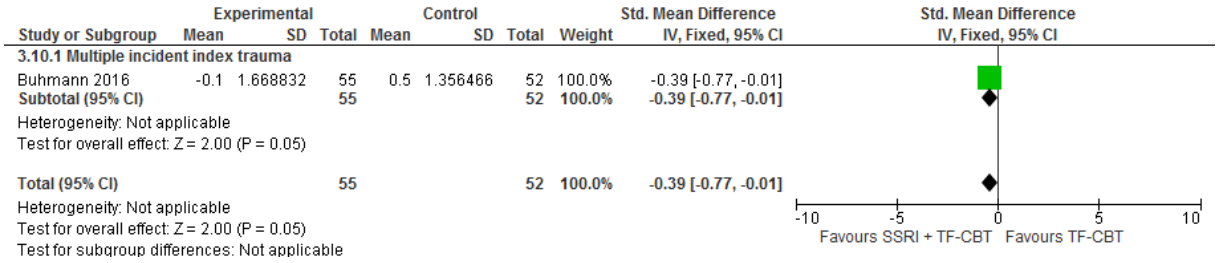


Figure 138: SSRI + trauma-focused CBT versus trauma-focused CBT (±placebo) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Quality of life (WHO-5 change score)

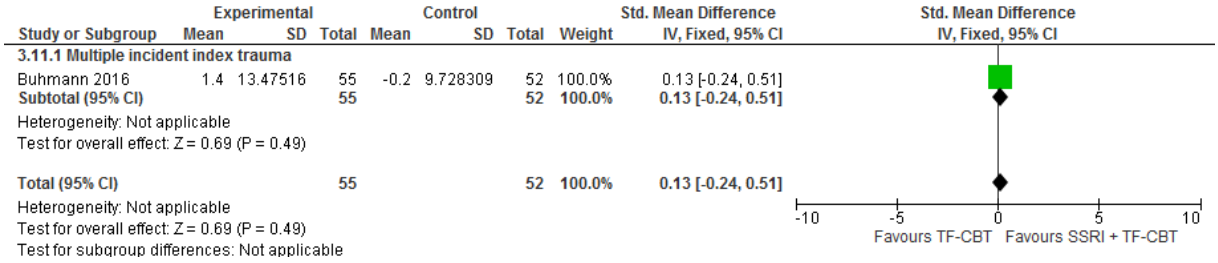


Figure 139: SSRI + trauma-focused CBT versus trauma-focused CBT (±placebo) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

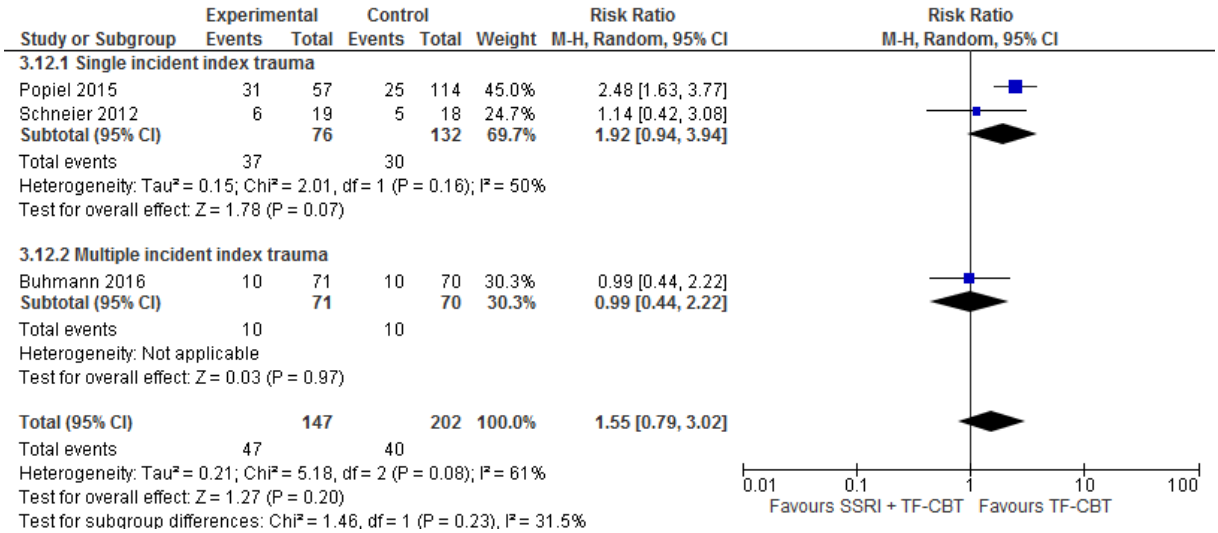
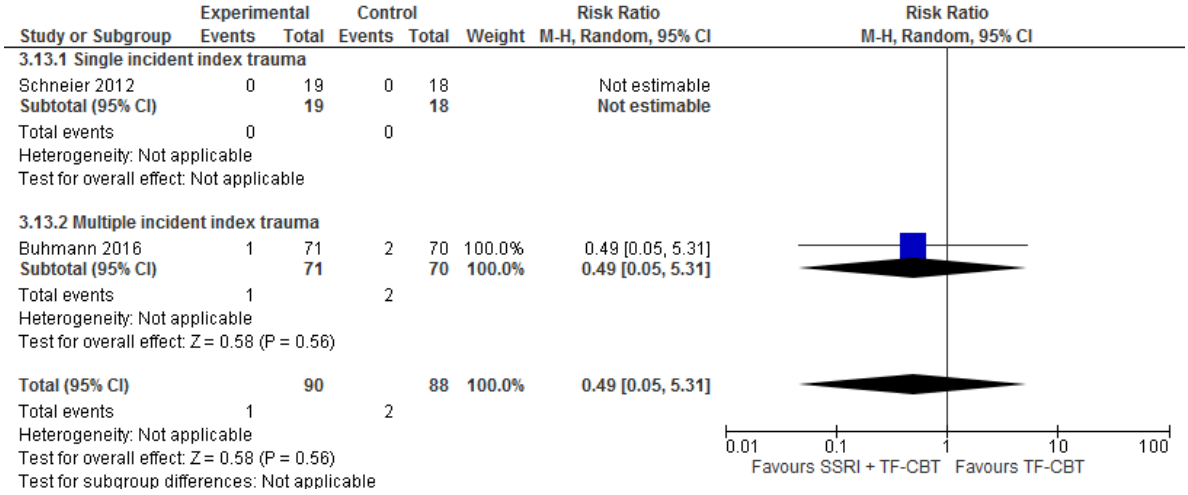


Figure 140: SSRI + trauma-focused CBT versus trauma-focused CBT (±placebo) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Antidepressants: Tricyclic antidepressants (TCAs)

TCA versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 141: TCA versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (IES change score); Multiple incident index trauma

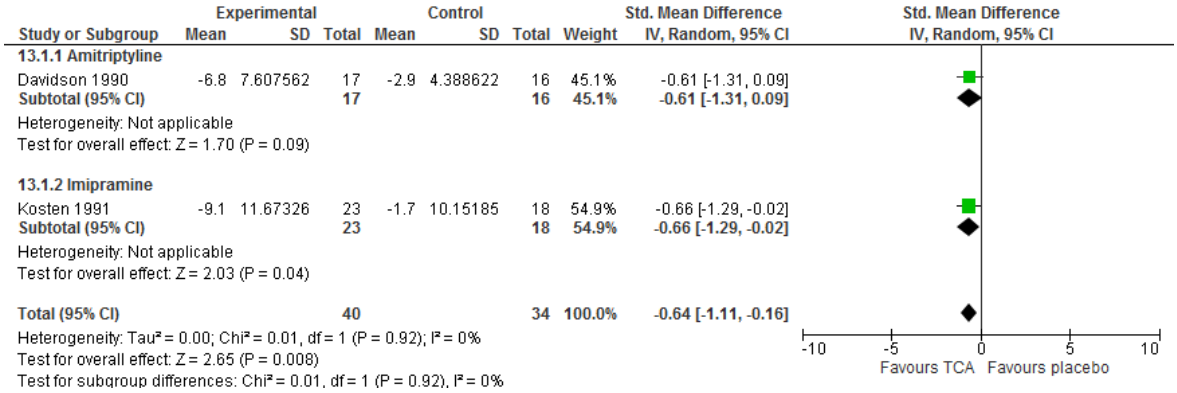


Figure 142: TCA versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (SI–PTSD change score); Multiple incident index trauma

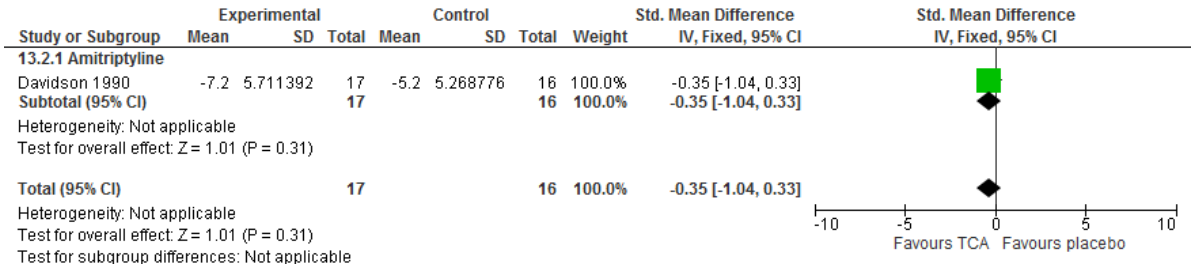


Figure 143: TCA versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people showing ≥50% improvement on SI–PTSD/rated as 'much or very much improved' on CGI-I); Multiple incident index trauma

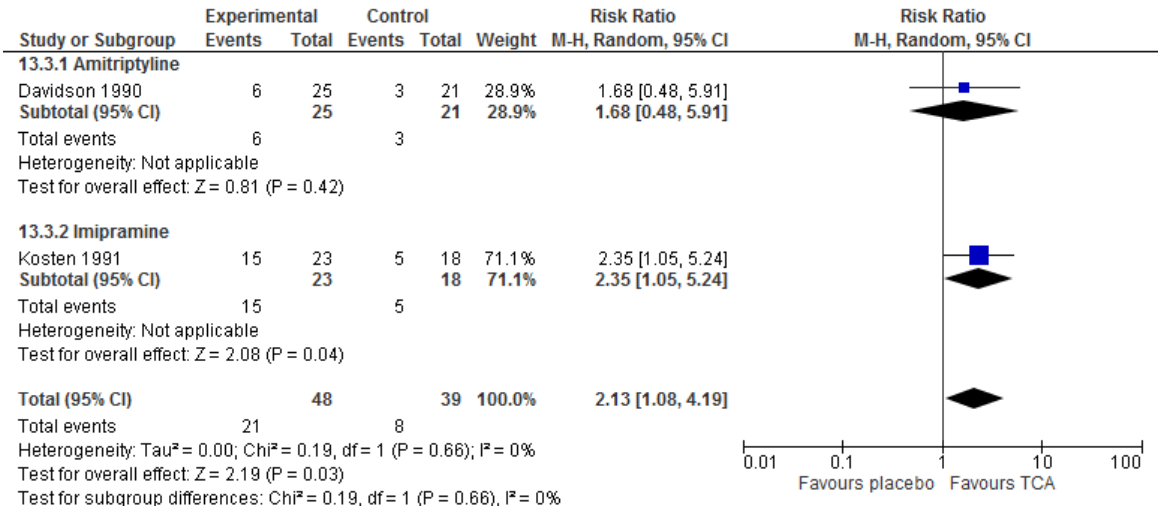


Figure 144: TCA versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms (HAM-A/CAS change score); Multiple incident index trauma

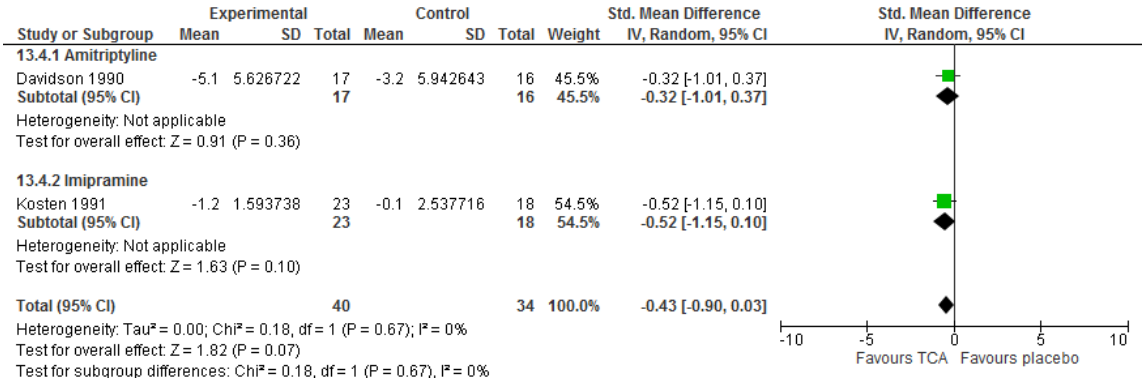


Figure 145: TCA versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (HAM-D change score); Multiple incident index trauma

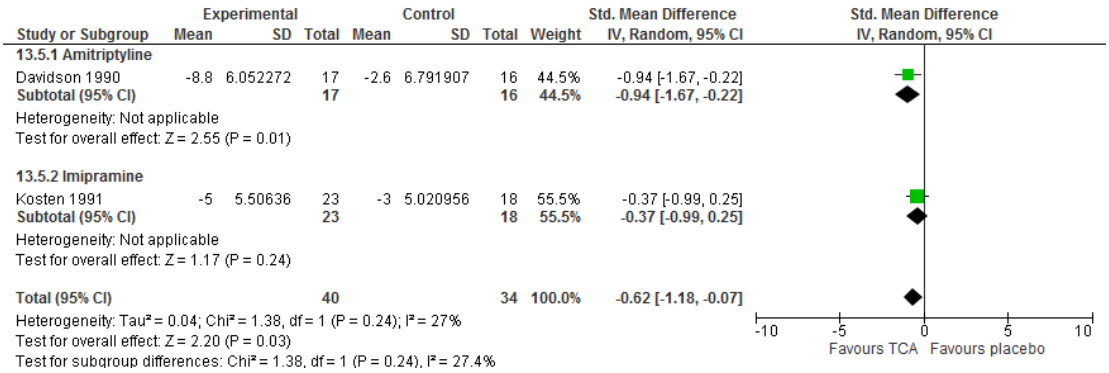


Figure 146: TCA versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events); Multiple incident index trauma

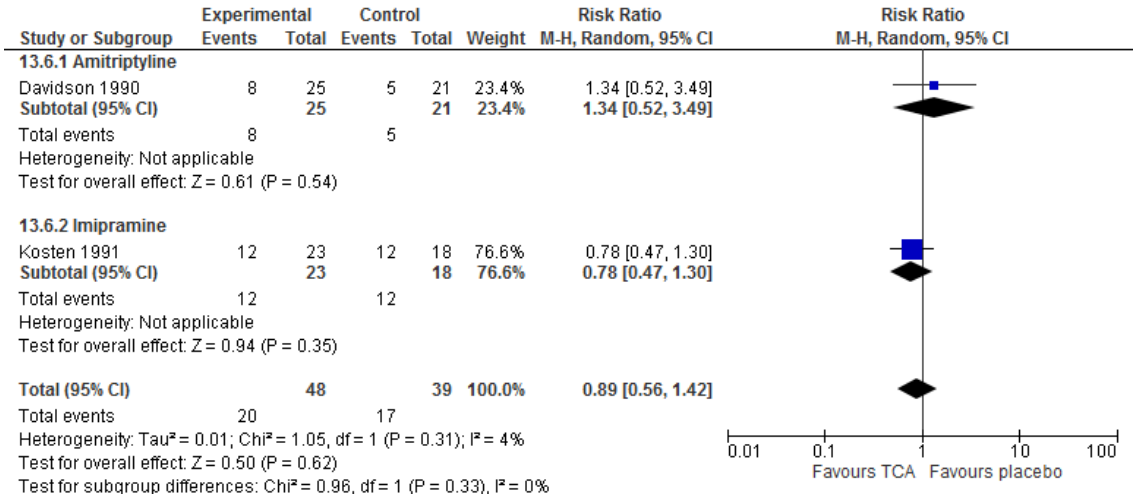
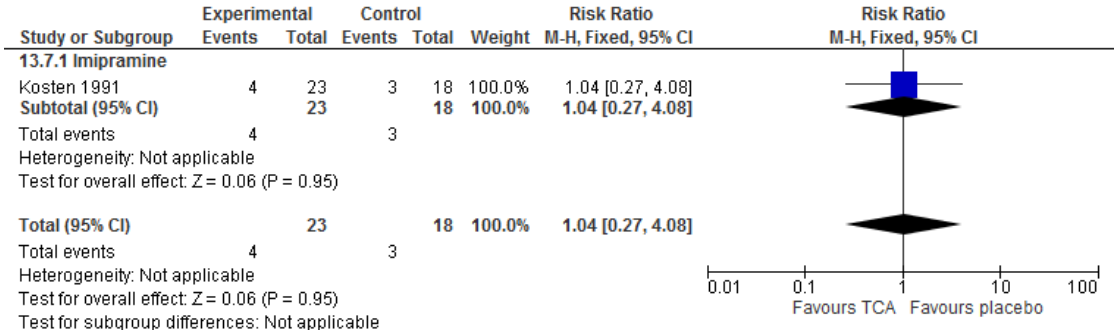


Figure 147: TCA versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events; Multiple incident index trauma



Antidepressants: Serotonin-norepinephrine reuptake inhibitors (SNRIs)

Venlafaxine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 148: Venlafaxine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomology at endpoint (CAPS)

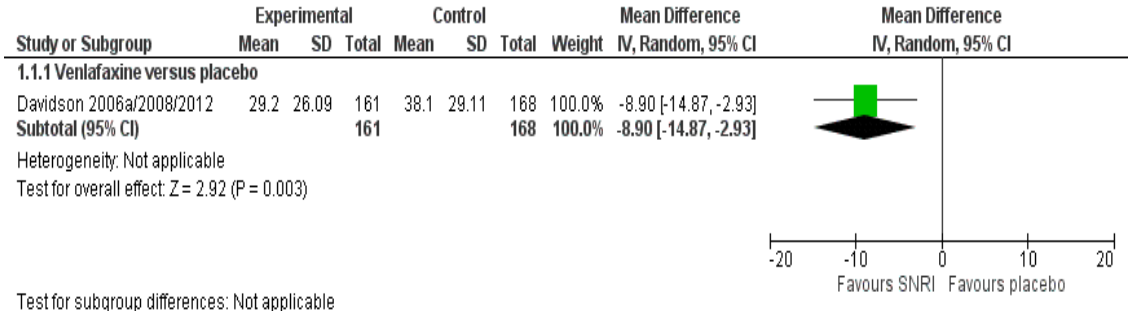


Figure 149: Venlafaxine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Symptoms of/recovery from depression at endpoint (HAM-D 17)

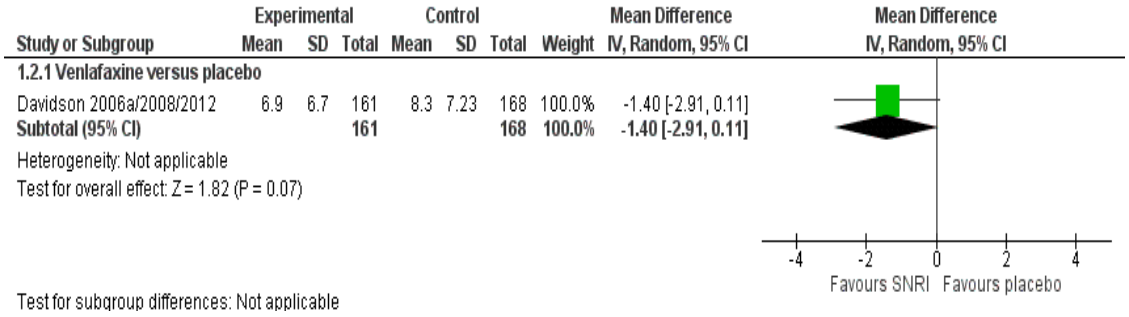


Figure 150: Venlafaxine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Global functioning at endpoint (GAF)

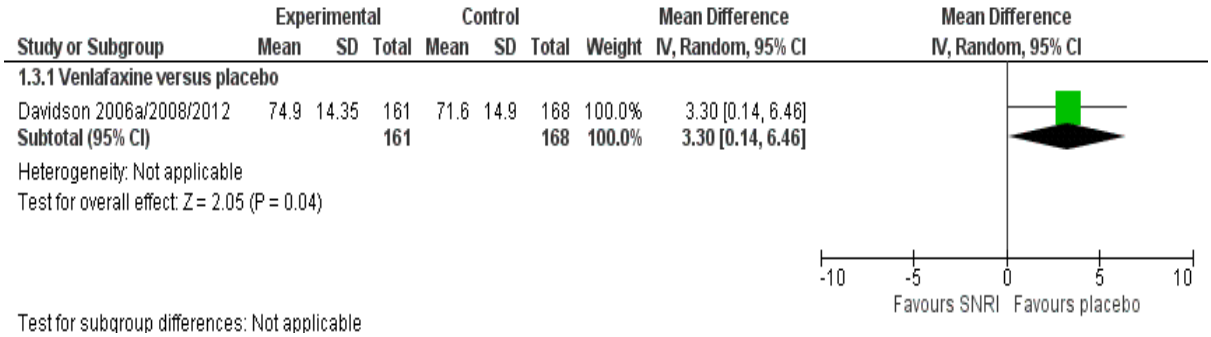


Figure 151: Venlafaxine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Quality of life at endpoint (Quality of Life Enjoyment and Life Satisfaction Short Form)

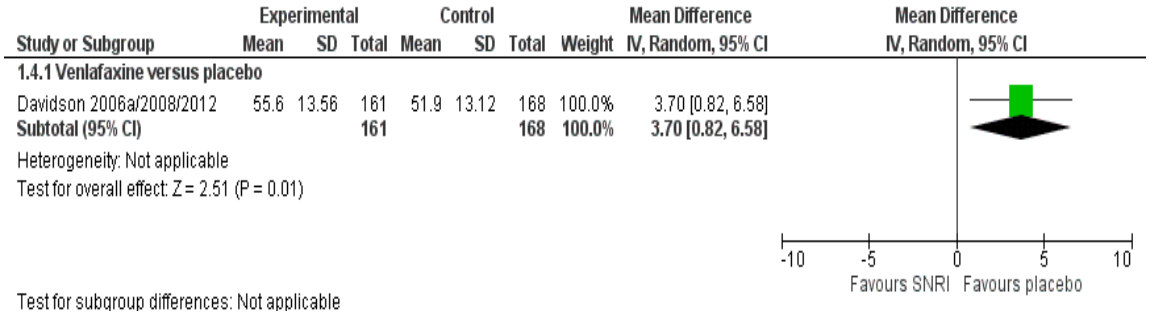


Figure 152: Venlafaxine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Functional impairment at endpoint (Sheehan Disability Scale)

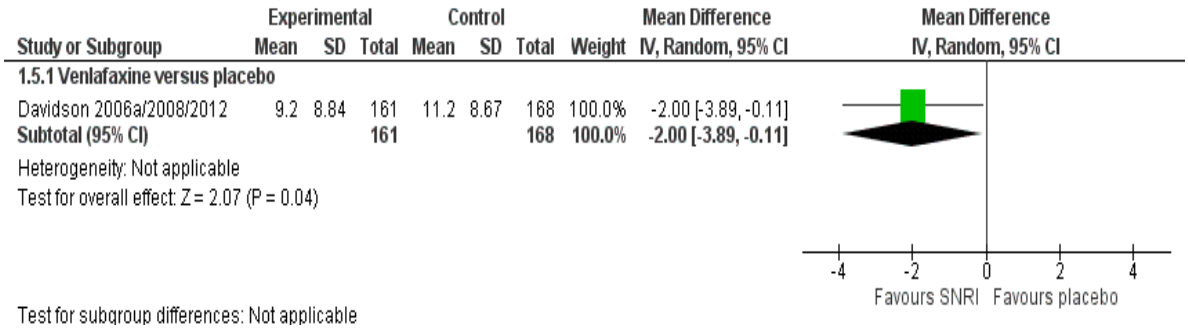


Figure 153: Venlafaxine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse effects) at endpoint

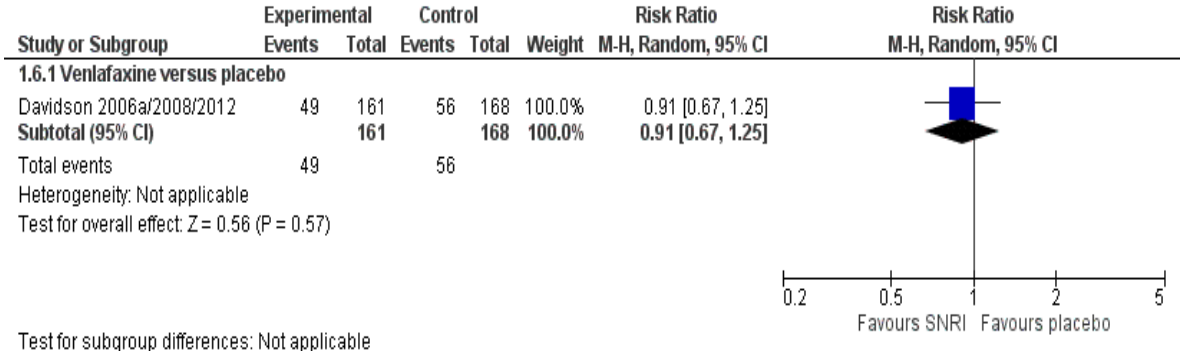
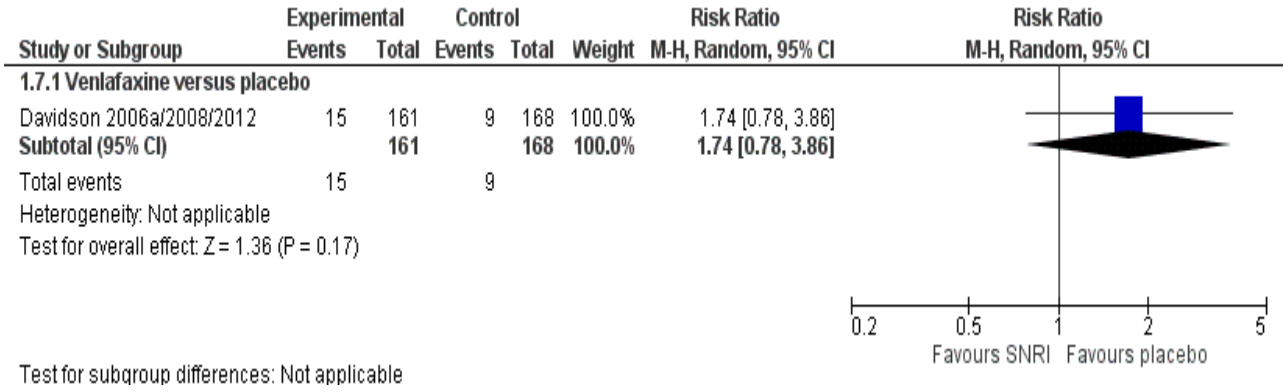


Figure 154: Venlafaxine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse effects



Antidepressants: Monoamine-oxidase inhibitors (MAOIs)

MAOI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms

Figure 155: MAOI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (IES change score); Multiple incident index trauma

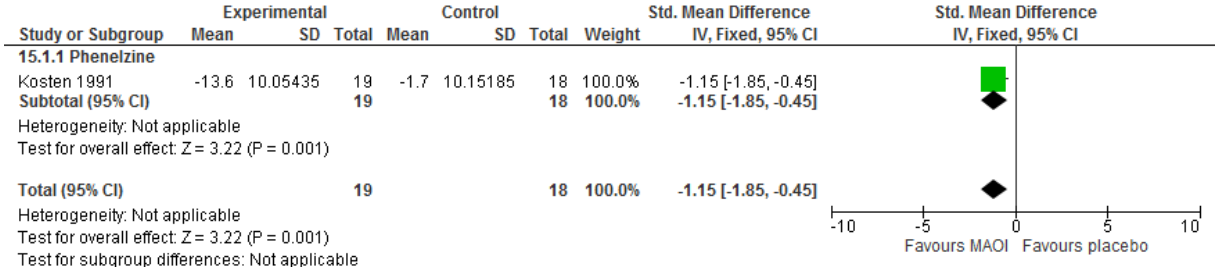


Figure 156: MAOI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score); Single incident index trauma

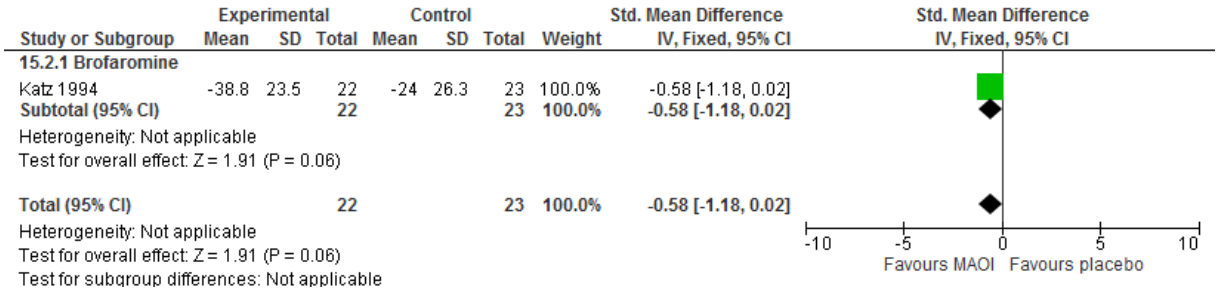


Figure 157: MAOI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Remission (number of people no longer meeting diagnostic criteria for PTSD); Single incident index trauma

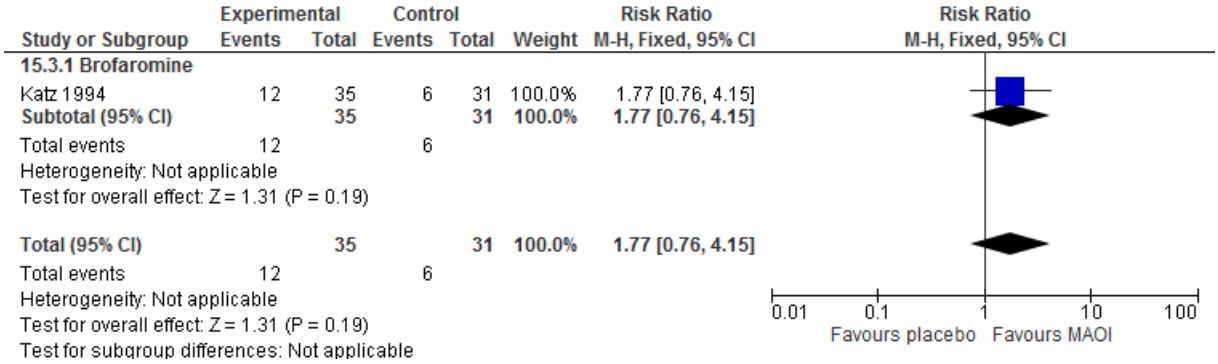


Figure 158: MAOI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people rated as 'much' or 'very much' improved on CGI-I); Multiple incident index trauma

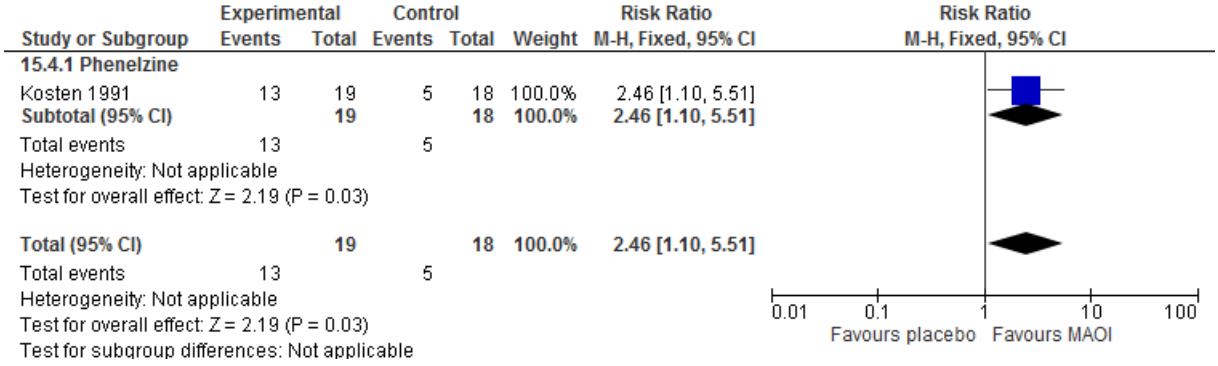


Figure 159: MAOI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms (CAS change score); Multiple incident index trauma

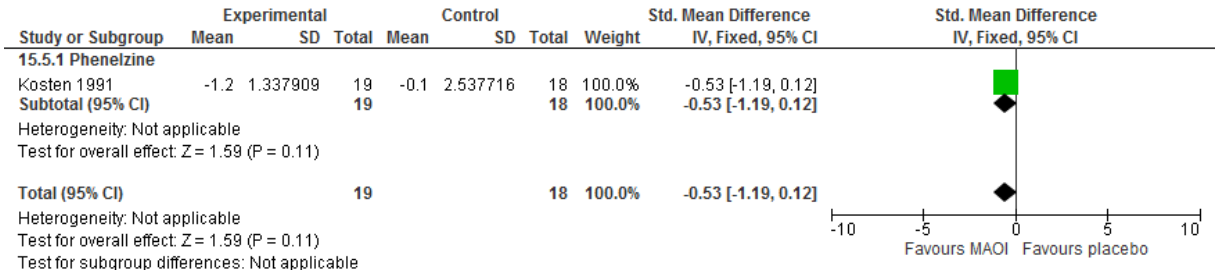


Figure 160: MAOI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (HAM-D change score); Multiple incident index trauma

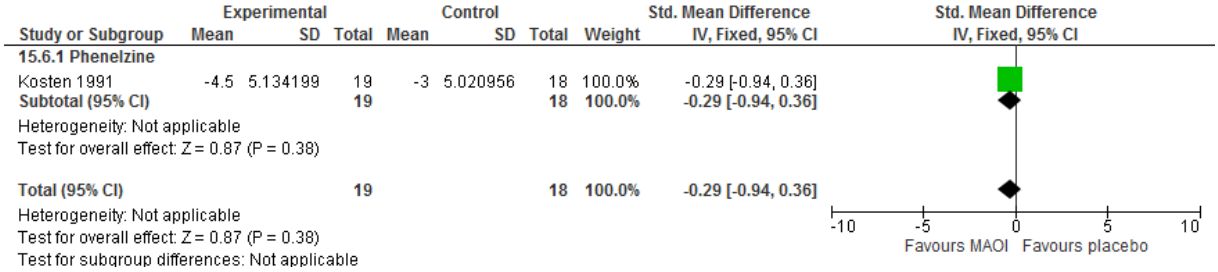


Figure 161: MAOI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

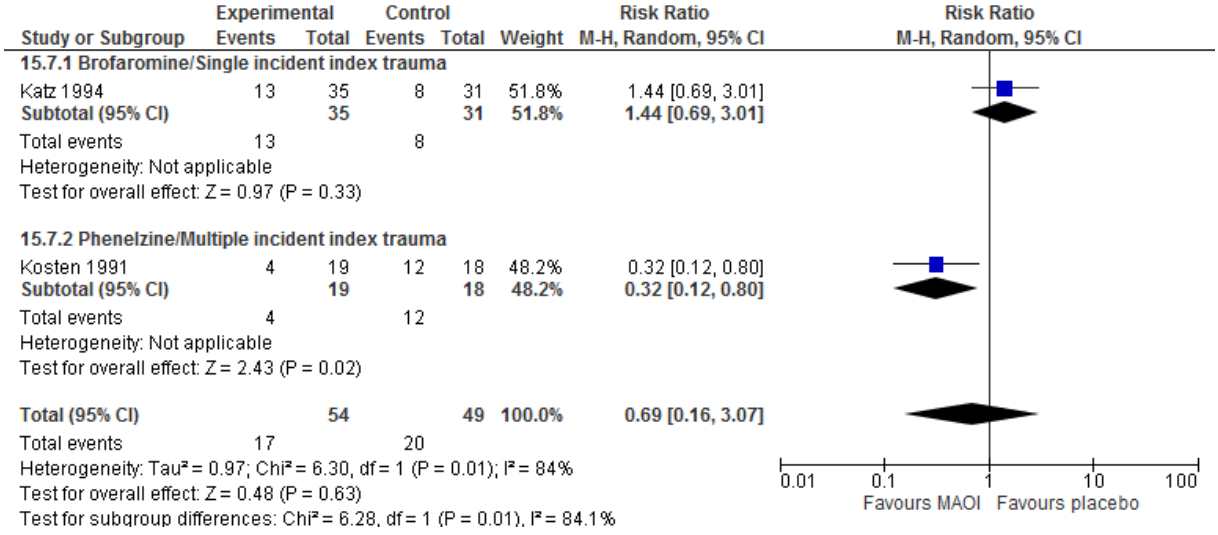
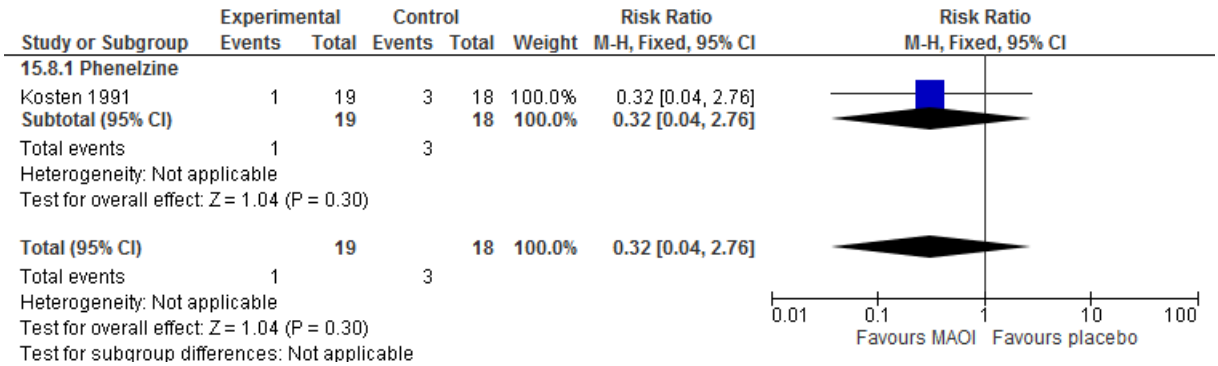


Figure 162: MAOI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events; Multiple incident index trauma



Phenelzine versus imipramine for the delayed treatment (>3 months) of clinically important PTSD symptoms

Figure 163: Phenelzine versus imipramine for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (IES change score)

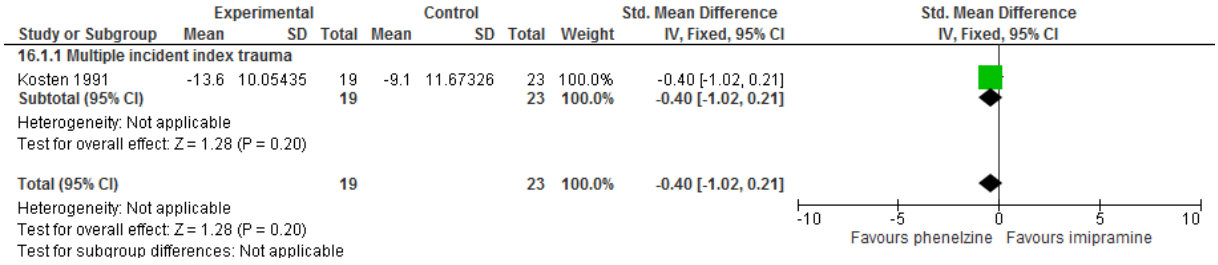


Figure 164: Phenelzine versus imipramine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people rated as 'much' or 'very much' improved on CGI-I)

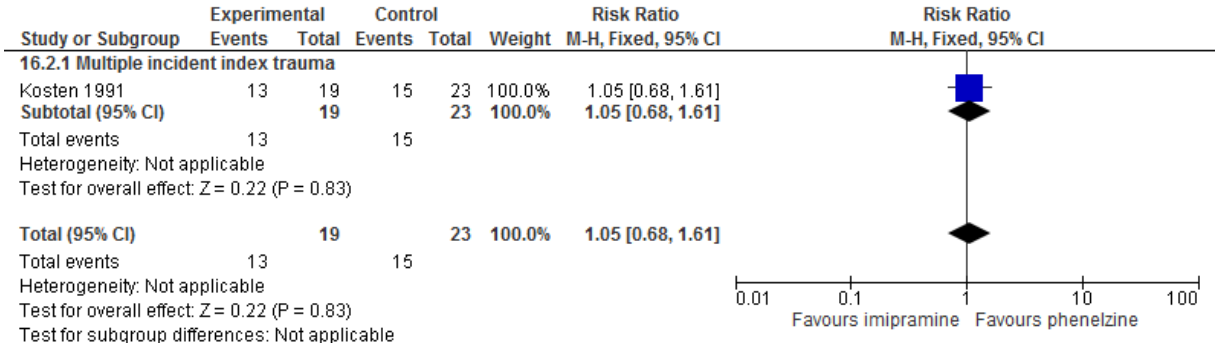


Figure 165: Phenelzine versus imipramine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms (CAS change score)

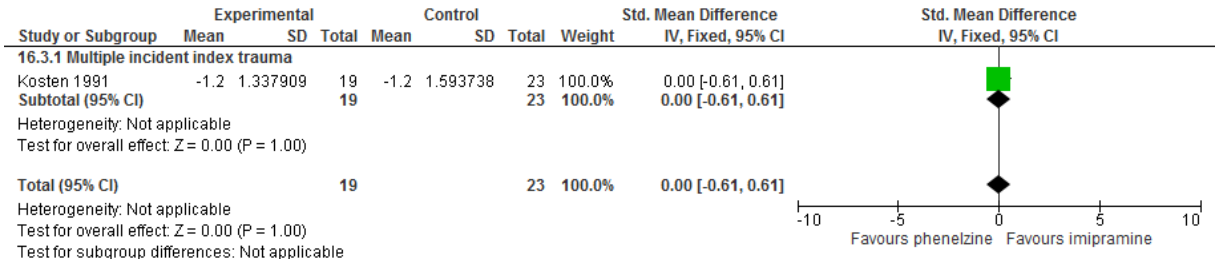


Figure 166: Phenelzine versus imipramine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (HAM-D change score)

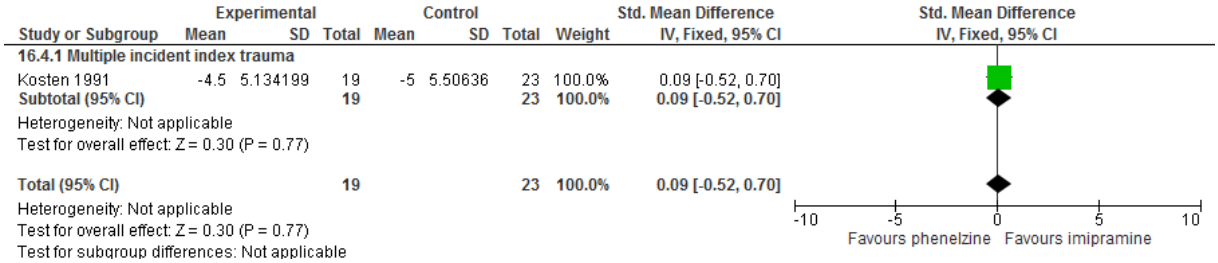


Figure 167: Phenelzine versus imipramine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

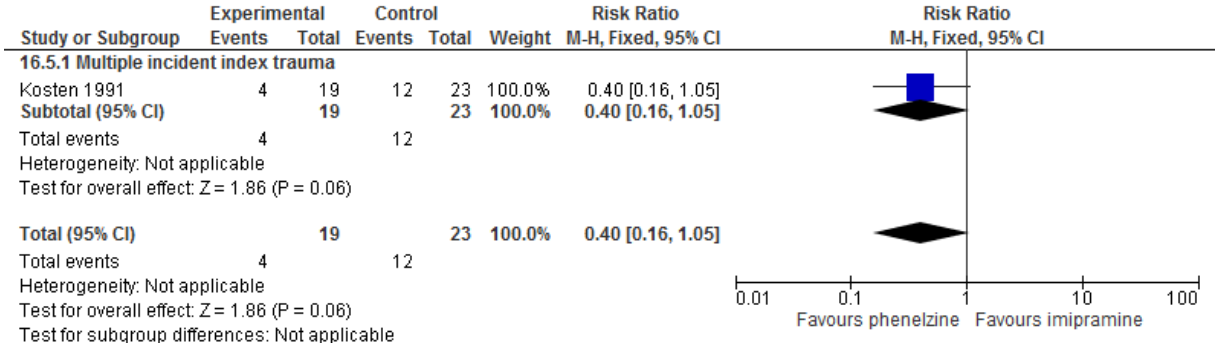
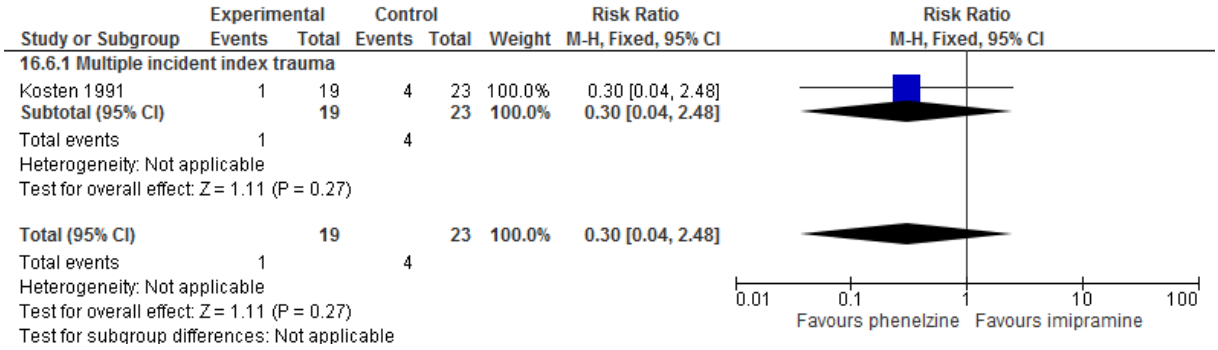


Figure 168: Phenelzine versus imipramine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Antidepressants: Other antidepressants

Nefazodone versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 169: Nefazodone versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (PCL change score)

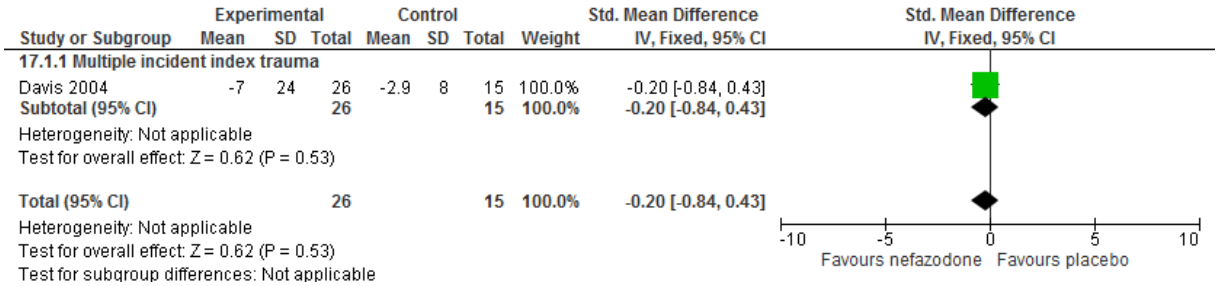


Figure 170: Nefazodone versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

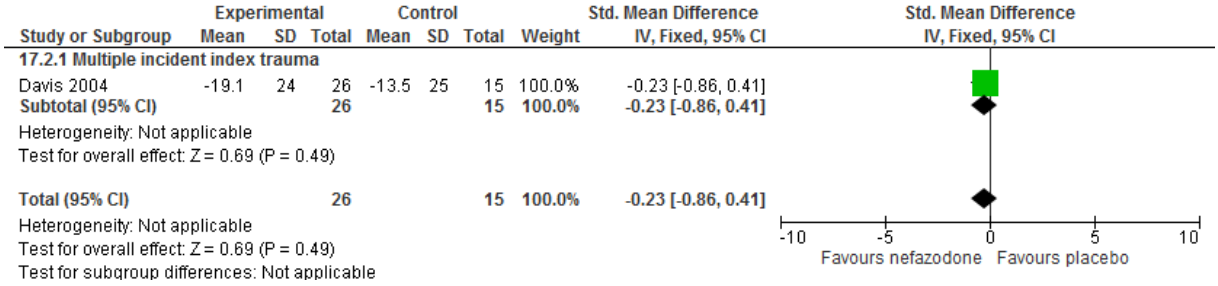


Figure 171: Nefazodone versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people showing ≥30% improvement on CAPS)

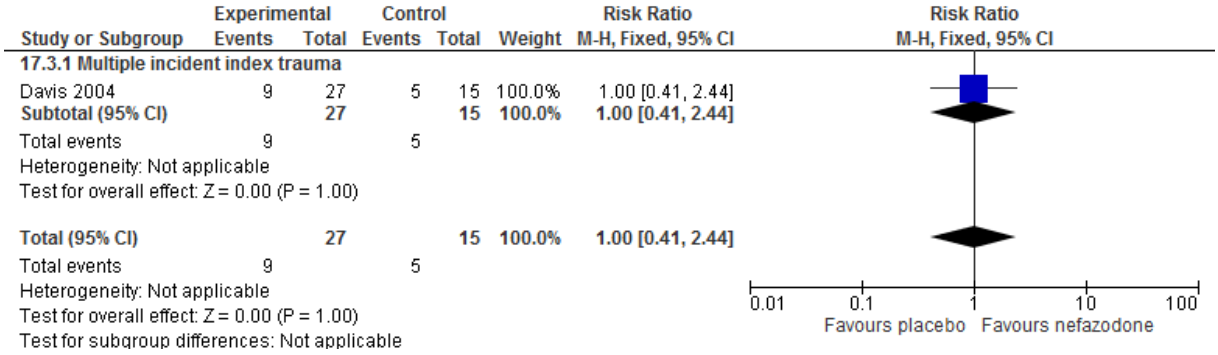


Figure 172: Nefazodone versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (HAM-D change score)

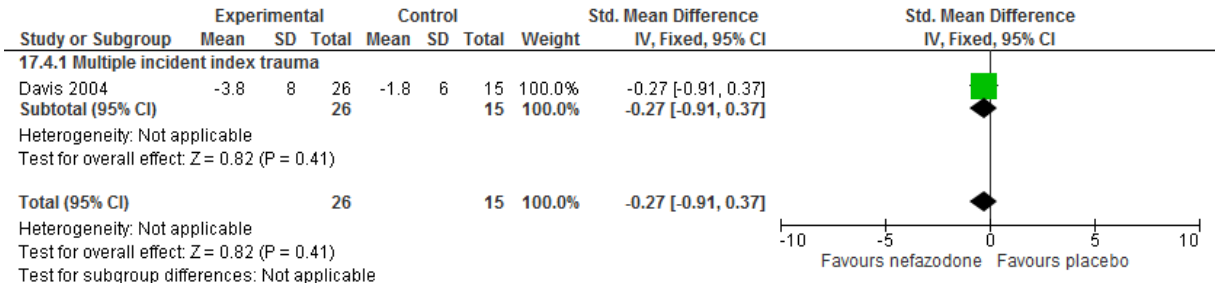


Figure 173: Nefazodone versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Dissociative symptoms (CADSS change score)

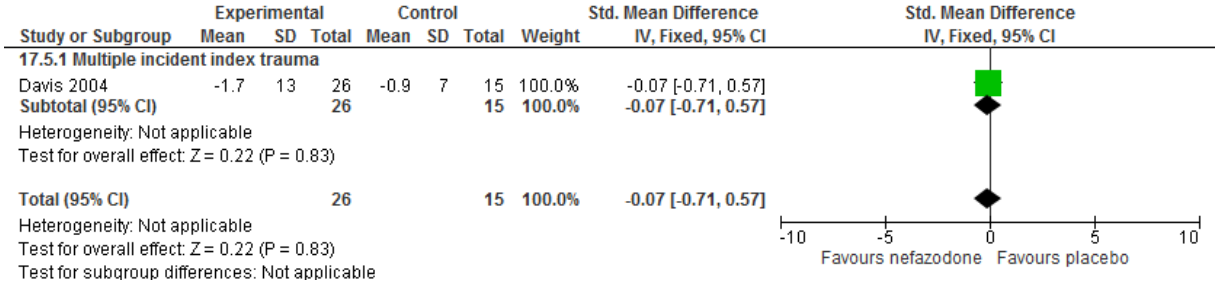


Figure 174: Nefazodone versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

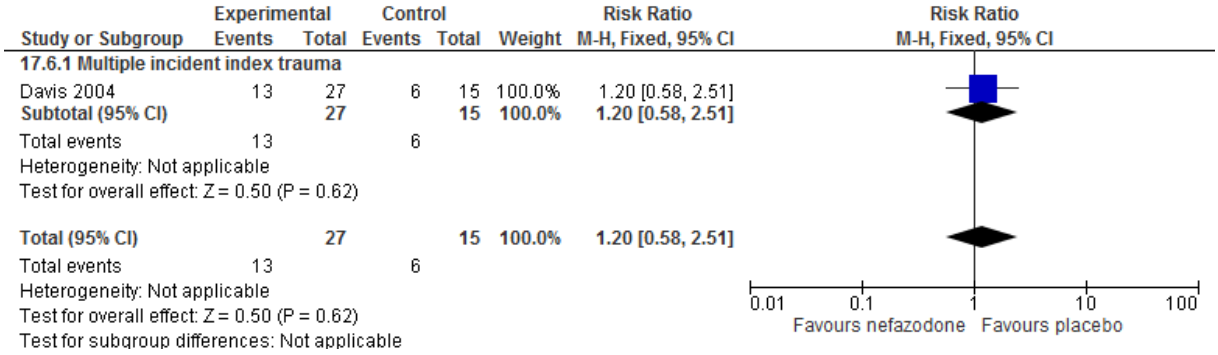
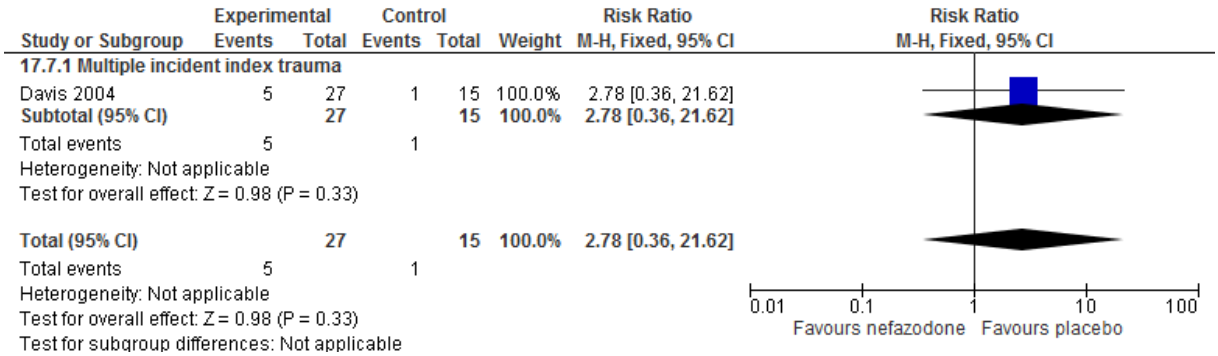


Figure 175: Nefazodone versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Bupropion (+TAU) versus placebo (+TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 176: Bupropion (+TAU) versus placebo (+TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (DTS change score)

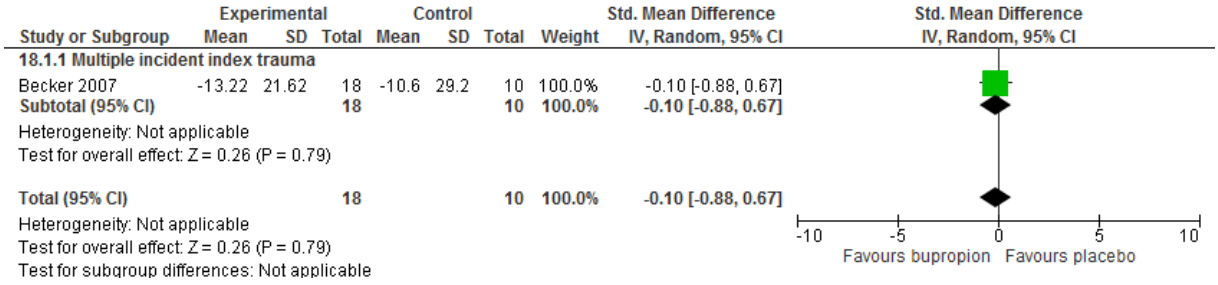
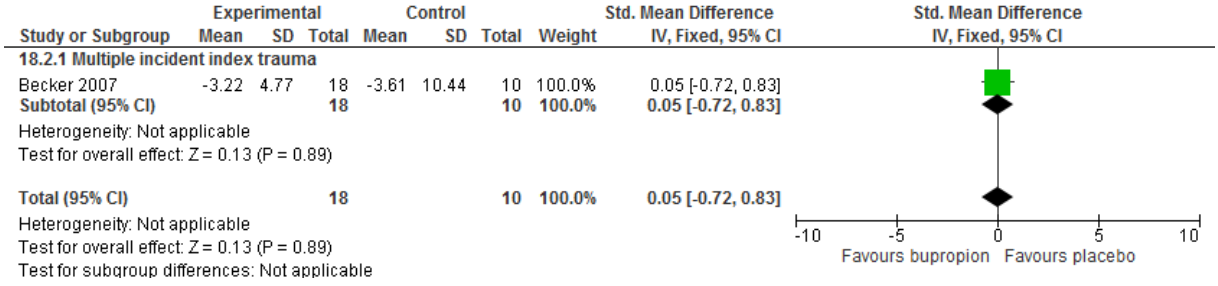


Figure 177: Bupropion (+TAU) versus placebo (+TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (BDI change score)



Moclobemide versus tianeptine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 178: Moclobemide versus tianeptine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults: PTSD symptomatology clinician-rated (CAPS change score)

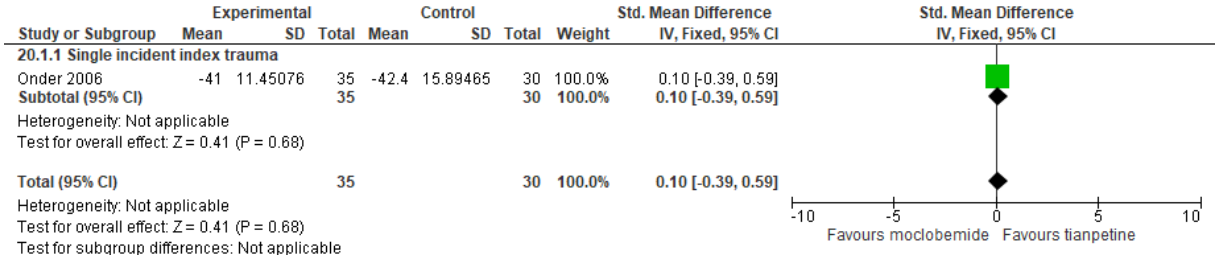


Figure 179: Moclobemide versus tianeptine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults: Response (number of people showing >50% improvement on CAPS)

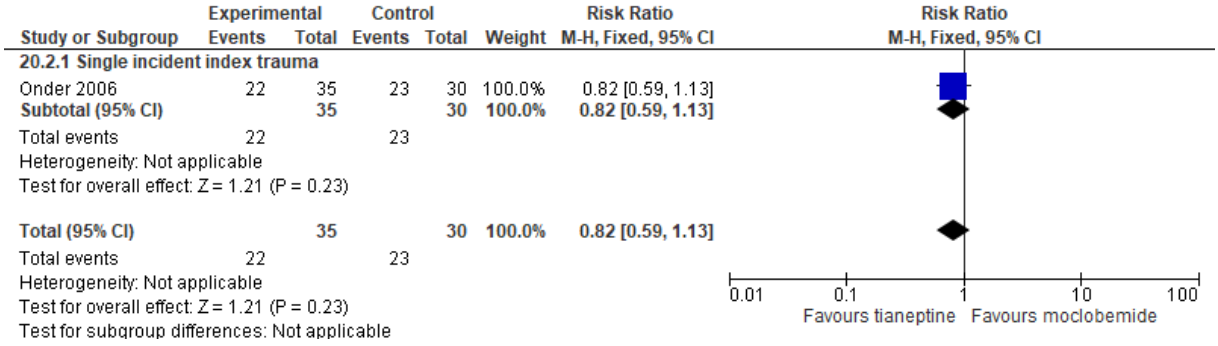


Figure 180: Moclobemide versus tianeptine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults: Discontinuation due to any reason (including adverse events)

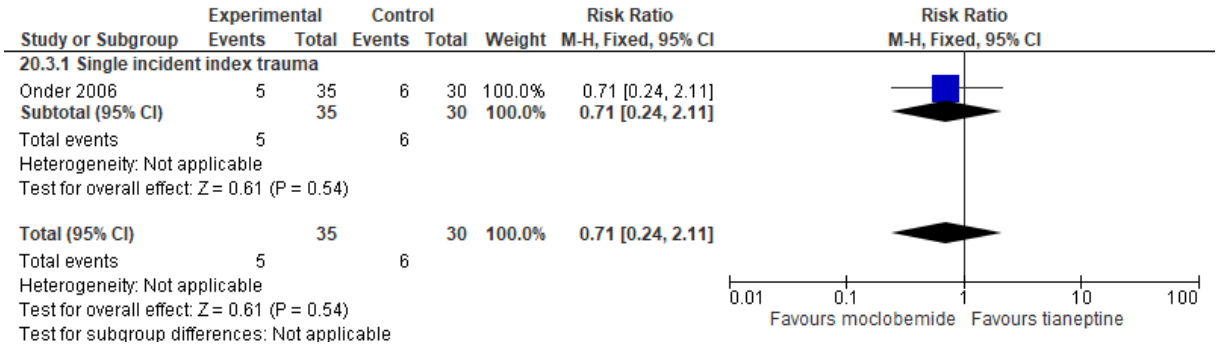
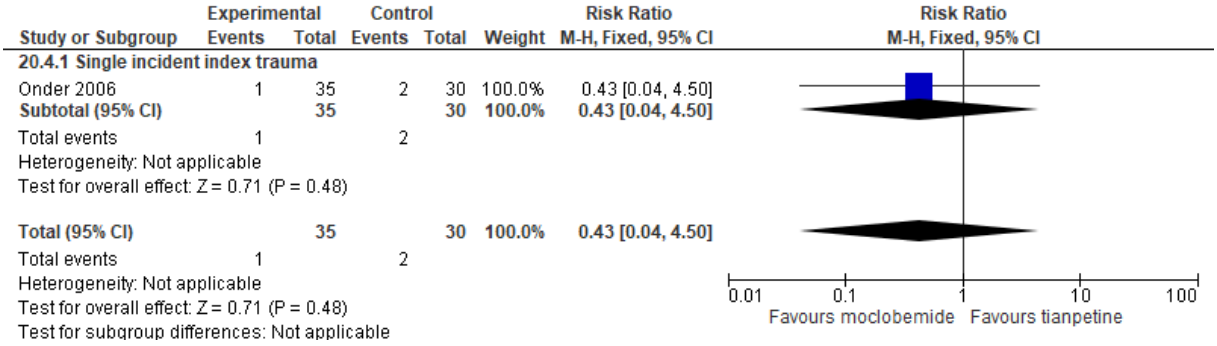


Figure 181: Moclobemide versus tianeptine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults: Discontinuation due to adverse events



Anticonvulsants

Topiramate versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 182: Topiramate versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (DTS change score)

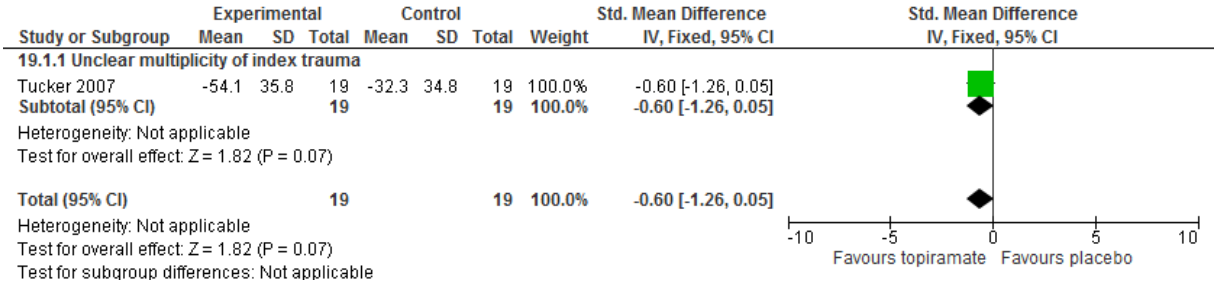


Figure 183: Topiramate versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

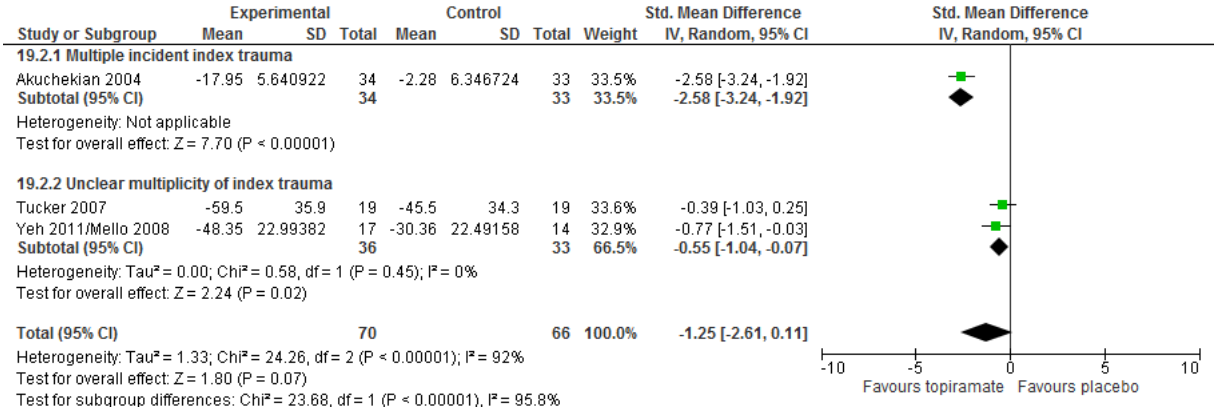


Figure 184: Topiramate versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people showing ≥30% improvement on CAPS)

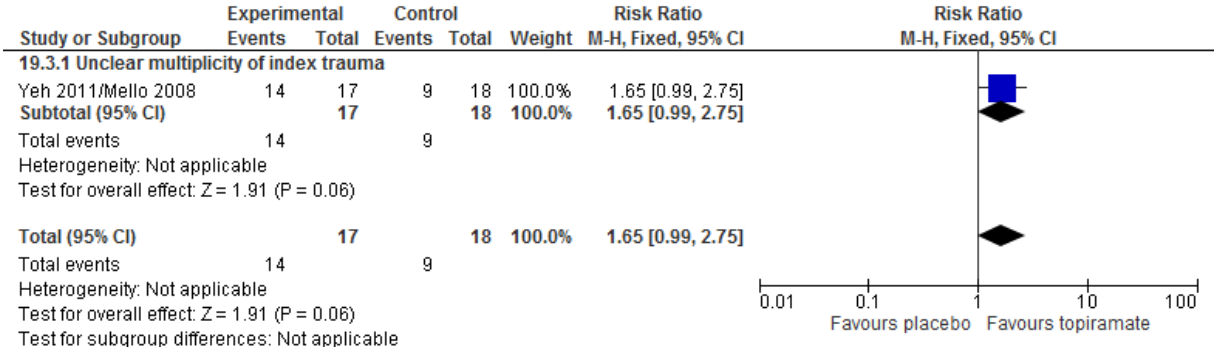


Figure 185: Topiramate versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms (HAM-A change score)

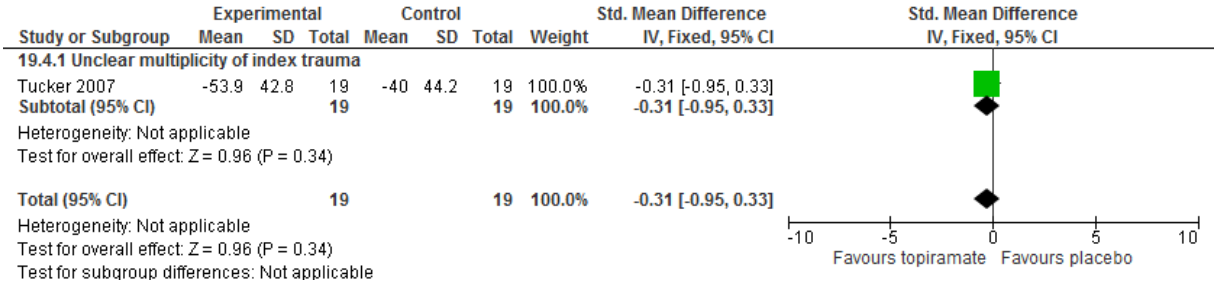


Figure 186: Topiramate versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (HAM-D/BDI change score)

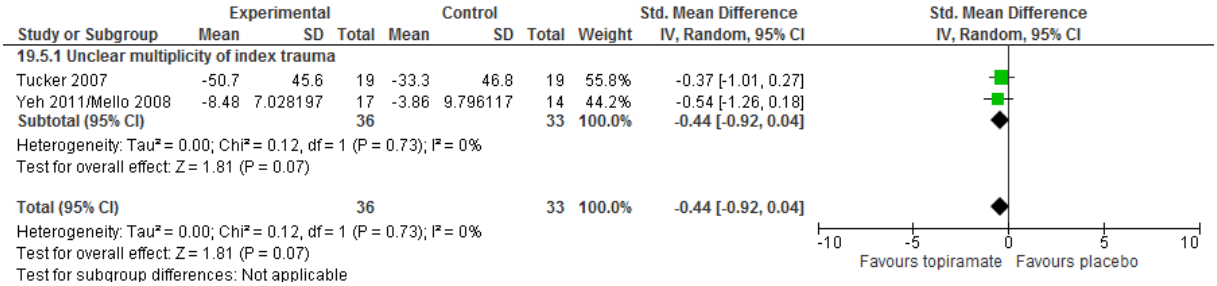


Figure 187: Topiramate versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Functional impairment (SDS change score)

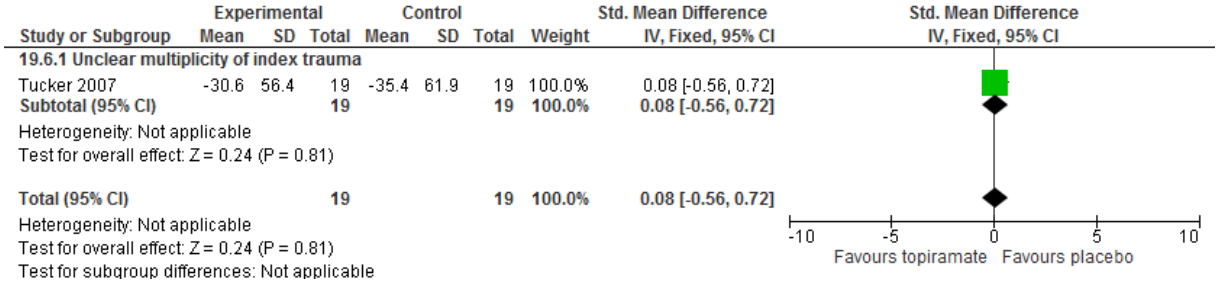


Figure 188: Topiramate versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

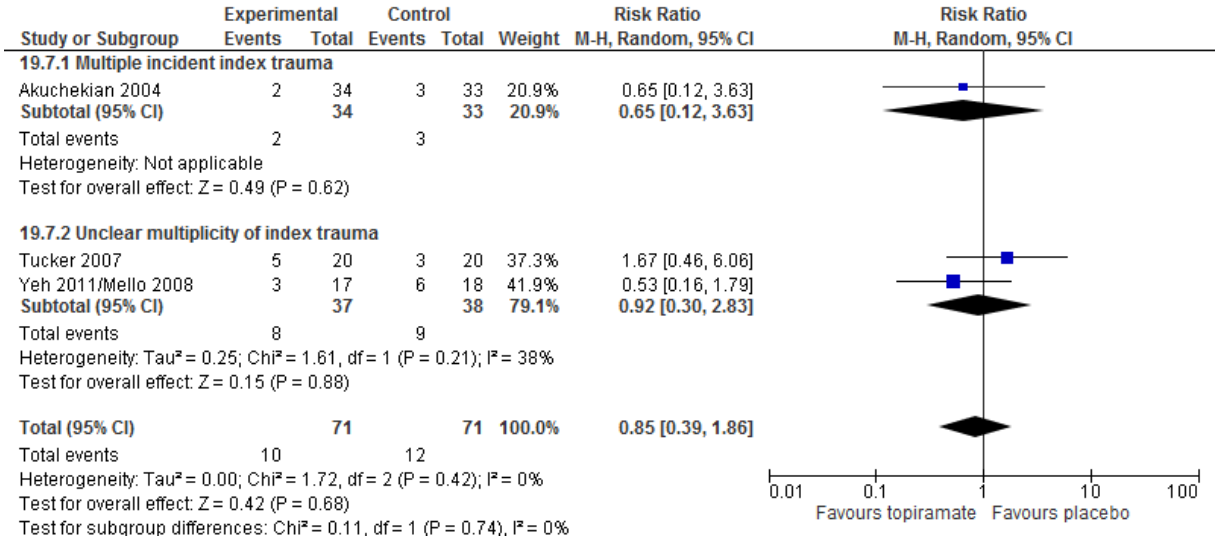
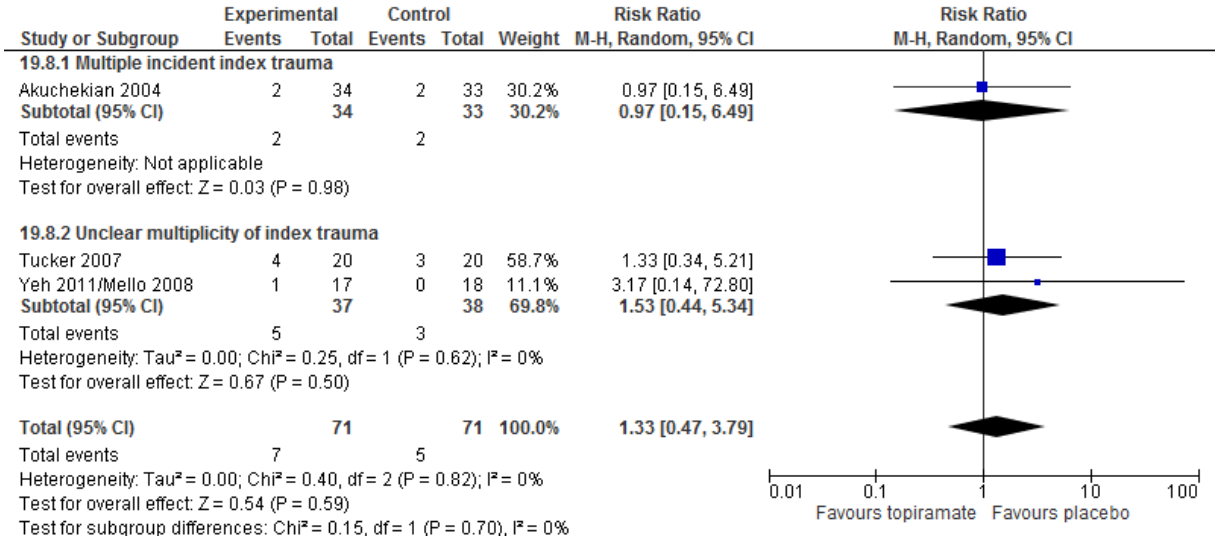


Figure 189: Topiramate versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Divalproex versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 190: Divalproex versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

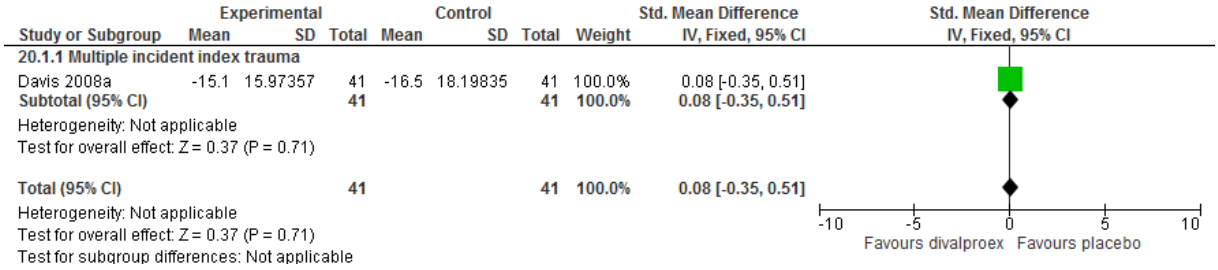


Figure 191: Divalproex versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms (HAM-A change score)

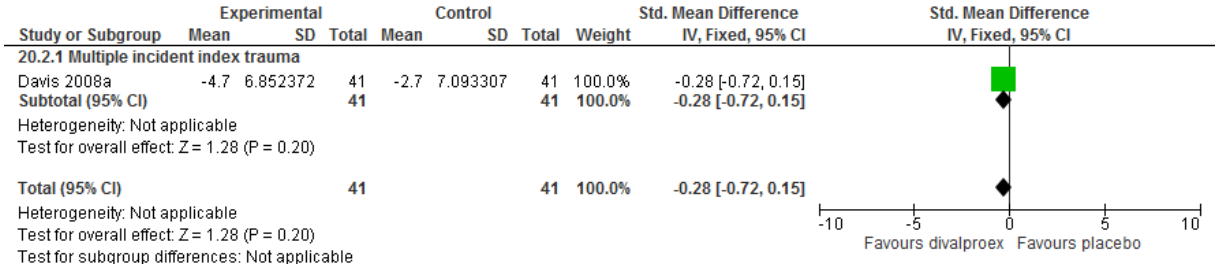


Figure 192: Divalproex versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (MADRS change score)

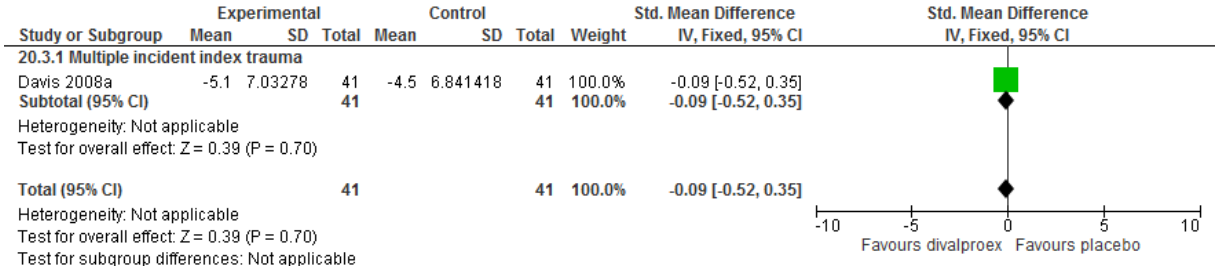


Figure 193: Divalproex versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

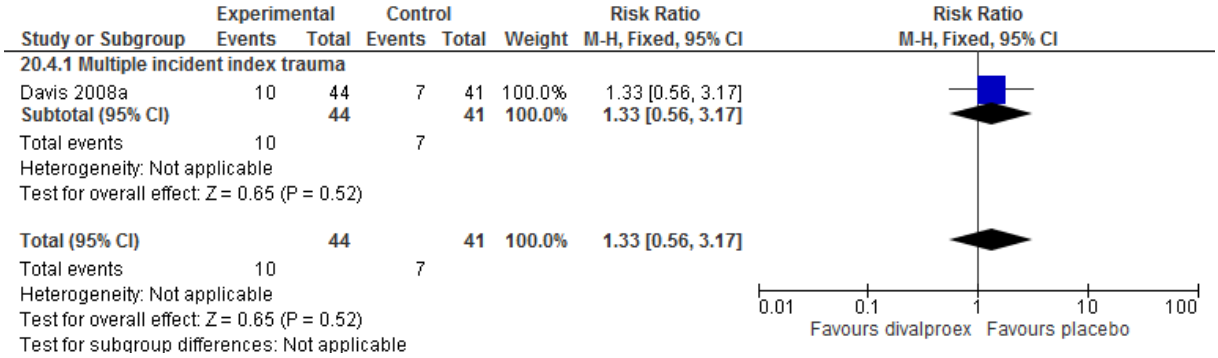
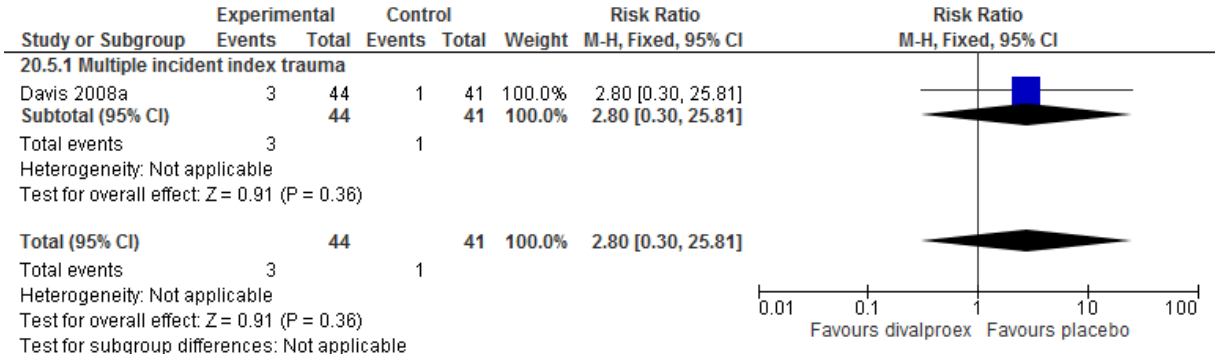


Figure 194: Divalproex versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Tiagabine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 195: Tiagabine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

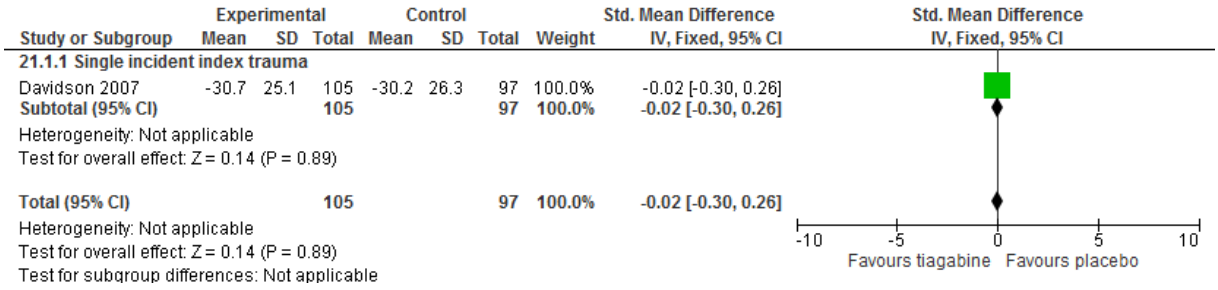


Figure 196: Tiagabine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people rated as 'much' or 'very much' improved on CGI-I)

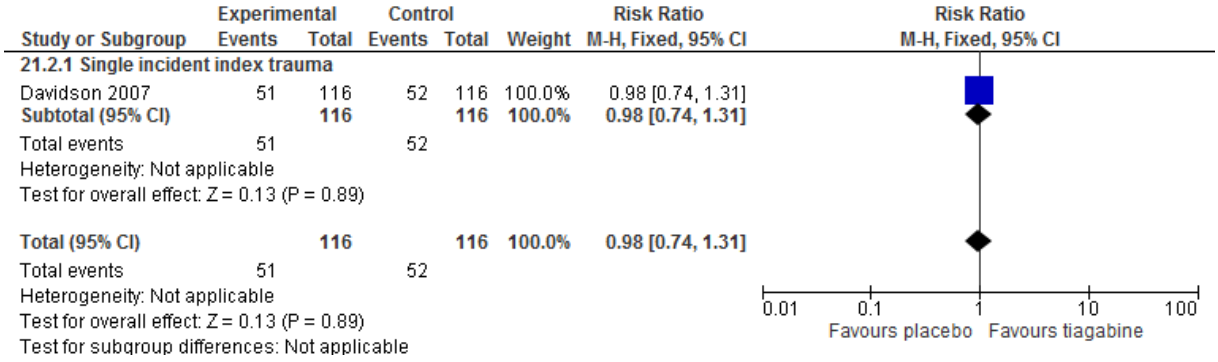


Figure 197: Tiagabine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Remission (number of people scoring <20 on CAPS)

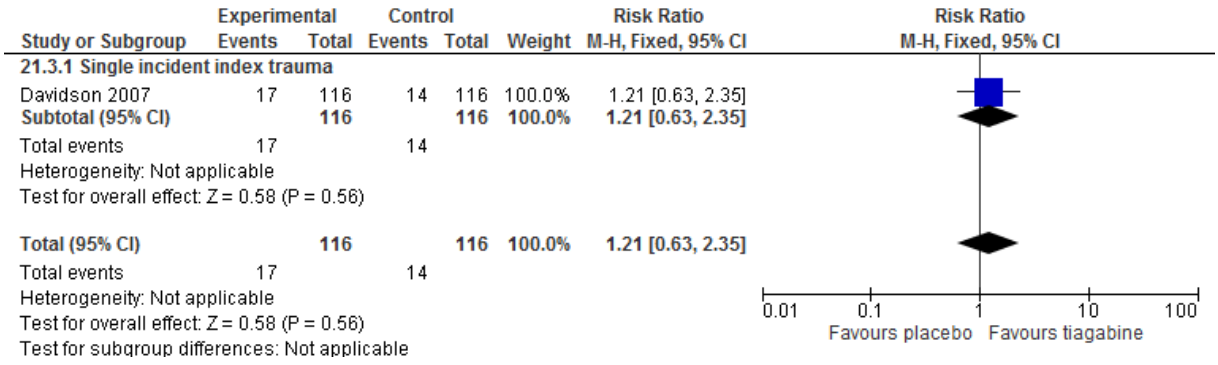


Figure 198: Tiagabine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (MADRS change score)

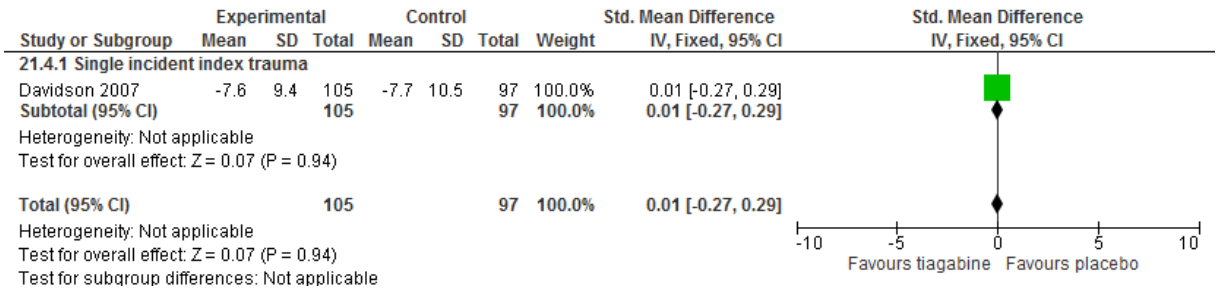


Figure 199: Tiagabine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Functional impairment (SDS change score)

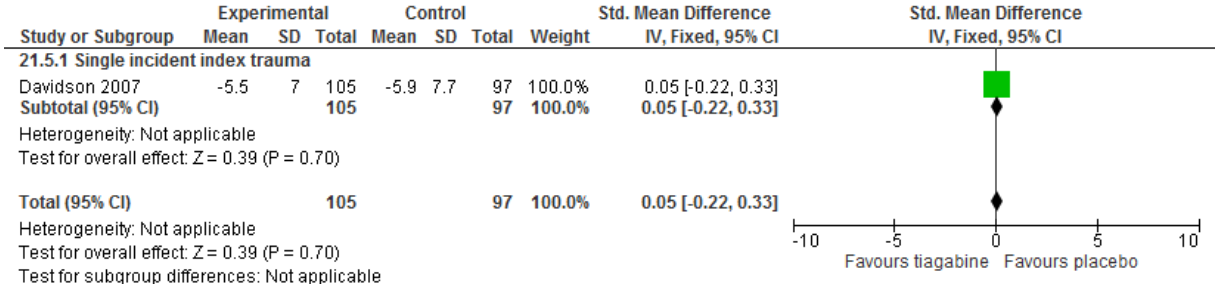


Figure 200: Tiagabine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

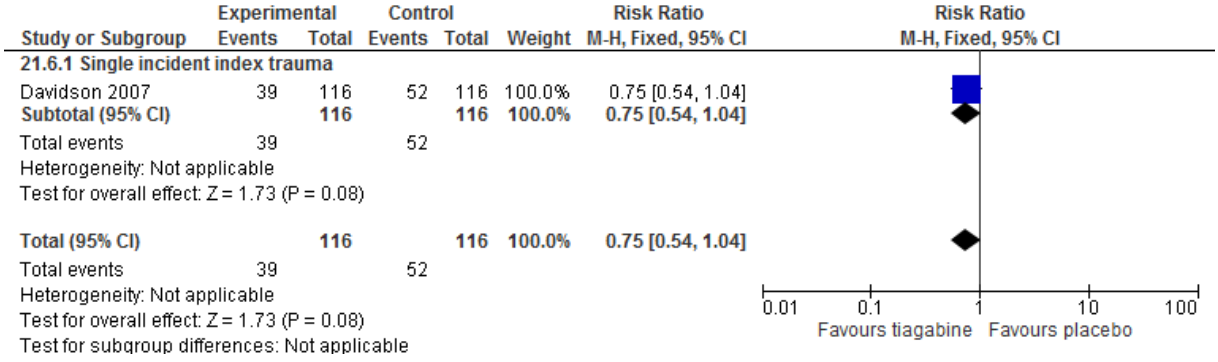
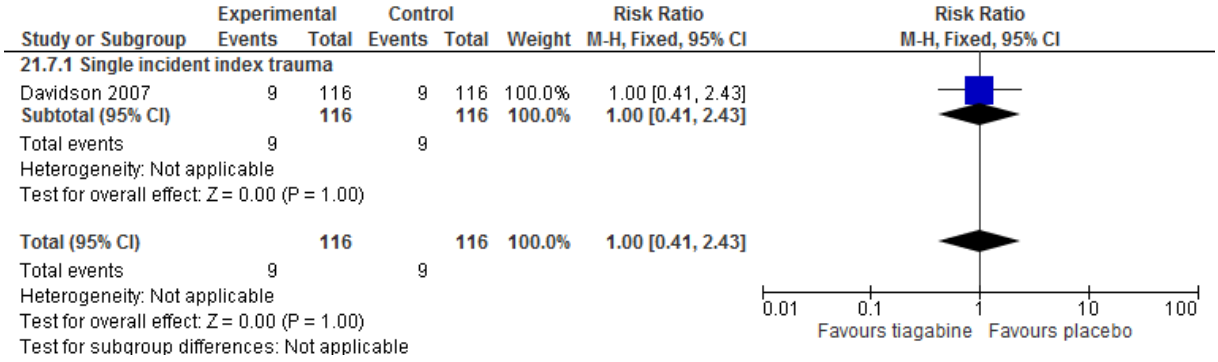


Figure 201: Tiagabine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Pregabalin (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 202: Pregabalin (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (PCL change score)

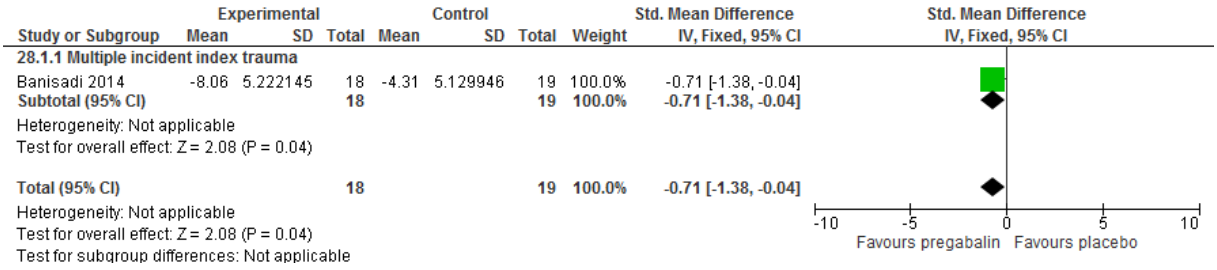


Figure 203: Pregabalin (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms (HAM-A change score)

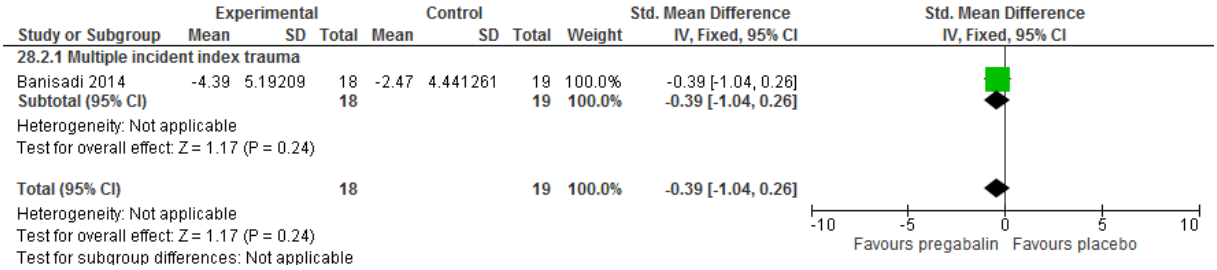


Figure 204: Pregabalin (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (HAM-D change score)

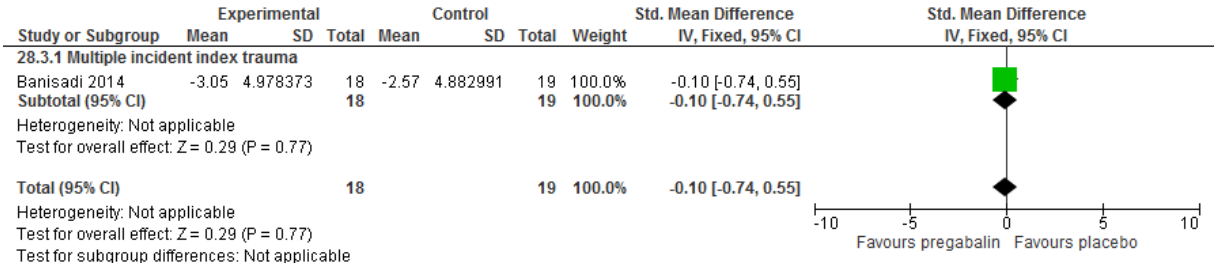
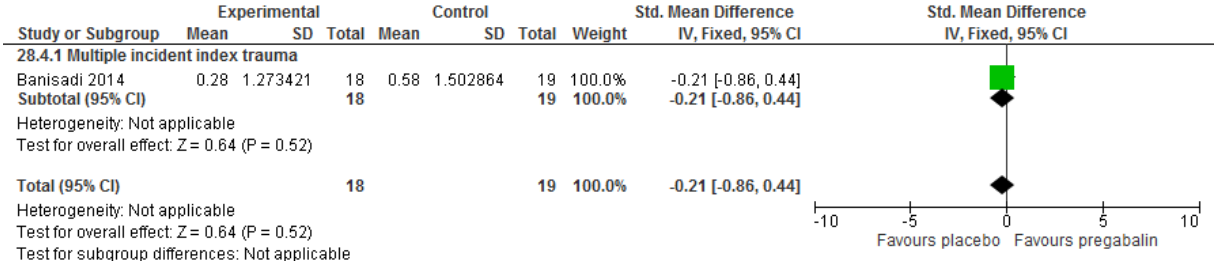


Figure 205: Pregabalin (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Quality of life (Spitzer Quality of Life Index change score)



Antipsychotics

Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 206: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (DTS change score)

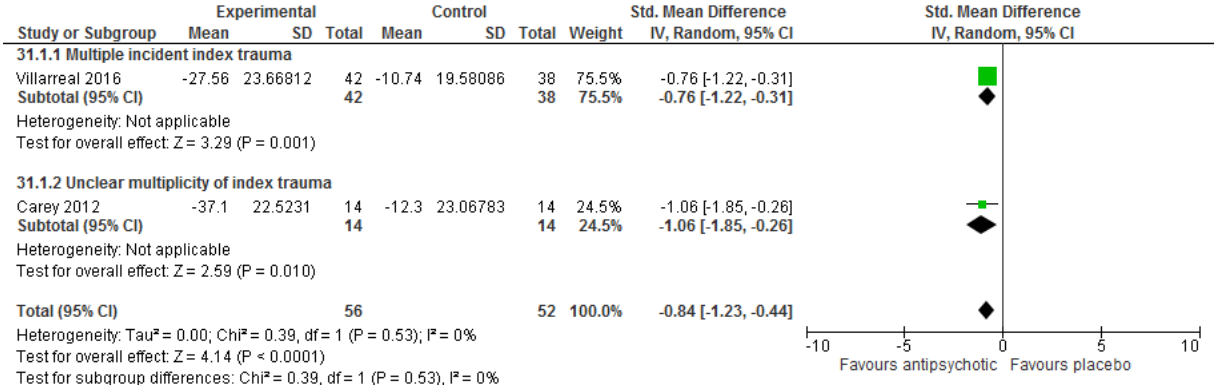


Figure 207: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

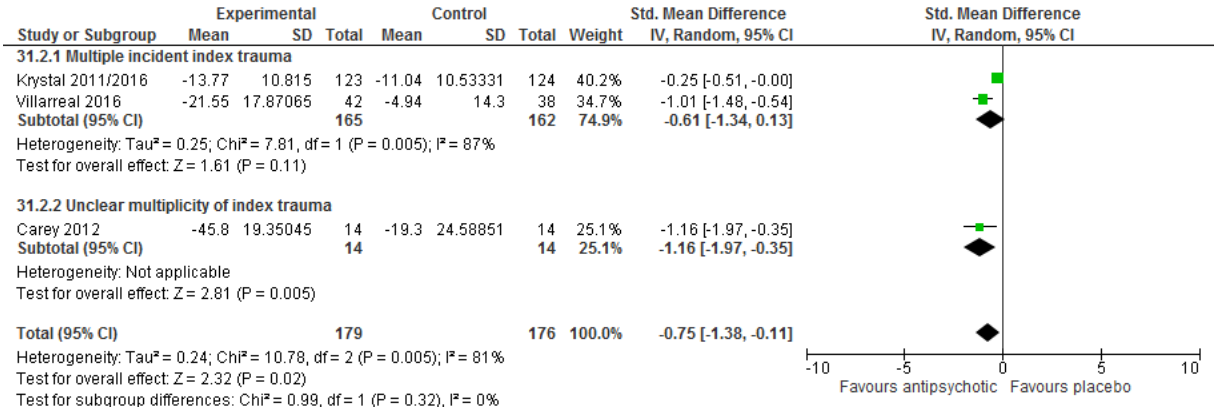


Figure 208: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Remission (number of people scoring <50 on CAPS)

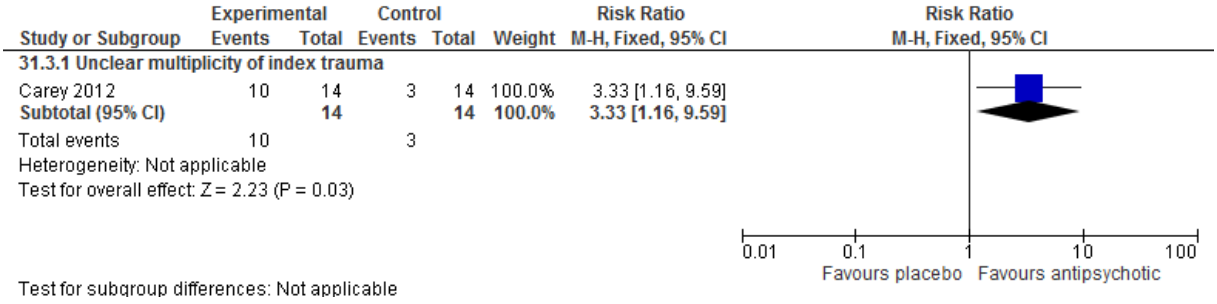


Figure 209: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people showing >50% improvement on CAPS)

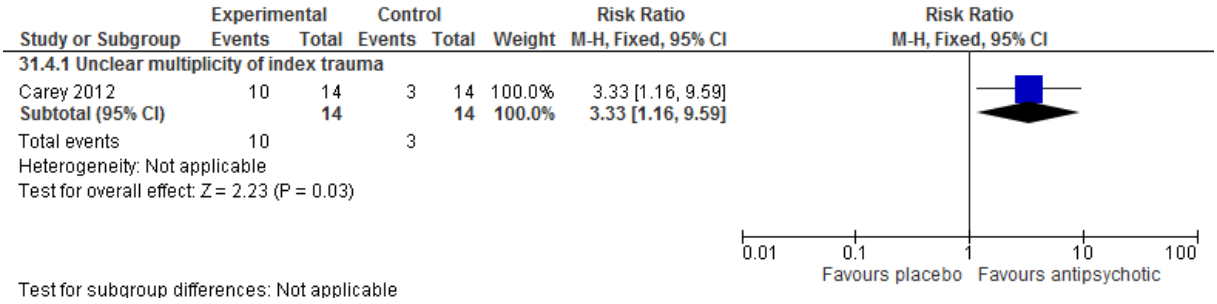


Figure 210: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms (HAM-A change score)

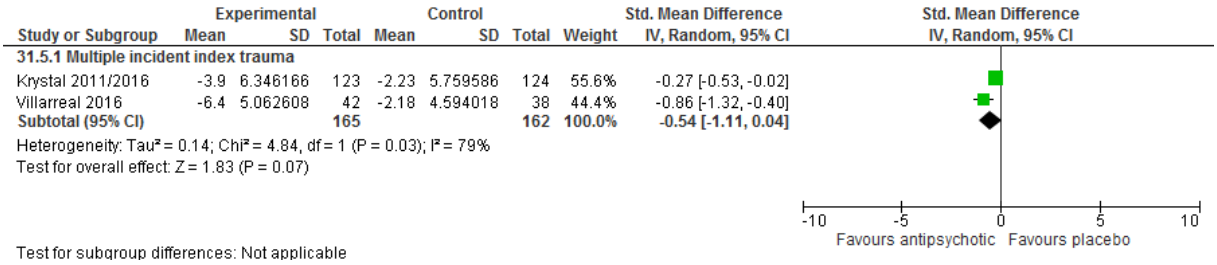


Figure 211: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (MADRS/HAM-D change score)

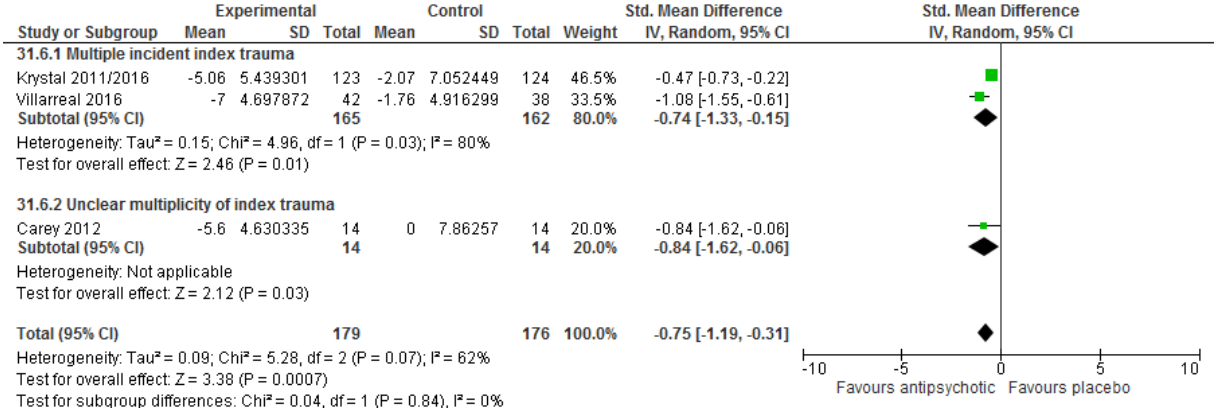


Figure 212: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Functional impairment (SDS change score)

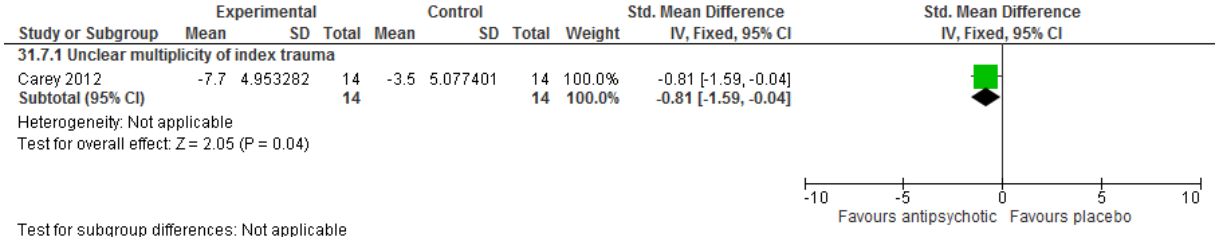


Figure 213: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Quality of life (BLSI change score)

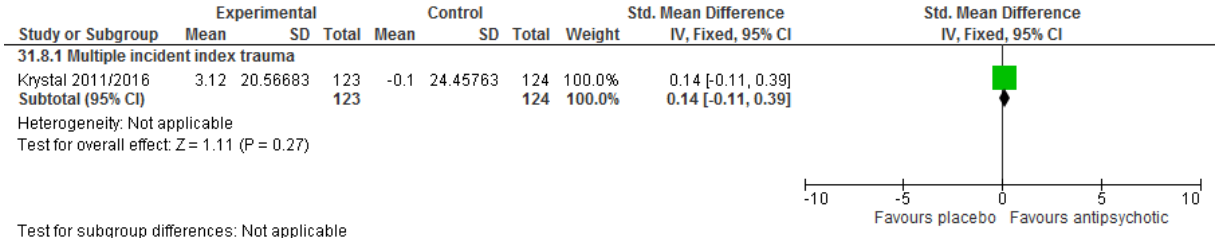


Figure 214: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Sleeping difficulties (PSQI change score)

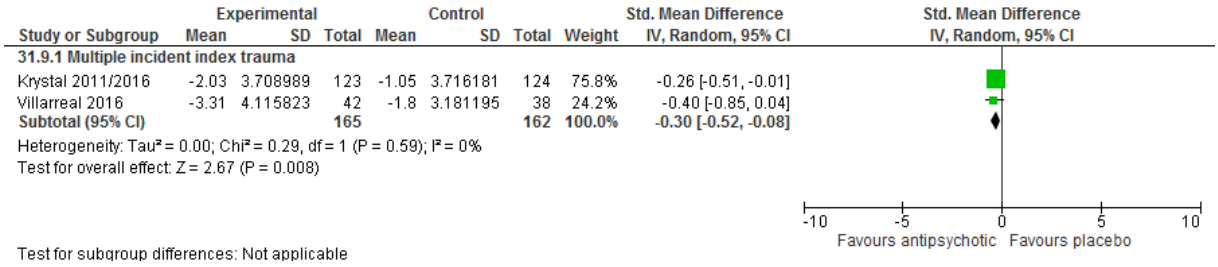


Figure 215: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

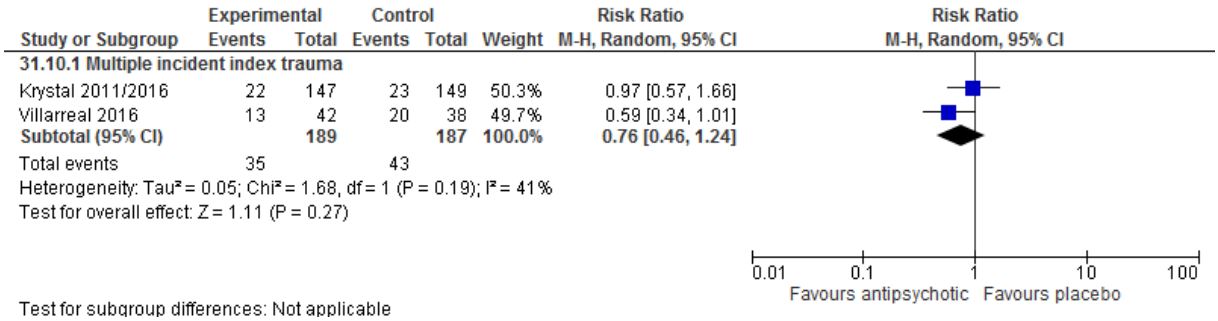


Figure 216: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events

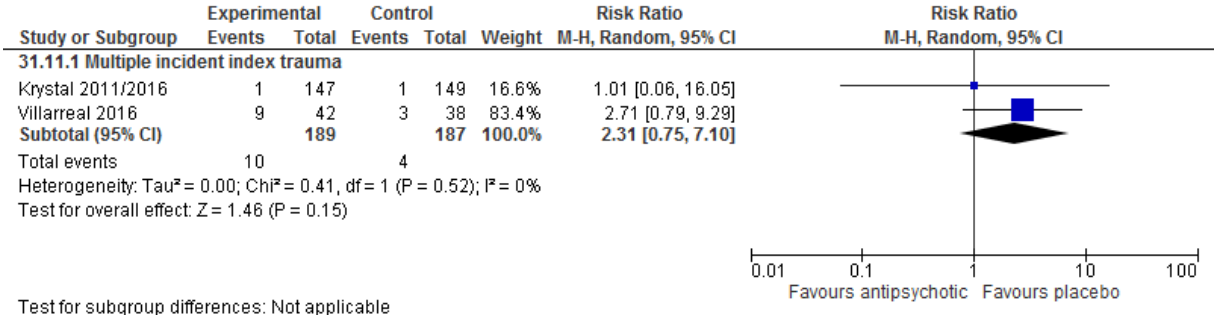
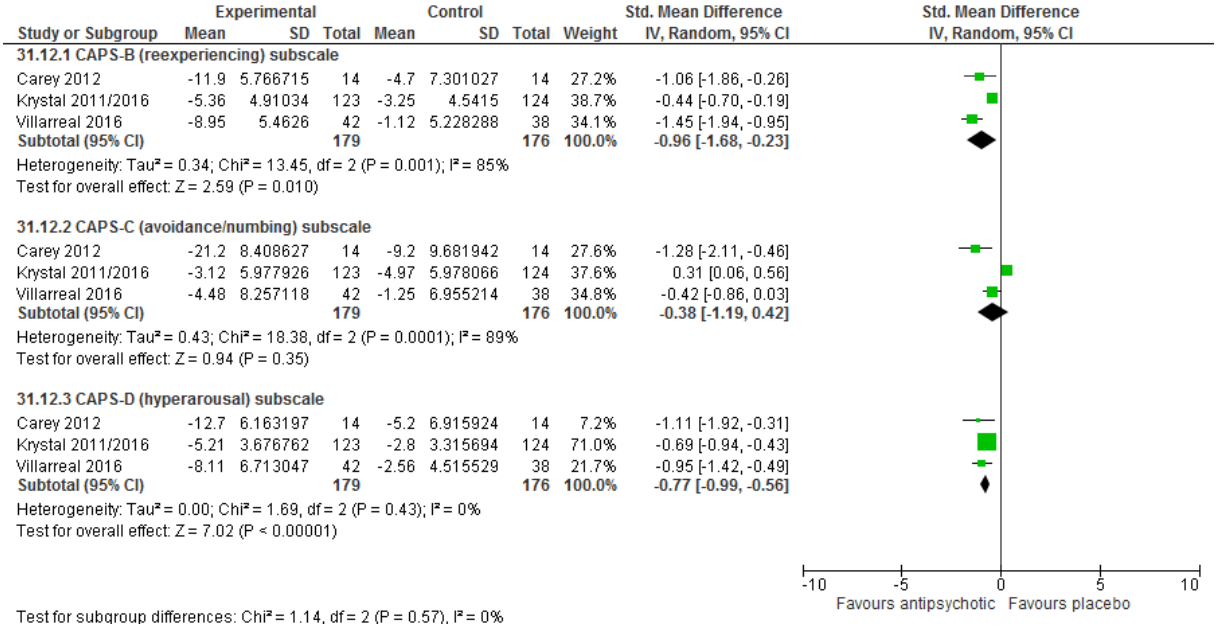


Figure 217: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomology by subscale



Sub-analysis by specific intervention: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 218: Sub-analysis by specific intervention: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (DTS change score)

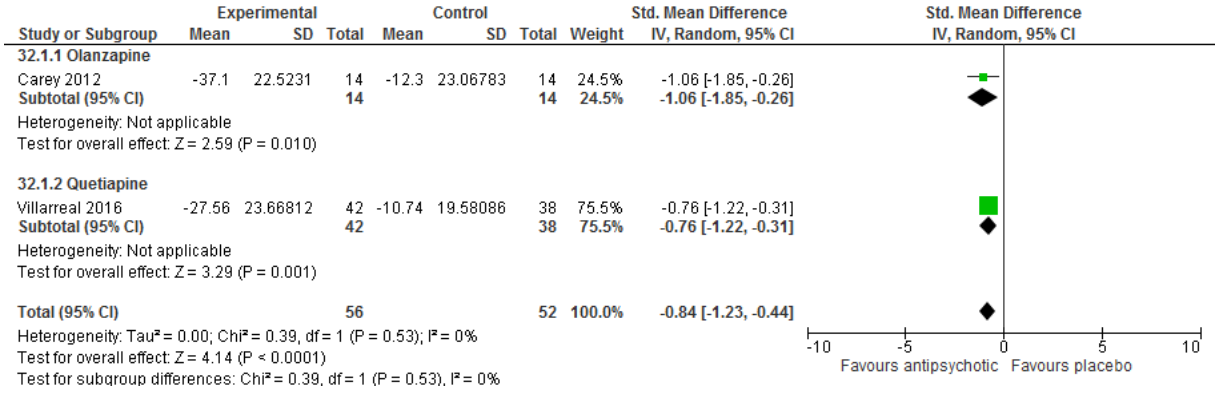


Figure 219: Sub-analysis by specific intervention: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

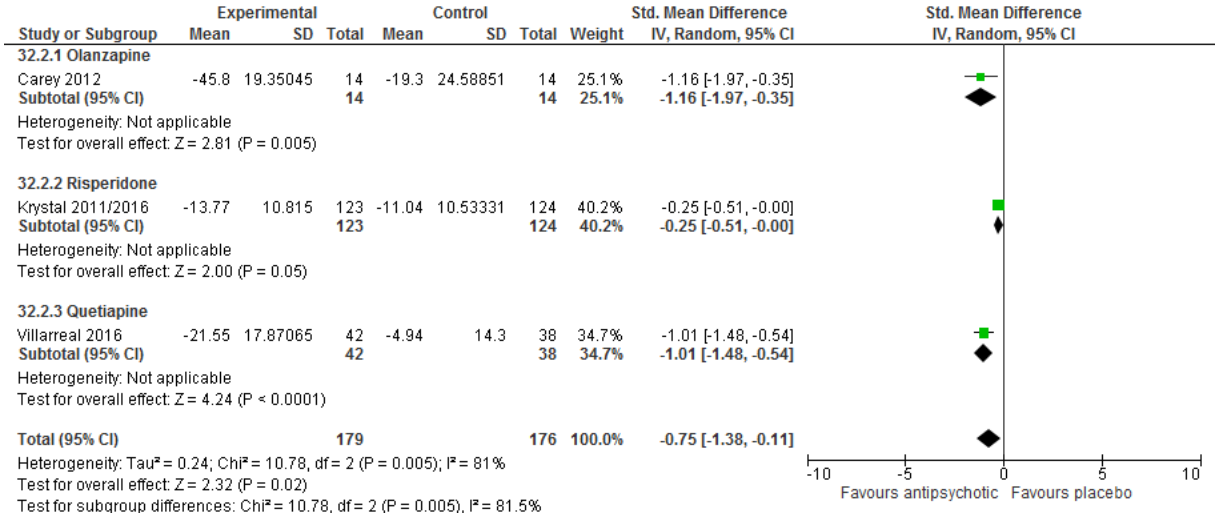


Figure 220: Sub-analysis by specific intervention: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Remission (number of people scoring <50 on CAPS)

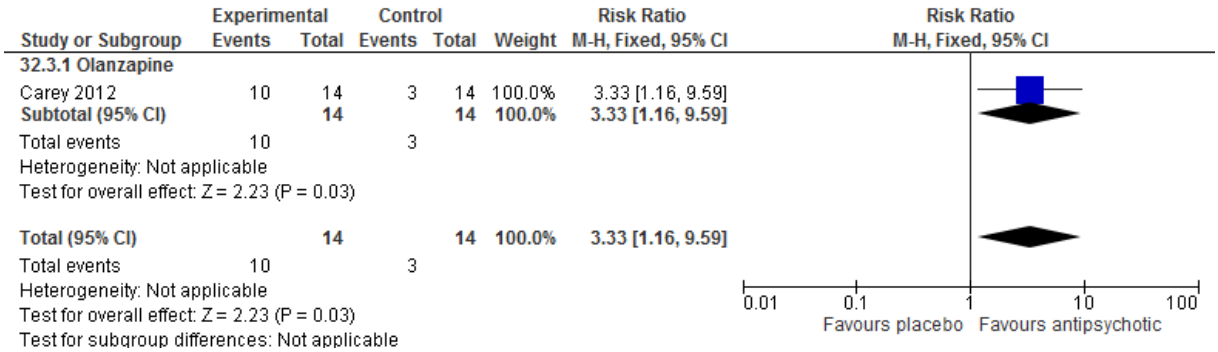


Figure 221: Sub-analysis by specific intervention: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people showing >50% improvement on CAPS)

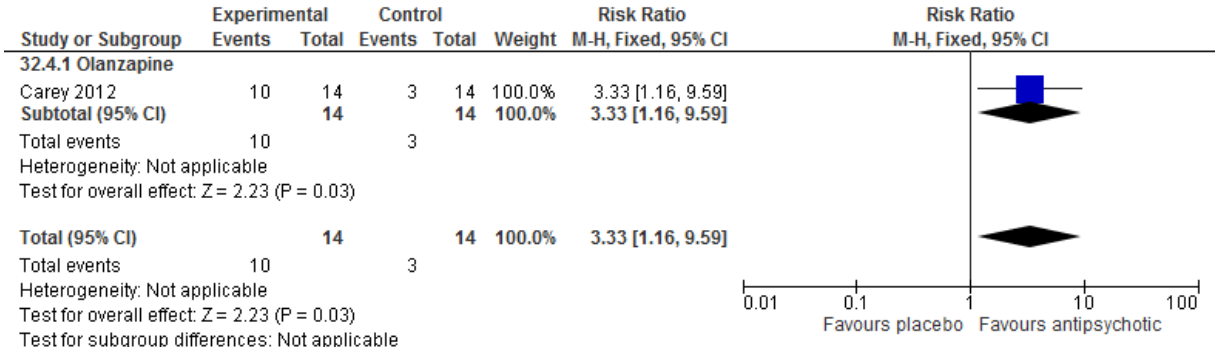


Figure 222: Sub-analysis by specific intervention: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms (HAM-A change score)

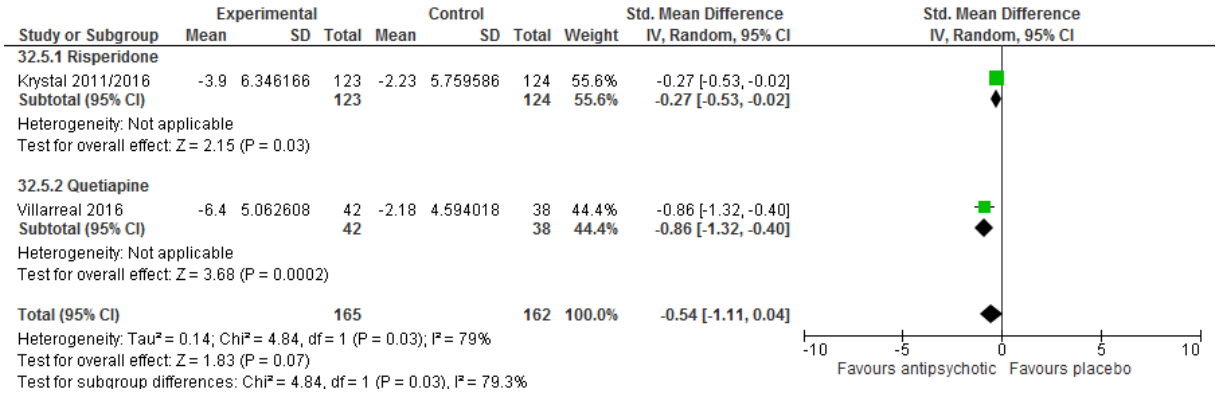


Figure 223: Sub-analysis by specific intervention: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (MADRS/HAM-D change score)

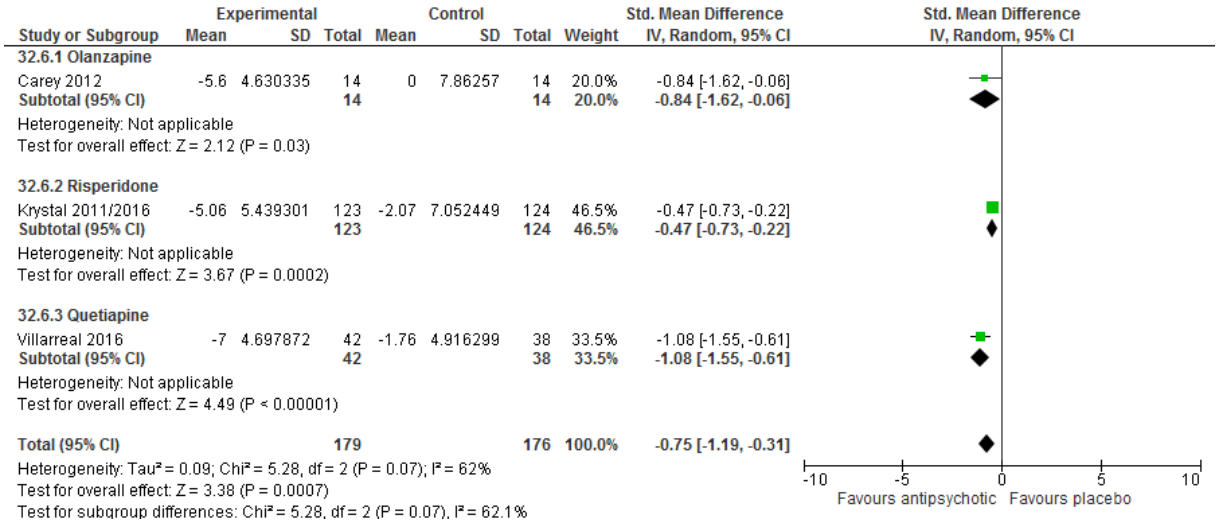


Figure 224: Sub-analysis by specific intervention: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Functional impairment (SDS change score)

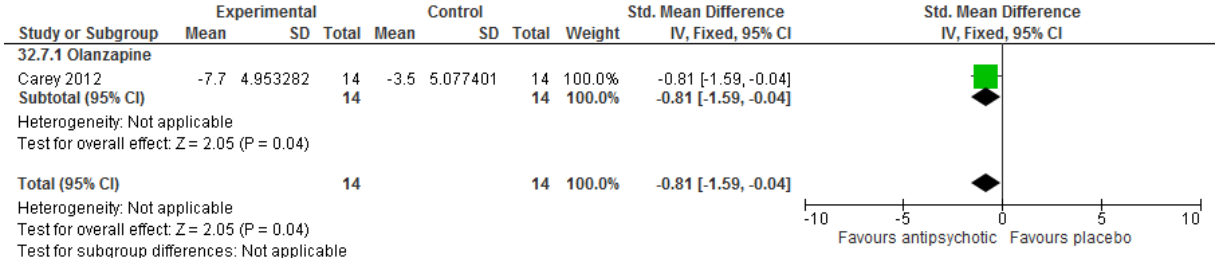


Figure 225: Sub-analysis by specific intervention: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Quality of life (BLSI change score)

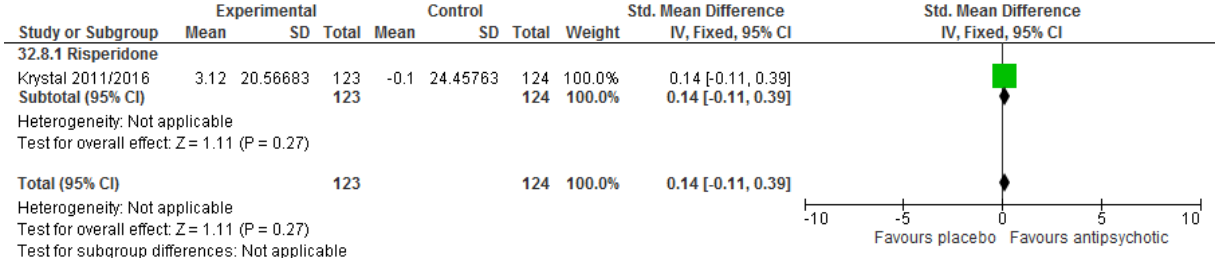


Figure 226: Sub-analysis by specific intervention: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Sleeping difficulties (PSQI change score)

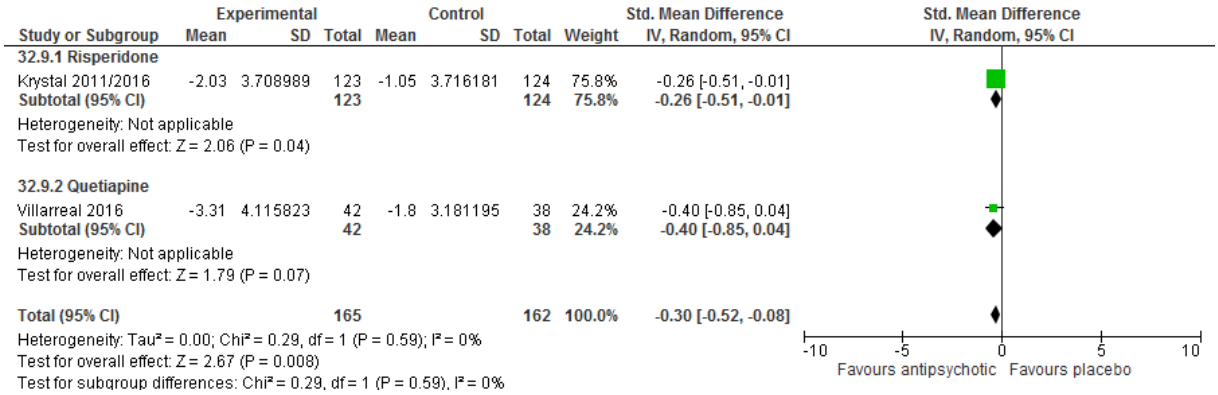


Figure 227: Sub-analysis by specific intervention: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

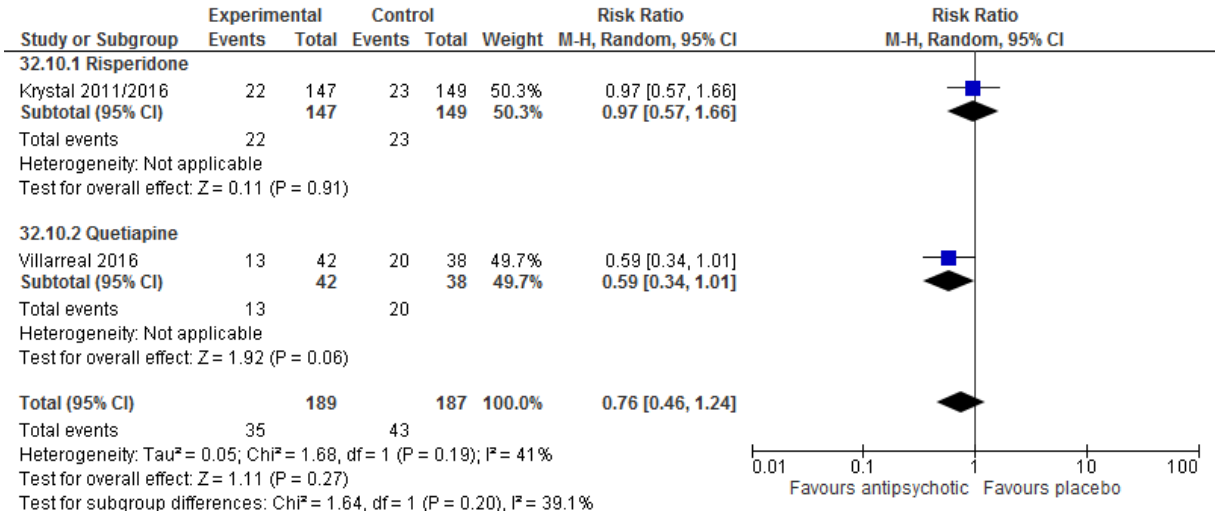
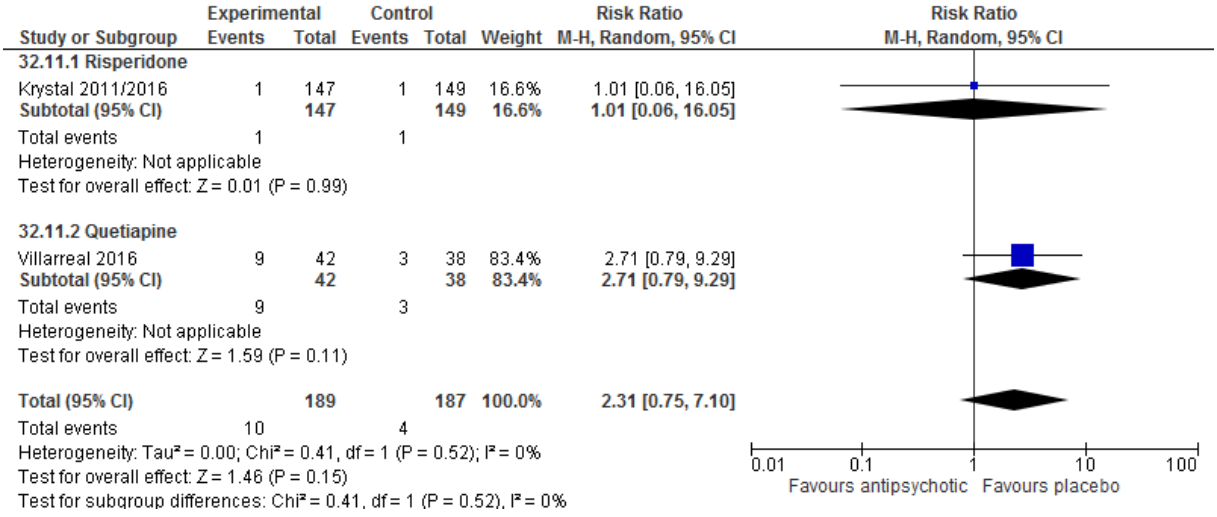


Figure 228: Sub-analysis by specific intervention: Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medication)

Figure 229: Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medication) of for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

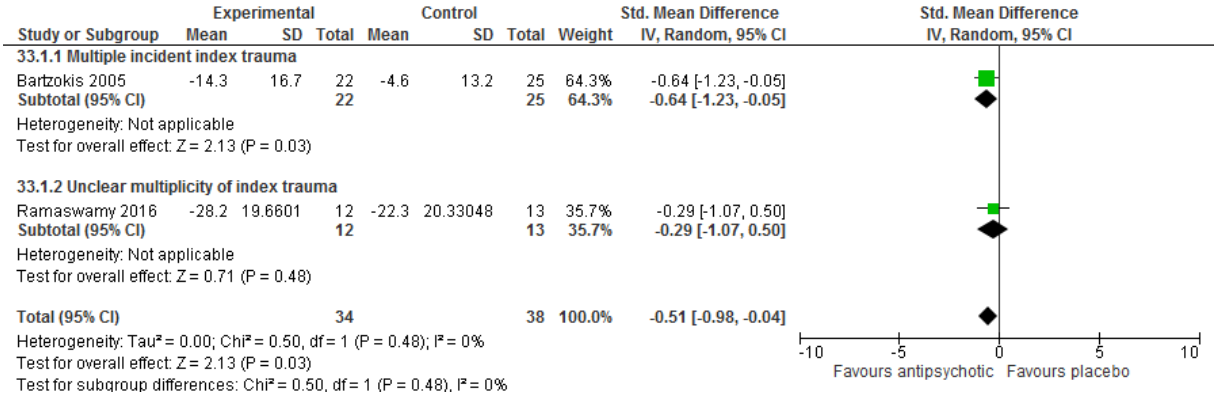


Figure 230: Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medication) of for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people showing ≥20/50% improvement on CAPS)

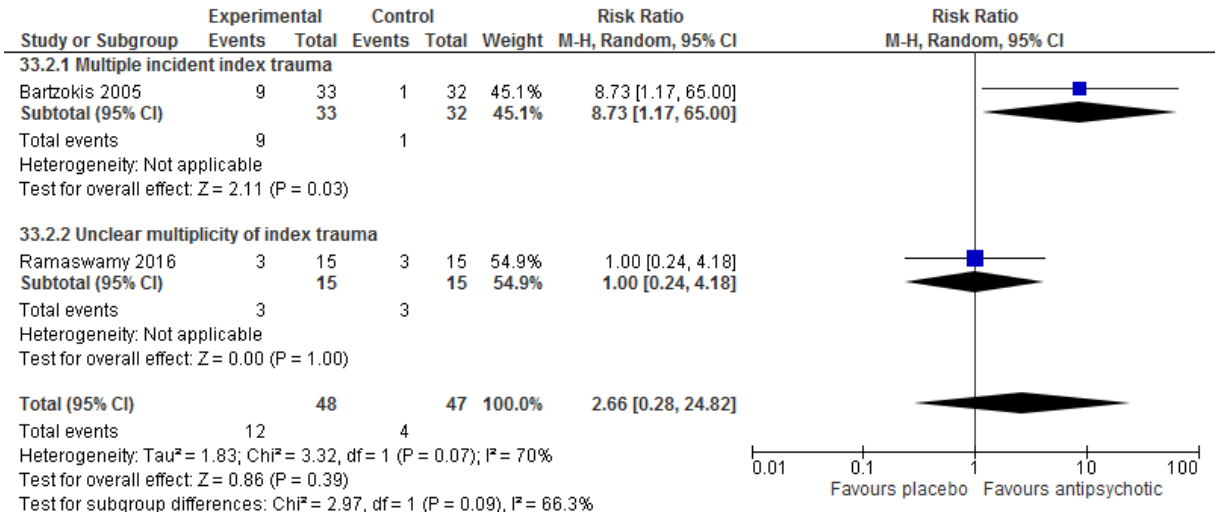


Figure 231: Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medication) of for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms (HAM-A change score)

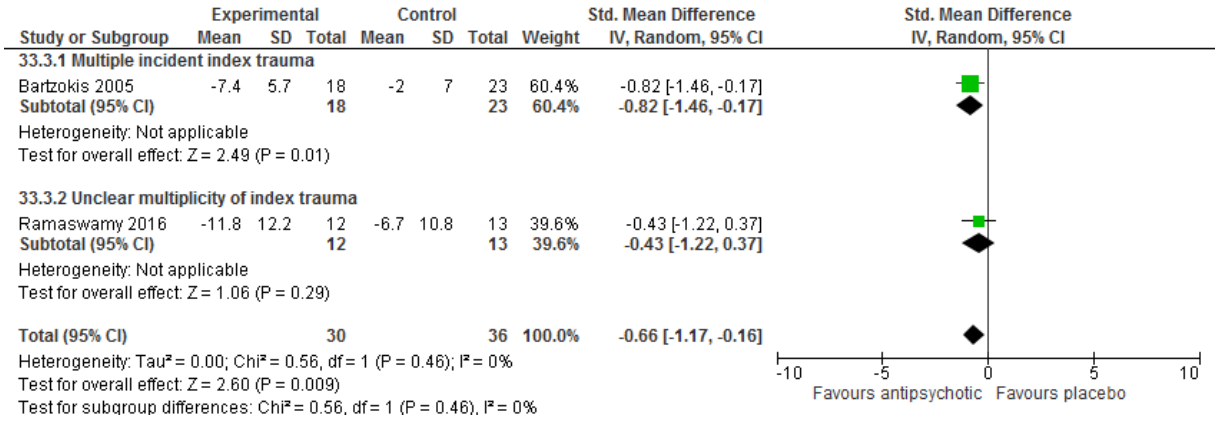


Figure 232: Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medication) of for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (HAM-D change score)

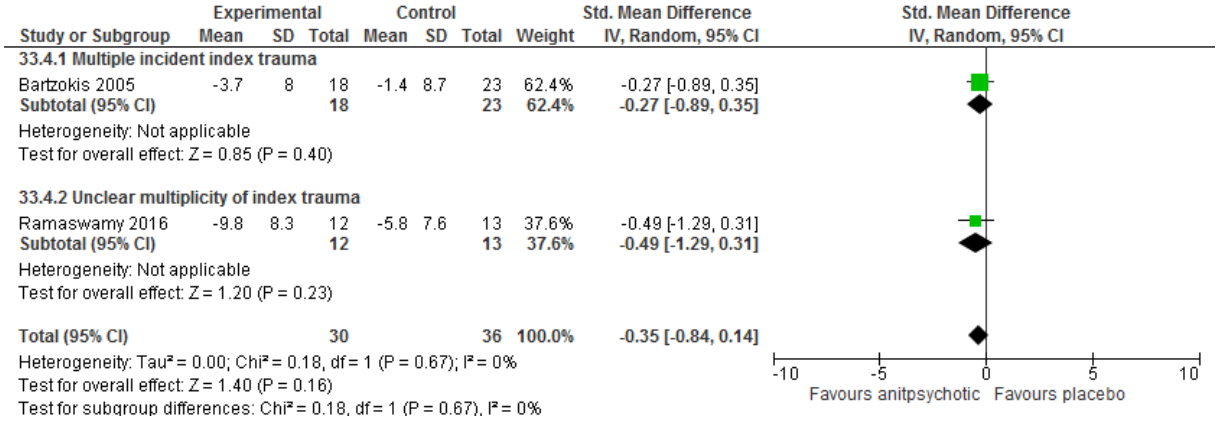


Figure 233: Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medication) of for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

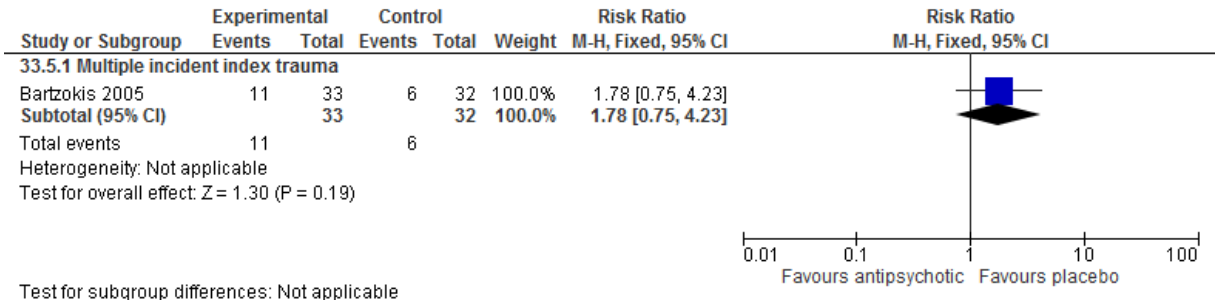


Figure 234: Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medication) of for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events

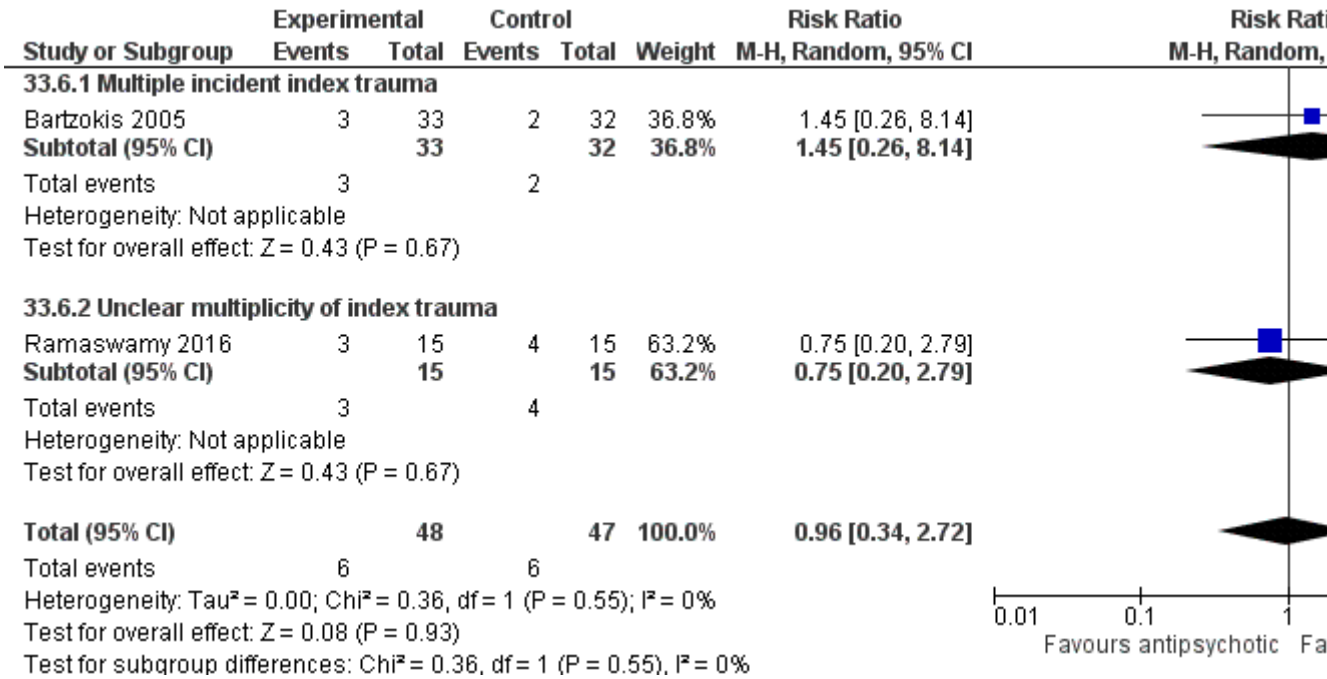
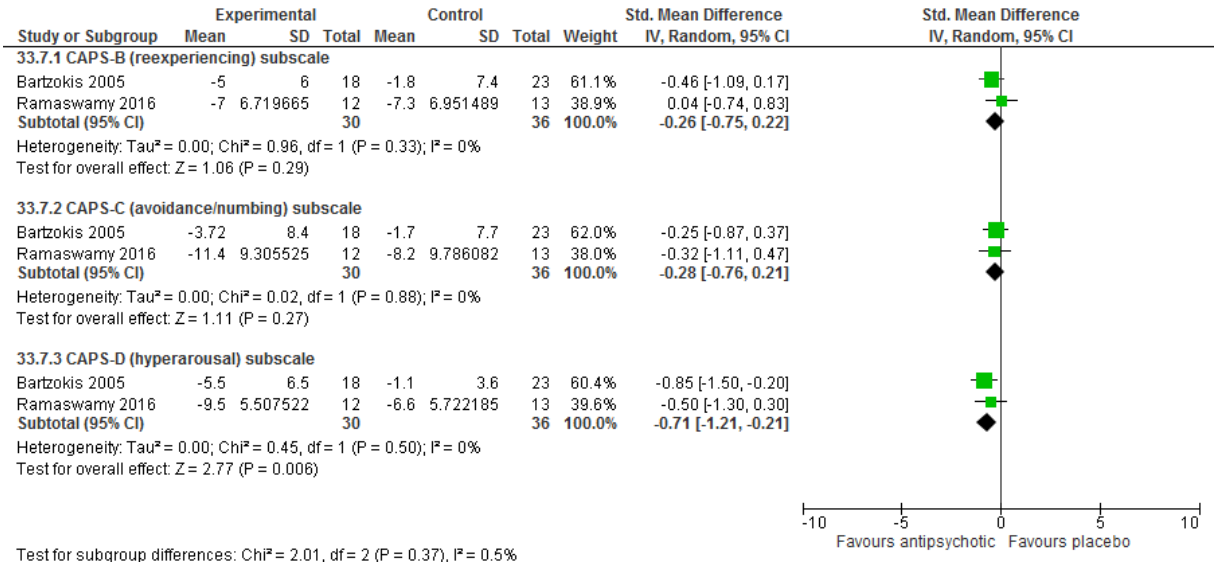


Figure 235: Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medication) of for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomology by subscale



Sub-analysis by specific intervention: Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 236: Sub-analysis by specific intervention: Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medications) of for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

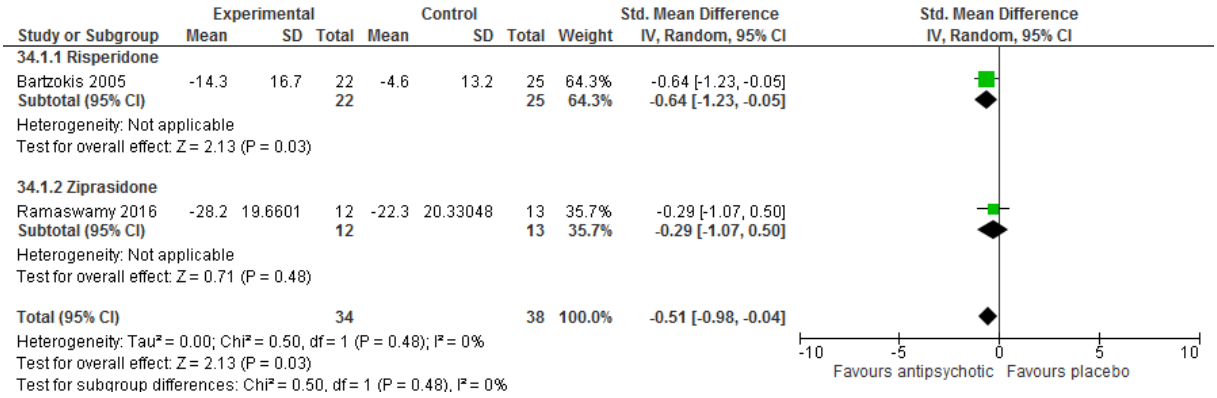


Figure 237: Sub-analysis by specific intervention: Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medications) of for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people showing ≥20% improvement on CAPS)

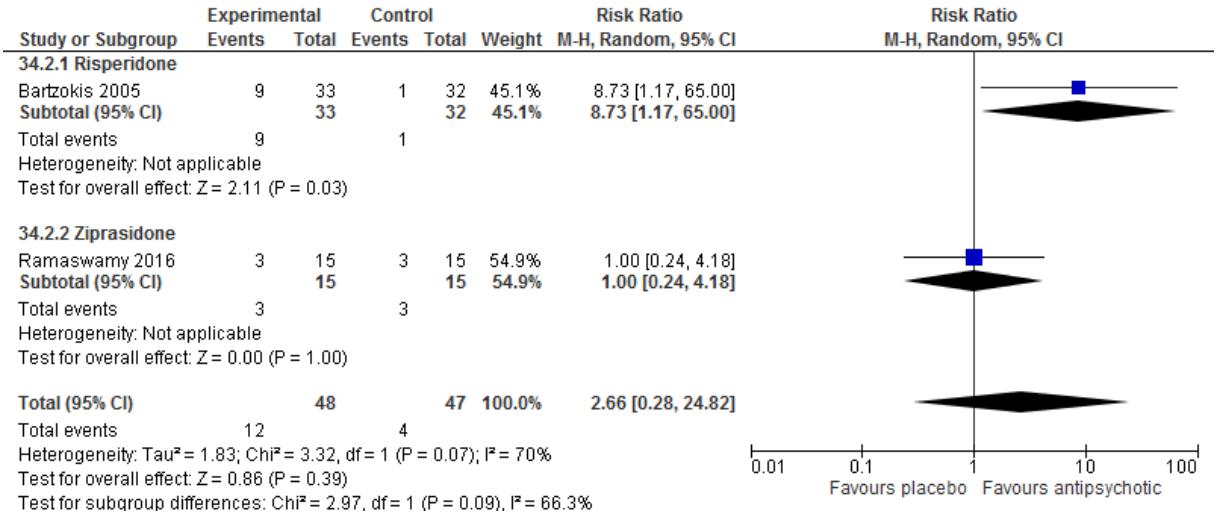


Figure 238: Sub-analysis by specific intervention: Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medications) of for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms (HAM-A change score)

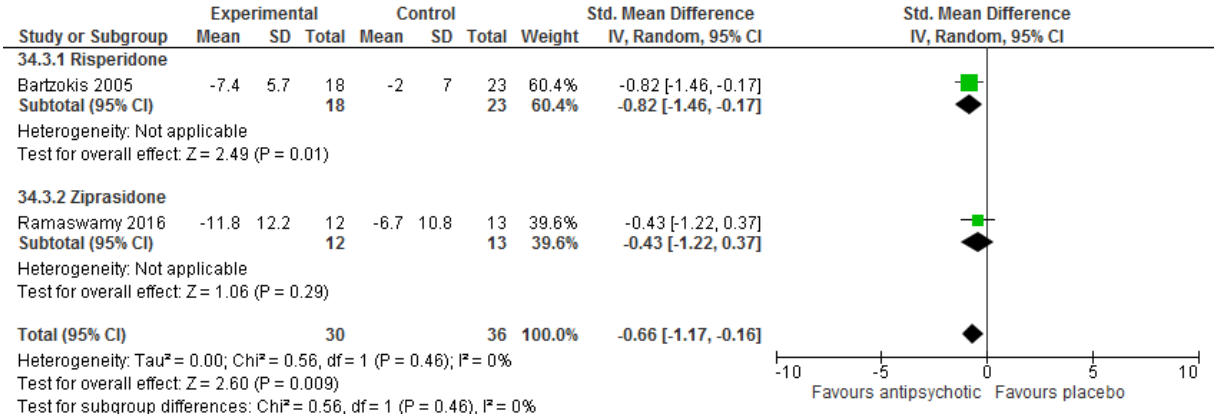


Figure 239: Sub-analysis by specific intervention: Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medications) of for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (HAM-D change score)

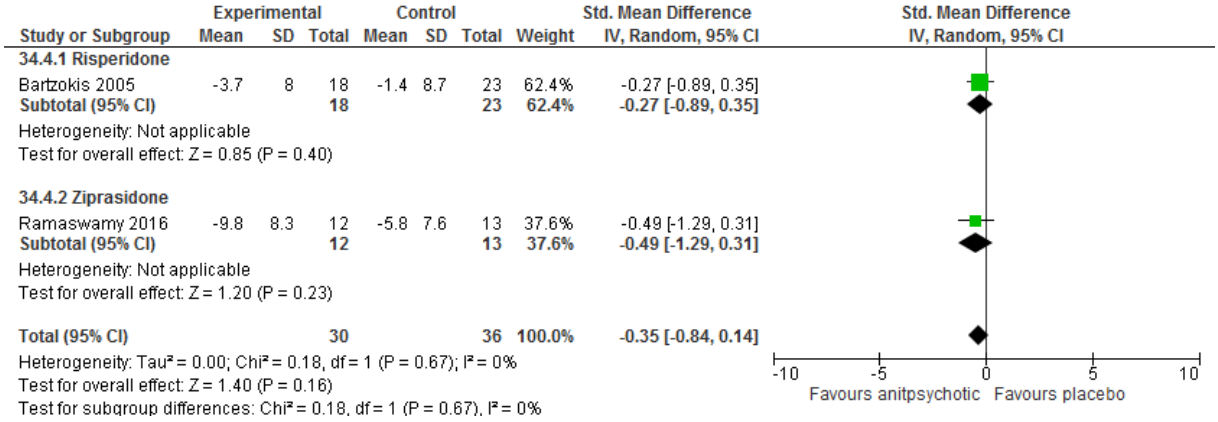


Figure 240: Sub-analysis by specific intervention: Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medications) of for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

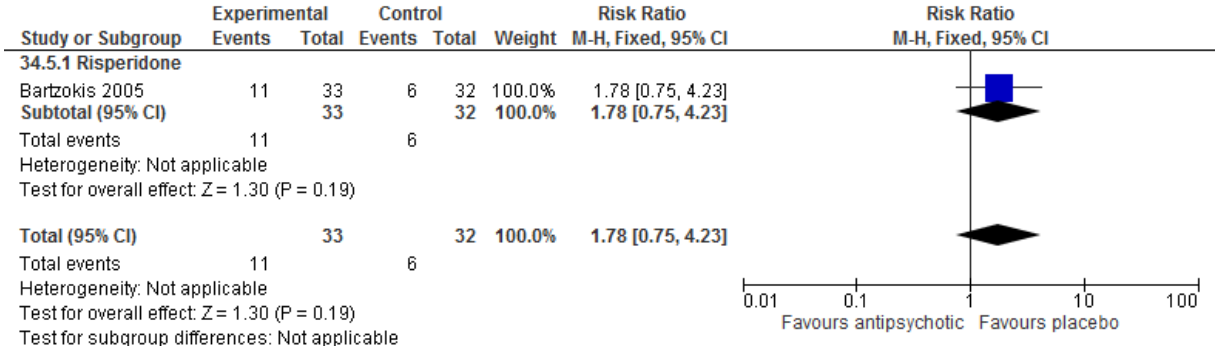
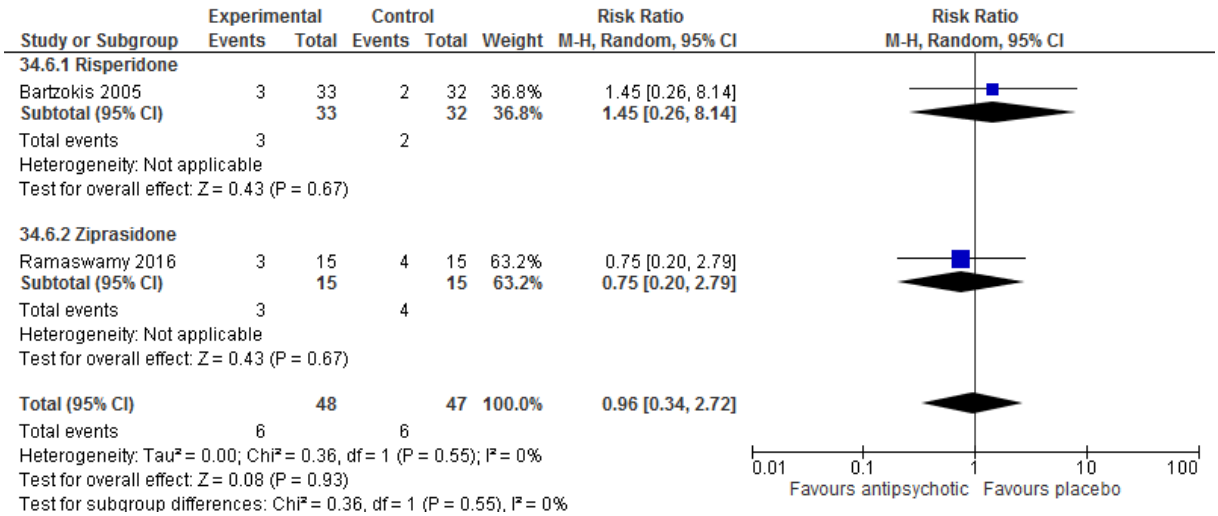


Figure 241: Sub-analysis by specific intervention: Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medications) of for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Benzodiazepines

Alprazolam (+ virtual reality exposure therapy) versus placebo (+ virtual reality exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms

Figure 242: Alprazolam (+virtual reality exposure therapy) versus placebo (+virtual reality exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-report (PSS-SR change score); Multiple incident index trauma

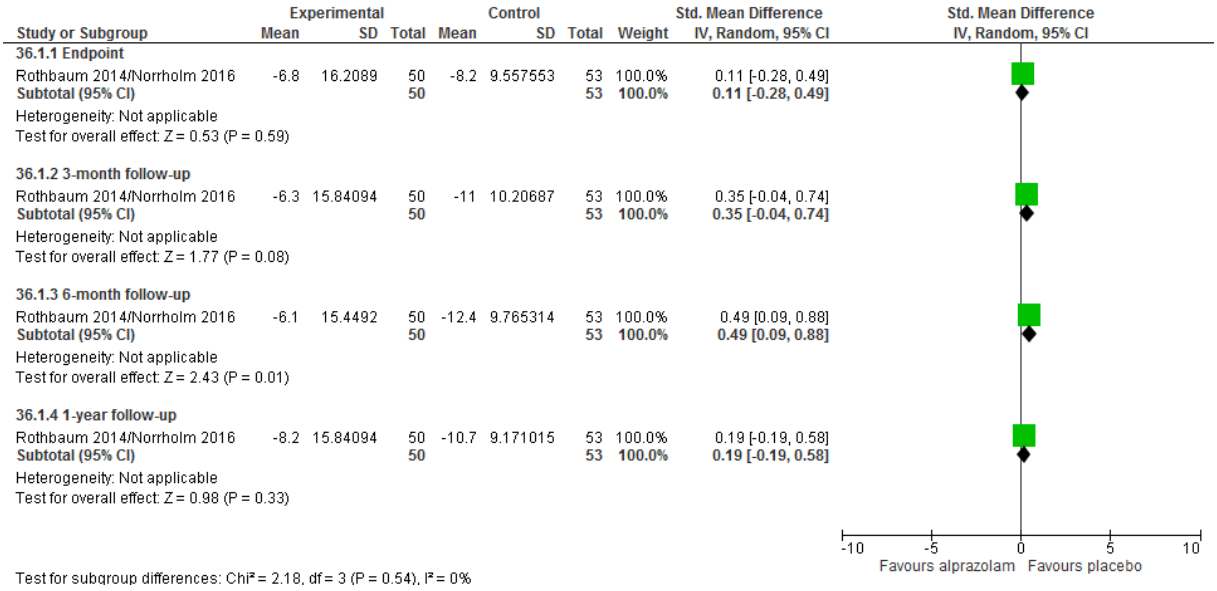


Figure 243: Alprazolam (+virtual reality exposure therapy) versus placebo (+virtual reality exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score); Multiple incident index trauma

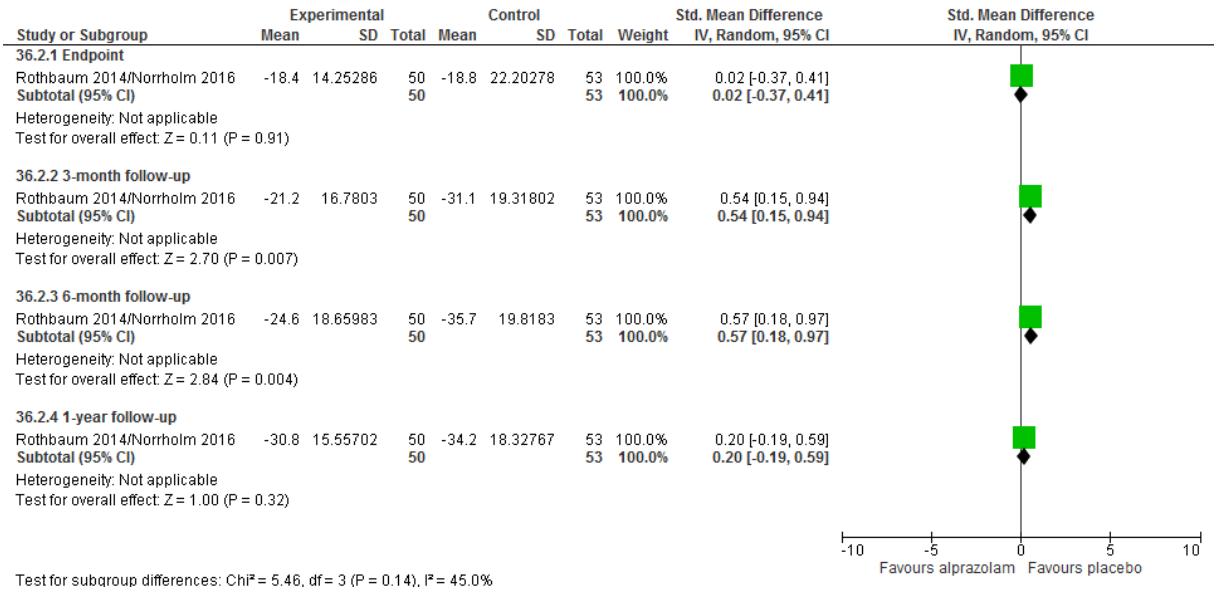


Figure 244: Alprazolam (+virtual reality exposure therapy) versus placebo (+virtual reality exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Remission (number of people no longer meeting diagnostic criteria for PTSD); Multiple incident index trauma

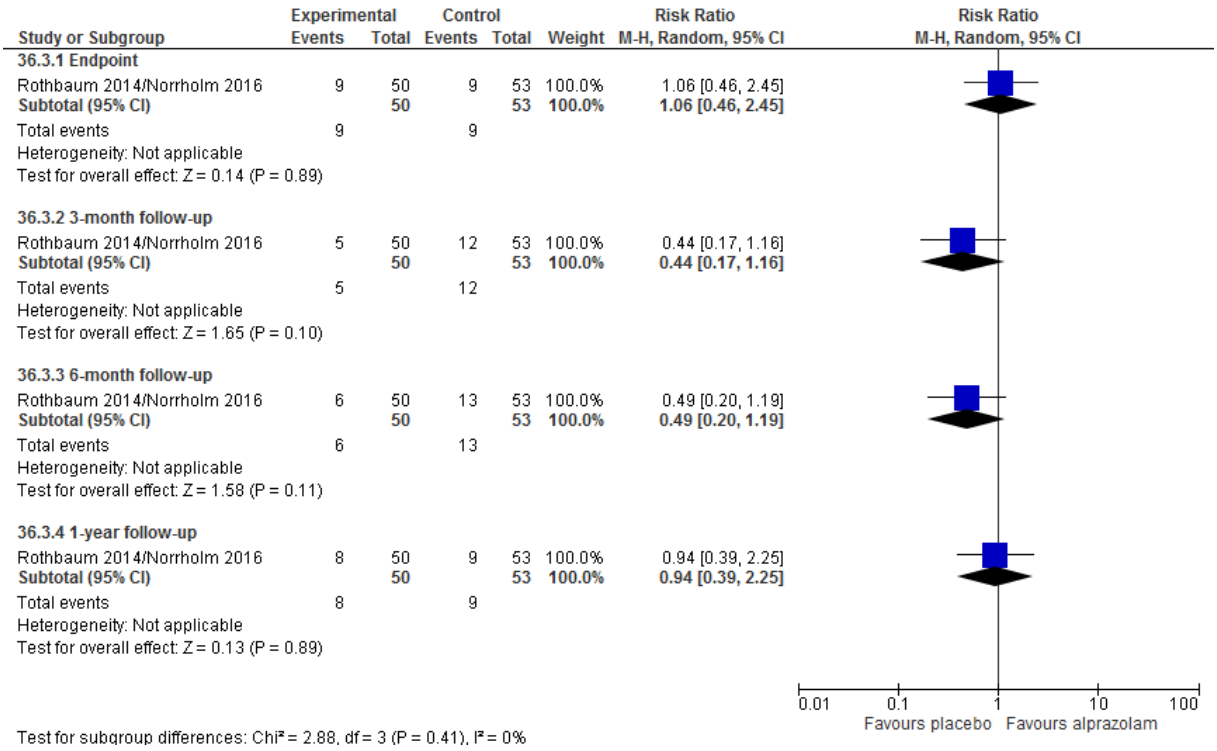
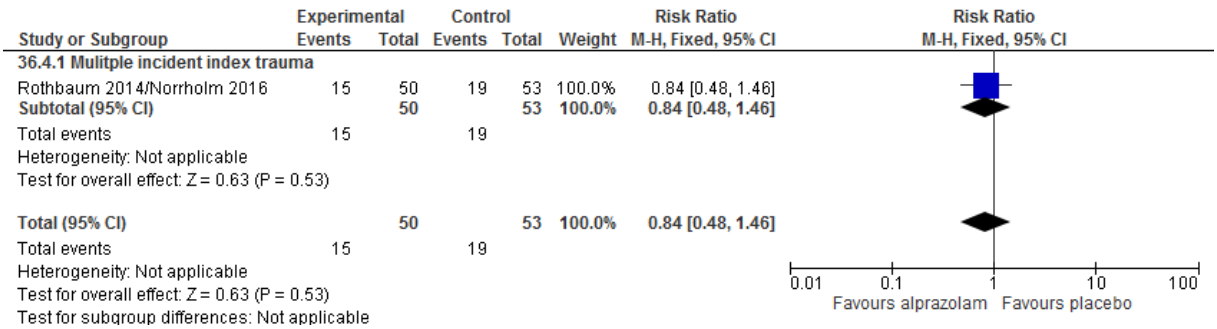


Figure 245: Alprazolam (+virtual reality exposure therapy) versus placebo (+virtual reality exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)



Alprazolam (+ virtual reality exposure therapy) versus d-cycloserine (+ virtual reality exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 246: Alprazolam (+virtual reality exposure therapy) versus d-cycloserine (+virtual reality exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-report (PSS-SR change score); Multiple incident index trauma

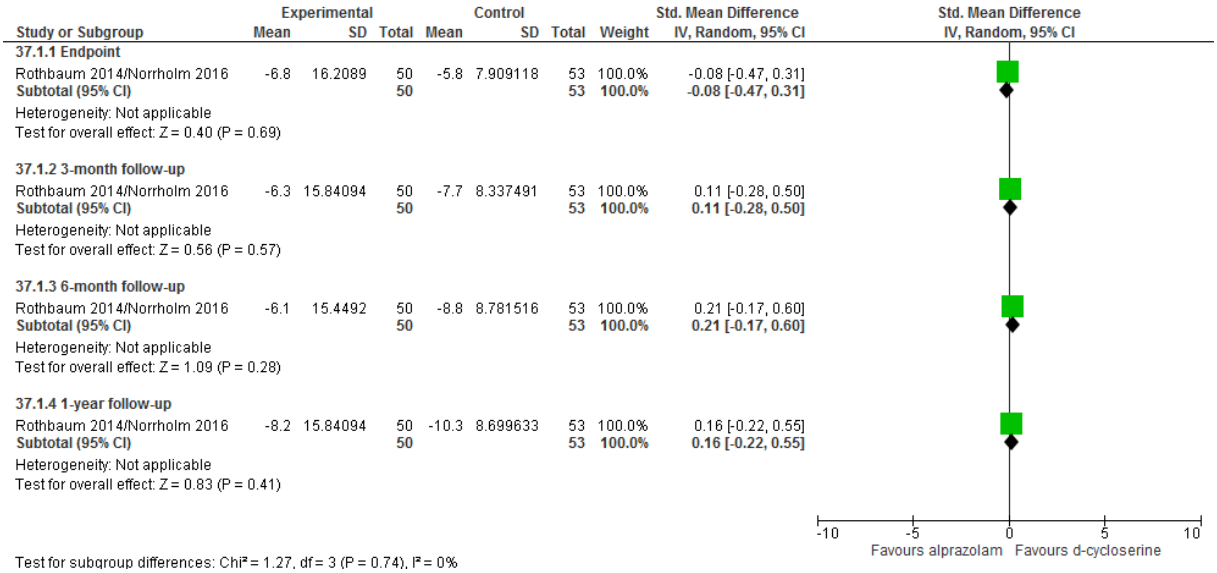


Figure 247: Alprazolam (+virtual reality exposure therapy) versus d-cycloserine (+virtual reality exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score); Multiple incident index trauma

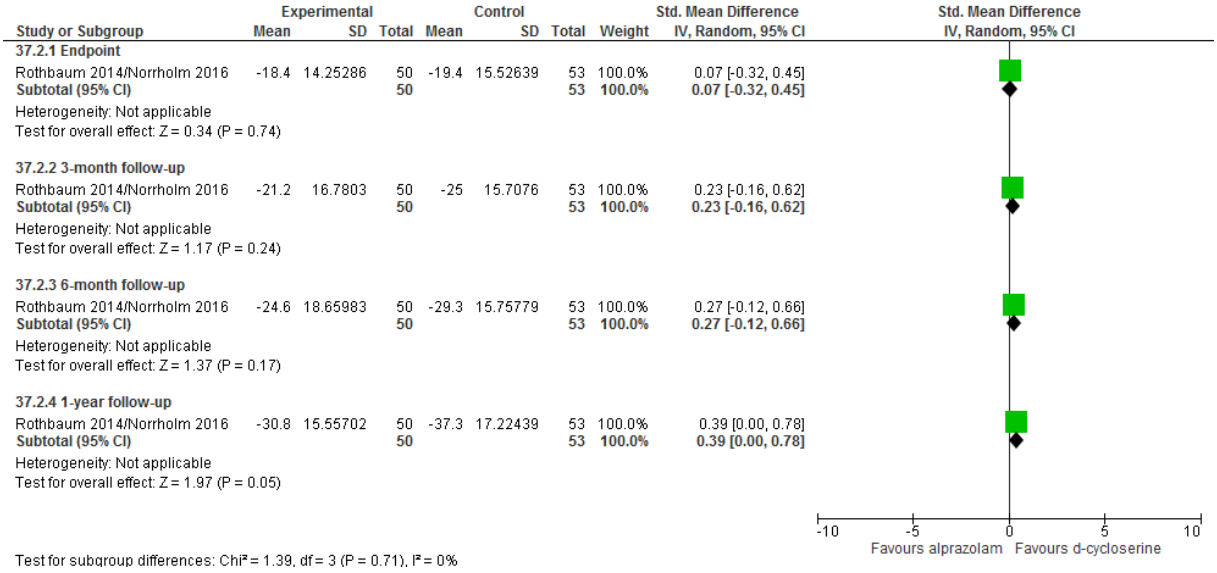


Figure 248: Alprazolam (+virtual reality exposure therapy) versus d-cycloserine (+virtual reality exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Remission (number of people no longer meeting diagnostic criteria for PTSD); Multiple incident index trauma

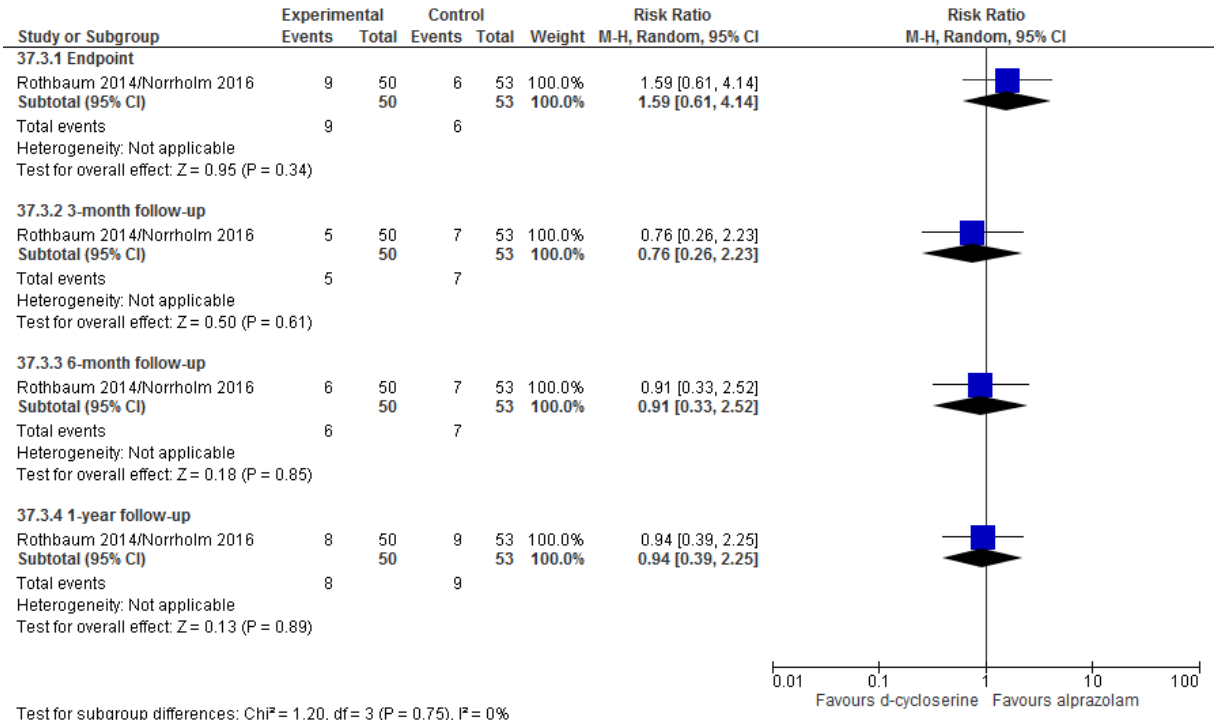
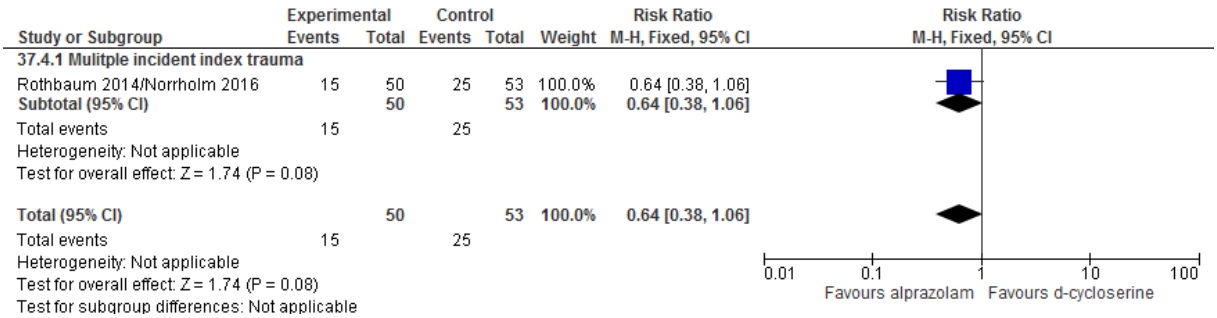


Figure 249: Alprazolam (+virtual reality exposure therapy) versus d-cycloserine (+virtual reality exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)



Other drugs: Prazosin

Prazosin (±TAU) versus placebo (± TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 250: Prazosin (±TAU) versus placebo (±TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated at endpoint (PCL change score)

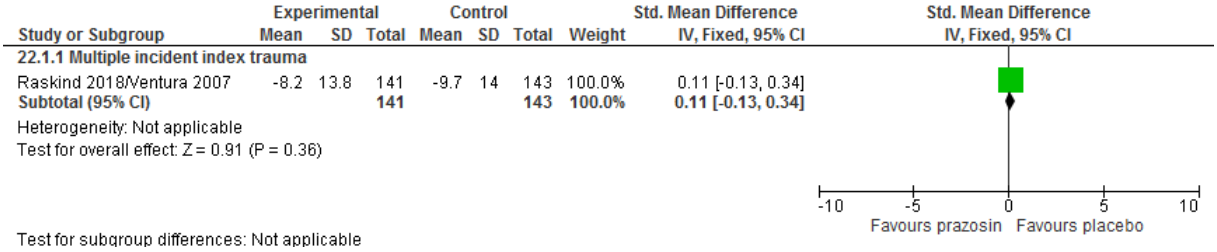


Figure 251: Prazosin (±TAU) versus placebo (±TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS/MINI change score)

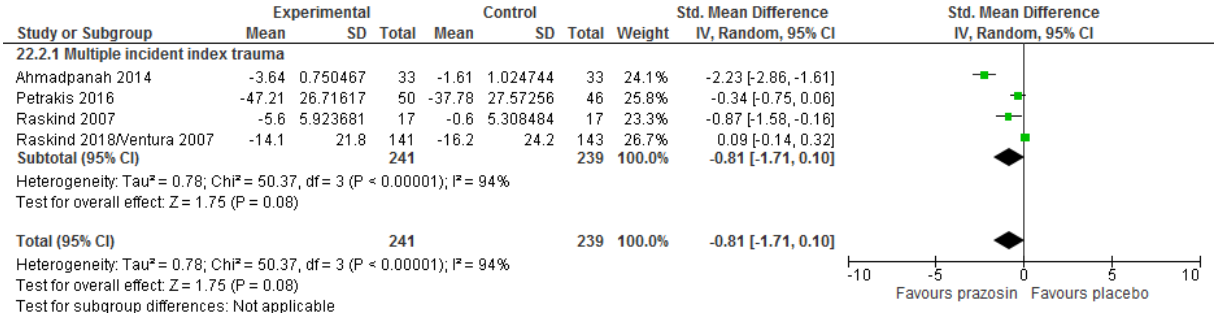


Figure 252: Prazosin (±TAU) versus placebo (±TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response (number of people rated as 'much' or 'very much' improved on CGI-I)

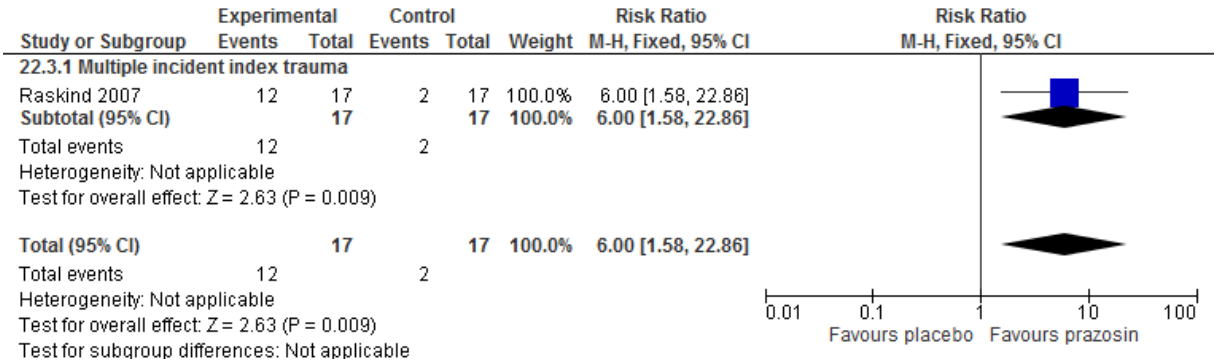


Figure 253: Prazosin (±TAU) versus placebo (±TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms at endpoint (BDI/HAM-D/PHQ-9 change score)

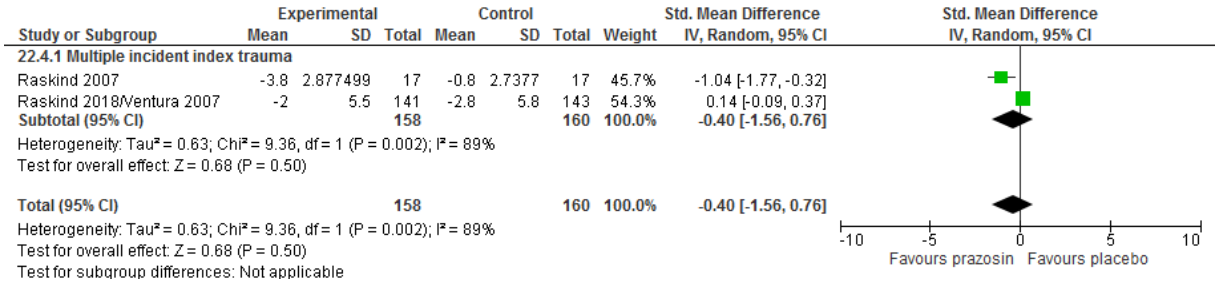


Figure 254: Prazosin (±TAU) versus placebo (±TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Alcohol use (TLFB): Number of participants abstinent from alcohol during the trial

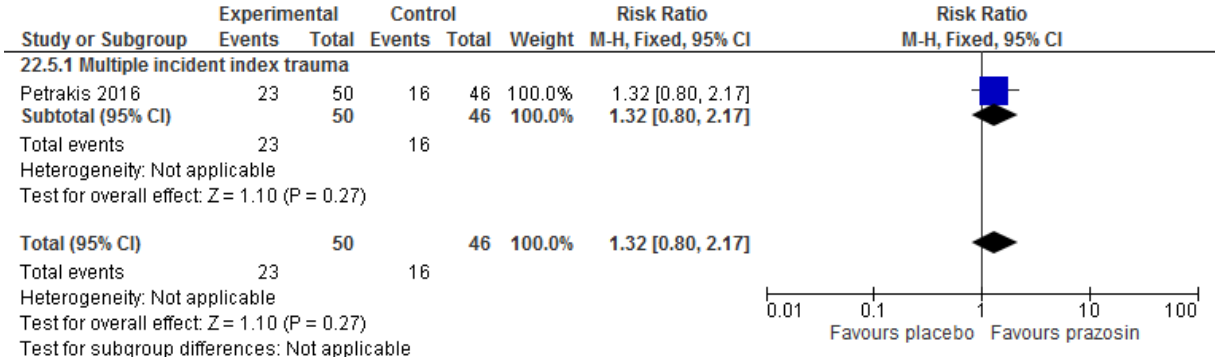


Figure 255: Prazosin (±TAU) versus placebo (±TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Alcohol craving/consumption (OCDS/AUDIT-C change score)

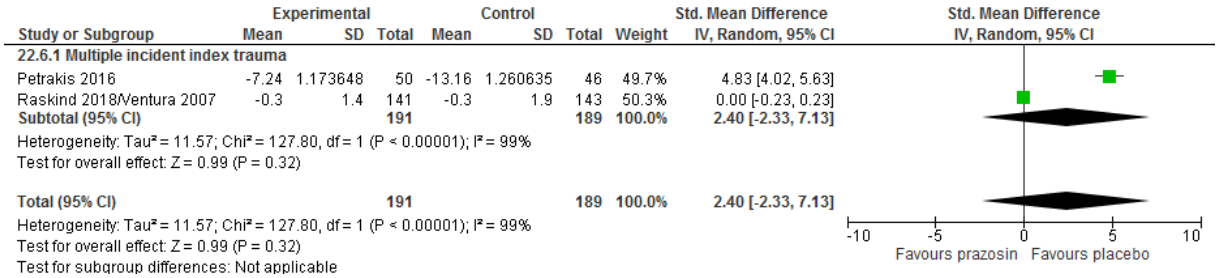


Figure 256: Prazosin (±TAU) versus placebo (±TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Sleeping difficulties at endpoint (PSQI change score)

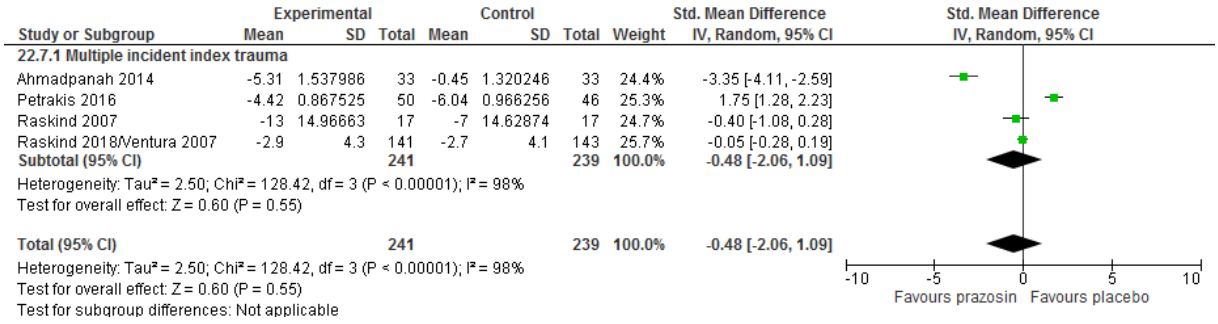


Figure 257: Prazosin (±TAU) versus placebo (±TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Quality of life (QOLI change score)

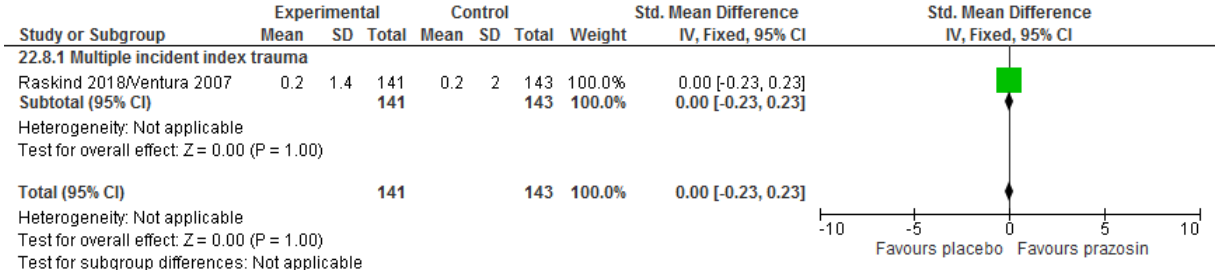


Figure 258: Prazosin (±TAU) versus placebo (±TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

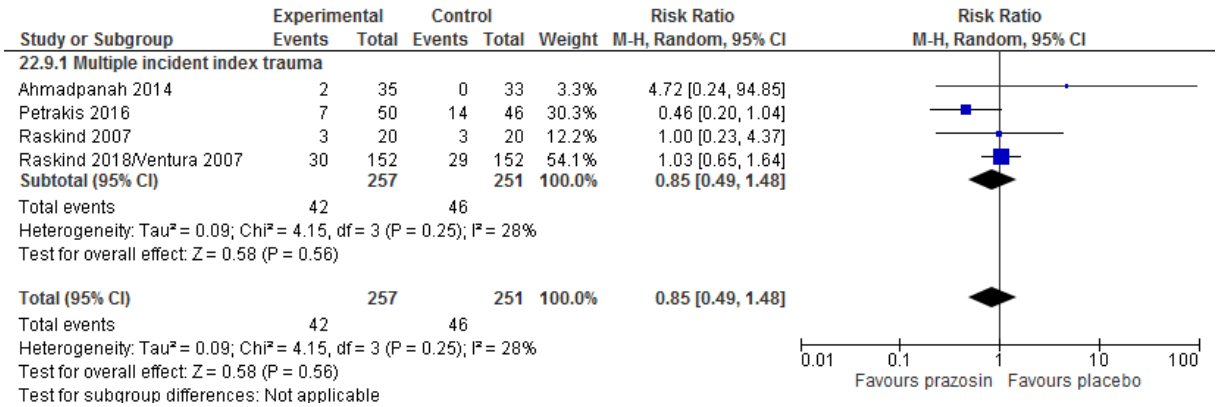
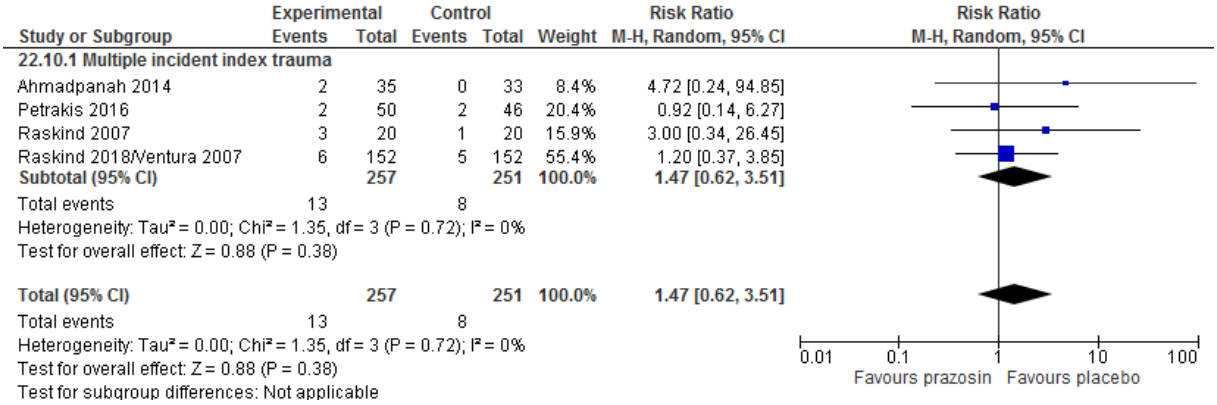


Figure 259: Prazosin (±TAU) versus placebo (±TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Prazosin versus hydroxyzine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 260: Prazosin versus hydroxyzine for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (MINI change score)

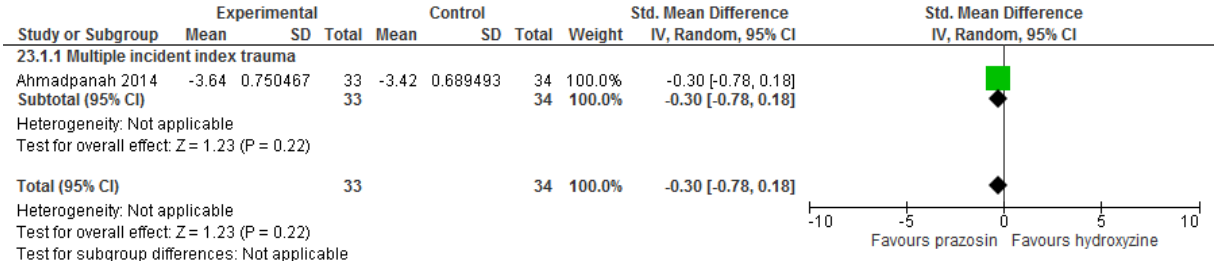


Figure 261: Prazosin versus hydroxyzine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Sleeping difficulties (PSQI change score)

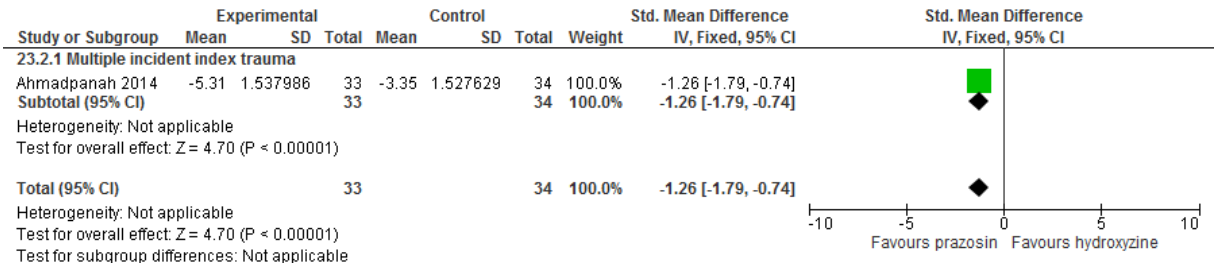


Figure 262: Prazosin versus hydroxyzine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

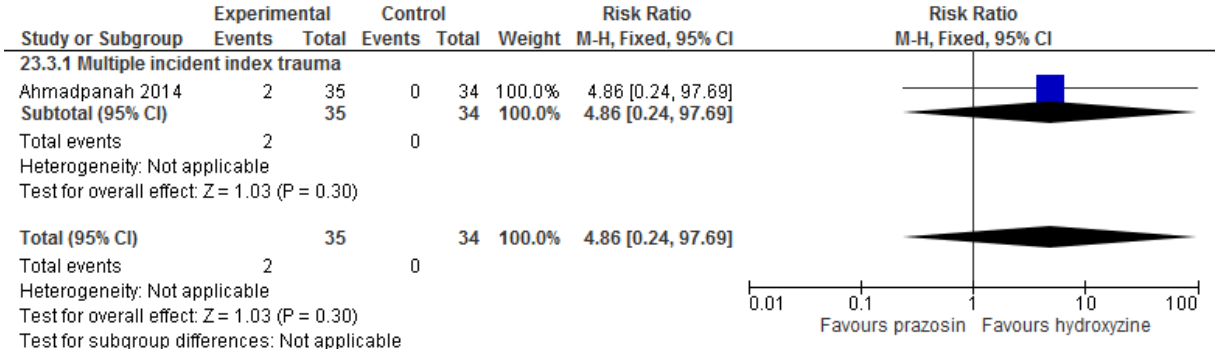
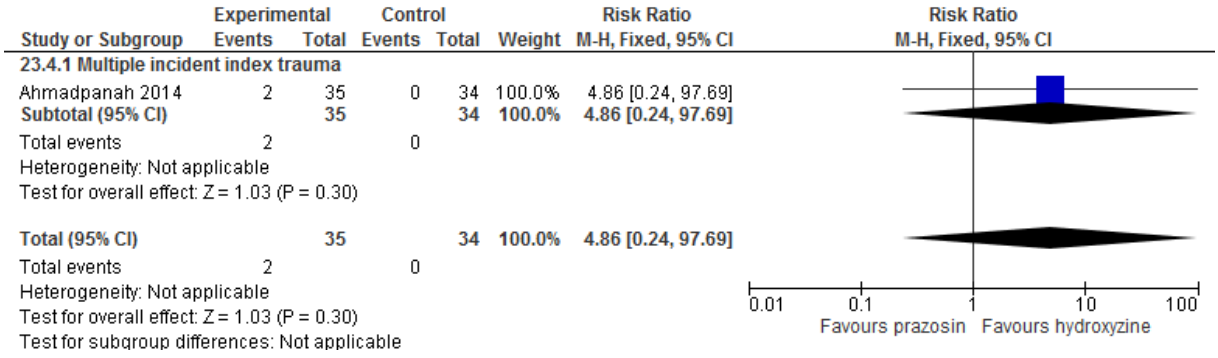


Figure 263: Prazosin versus hydroxyzine for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Other drugs: Hydroxyzine

Hydroxyzine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 264: Hydroxyzine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (MINI change score)

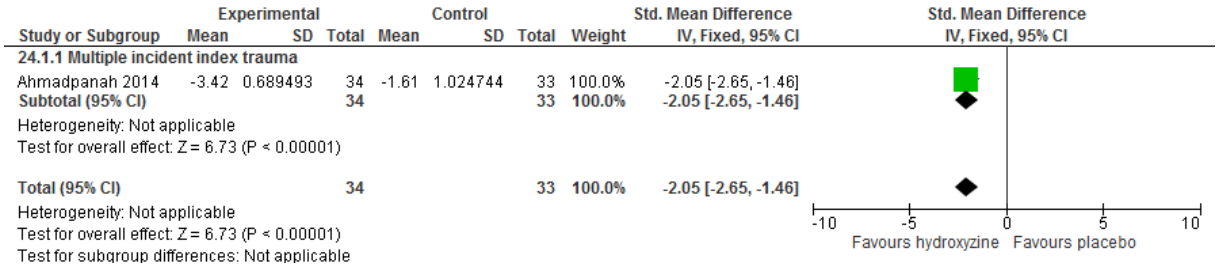
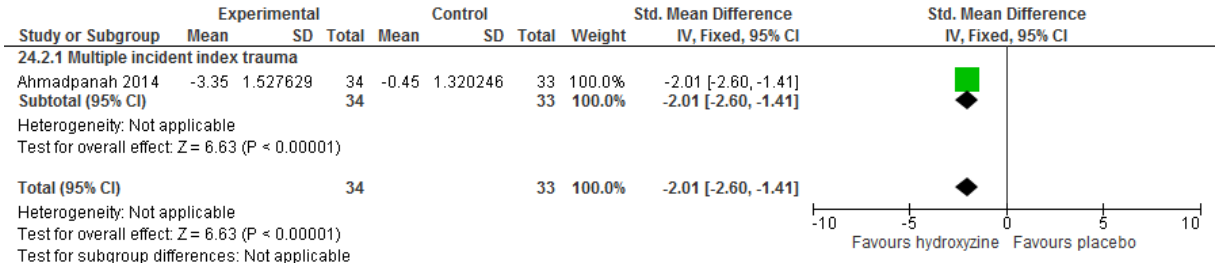


Figure 265: Hydroxyzine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Sleeping difficulties (PSQI change score)



Other drugs: Eszopiclone

Eszopiclone versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 266: Eszopiclone versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

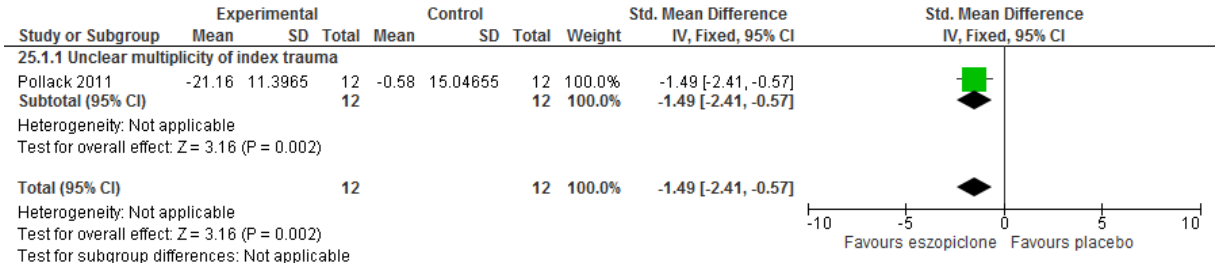
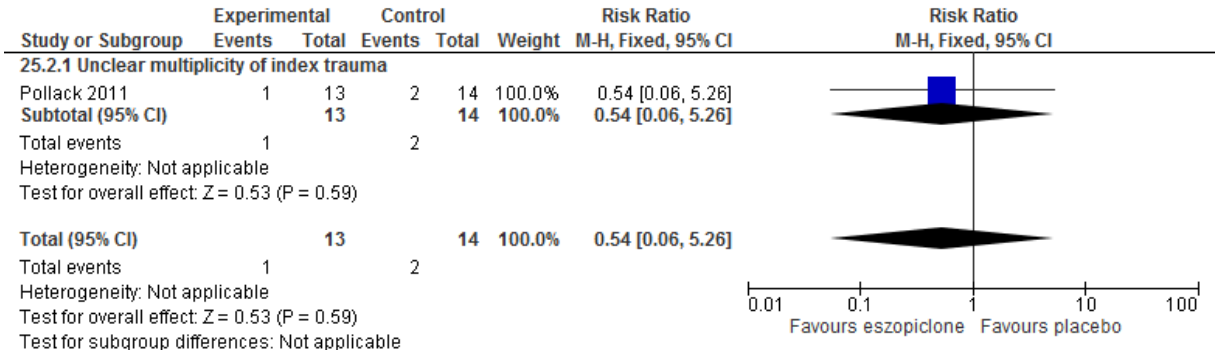


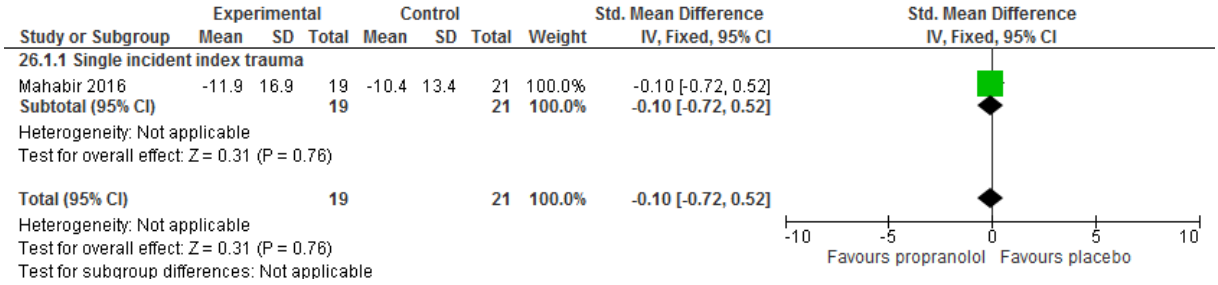
Figure 267: Eszopiclone versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)



Other drugs: Propranolol

Propranolol (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

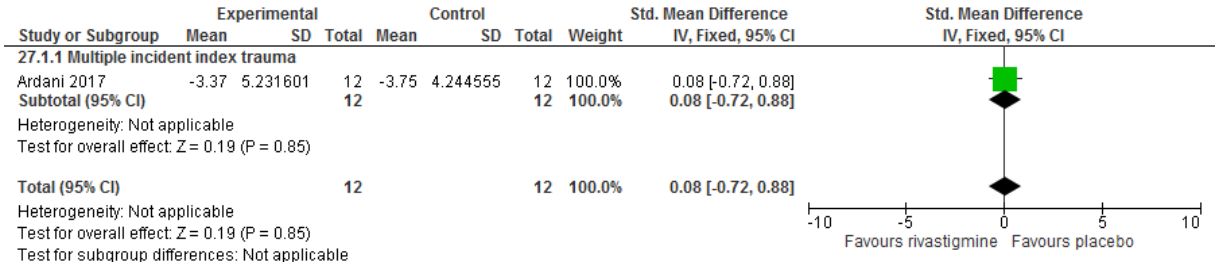
Figure 268: Propranolol (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (IES-R change score)



Other drugs: Rivastigmine

Rivastigmine (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 269: Rivastigmine (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (PCL change score)



Other drugs: Guanfacine

Guanfacine (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 270: Guanfacine (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated (IES-R change score)

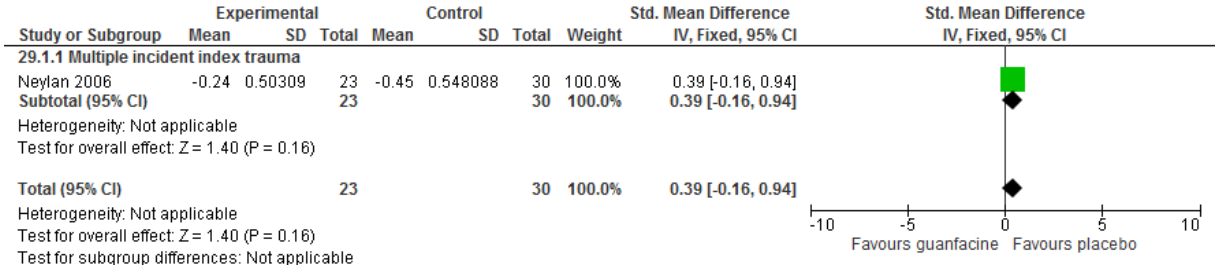


Figure 271: Guanfacine (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated (CAPS change score)

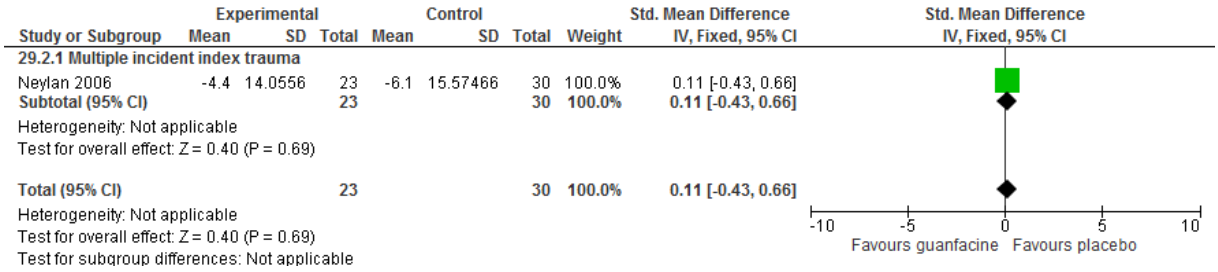


Figure 272: Guanfacine (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms (HAM-D change score)

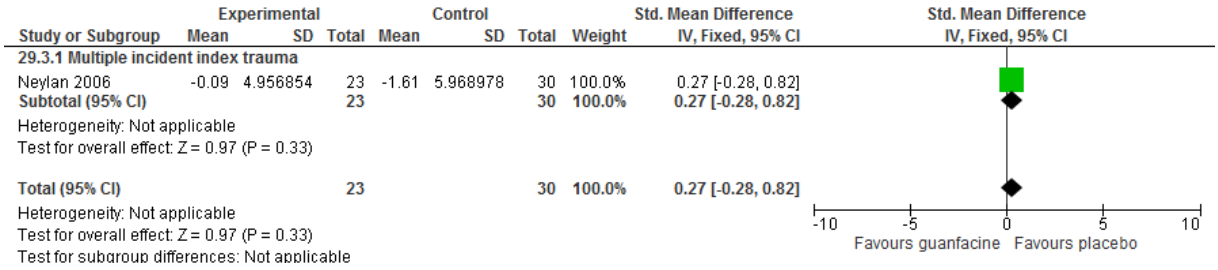


Figure 273: Guanfacine (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Quality of life (QOLI change score)

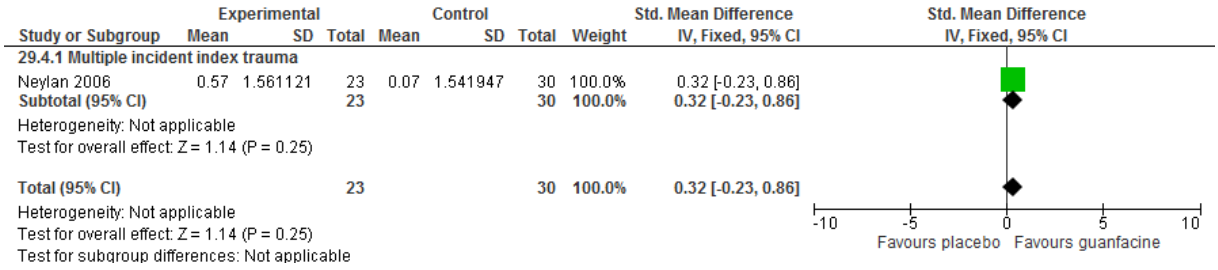


Figure 274: Guanfacine (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Sleeping difficulties (Sleep Quality Index change score)

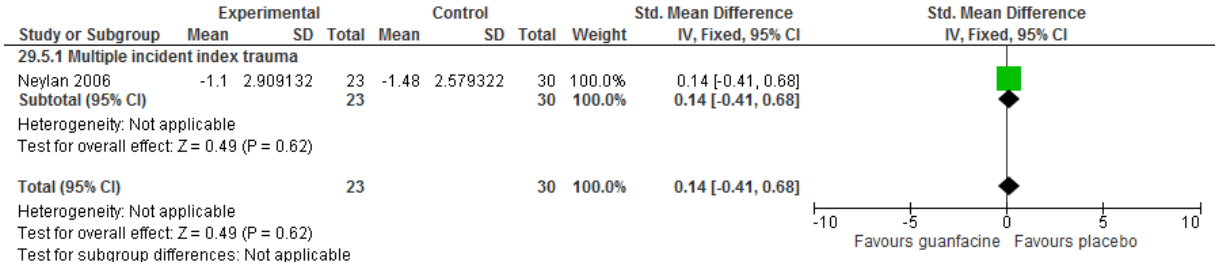


Figure 275: Guanfacine (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

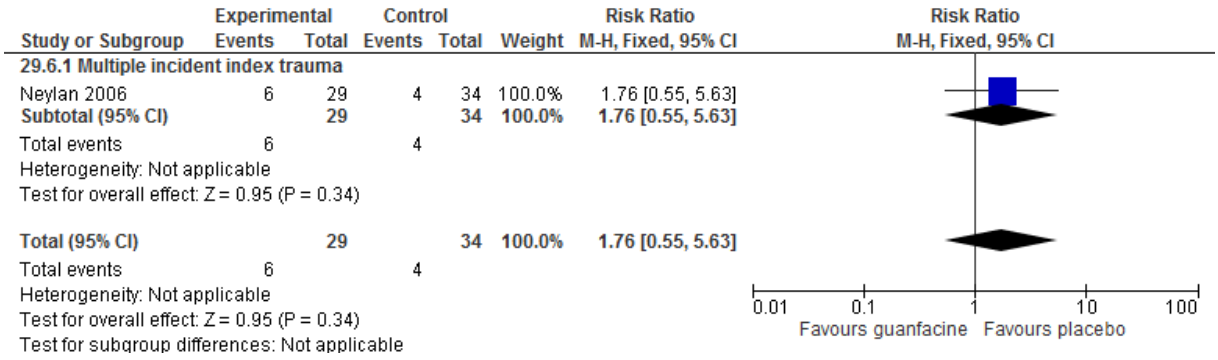
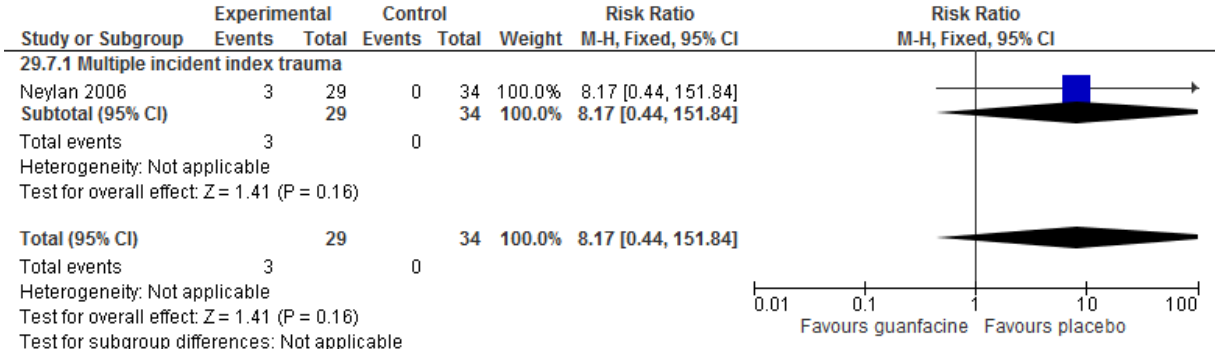


Figure 276: Guanfacine (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Other drugs: D-cycloserine

D-cycloserine (+ exposure therapy) versus placebo (+ exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Figure 277: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated at endpoint (PCL/PSS-SR change score)

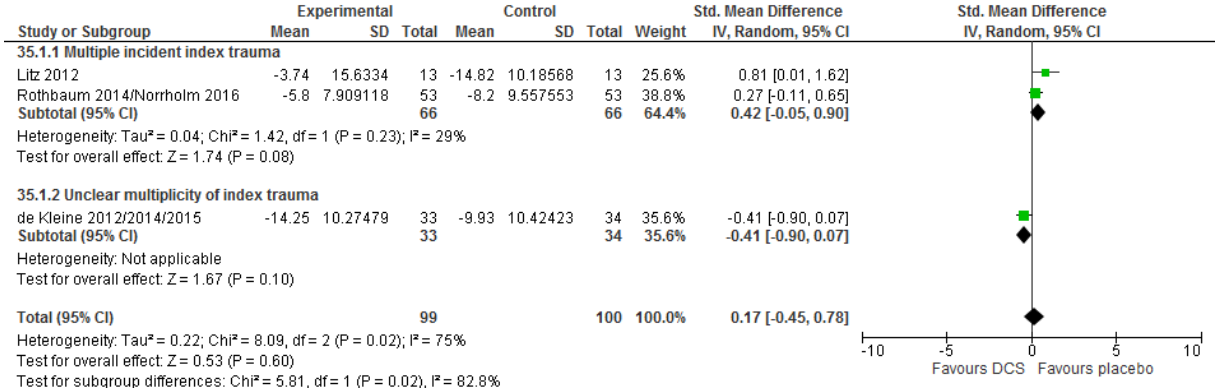


Figure 278: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated at 3-month follow-up (PSS-SR change score)

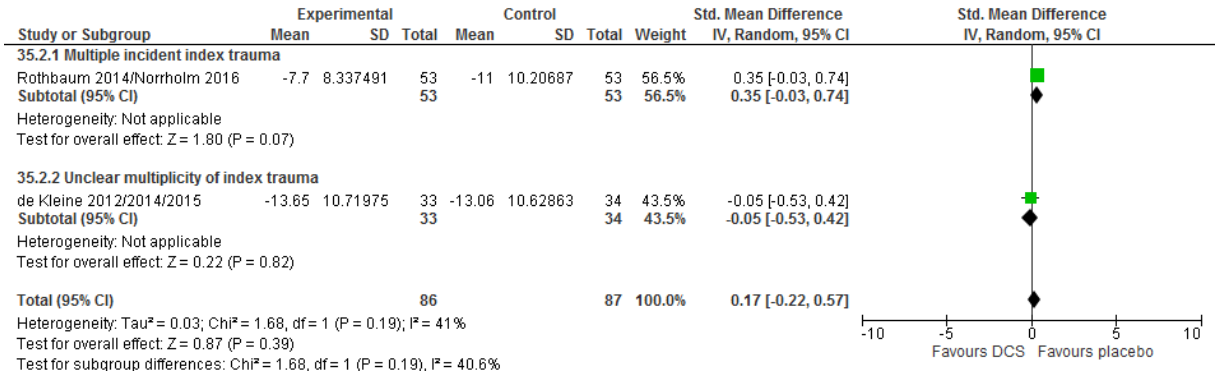


Figure 279: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated at 6-month follow-up (PSS-SR change score)

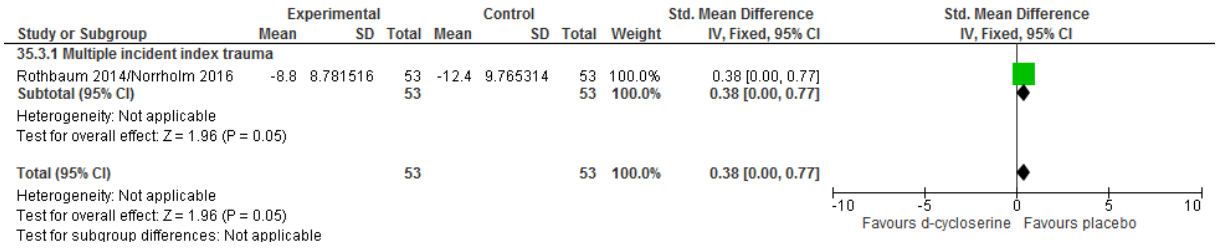


Figure 280: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology self-rated at 1-year follow-up (PSS-SR change score)

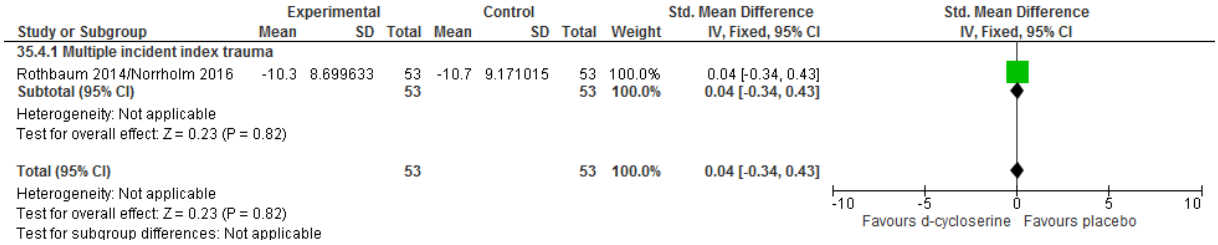


Figure 281: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated at endpoint (CAPS change score)

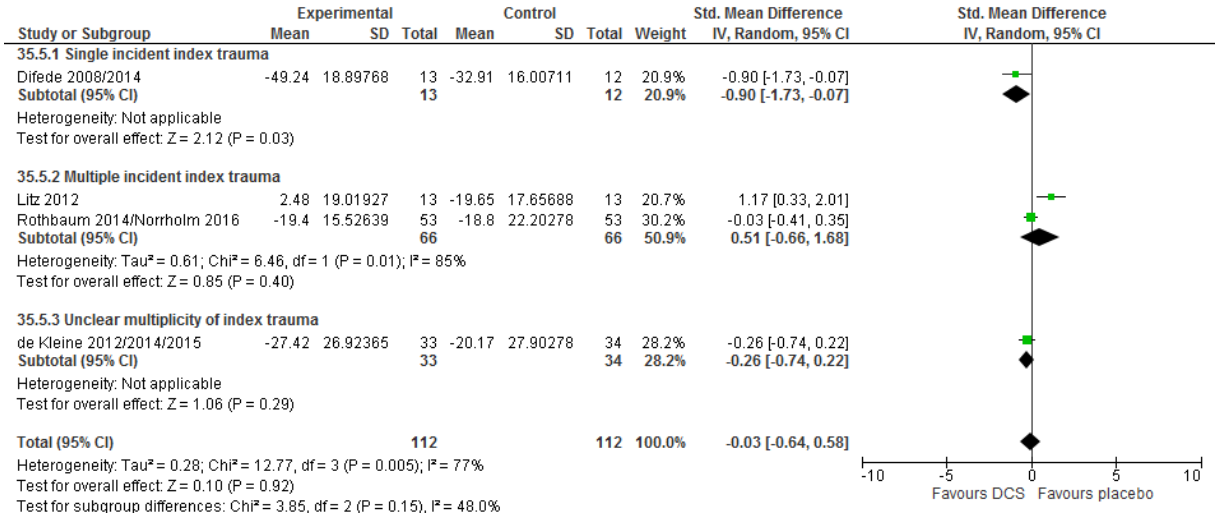


Figure 282: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated at 3-month follow-up (CAPS change score)

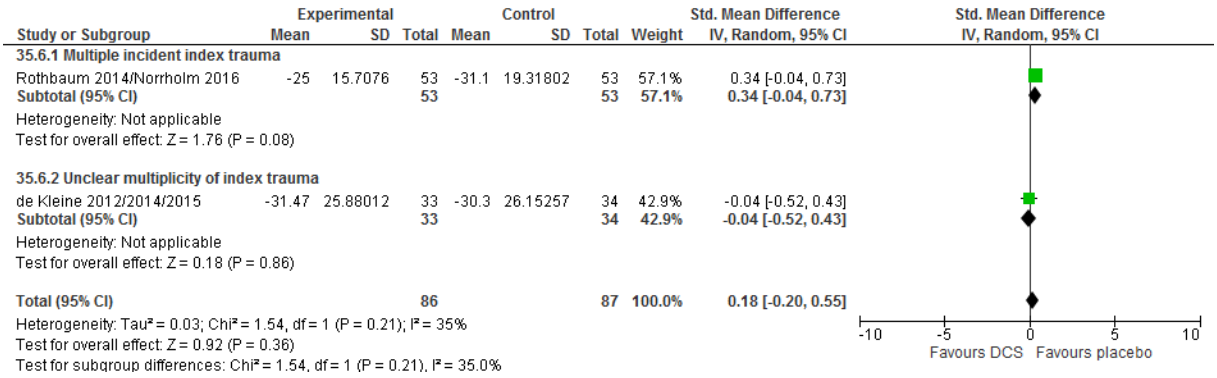


Figure 283: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated at 6-month follow-up (CAPS change score)

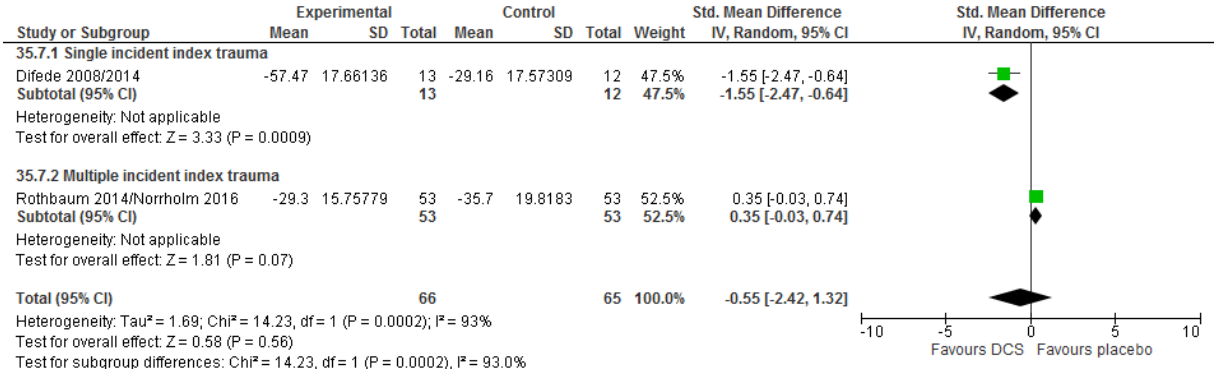


Figure 284: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: PTSD symptomatology clinician-rated at 1-year follow-up (CAPS change score)

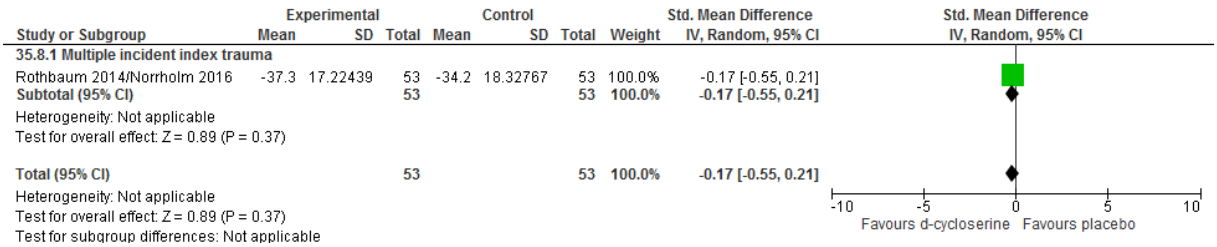


Figure 285: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Remission at endpoint (number of people scoring <20 on CAPS/no longer meeting diagnostic criteria)

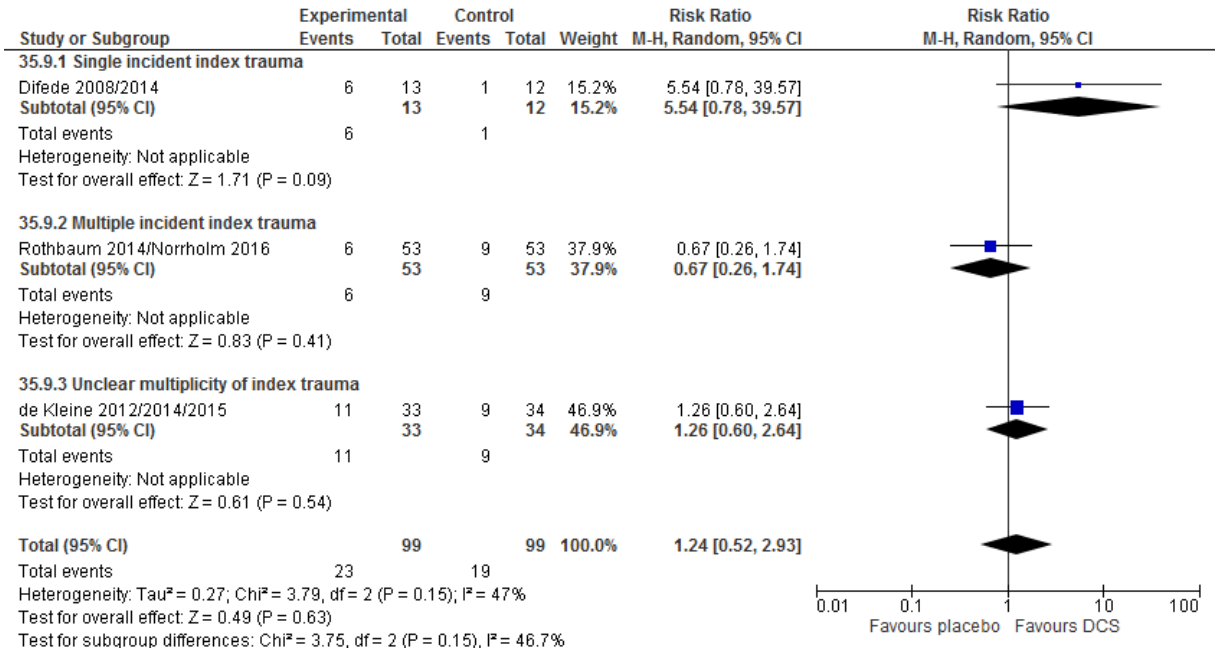


Figure 286: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Remission at 3-month follow-up (number of people scoring <20 on CAPS/no longer meeting diagnostic criteria)

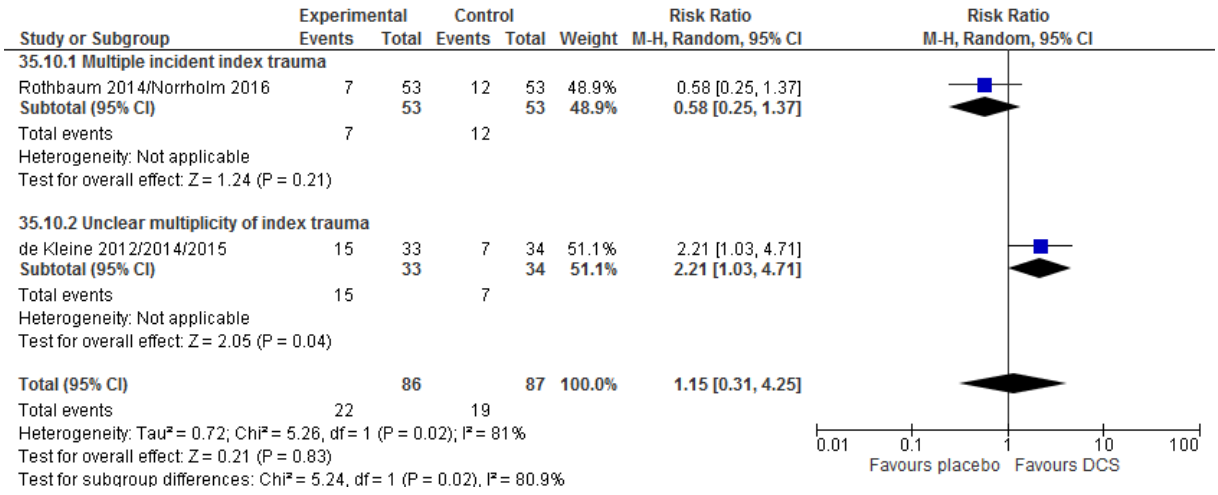


Figure 287: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Remission at 6-month follow-up (number of people scoring <20 on CAPS/no longer meeting diagnostic criteria)

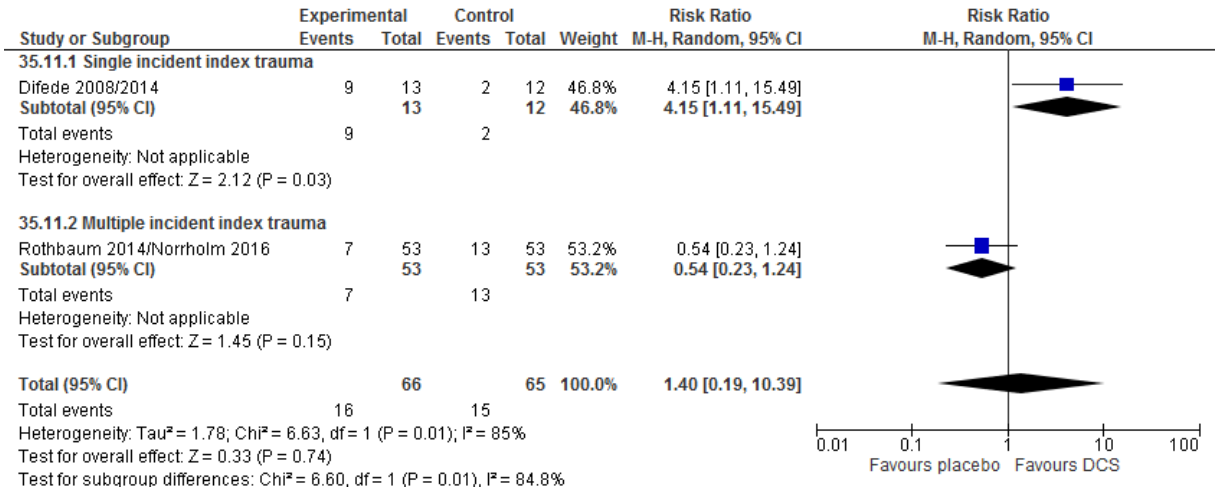


Figure 288: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Remission at 1-year follow-up (number of people no longer meeting diagnostic criteria)

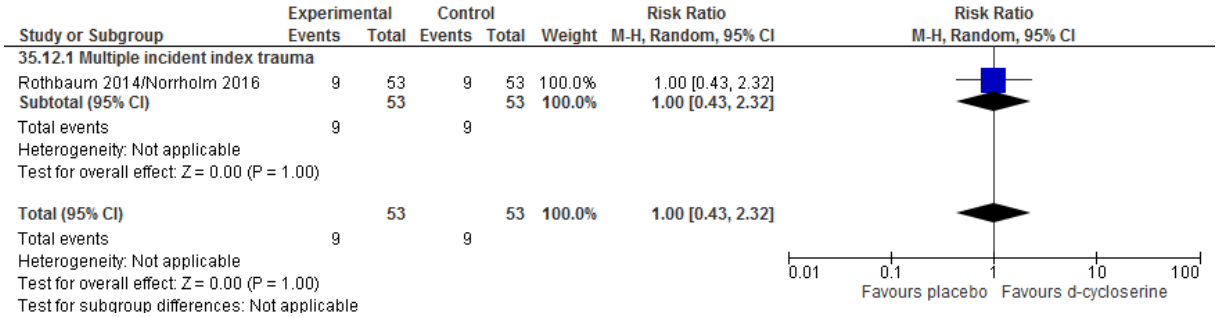


Figure 289: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response at endpoint (number of people showing improvement of at least 10 points on CAPS)

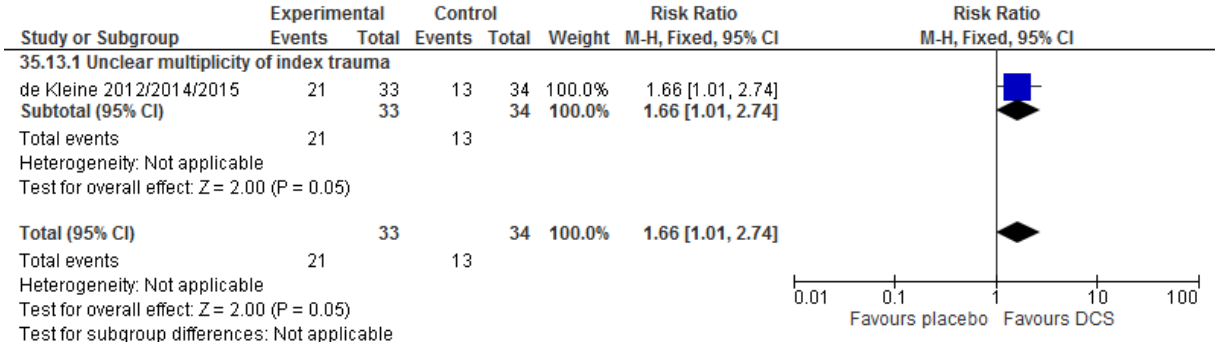


Figure 290: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Response at 3-month follow-up (number of people showing improvement of at least 10 points on CAPS)

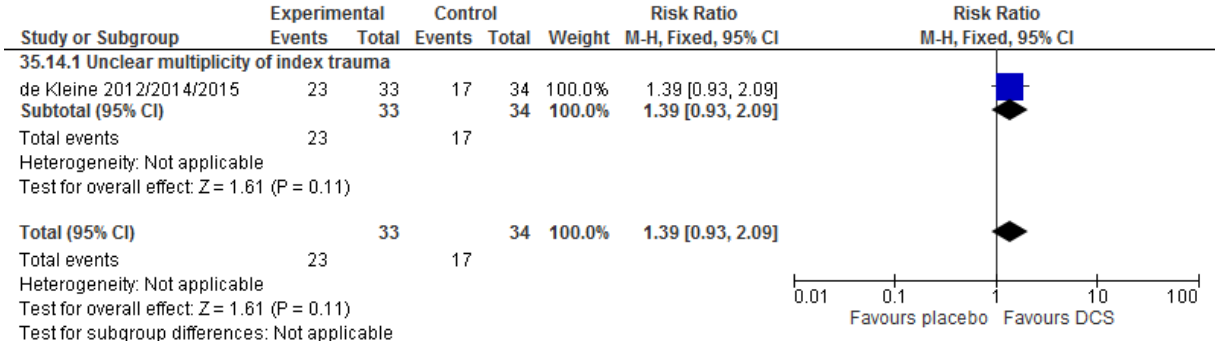


Figure 291: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms at endpoint (STAI State change score)

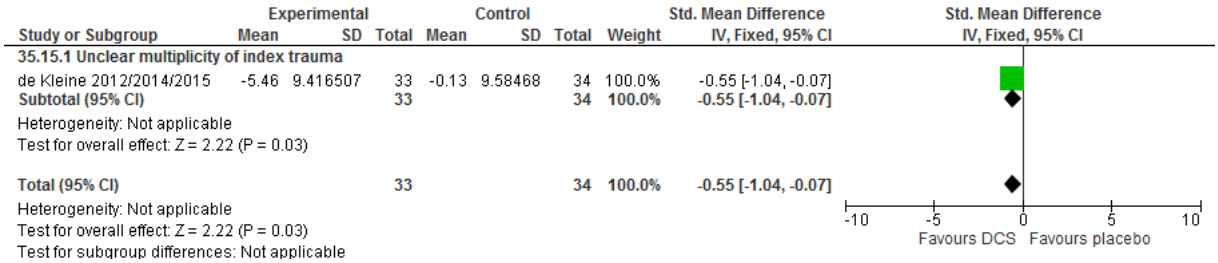


Figure 292: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Anxiety symptoms at 3-month follow-up (STAI State change score)

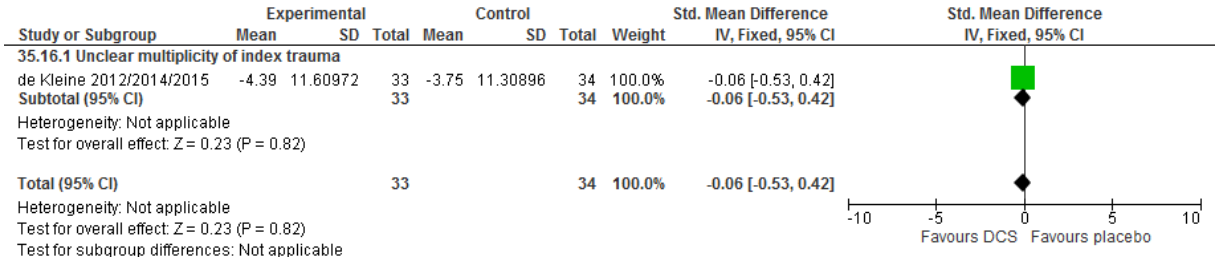


Figure 293: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms at endpoint (BDI/BDI-II change score)

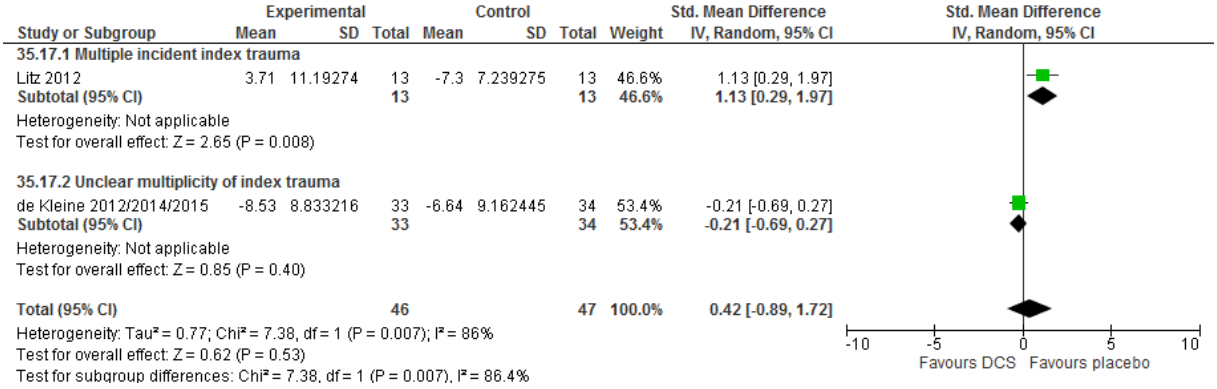


Figure 294: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Depression symptoms at 3-month follow-up (BDI change score)

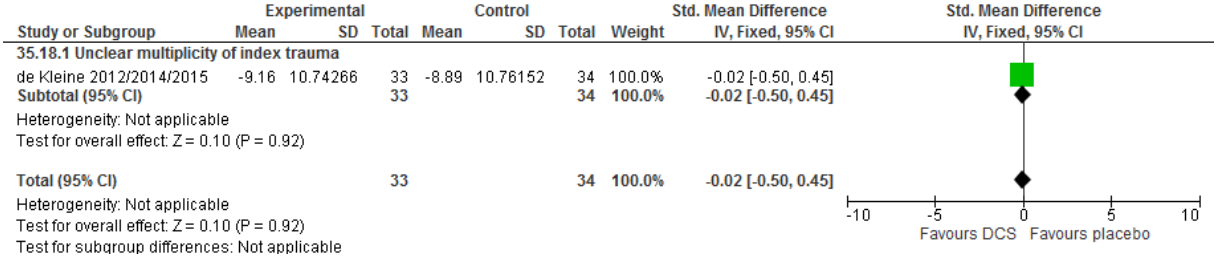


Figure 295: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to any reason (including adverse events)

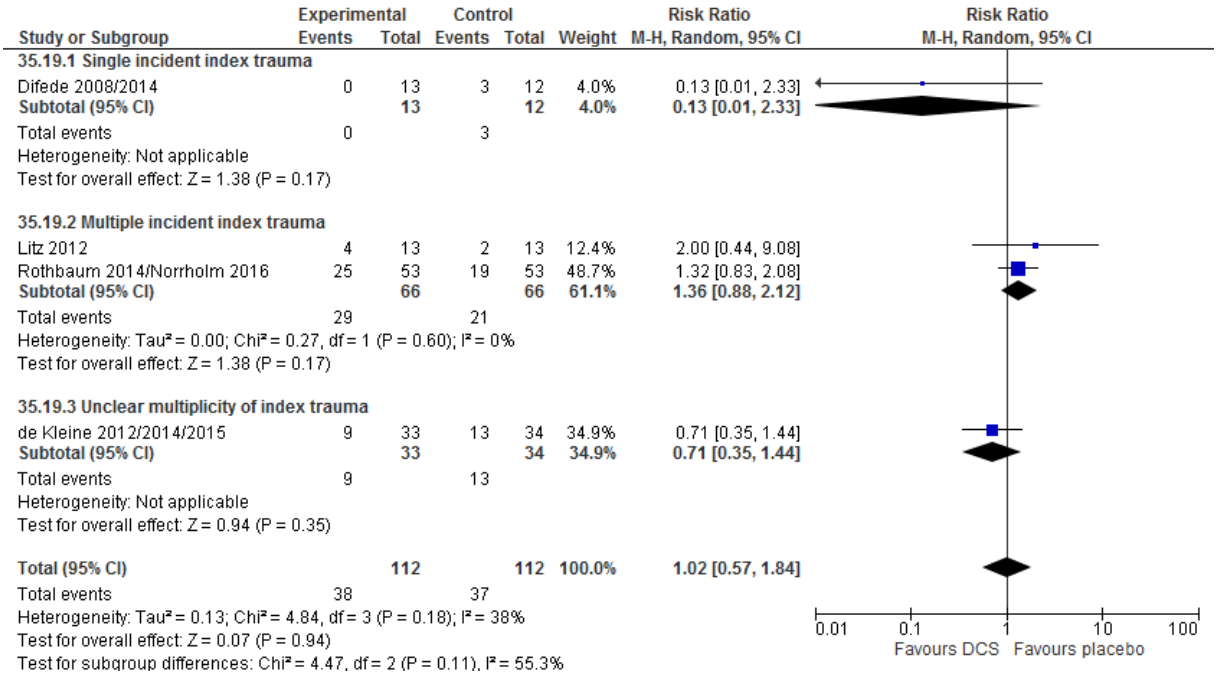
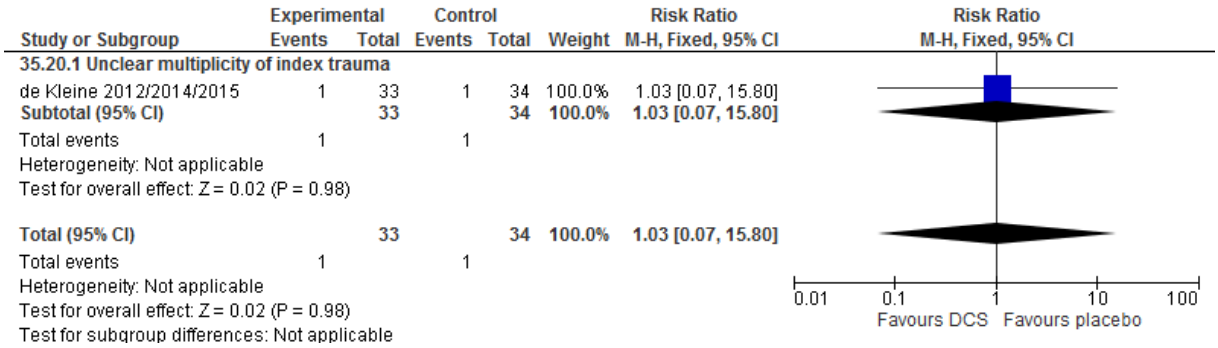


Figure 296: D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms: Discontinuation due to adverse events



Appendix F – GRADE tables

GRADE tables for "For adults at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Antidepressants: Selective serotonin reuptake inhibitors (SSRIs)

Escitalopram versus placebo for the early prevention (<1 month) of PTSD in adults

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Escitalopram**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
PTSD symptomatology clinician-rated (follow-up mean 24 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	12	17	-	SMD 0.9 higher (0.12 to 1.68 higher)	VERY LOW	CRITICAL
Depression symptoms (follow-up mean 24 weeks; measured with: MADRS change score; Better indicated by lower values)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[3]	12	17	-	SMD 0.5 higher (0.25 lower to 1.25 higher)	VERY LOW	IMPORTANT
Functional impairment (follow-up mean 24 weeks; measured with: SDS change score; Better indicated by lower values)												
1	randomised trials	serious [5]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[3]	12	17	-	SMD 0.49 higher (0.26 lower to 1.24 higher)	VERY LOW	IMPORTANT
Discontinuation due to any reason (including adverse events) - Clinically important PTSD symptoms at baseline (follow-up mean 24 weeks; assessed with: Number of participants lost to follow-up for any reason)												
1	randomised trials	serious [5]	no serious inconsistency	no serious indirectness	very serious[6]	none	1/12 (8.3%)	1/17 (5.9%)	RR 1.42 (0.1 to 20.49)	25 more per 1000 (from 53 fewer to 1000 more)	VERY LOW	CRITICAL

CAPS, Clinician Administered PTSD Scale; CI, Confidence interval; PTSD, Post-traumatic stress disorder; SMD, Standard mean difference.
1 Significant group difference at baseline and non-blind outcome assessment
2 OIS not met (N<400)
3 Funding from pharmaceutical company
4 95% CI crosses line of no effect and threshold for clinically important harm

5 Significant group difference at baseline
6 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Anticonvulsants

Gabapentin versus placebo for the early prevention (<1 month) of PTSD in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Gabapentin**	**Placebo**	**Relative (95% CI)**	**Absolute**		
PTSD/ASD symptomatology (follow-up mean 1 months; measured with: ASDS endpoint score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	14	15	-	SMD 0.16 higher (0.57 lower to 0.89 higher)	LOW	CRITICAL
Diagnosis of PTSD at 3-month follow-up (follow-up mean 3 months; assessed with: CIDI)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/14 (42.9%)	5/17 (29.4 %)	RR 1.46 (0.56 to 3.78)	135 more per 1000 (from 129 fewer to 818 more)	LOW	CRITICAL
Discontinuation due to any reason (including adverse events) - Non-significant PTSD symptoms at baseline (follow-up mean 1 months; assessed with: Number of participants lost to follow-up for any reason)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/14 (0%)	2/17 (11.8 %)	RR 0.24 (0.01 to 4.62)	89 fewer per 1000 (from 116 fewer to 426 more)	LOW	CRITICAL

ASD, Acute Stress Disorder; CI, Confidence Interval; CIDI, Composite International Diagnostic Interview; PTSD, Post-traumatic stress disorder; SMD, Standard mean difference
[1] 95% CI crosses both line of no effect and thresholds for both clinically important benefit and harm

Benzodiazepines

Temazepam versus placebo for the early prevention (<1 month) of PTSD in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Temazepam**	**Placebo**	**Relative (95% CI)**	**Absolute**		
PTSD symptomatology clinician-rated at endpoint (follow-up mean 1 weeks; measured with: CAPS change score; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Temazepam	Placebo	Relative (95% CI)	Absolute		
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	10	10	-	SMD 0.55 higher (0.35 lower to 1.45 higher)	LOW	CRITICAL
PTSD symptomatology clinician-rated at 1-month follow-up (follow-up mean 1 months; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	11	11	-	SMD 0.18 higher (0.65 lower to 1.02 higher)	VERY LOW	CRITICAL
Diagnosis of PTSD at 1-month follow-up (follow-up mean 1 months; assessed with: CAPS)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/11 (54.5%)	3/11 (27.3 %)	RR 2 (0.66 to 6.04)	273 more per 1000 (from 93 fewer to 1000 more)	VERY LOW	CRITICAL

CAPS, Clinician Administered PTSD Scale; CI, Confidence interval; PTSD, Post-traumatic stress disorder; SMD, Standard Mean Difference.
[1] Risk of bias is unclear across multiple domains
[2] 95% CI crosses both line of no effect and threshold for clinically important harm
[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Other drugs

Hydrocortisone versus placebo for the early prevention (<1 month) of PTSD in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydrocortisone	Placebo	Relative (95% CI)	Absolute		
PTSD symptomatology clinician-rated at endpoint (follow-up mean 1 months; measured with: CAPS endpoint score; Better indicated by lower values)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	24	27	-	SMD 2.62 lower (3.38 to 1.86 lower)	VERY LOW	CRITICAL
PTSD symptomatology clinician-rated at 2-month follow-up (follow-up mean 2 months; measured with: CAPS endpoint score; Better indicated by lower values)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	19	24	-	SMD 2.96 lower (3.85 to 2.07 lower)	VERY LOW	CRITICAL
Diagnosis of PTSD at endpoint (follow-up mean 1 months; assessed with: CAPS)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/24 (8.3%)	3/27 (11.1 %)	RR 0.75 (0.14 to 4.12)	28 fewer per 1000 (from 96 fewer to 347 more)	VERY LOW	CRITICAL
Diagnosis of PTSD at 2-month follow-up (follow-up mean 2 months; assessed with: CAPS)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydrocortisone	Placebo	Relative (95% CI)	Absolute		
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious [3]	none	0/19 (0%)	3/24 (12.5 %)	RR 0.18 (0.01 to 3.26)	102 fewer per 1000 (from 124 fewer to 282 more)	VERY LOW	CRITICAL
Depression symptoms at endpoint (follow-up mean 1 months; measured with: CES-D endpoint score; Better indicated by lower values)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious [2]	none	24	27	-	SMD 3.57 lower (4.48 to 2.66 lower)	VERY LOW	IMPORTANT
Depression symptoms at 2-month follow-up (follow-up mean 2 months; measured with: CES-D endpoint score; Better indicated by lower values)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious [2]	none	19	24	-	SMD 3.71 lower (4.73 to 2.69 lower)	VERY LOW	IMPORTANT
Quality of life (follow-up mean 1 months; measured with: SF-36 General health change score; Better indicated by higher values)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious [2]	none	24	27	-	SMD 3.51 higher (2.61 to 4.41 higher)	VERY LOW	IMPORTANT
Discontinuation due to adverse events (follow-up mean 1 months; assessed with: Number of participants who dropped out due to adverse events)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious [3]	none	1/31 (3.2%)	0/33 (0%)	RR 3.19 (0.13 to 75.43)	-	VERY LOW	CRITICAL

CAPS, Clinician Administered PTSD Scale; CES-D, Short Self-report scale measuring depressive symptomatology; CI, Confidence interval; PTSD, Post-traumatic stress disorder; SMD, Standard Mean Difference.
[1] Risk of bias is high or unclear across multiple domains
[2] OIS not met (N<400)
[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Oxytocin versus placebo for the early prevention (<1 month) of PTSD in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin	Placebo	Relative (95% CI)	Absolute		
PTSD symptomatology self-rated at 1-month follow-up (follow-up mean 1 months; measured with: IES-R change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious [1]	none	53	54	-	SMD 0.39 lower (0.78 to 0.01 lower)	MODERATE	CRITICAL
PTSD symptomatology self-rated at 2-month follow-up (follow-up mean 2 months; measured with: IES-R change score; Better indicated by lower values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	53	54	-	SMD 0.27 lower (0.65 lower to 0.11 higher)	MODERATE	CRITICAL
PTSD symptomatology self-rated at 5-month follow-up (follow-up mean 5 months; measured with: IES-R change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	53	54	-	SMD 0.08 lower (0.46 lower to 0.3 higher)	MODERATE	CRITICAL
PTSD symptomatology clinician-rated at 1-month follow-up (follow-up mean 1 months; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	serious[2]	none	53	54	-	SMD 0.2 lower (0.58 lower to 0.18 higher)	LOW	CRITICAL
PTSD symptomatology clinician-rated at 2-month follow-up (follow-up mean 2 months; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	serious[1]	none	53	54	-	SMD 0.44 lower (0.83 to 0.06 lower)	LOW	CRITICAL
PTSD symptomatology clinician-rated at 5-month follow-up (follow-up mean 5 months; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	serious[2]	none	53	54	-	SMD 0.16 lower (0.54 lower to 0.22 higher)	LOW	CRITICAL
Anxiety symptoms at 1-month follow-up (follow-up mean 1 months; measured with: HADS-A change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	53	54	-	SMD 0.31 lower (0.7 lower to 0.07 higher)	MODERATE	IMPORTANT
Anxiety symptoms at 2-month follow-up (follow-up mean 2 months; measured with: HADS-A change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	53	54	-	SMD 0.33 lower (0.71 lower to 0.05 higher)	MODERATE	IMPORTANT
Anxiety symptoms at 5-month follow-up (follow-up mean 5 months; measured with: HADS-A change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	53	54	-	SMD 0.51 lower (0.89 to 0.12 lower)	MODERATE	IMPORTANT
Depression symptoms at 1-month follow-up (follow-up mean 1 months; measured with: HADS-D change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	53	54	-	SMD 0.13 lower (0.51 lower to 0.25 higher)	MODERATE	IMPORTANT
Depression symptoms at 2-month follow-up (follow-up mean 2 months; measured with: HADS-D change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	53	54	-	SMD 0.07 lower (0.45 lower to 0.31 higher)	MODERATE	IMPORTANT
Depression symptoms at 5-month follow-up (follow-up mean 5 months; measured with: HADS-D change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	53	54	-	SMD 0.13 lower (0.51 lower to 0.25 higher)	MODERATE	IMPORTANT
Discontinuation due to any reason (including adverse events) - Subthreshold symptoms (below threshold but ≥50% maximum score on scale) at baseline (follow-up mean 1 months; assessed with: Number of participants lost to follow-up for any reason)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	21/62 (33.9%)	17/58 (29.3%)	RR 1.16 (0.68 to 1.96)	47 more per 1000 (from 94 fewer to 281 more)	LOW	CRITICAL

CAPS, Clinician administered PTSD scale; CI, Confidence interval, HADS, Hospital Anxiety and Depression Scale; PTSD, Post-traumatic stress disorder; SMD, Standard Mean Difference.
[1] OIS not met (N<400)
[2] 95% CI crosses both line of no effect and threshold for clinically important benefit
[3] Non-blind outcome assessment
[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Propranolol versus placebo for the early prevention (<1 month) of PTSD in adults

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Propranolol**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
PTSD/ASD symptomatology self-rated (follow-up mean 1 months; measured with: ASDS endpoint score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	13	15	-	SMD 0.36 lower (1.11 lower to 0.39 higher)	MODERATE	CRITICAL
PTSD symptomatology clinician-rated at endpoint (follow-up mean 1 months; measured with: CAPS endpoint score; Better indicated by lower values)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	32	40	-	SMD 0.16 lower (0.63 lower to 0.31 higher)	LOW	CRITICAL
PTSD symptomatology clinician-rated at 2-month follow-up (follow-up mean 2 months; measured with: CAPS endpoint score; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	21	20	-	SMD 0.08 higher (0.53 lower to 0.7 higher)	VERY LOW	CRITICAL
Diagnosis of PTSD at endpoint (follow-up mean 1 months; assessed with: CAPS)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	15/40 (37.5%)	15/41 (36.6 %)	RR 1.06 (0.61 to 1.83)	22 more per 1000 (from 143 fewer to 304 more)	VERY LOW	CRITICAL
Diagnosis of PTSD at 2-3 month follow-up (follow-up 2-3 months; assessed with: CAPS/CIDI)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	23/57 (40.4%)	21/61 (34.4 %)	RR 1.18 (0.74 to 1.89)	62 more per 1000 (from 90 fewer to 306 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (including adverse events) (follow-up mean 1 months; assessed with: Number of participants lost to follow-up for any reason)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	12/57 (21.1%)	6/61 (9.8%)	RR 2.3 (0.94 to 5.66)	128 more per 1000 (from 6 fewer to 458 more)	MODERATE	CRITICAL

ASD, Acute Stress Disorder; CI, Confidence interval; CIDI, Composite International Diagnostic Interview; PTSD, Post-traumatic stress disorder; SMD, Standard mean difference.
[1] 95% CI crosses both line of no effect and threshold for clinically important benefit
[2] Risk of bias is high or unclear across multiple domains
[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm
[4] 95% CI crosses both line of no effect and threshold for clinically important harm

Propranolol versus gabapentin for the early prevention (<1 month) of PTSD in adults

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propranolol versus gabapentin for the early prevention (<1 month) of PTSD in adults	Control	Relative (95% CI)	Absolute	Quality	Importance
PTSD/ASD symptomatology self-rated (follow-up mean 1 months; measured with: ASDS endpoint score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	13	14	-	SMD 0.48 lower (1.25 lower to 0.29 higher)	MODERATE	CRITICAL
Diagnosis of PTSD at 3-month follow-up (follow-up mean 3 months; assessed with: CIDI)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/17 (47.1%)	6/14 (42.9%)	RR 1.1 (0.5 to 2.41)	43 more per 1000 (from 214 fewer to 604 more)	LOW	CRITICAL
Discontinuation due to any reason (including adverse events) - Non-significant PTSD symptoms at endpoint (follow-up mean 1 months; assessed with: Number of participants lost to follow-up for any reason)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4/17 (23.5%)	0/14 (0%)	RR 7.5 (0.44 to 128.4)	-	LOW	CRITICAL

ASD, Acute Stress Disorder; CI-confidence interval; CIDI, Composite International Diagnostic Interview; PTSD, post-traumatic stress disorder; SMD, Standard mean difference.
[1] 95% CI crosses both line of no effect and threshold for clinically important benefit
[2] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Prazosin versus placebo for the delayed treatment (>3 months) of non-significant PTSD symptoms in adults

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prazosin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
PTSD symptomatology self-rated at endpoint (follow-up mean 8 weeks; measured with: PCL change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	15	13	-	SMD 0.94 lower (1.72 to 0.15 lower)	MODERATE	CRITICAL
PTSD symptomatology self-rated at 4-month follow-up (follow-up mean 4 months; measured with: PCL change score; Better indicated by lower values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prazosin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	12	11	-	SMD 1.12 lower (2.02 to 0.23 lower)	MODERATE	CRITICAL
Anxiety symptoms at endpoint (follow-up mean 8 weeks; measured with: BAI change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	15	12	-	SMD 0.32 lower (1.08 lower to 0.45 higher)	MODERATE	IMPORTANT
Anxiety symptoms at 4-month follow-up (follow-up mean 4 months; measured with: BAI change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	12	11	-	SMD 0.76 lower (1.61 lower to 0.1 higher)	MODERATE	IMPORTANT
Depression symptoms at endpoint (follow-up mean 8 weeks; measured with: BDI change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	15	13	-	SMD 0.54 lower (1.3 lower to 0.22 higher)	MODERATE	IMPORTANT
Depression symptoms at 4-month follow-up (follow-up mean 4 months; measured with: BDI change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	12	11	-	SMD 0.96 lower (1.83 to 0.09 lower)	MODERATE	IMPORTANT
Functional impairment at endpoint (follow-up mean 8 weeks; measured with: SDS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	15	13	-	SMD 0.23 lower (0.98 lower to 0.52 higher)	LOW	IMPORTANT
Functional impairment at 4-month follow-up (follow-up mean 4 months; measured with: SDS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	11	11	-	SMD 0.52 lower (1.38 lower to 0.33 higher)	MODERATE	IMPORTANT
Sleeping difficulties at endpoint (follow-up mean 8 weeks; measured with: PSQI change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	14	13	-	SMD 1.01 lower (1.82 to 0.2 lower)	MODERATE	IMPORTANT
Sleeping difficulties at 4-month follow-up (follow-up mean 4 months; measured with: PSQI change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	12	11	-	SMD 1.15 lower (2.04 to 0.25 lower)	MODERATE	IMPORTANT
Discontinuation due to any reason (including adverse events) (follow-up mean 8 weeks; assessed with: Number of participants lost to follow-up for any reason)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	5/18 (27.8 %)	4/16 (25%)	RR 1.11 (0.36 to 3.44)	28 more per 1000 (from 160 fewer to 610 more)	LOW	CRITICAL
Discontinuation due to adverse events (follow-up mean 8 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1/18 (5.6%)	2/16 (12.5 %)	RR 0.44 (0.04 to 4.45)	70 fewer per 1000 (from 120 fewer to 431 more)	LOW	CRITICAL

CI-confidence interval; PCL, Self-report measure that assesses the 2o DSM-5 symptoms of PTSD; PTSD, post-traumatic stress disorder; SMD, Standard mean difference

[1] *OIS not met (N<400)*

[2] *95% CI crosses both line of no effect and threshold for clinically important benefit*

[3] *95% CI crosses line of no effect and thresholds for both clinically important benefit and harm*

GRADE tables for "For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

Antidepressants: Selective serotonin reuptake inhibitors (SSRIs)

SSRI versus placebo

SSRI versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRIs	Placebo	Relative (95% CI)	Absolute	Quality	Importance
PTSD symptomatology self-rated (follow-up 10-12 weeks; measured with: DTS/IES-R change score; Better indicated by lower values)												
16	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	reporting bias[2]	2091	1502	-	SMD 0.26 lower (0.39 to 0.14 lower)	LOW	CRITICAL
PTSD symptomatology clinician-rated (follow-up 8-12 weeks; measured with: CAPS/SI–PTSD change score; Better indicated by lower values)												
17	randomised trials	serious3	serious[1]	no serious indirectness	no serious imprecision	reporting bias[2]	2008	1467	-	SMD 0.28 lower (0.4 to 0.16 lower)	VERY LOW	CRITICAL
Remission clinician-rated (follow-up 8-12 weeks; assessed with: Number of people scoring <20 on CAPS/no longer meeting diagnostic criteria for PTSD)												
5	randomised trials	serious4	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	262/880 (29.8%)	124/647 (19.2%)	RR 1.31 (1.07 to 1.59)	59 more per 1000 (from 13 more to 113 more)	LOW	CRITICAL
Remission self-rated (assessed with: Number of people scoring <18 on DTS)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[2]	47/190 (24.7%)	29/194 (14.9%)	RR 1.65 (1.09 to 2.51)	97 more per 1000 (from 13 more to 226 more)	LOW	CRITICAL
Response (follow-up 10-12 weeks; assessed with: Number of people showing ≥30% improvement on CAPS or IES-R/≥50% improvement on TOP-8 and/or CGI-I much or very much improved)												
11	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	703/1250 (56.2%)	371/905 (41%)	RR 1.35 (1.2 to 1.52)	143 more per 1000 (from 82	LOW	CRITICAL

										more to 213 more)		
Anxiety symptoms (follow-up 10-12 weeks; measured with: HAM-A change score; Better indicated by lower values)												
5	randomised trials	serious[3]	serious[1]	no serious indirectness	no serious imprecision	reporting bias[2]	709	351	-	SMD 0.15 lower (0.37 lower to 0.06 higher)	VERY LOW	IMPORTANT
Depression symptoms (follow-up 8-12 weeks; measured with: HAM-D/MADRS/BDI/BDI-II change score; Better indicated by lower values)												
14	randomised trials	serious[3]	serious[1]	no serious indirectness	no serious imprecision	reporting bias[2]	1853	1282	-	SMD 0.24 lower (0.37 to 0.11 lower)	VERY LOW	IMPORTANT
Dissociative symptoms (follow-up mean 10 weeks; measured with: DES change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[2]	17	13	-	SMD 0.86 lower (1.62 to 0.1 lower)	LOW	IMPORTANT
Functional impairment (follow-up mean 12 weeks; measured with: SDS change score; Better indicated by lower values)												
5	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	reporting bias[2]	840	666	-	SMD 0.33 lower (0.49 to 0.17 lower)	LOW	IMPORTANT
Global functioning (follow-up mean 12 weeks; measured with: GAF change score; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[2]	173	179	-	SMD 0.32 higher (0.11 to 0.53 higher)	LOW	IMPORTANT
Quality of life (follow-up mean 12 weeks; measured with: Q-LES-Q-SF change score; Better indicated by higher values)												
2	randomised trials	no serious risk of bias	very serious[7]	no serious indirectness	no serious imprecision	reporting bias[2]	266	269	-	SMD 0.59 higher (0.16 to 1.03 higher)	VERY LOW	IMPORTANT
Sleeping difficulties (follow-up mean 12 weeks; measured with: PSQI change score; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[2]	182	186	-	SMD 0.04 higher (0.25 lower to 0.32 higher)	LOW	IMPORTANT
Relationship difficulties (follow-up mean 10 weeks; measured with: IIP change score; Better indicated by lower values)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[2]	17	13	-	SMD 0.73 lower (1.48 lower to 0.02 higher)	LOW	IMPORTANT
Discontinuation due to any reason (follow-up 8-12 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
17	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	582/2015 (28.9%)	467/1554 (30.1%)	RR 1.01 (0.92 to 1.12)	3 more per 1000 (from 24 fewer to 36 more)	MODERATE	CRITICAL
Discontinuation due to adverse events (follow-up 10-12 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
13	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[2]	171/1821 (9.4%)	84/1253 (6.7%)	RR 1.42 (1.1 to 1.82)	28 more per 1000 (from 7 more to 55 more)	LOW	CRITICAL

BDI, Beck Depression Inventory; CAPS, Clinician Administered PTSD Scale; CGI-I, Clinical Global Impression scale-Global Improvement; CI, confidence interval; DES, Dissociative Experiences Scale; DTS, Davidson Trauma Scale; GAF, Global Assessment of Functioning; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; IES-R, Impact of Event Scale-Revised; IIP, Inventory of Interpersonal Problems; MADRS, Montgomery-Asberg Depression Rating Scale; PTSD, Post-traumatic stress disorder; PSQI, Pittsburgh Sleep Quality Index; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; RR, risk ratio; SDS, Sheehan Disability Scale; SI-PTSD, Structured Interview for PTSD; SMD, standard mean difference; SSRIs, Selective Serotonin Reuptake Inhibitors; TOP-8, Treatment Outcome PTSD scale

[1] *Substantial heterogeneity (I2>50%)*
[2] *Funding from pharmaceutical company*
[3] *Unclear blinding of outcome assessor(s) and unclear risk of attrition bias*
[4] *Unclear blinding of outcome assessor(s)*
[5] *OIS not met (events<300)*
[6] *OIS not met (N<400)*
[7] *Considerable heterogeneity (I2>80%)*

Sertraline (+non-trauma-focused cognitive therapy) versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline (+ non-trauma-focused cognitive therapy)	Placebo (+ non-trauma-focused cognitive therapy)	Relative (95% CI)	Absolute	Quality	Importance
PTSD symptomatology clinician-rated at endpoint (follow-up mean 12 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	24	25	-	SMD 0.6 lower (1.17 to 0.02 lower)	MODERATE	CRITICAL
PTSD symptomatology clinician-rated at 6-month follow-up (follow-up mean 26 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21	28	-	SMD 0.82 lower (1.41 to 0.23 lower)	MODERATE	CRITICAL
PTSD symptomatology clinician-rated at 12-month follow-up (follow-up mean 52 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21	22	-	SMD 0.83 lower (1.46 to 0.21 lower)	MODERATE	CRITICAL
Response at endpoint (follow-up mean 12 weeks; assessed with: Number of people showing improvement of at least 15 points on CAPS)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	25/32 (78.1%)	18/37 (48.6%)	RR 1.61 (1.1 to 2.34)	297 more per 1000 (from 49 more to 652 more)	MODERATE	CRITICAL
Response at 6-month follow-up (follow-up mean 26 weeks; assessed with: Number of people showing improvement of at least 15 points on CAPS)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	26/32 (81.3%)	24/37 (64.9%)	RR 1.25 (0.94 to 1.67)	162 more per 1000 (from 39 fewer to 435 more)	MODERATE	CRITICAL
Response at 12-month follow-up (follow-up mean 52 weeks; assessed with: Number of people showing improvement of at least 15 points on CAPS)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	30/32 (93.8%)	24/37 (64.9%)	RR 1.45 (1.12 to 1.86)	292 more per 1000 (from 78	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline (+ non-trauma-focused cognitive therapy)	Placebo (+ non-trauma-focused cognitive therapy)	Relative (95% CI)	Absolute	Quality	Importance
										more to 558 more)		
Alcohol use: Number of heavy drinking days in the past 7 days at endpoint (follow-up mean 12 weeks; measured with: TLFB HDD (≥5 drinks/day for men and ≥4 drinks/day for women) change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	22	25	-	SMD 0.22 higher (0.36 lower to 0.79 higher)	MODERATE	IMPORTANT
Alcohol use: Number of heavy drinking days in the past 7 days at 6-month follow-up (follow-up mean 26 weeks; measured with: TLFB HDD (≥5 drinks/day for men and ≥4 drinks/day for women) change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	22	28	-	SMD 0.08 lower (0.64 lower to 0.47 higher)	MODERATE	IMPORTANT
Alcohol use: Number of heavy drinking days in the past 7 days at 12-month follow-up (follow-up mean 52 weeks; measured with: TLFB HDD (≥5 drinks/day for men and ≥4 drinks/day for women) change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	20	21	-	SMD 0.09 lower (0.7 lower to 0.52 higher)	LOW	IMPORTANT
Alcohol use: Drinks per drinking day at endpoint (follow-up mean 12 weeks; measured with: TLFB DDD change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	22	25	-	SMD 0.27 higher (0.31 lower to 0.85 higher)	MODERATE	IMPORTANT
Alcohol use: Drinks per drinking day at 6-month follow-up (follow-up mean 26 weeks; measured with: TLFB DDD change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	22	28	-	SMD 0.25 lower (0.81 lower to	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sertraline (+ non-trauma-focused cognitive therapy)**	**Placebo (+ non-trauma-focused cognitive therapy)**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
										0.31 higher)		
Alcohol use: Drinks per drinking day at 12-month follow-up (follow-up mean 52 weeks; measured with: TLFB DDD change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	20	21	-	SMD 0.06 lower (0.67 lower to 0.55 higher)	LOW	IMPORTANT
Alcohol use: Abstinence at endpoint (follow-up mean 12 weeks; assessed with: Number of participants abstinent from alcohol (in the prior 7 days; TLFB))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	10/22 (45.5%)	15/25 (60%)	RR 0.76 (0.43 to 1.32)	144 fewer per 1000 (from 342 fewer to 192 more)	LOW	IMPORTANT
Alcohol use: Abstinence at 6-month follow-up (follow-up mean 26 weeks; assessed with: Number of participants abstinent from alcohol (in the prior 7 days; TLFB))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	12/22 (54.5%)	13/28 (46.4%)	RR 1.17 (0.68 to 2.04)	79 more per 1000 (from 149 fewer to 483 more)	LOW	IMPORTANT
Alcohol use: Abstinence at 12-month follow-up (follow-up mean 52 weeks; assessed with: Number of participants abstinent from alcohol (in the prior 7 days; TLFB))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	8/20 (40%)	12/21 (57.1%)	RR 0.7 (0.36 to 1.34)	171 fewer per 1000 (from 366 fewer to 194 more)	LOW	IMPORTANT
Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	8/32 (25%)	12/37 (32.4%)	RR 0.77 (0.36 to 1.65)	75 fewer per 1000 (from 208 fewer to 211 more)	LOW	CRITICAL
Discontinuation due to adverse events (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	1/32 (3.1%)	2/37 (5.4%)	RR 0.58 (0.05 to 6.08)	23 fewer per 1000 (from 51	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline (+ non-trauma-focused cognitive therapy)	Placebo (+ non-trauma-focused cognitive therapy)	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 275 more)		

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; PTSD, Post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference; TLFB-DDD/HDD, alcohol timeline feedback-drinks per drinking days/heavy drinking days

[1] OIS not met (N<400)

[2] OIS not met (events<300)

[3] 95% CI crosses both line of no effect and threshold for clinically important benefit

[4] 95% CI crosses both line of no effect and threshold for clinically important harm

[5] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

SSRI versus other antidepressants

SSRI versus mirtazapine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRI	Mirtazapine	Relative (95% CI)	Absolute	Quality	Importance
PTSD symptomatology clinician-rated (follow-up 6-8 weeks; measured with: CAPS change score; Better indicated by lower values)												
2	randomised trials	very serious[1]	serious[2]	no serious indirectness	serious[3]	reporting bias[4]	69	71	-	SMD 0.29 higher (0.34 lower to 0.93 higher)	VERY LOW	CRITICAL
Response (follow-up 6-8 weeks; assessed with: Number of people showing ≥30% improvement on CAPS)												
2	randomised trials	very serious[1]	serious[2]	no serious indirectness	very serious5	reporting bias[4]	51/75 (68%)	59/78 (75.6%)	RR 0.97 (0.64 to 1.47)	23 fewer per 1000 (from 272 fewer to 356 more)	VERY LOW	CRITICAL
Depression symptoms (follow-up 6-8 weeks; measured with: HAM-D/BDI-II change score; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRI	Mirtazapine	Relative (95% CI)	Absolute		
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	69	71	-	SMD 0.15 higher (0.32 lower to 0.63 higher)	VERY LOW	IMPORTANT
Discontinuation due to any reason (follow-up 6-8 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[4]	8/75 (10.7%)	13/78 (16.7%)	RR 0.64 (0.25 to 1.62)	60 fewer per 1000 (from 125 fewer to 103 more)	VERY LOW	CRITICAL
Discontinuation due to adverse events **(follow-up 6-8 weeks; assessed with: Number of people who dropped out of the study due to adverse events)**												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	1/75 (1.3%)	3/78 (3.8%)	RR 0.44 (0.07 to 2.88)	22 fewer per 1000 (from 36 fewer to 72 more)	LOW	CRITICAL

BDI, Beck Depression Inventory; CI, confidence interval; CAPS, clinician administered PTSD scale; HAM-D, Hamilton Depression Rating Scale-Depression; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference; SSRI, selective serotonin reuptake inhibitor

[1] Risk of bias is high or unclear across multiple domains

[2] Substantial heterogeneity (I2>50%)

[3] 95% CI crosses both line of no effect and threshold for clinically important effect

[4] Funding from pharmaceutical company

[5] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Sertraline versus nefazodone for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline	Nefazodone	Relative (95% CI)	Absolute		
PTSD symptomatology self-rated (follow-up mean 12 weeks; measured with: DTS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	13	13	-	SMD 0.46 higher (0.32 lower to	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline	Nefazodone	Relative (95% CI)	Absolute	Quality	Importance
										1.24 higher)		
PTSD symptomatology clinician-rated (follow-up 12-22 weeks; measured with: CAPS/TOP-8 change score; Better indicated by lower values)												
2	randomised trials	very serious[3]	serious[4]	no serious indirectness	serious[1]	reporting bias[2]	43	37	-	SMD 0.7 lower (1.47 lower to 0.07 higher)	VERY LOW	CRITICAL
Anxiety symptoms (follow-up mean 12 weeks; measured with: HAM-A change score; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	13	13	-	SMD 0.4 higher (0.37 lower to 1.18 higher)	VERY LOW	IMPORTANT
Depression symptoms (follow-up mean 12 weeks; measured with: MADRS change score; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	13	13	-	SMD 0.28 higher (0.49 lower to 1.05 higher)	VERY LOW	IMPORTANT
Functional impairment (follow-up mean 12 weeks; measured with: SDS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[2]	13	13	-	SMD 0.09 higher (0.68 lower to 0.86 higher)	VERY LOW	IMPORTANT
Sleeping difficulties (follow-up mean 12 weeks; measured with: PSQI change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[2]	13	13	-	SMD 0.06 lower (0.83 lower to 0.71 higher)	VERY LOW	IMPORTANT
Discontinuation due to any reason (follow-up 12-22 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
2	randomised trials	no serious	serious[4]	no serious indirectness	very serious[5]	reporting bias[2]	6/49 (12.2%)	11/48 (22.9%)	RR 0.39 (0.02 to 7.14)	140 fewer per 1000 (from 225	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline	Nefazodone	Relative (95% CI)	Absolute		
		risk of bias								fewer to 1000 more)		
Discontinuation due to adverse events (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[2]	2/19 (10.5%)	2/18 (11.1%)	RR 0.95 (0.15 to 6.03)	6 fewer per 1000 (from 94 fewer to 559 more)	VERY LOW	CRITICAL

CAPS, clinician administered PTSD scale; CI, confidence interval; DTS, Davidson Trauma Scale; PSQI, Pittsburgh Sleep Quality Index; RR, risk ration; SDS, Sheehan Disability Scale; TOP-8, Treatment Outcome PTSD scale; SMD, standard mean difference
[1] 95% CI crosses both line of no effect and threshold for clinically important effect
[2] Funding from pharmaceutical company
[3] Risk of bias is high or unclear across multiple domains
[4] Substantial heterogeneity (I2>50%)
[5] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Fluoxetine versus moclobemide for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoxetine	Moclobemide	Relative (95% CI)	Absolute		
PTSD symptomatology clinician-rated (follow-up mean 12 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	38	35	-	SMD 0.13 lower (0.59 lower to 0.33 higher)	VERY LOW	CRITICAL
Response (follow-up mean 12 weeks; assessed with: Number of people showing >50% improvement on CAPS)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29/38 (76.3%)	22/35 (62.9%)	RR 1.21 (0.89 to 1.66)	132 more per 1000 (from 69 fewer to 415 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoxetine	Moclobemide	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/38 (18.4%)	5/35 (14.3%)	RR 1.29 (0.45 to 3.69)	41 more per 1000 (from 79 fewer to 384 more)	VERY LOW	CRITICAL
Discontinuation due to adverse events (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/38 (10.5%)	1/35 (2.9%)	RR 3.68 (0.43 to 31.4)	77 more per 1000 (from 16 fewer to 869 more)	VERY LOW	CRITICAL

CAPS, clinician administered PTSD scale; CI, confidence interval; PTSD, Post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] Open-label
[2] 95% CI crosses both line of no effect and threshold for clinically important effect
[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Fluoxetine versus tianeptine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoxetine	Tianeptine	Relative (95% CI)	Absolute		
PTSD symptomatology clinician-rated (follow-up mean 12 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	38	30	-	SMD 0.03 higher (0.45 lower to 0.51 higher)	VERY LOW	CRITICAL
Response (follow-up mean 12 weeks; assessed with: Number of people showing >50% improvement on CAPS)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	29/38 (76.3%)	23/30 (76.7%)	RR 1 (0.76 to 1.3)	0 fewer per 1000 (from 184 fewer to 230 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/38 (18.4%)	6/30 (20%)	RR 0.92 (0.35 to 2.45)	16 fewer per 1000 (from 130	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoxetine	Tianeptine	Relative (95% CI)	Absolute		
										fewer to 290 more)		
Discontinuation due to adverse events (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/38 (10.5%)	2/30 (6.7%)	RR 1.58 (0.31 to 8.05)	39 more per 1000 (from 46 fewer to 470 more)	VERY LOW	CRITICAL

CAPS, clinician administered PTSD scale; CI, confidence interval; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] Open-label
[2] 95% CI crosses line of no effect and threshold for clinically important effect
[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Fluvoxamine versus reboxetine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluvoxamine	Reboxetine	Relative (95% CI)	Absolute		
PTSD symptomatology clinician-rated (follow-up mean 8 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	17	11	-	SMD 0.57 lower (1.34 lower to 0.21 higher)	VERY LOW	CRITICAL
Anxiety symptoms (follow-up mean 8 weeks; measured with: HAM-A change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	17	11	-	SMD 0 higher (0.76 lower to 0.76 higher)	VERY LOW	IMPORTANT
Depression symptoms (follow-up mean 8 weeks; measured with: HAM-D change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	17	11	-	SMD 0.24 lower (1 lower to	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluvoxamine	Reboxetine	Relative (95% CI)	Absolute		
										0.52 higher)		
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	3/20 (15%)	9/20 (45%)	RR 0.33 (0.11 to 1.05)	301 fewer per 1000 (from 400 fewer to 22 more)	LOW	CRITICAL

CAPS, clinician-administered PTSD scale; CI, confidence interval; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference;
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses both line of no effect and threshold for clinically important effect
[3] Funding from pharmaceutical company
[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

SSRI versus SNRI

Sertraline versus venlafaxine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline	Venlafaxine	Relative (95% CI)	Absolute		
PTSD symptomatology self-rated (follow-up mean 12 weeks; measured with: DTS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	173	179	-	SMD 0.25 higher (0.04 to 0.46 higher)	LOW	CRITICAL
PTSD symptomatology clinician-rated (follow-up mean 12 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	173	179	-	SMD 0.15 higher (0.06 lower to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline	Venlafaxine	Relative (95% CI)	Absolute	Quality	Importance
										0.35 higher)		
Remission (follow-up mean 12 weeks; assessed with: Number of people scoring <20 on CAPS)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[2]	42/173 (24.3%)	54/179 (30.2%)	RR 0.8 (0.57 to 1.14)	60 fewer per 1000 (from 130 fewer to 42 more)	VERY LOW	CRITICAL
Depression symptoms (follow-up mean 12 weeks; measured with: HAM-D change score; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	173	179	-	SMD 0.19 higher (0.02 lower to 0.4 higher)	VERY LOW	IMPORTANT
Functional impairment (follow-up mean 12 weeks; measured with: SDS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	173	179	-	SMD 0.09 higher (0.12 lower to 0.3 higher)	LOW	IMPORTANT
Global functioning (follow-up mean 12 weeks; measured with: GAF change score; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	173	179	-	SMD 0.08 lower (0.29 lower to 0.13 higher)	LOW	IMPORTANT
Quality of life (follow-up mean 12 weeks; measured with: Q-LES-Q-SF change score; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	173	179	-	SMD 0.06 lower (0.27 lower to 0.15 higher)	LOW	IMPORTANT
Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[2]	62/173 (35.8%)	54/179 (30.2%)	RR 1.19 (0.88 to 1.6)	57 more per 1000 (from 36 fewer to 181 more)	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline	Venlafaxine	Relative (95% CI)	Absolute		
Discontinuation due to adverse events (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[2]	22/173 (12.7%)	17/179 (9.5%)	RR 1.34 (0.74 to 2.43)	32 more per 1000 (from 25 fewer to 136 more)	VERY LOW	CRITICAL

CAPS, clinician administered PTSD scale; CI, confidence interval; DTS, Davidson Trauma Scale; GAF, Global Assessment of Functioning; HAM-D, Hamilton Anxiety Rating scale-Depression; PTSD, post-traumatic stress disorder; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; RR, risk ratio; SMD, standard mean difference

[1] OIS not met (N<400)

[2] Funding from pharmaceutical company

[3] Risk of bias is unclear across multiple domains

[4] 95% CI crosses both line of no effect and threshold for clinically important effect

[5] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Sertraline (+trauma-focused CBT) versus venlafaxine (+trauma-focused CBT) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline (+ trauma-focused CBT)	Venlafaxine (+ trauma-focused CBT)	Relative (95% CI)	Absolute		
PTSD symptomatology self-rated (follow-up mean 30 weeks; measured with: HTQ change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	104	91	-	SMD 0.15 lower (0.43 lower to 0.13 higher)	LOW	CRITICAL
Anxiety symptoms (follow-up mean 30 weeks; measured with: HAM-A change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	104	91	-	SMD 0.08 higher (0.2 lower to 0.36 higher)	LOW	IMPORTANT
Depression symptoms (follow-up mean 30 weeks; measured with: HAM-D change score; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline (+ trauma-focused CBT)	Venlafaxine (+ trauma-focused CBT)	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	104	91	-	SMD 0.02 lower (0.3 lower to 0.27 higher)	LOW	IMPORTANT
Functional impairment (follow-up mean 30 weeks; measured with: SDS change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	104	91	-	SMD 0.39 lower (0.68 to 0.11 lower)	LOW	IMPORTANT
Quality of life (follow-up mean 30 weeks; measured with: WHO-5 change score; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	104	91	-	SMD 0.29 higher (0.01 to 0.58 higher)	LOW	IMPORTANT
Discontinuation due to any reason (follow-up mean 30 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	21/109 (19.3%)	30/98 (30.6%)	RR 0.63 (0.39 to 1.02)	113 fewer per 1000 (from 187 fewer to 6 more)	MODERATE	CRITICAL

CBT, cognitive behavioural therapy; CI, confidence interval; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; HTQ, Harvard Trauma Questionnaire; PTSD, post-traumatic stress disorder; RR, risk ratio; SDS, Sheehan Disability Scale; SMD, standard mean difference

[1] Open-label

[2] OIS not met (N<400)

[3] 95% CI crosses both line of no effect and threshold for clinically important effect

SSRI versus TCA

Paroxetine versus amitriptyline for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paroxetine	Amitriptyline	Relative (95% CI)	Absolute		
PTSD symptomatology clinician-rated (follow-up mean 12 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	20	-	SMD 0.66 higher (0.03 to 1.28 higher)	VERY LOW	CRITICAL
Response (follow-up mean 12 weeks; assessed with: Number of people showing ≥30% improvement on CAPS & CGI-I much or very much improved)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/25 (28%)	11/25 (44%)	RR 0.64 (0.3 to 1.37)	158 fewer per 1000 (from 308 fewer to 163 more)	VERY LOW	CRITICAL
Anxiety symptoms (follow-up mean 12 weeks; measured with: BAI change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	22	20	-	SMD 0.61 higher (0.01 lower to 1.23 higher)	LOW	IMPORTANT
Depression symptoms (follow-up mean 12 weeks; measured with: BDI change score; Better indicated by lower values)												
1	randomised trials	seriou[s1]	no serious inconsistency	no serious indirectness	very serious[3]	none	22	20	-	SMD 0.04 lower (0.65 lower to 0.56 higher)	VERY LOW	IMPORTANT
Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	3/25 (12%)	5/25 (20%)	RR 0.6 (0.16 to 2.25)	80 fewer per 1000 (from 168 fewer to 250 more)	LOW	CRITICAL
Discontinuation due to adverse events (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	3/25 (12%)	5/25 (20%)	RR 0.6 (0.16 to 2.25)	80 fewer per 1000 (from 168 fewer to 250 more)	LOW	CRITICAL

BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CAPS, clinician-administered PTSD scale; CGI-I, Clinical Global Impression scale-Global Improvement; CI, confidence interval; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] Open-label (no blinding)
[2] OIS not met (N<400)
[3] 95% CI crosses line of no effect and threshold for both clinically important benefit and harm
[4] 95% CI crosses both line of no effect and threshold for clinically important effect

SSRI versus placebo for maintenance treatment of PTSD symptoms in adults

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SSRIs**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Relapse (follow-up 24-28 weeks; assessed with: Number of participants who relapsed)												
3	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	reporting bias[4]	38/156 (24.4%)	64/166 (38.6%)	RR 0.51 (0.25 to 1.06)	189 fewer per 1000 (from 289 fewer to 23 more)	VERY LOW	CRITICAL
PTSD symptomatology self-rated (follow-up 24-28 weeks; measured with: DTS change score; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	very serious[5]	no serious indirectness	serious[3]	reporting bias[4]	103	108	-	SMD 0.24 lower (0.87 lower to 0.39 higher)	VERY LOW	CRITICAL
PTSD symptomatology clinician-rated (follow-up mean 24 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[4]	68	61	-	SMD 0.19 higher (0.15 lower to 0.54 higher)	VERY LOW	CRITICAL
Depression symptoms (follow-up mean 28 weeks; measured with: HAM-D change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	reporting bias[4]	38	46	-	SMD 3.19 lower (3.85 to 2.54 lower)	VERY LOW	IMPORTANT
Quality of life (follow-up mean 28 weeks; measured with: Q-LES-Q-SF change score; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	reporting bias[4]	38	46	-	SMD 3.47 higher (2.78 to 4.16 higher)	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRIs	Placebo	Relative (95% CI)	Absolute		
Discontinuation due to any reason (follow-up 24-28 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	reporting bias[4]	40/156 (25.6%)	69/166 (41.6%)	RR 0.61 (0.42 to 0.89)	162 fewer per 1000 (from 46 fewer to 241 fewer)	LOW	CRITICAL
Discontinuation due to adverse events (follow-up 26-28 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	reporting bias[4]	5/68 (7.4%)	3/78 (3.8%)	RR 1.81 (0.49 to 6.69)	31 more per 1000 (from 20 fewer to 219 more)	VERY LOW	CRITICAL

CAPS, clinician administered PTSD scale; CI, confidence interval; DTS, Davidson Trauma Scale; HAM-D, Hamilton Anxiety Rating scale-Depression; PTSD, post-traumatic stress disorder; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; RR, risk ratio; SMD, standard mean difference; SSRIs, selective serotonin reuptake inhibitors

[1] Risk of bias is high or unclear across multiple domains
[2] Substantial heterogeneity (I2>50%)
[3] 95% CI crosses both line of no effect and threshold for clinically important benefit
[4] Funding from pharmaceutical company
[5] Considerable heterogeneity (I2=>80%)
[6] 95% CI crosses both line of no effect and threshold for clinically important harm
[7] OIS not met (N<400)
[8] OIS not met (events<300)
[9] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

SSRI versus psychological therapies

SSRI + trauma-focused CBT versus trauma-focused CBT (±placebo) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRI + trauma-focused CBT	Trauma-focused CBT (+/- placebo)	Relative (95% CI)	Absolute		
PTSD symptomatology self-rated at endpoint (follow-up 12-26 weeks; measured with: HTQ/PDS change score; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	81	141	-	SMD 0.1 lower	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRI + trauma-focused CBT	Trauma-focused CBT (+/- placebo)	Relative (95% CI)	Absolute		
										(0.39 lower to 0.18 higher)		
PTSD symptomatology self-rated at 1-year follow-up (follow-up mean 52 weeks; measured with: PDS change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	26	89	-	SMD 0.21 lower (0.65 lower to 0.23 higher)	LOW	CRITICAL
PTSD symptomatology clinician-rated (follow-up 10-12 weeks; measured with: CAPS/SI–PTSD change score; Better indicated by lower values)												
2	randomised trials	serious[1]	serious[4]	no serious indirectness	serious[3]	none	39	102	-	SMD 0.6 lower (1.39 lower to 0.19 higher)	VERY LOW	CRITICAL
Remission (follow-up 10-12 weeks; assessed with: Number of people no longer meeting diagnostic criteria for PTSD/scoring ≤20 on CAPS & CGI-I score=1)												
2	randomised trials	serious[1]	very serious5	no serious indirectness	very serious[6]	none	28/76 (36.8%)	75/132 (56.8%)	RR 1.07 (0.24 to 4.69)	40 more per 1000 (from 432 fewer to 1000 more)	VERY LOW	CRITICAL
Response (follow-up mean 10 weeks; assessed with: Number of people rated as 'much' or 'very much' improved on CGI-I)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	12/19 (63.2%)	7/18 (38.9%)	RR 1.62 (0.83 to 3.18)	241 more per 1000 (from 66 fewer to 848 more)	LOW	CRITICAL
Anxiety symptoms at endpoint (follow-up 12-26 weeks; measured with: HAM-A/STAI State change score; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	81	141	-	SMD 0.23 lower (0.52 lower to 0.06 higher)	VERY LOW	IMPORTANT
Anxiety symptoms at 1-year follow-up (follow-up mean 52 weeks; measured with: STAI State change score; Better indicated by lower values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRI + trauma-focused CBT	Trauma-focused CBT (+/- placebo)	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	26	89	-	SMD 0.08 lower (0.52 lower to 0.35 higher)	LOW	IMPORTANT
Depression symptoms at endpoint (follow-up 10-26 weeks; measured with: HAM-D/BDI-II change score; Better indicated by lower values)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	94	155	-	SMD 0.61 lower (0.88 to 0.34 lower)	VERY LOW	IMPORTANT
Depression symptoms at 1-year follow-up (follow-up mean 52 weeks; measured with: BDI-II change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	89	-	SMD 0.74 lower (1.19 to 0.3 lower)	LOW	IMPORTANT
Functional impairment (follow-up mean 26 weeks; measured with: SDS change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	55	52	-	SMD 0.39 lower (0.77 to 0.01 lower)	LOW	IMPORTANT
Quality of life (follow-up mean 26 weeks; measured with: WHO-5 change score; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	55	52	-	SMD 0.13 higher (0.24 lower to 0.51 higher)	LOW	IMPORTANT
Discontinuation due to any reason (follow-up 10-26 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
3	randomised trials	serious[1]	serious[4]	no serious indirectness	very serious[6]	none	47/147 (32%)	40/202 (19.8%)	RR 1.55 (0.79 to 3.02)	109 more per 1000 (from 42 fewer to 400 more)	VERY LOW	CRITICAL
Discontinuation due to adverse events (follow-up 10-26 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	1/90 (1.1%)	2/88 (2.3%)	RR 0.49 (0.05 to 5.31)	12 fewer per 1000 (from 22	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRI + trauma-focused CBT	Trauma-focused CBT (+/- placebo)	Relative (95% CI)	Absolute		
										fewer to 98 more)		

BDI, Beck Depression Inventory; CAPS, Clinician Administered PTSD Scale; CBT, cognitive behavioural therapy; CGI, Clinical Global Impression scale; CI, confidence interval; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; HTQ, Harvard Trauma Questionnaire; PDS, Post-traumatic Diagnostic Scale; PTSD, post-traumatic stress disorder; RR, risk ratio; SDS, Sheehan Disability Scale; SI-PTSD, Structured Interview for PTSD; SMD, standard mean difference; SSRI, selective serotonin reuptake inhibitor; STAI, State-Trait Anxiety Inventory

[1] Risk of bias is high or unclear across multiple domains
[2] OIS not met (N<400)
[3] 95% CI crosses both line of no effect and threshold for clinically important benefit
[4] Substantial heterogeneity (I2>50%)
[5] Considerable heterogeneity (I2>80%)
[6] 95% CI crosses line of no effect and threshold for both clinical benefit and harm

Antidepressants: Tricyclic antidepressants (TCAs)

TCA versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCAs	Placebo	Relative (95% CI)	Absolute		
PTSD symptomatology self-rated (follow-up mean 8 weeks; measured with: IES change score; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40	34	-	SMD 0.64 lower (1.11 to 0.16 lower)	VERY LOW	CRITICAL
PTSD symptomatology clinician-rated (follow-up mean 8 weeks; measured with: SI–PTSD change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	17	16	-	SMD 0.35 lower (1.04 lower to 0.33 higher)	LOW	CRITICAL
Response (follow-up mean 8 weeks; assessed with: Number of people showing ≥50% improvement on SI–PTSD/rated as 'much or very much improved' on CGI-I)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TCAs**	**Placebo**	**Relative (95% CI)**	**Absolute**		
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	21/48 (43.8%)	8/39 (20.5%)	RR 2.13 (1.08 to 4.19)	232 more per 1000 (from 16 more to 654 more)	VERY LOW	CRITICAL
Anxiety symptoms (follow-up mean 8 weeks; measured with: HAM-A/CAS change score; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	40	34	-	SMD 0.43 lower (0.9 lower to 0.03 higher)	VERY LOW	IMPORTANT
Depression symptoms (follow-up mean 8 weeks; measured with: HAM-D change score; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40	34	-	SMD 0.62 lower (1.18 to 0.07 lower)	VERY LOW	IMPORTANT
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	20/48 (41.7%)	17/39 (43.6%)	RR 0.89 (0.56 to 1.42)	48 fewer per 1000 (from 192 fewer to 183 more)	VERY LOW	CRITICAL
Discontinuation due to adverse events (follow-up mean 8 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	4/23 (17.4%)	3/18 (16.7%)	RR 1.04 (0.27 to 4.08)	7 more per 1000 (from 122 fewer to 513 more)	VERY LOW	CRITICAL

CAS, Clinical Anxiety Scale; CI, confidence interval; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; IES, Impact of Event Scale; PTSD, post-traumatic stress disorder; RR, risk ratio; SI-PTSD, Structured Interview for PTSD; SMD, standard mean difference; TCA, tricyclic antidepressant

[1] Risk of bias is high or unclear across multiple domains

[2] OIS not met (N<400)

[3] 95% CI crosses both line of no effect and threshold for clinically important benefit

[4] OIS not met (events<300)

[5] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Antidepressants: Serotonin-norepinephrine reuptake inhibitors (SNRIs)

Venlafaxine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Venlafaxine**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
PTSD symptomatology self-rated (follow-up mean 12 weeks; measured with: DTS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	179	179	-	SMD 0.52 lower (0.73 to 0.31 lower)	LOW	CRITICAL
PTSD symptomatology clinician-rated (follow-up 12-26 weeks; measured with: CAPS change score; Better indicated by lower values)												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	340	347	-	SMD 0.44 lower (0.59 to 0.29 lower)	LOW	CRITICAL
Remission (follow-up 12-26 weeks; assessed with: Number of people scoring <20 on CAPS)												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[2]	136/340 (40%)	98/347 (28.2%)	RR 1.41 (1.15 to 1.74)	116 more per 1000 (from 42 more to 209 more)	VERY LOW	CRITICAL
Depression symptoms (follow-up 12-26 weeks; measured with: HAM-D change score; Better indicated by lower values)												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	340	347	-	SMD 0.49 lower (0.64 to 0.33 lower)	LOW	IMPORTANT
Functional impairment (follow-up 12-26 weeks; measured with: SDS change score; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	340	347	-	SMD 0.42 lower (0.57 to 0.27 lower)	MODERATE	IMPORTANT
Global functioning (follow-up 12-26 weeks; measured with: GAF change score; Better indicated by higher values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	340	347	-	SMD 0.4 higher (0.24 to 0.55 higher)	MODERATE	IMPORTANT
Quality of life (follow-up 12-26 weeks; measured with: Q-LES-Q-SF change score; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Venlafaxine	Placebo	Relative (95% CI)	Absolute		
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	340	347	-	SMD 0.46 higher (0.3 to 0.61 higher)	MODERATE	IMPORTANT
Discontinuation due to any reason (follow-up 12-26 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[2]	103/340 (30.3%)	121/347 (34.9%)	RR 0.87 (0.7 to 1.08)	45 fewer per 1000 (from 105 fewer to 28 more)	LOW	CRITICAL
Discontinuation due to adverse events (follow-up 12-26 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	reporting bias[2]	32/340 (9.4%)	28/347 (8.1%)	RR 1.19 (0.62 to 2.26)	15 more per 1000 (from 31 fewer to 102 more)	VERY LOW	CRITICAL

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; DTS, Davidson Trauma Scale; GAF, Global Assessment of Functioning; HAM-D, Hamilton Anxiety Rating scale-Depression; PTSD, post-traumatic stress disorder; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire; RR, risk ratio; SDS, Sheehan Disability Scale; SMD, standard mean difference

[1] OIS not met (N<400)

[2] Funding from pharmaceutical company

[3] Blinding of outcome assessor(s) unclear

[4] OIS not met (events<300)

[5] 95% CI crosses both line of no effect and threshold for clinically important benefit

[6] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Antidepressants: Monoamine-oxidase inhibitors (MAOIs)

MAOI versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MAOIs	Placebo	Relative (95% CI)	Absolute		
PTSD symptomatology self-rated (follow-up mean 8 weeks; measured with: IES change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19	18	-	SMD 1.15 lower	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MAOIs	Placebo	Relative (95% CI)	Absolute		
										(1.85 to 0.45 lower)		
PTSD symptomatology clinician-rated (follow-up mean 14 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	22	23	-	SMD 0.58 lower (1.18 lower to 0.02 higher)	LOW	CRITICAL
Remission (follow-up mean 14 weeks; assessed with: Number of people no longer meeting diagnostic criteria for PTSD)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	12/35 (34.3%)	6/31 (19.4%)	RR 1.77 (0.76 to 4.15)	149 more per 1000 (from 46 fewer to 610 more)	VERY LOW	CRITICAL
Response (follow-up mean 8 weeks; assessed with: Number of people rated as 'much' or 'very much' improved on CGI-I)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	13/19 (68.4%)	5/18 (27.8%)	RR 2.46 (1.1 to 5.51)	406 more per 1000 (from 28 more to 1000 more)	VERY LOW	CRITICAL
Anxiety symptoms (follow-up mean 8 weeks; measured with: CAS change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	19	18	-	SMD 0.53 lower (1.19 lower to 0.12 higher)	LOW	IMPORTANT
Depression symptoms (follow-up mean 8 weeks; measured with: HAM-D change score; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	19	18	-	SMD 0.29 lower (0.94 lower to 0.36 higher)	VERY LOW	IMPORTANT
Discontinuation due to any reason (follow-up 8-14 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
2	randomised trials	no serious risk of bias	very serious[6]	no serious indirectness	very serious[4]	none	17/54 (31.5%)	20/49 (40.8%)	RR 0.69 (0.16 to 3.07)	127 fewer per 1000 (from 343	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MAOIs	Placebo	Relative (95% CI)	Absolute		
										fewer to 845 more)		
Discontinuation due to adverse events (follow-up mean 8 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/19 (5.3%)	3/18 (16.7%)	RR 0.32 (0.04 to 2.76)	113 fewer per 1000 (from 160 fewer to 293 more)	VERY LOW	CRITICAL

CAPS, Clinician Administered PTSD Scale; CAS, Clinical Anxiety Scale; CGI-I, Clinical Global Impression scale-Global Improvement; CI, confidence interval; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; IES, Impact of Event Scale; MAOIs, monoamine oxidase inhibitors; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference

[1] Risk of bias is high or unclear across multiple domains
[2] OIS not met (N<400)
[3] 95% CI crosses both line of no effect and threshold for clinically important benefit
[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm
[5] OIS not met (events<300)
[6] Considerable heterogeneity (I2>80%)

Phenelzine versus imipramine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenelzine	Imipramine	Relative (95% CI)	Absolute		
PTSD symptomatology self-rated (follow-up mean 8 weeks; measured with: IES change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19	23	-	SMD 0.4 lower (1.02 lower to 0.21 higher)	LOW	CRITICAL
Response (follow-up mean 8 weeks; assessed with: Number of people rated as 'much' or 'very much' improved on CGI-I)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	13/19 (68.4%)	15/23 (65.2%)	RR 1.05 (0.68 to 1.61)	33 more per 1000 (from 209 fewer to 398 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenelzine	Imipramine	Relative (95% CI)	Absolute		
Anxiety symptoms (follow-up mean 8 weeks; measured with: CAS change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	19	23	-	SMD 0 higher (0.61 lower to 0.61 higher)	VERY LOW	IMPORTANT
Depression symptoms (follow-up mean 8 weeks; measured with: HAM-D change score; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	19	23	-	SMD 0.09 higher (0.52 lower to 0.7 higher)	VERY LOW	IMPORTANT
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/19 (21.1%)	12/23 (52.2%)	RR 0.4 (0.16 to 1.05)	313 fewer per 1000 (from 438 fewer to 26 more)	LOW	CRITICAL
Discontinuation due to adverse events (follow-up mean 8 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/19 (5.3%)	4/23 (17.4%)	RR 0.3 (0.04 to 2.48)	122 fewer per 1000 (from 167 fewer to 257 more)	VERY LOW	CRITICAL

CAS, Clinical Anxiety Scale; CGI-I, Clinical Global Impression scale-Global Improvement; CI, confidence interval; HAM-D, Hamilton Anxiety Rating scale-Depression; IES, Impact of Event Scale; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference

[1] Risk of bias is high or unclear across multiple domains

[2] 95% CI crosses both line of no effect and threshold for clinically important benefit

[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Antidepressants: Other antidepressants

Nefazodone versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nefazodone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
PTSD symptomatology self-rated (follow-up mean 12 weeks; measured with: PCL change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	26	15	-	SMD 0.2 lower (0.84 lower to 0.43 higher)	VERY LOW	CRITICAL
PTSD symptomatology clinician-rated (follow-up mean 12 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	26	15	-	SMD 0.23 lower (0.86 lower to 0.41 higher)	VERY LOW	CRITICAL
Response (follow-up mean 12 weeks; assessed with: Number of people showing ≥30% improvement on CAPS)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	9/27 (33.3%)	5/15 (33.3%)	RR 1 (0.41 to 2.44)	0 fewer per 1000 (from 197 fewer to 480 more)	VERY LOW	CRITICAL
Depression symptoms (follow-up mean 12 weeks; measured with: HAM-D change score; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	26	15	-	SMD 0.27 lower (0.91 lower to 0.37 higher)	VERY LOW	IMPORTANT
Dissociative symptoms (follow-up mean 12 weeks; measured with: CADSS change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	26	15	-	SMD 0.07 lower (0.71 lower to 0.57 higher)	VERY LOW	IMPORTANT
Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nefazodone	Placebo	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	13/27 (48.1%)	6/15 (40%)	RR 1.2 (0.58 to 2.51)	80 more per 1000 (from 168 fewer to 604 more)	VERY LOW	CRITICAL
Discontinuation due to adverse events (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	5/27 (18.5%)	1/15 (6.7%)	RR 2.78 (0.36 to 21.62)	119 more per 1000 (from 43 fewer to 1000 more)	VERY LOW	CRITICAL

CADSS, Clinician Administered Dissociative States Scale; CAPS, Clinician Administered PTSD Scale; CI, confidence interval; HAM-D, Hamilton Anxiety Rating scale-Depression; PCL, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; RR, relative risk; SMD, standard mean difference

[1] Risk of bias is high or unclear across multiple domains

[2] 95% CI crosses both line of no effect and threshold for clinically important benefit

[3] Funding from pharmaceutical company

[4] 95% CI crosses line of no effect and threshold for both clinically important benefit and harm

Bupropion (+TAU) versus placebo (+TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bupropion (+ TAU)	Placebo (+ TAU)	Relative (95% CI)	Absolute		
PTSD symptomatology self-rated (follow-up mean 8 weeks; measured with: DTS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	reporting bias[2]	18	10	-	SMD 0.1 lower (0.88 lower to 0.67 higher)	VERY LOW	CRITICAL
Depression symptoms (follow-up mean 8 weeks; measured with: BDI change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	reporting bias[2]	18	10	-	SMD 0.05 higher (0.72 lower to 0.83 higher)	VERY LOW	IMPORTANT

BDI, Beck Depression Inventory; CI, confidence interval; DTS, Davidson Trauma Scale; PTSD, post-traumatic stress disorder; TAU, treatment as usual; SMD, standard mean difference
[1] 95% CI crosses line of no effect and threshold for both clinically important benefit and harm
[2] Funding from pharmaceutical company

Moclobemide versus tianeptine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Moclobemide**	**Tianeptine**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
PTSD symptomatology clinician-rated (follow-up mean 12 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	35	30	-	SMD 0.1 higher (0.39 lower to 0.59 higher)	VERY LOW	CRITICAL
Response (follow-up mean 12 weeks; assessed with: Number of people showing >50% improvement on CAPS)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/35 (62.9%)	23/30 (76.7%)	RR 0.82 (0.59 to 1.13)	138 fewer per 1000 (from 314 fewer to 100 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/35 (14.3%)	6/30 (20%)	RR 0.71 (0.24 to 2.11)	58 fewer per 1000 (from 152 fewer to 222 more)	VERY LOW	CRITICAL
Discontinuation due to adverse events (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/35 (2.9%)	2/30 (6.7%)	RR 0.43 (0.04 to 4.5)	38 fewer per 1000 (from 64	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moclobemide	Tianeptine	Relative (95% CI)	Absolute		
										fewer to 233 more)		

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] Open-label
[2] 95% CI crosses both line of no effect and threshold for clinically important effect
[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Anticonvulsants

Topiramate versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Placebo	Relative (95% CI)	Absolute		
PTSD symptomatology self-rated (follow-up mean 12 weeks; measured with: DTS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	19	19	-	SMD 0.6 lower (1.26 lower to 0.05 higher)	LOW	CRITICAL
PTSD symptomatology clinician-rated (follow-up mean 12 weeks; measured with: CAPS change score; Better indicated by lower values)												
3	randomised trials	serious[3]	very serious[4]	no serious indirectness	serious[1]	none	70	66	-	SMD 1.25 lower (2.61 lower to 0.11 higher)	VERY LOW	CRITICAL
Response (follow-up mean 12 weeks; assessed with: Number of people showing ≥30% improvement on CAPS)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	14/17 (82.4%)	9/18 (50%)	RR 1.65 (0.99 to 2.75)	325 more per 1000 (from 5 fewer to 875 more)	MODERATE	CRITICAL
Anxiety symptoms (follow-up mean 12 weeks; measured with: HAM-A change score; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Placebo	Relative (95% CI)	Absolute		
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	19	19	-	SMD 0.31 lower (0.95 lower to 0.33 higher)	VERY LOW	IMPORTANT
Depression symptoms (follow-up mean 12 weeks; measured with: HAM-D/BDI change score; Better indicated by lower values)												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	36	33	-	SMD 0.44 lower (0.92 lower to 0.04 higher)	VERY LOW	IMPORTANT
Functional impairment (follow-up mean 12 weeks; measured with: SDS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[2]	19	19	-	SMD 0.08 higher (0.56 lower to 0.72 higher)	VERY LOW	IMPORTANT
Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	10/71 (14.1%)	12/71 (16.9%)	RR 0.85 (0.39 to 1.86)	25 fewer per 1000 (from 103 fewer to 145 more)	LOW	CRITICAL
Discontinuation due to adverse events (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	7/71 (9.9%)	5/71 (7%)	RR 1.33 (0.47 to 3.79)	23 more per 1000 (from 37 fewer to 196 more)	LOW	CRITICAL

BDI, Beck Depression Inventory; CAPS, Clinician Administered PTSD Scale; CI, confidence interval; DTS, Davidson Trauma Scale; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; PTSD, post-traumatic stress disorder; RR, risk ratio; SDS, Sheehan Disability Scale; SMD, standard mean difference

[1] 95% CI crosses both line of no effect and threshold for clinically important benefit

[2] Funding from pharmaceutical company

[3] Blinding of outcome assessor(s) is unclear

[4] Considerable heterogeneity (I2>80%)

[5] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Divalproex versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Divalproex**	**Placebo**	**Relative (95% CI)**	**Absolute**		
PTSD symptomatology clinician-rated (follow-up mean 8 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	41	41	-	SMD 0.08 higher (0.35 lower to 0.51 higher)	LOW	CRITICAL
Anxiety symptoms (follow-up mean 8 weeks; measured with: HAM-A change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[2]	41	41	-	SMD 0.28 lower (0.72 lower to 0.15 higher)	LOW	IMPORTANT
Depression symptoms (follow-up mean 8 weeks; measured with: MADRS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[2]	41	41	-	SMD 0.09 lower (0.52 lower to 0.35 higher)	LOW	IMPORTANT
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[2]	10/44 (22.7%)	7/41 (17.1%)	RR 1.33 (0.56 to 3.17)	56 more per 1000 (from 75 fewer to 370 more)	VERY LOW	CRITICAL
Discontinuation due to adverse events (follow-up mean 8 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[2]	3/44 (6.8%)	1/41 (2.4%)	RR 2.8 (0.3 to 25.81)	44 more per 1000 (from 17 fewer to 605 more)	VERY LOW	CRITICAL

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; HAM-A, Hamilton Anxiety Rating scale-Anxiety; MADRS, Montgomery-Asberg Depression Rating Scale; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference

[1] 95% CI crosses both line of no effect and threshold for clinically important harm

[2] Funding from pharmaceutical company

[3] 95% CI crosses both line of no effect and threshold for clinically important benefit

[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Tiagabine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tiagabine	Placebo	Relative (95% CI)	Absolute		
PTSD symptomatology clinician-rated (follow-up mean 12 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	105	97	-	SMD 0.02 lower (0.3 lower to 0.26 higher)	VERY LOW	CRITICAL
Response (follow-up mean 12 weeks; assessed with: Number of people rated as 'much' or 'very much' improved on CGI-I)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	51/116 (44%)	52/116 (44.8%)	RR 0.98 (0.74 to 1.31)	9 fewer per 1000 (from 117 fewer to 139 more)	VERY LOW	CRITICAL
Remission (follow-up mean 12 weeks; assessed with: Number of people scoring <20 on CAPS)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	17/116 (14.7%)	14/116 (12.1%)	RR 1.21 (0.63 to 2.35)	25 more per 1000 (from 45 fewer to 163 more)	VERY LOW	CRITICAL
Depression symptoms (follow-up mean 12 weeks; measured with: MADRS change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	105	97	-	SMD 0.01 higher (0.27 lower to 0.29 higher)	VERY LOW	IMPORTANT
Functional impairment (follow-up mean 12 weeks; measured with: SDS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	105	97	-	SMD 0.05 higher (0.22 lower to 0.33 higher)	LOW	IMPORTANT
Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	39/116 (33.6%)	52/116 (44.8%)	RR 0.75 (0.54 to 1.04)	112 fewer per 1000 (from 206 fewer to 18 more)	LOW	CRITICAL
Discontinuation due to adverse events (follow-up mean 12 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	9/116 (7.8%)	9/116 (7.8%)	RR 1 (0.41 to 2.43)	0 fewer per 1000 (from	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tiagabine	Placebo	Relative (95% CI)	Absolute		
										46 fewer to 111 more)		

CAPS, Clinician Administered PTSD Scale; CGI-I, Clinical Global Impression scale-Global Improvement; CI, confidence interval; MADRS, Montgomery-Asberg Depression Rating Scale; PTSD, post-traumatic stress disorder; RR, risk ratio; SDS, Sheehan Disability Scale; SMD, standard mean difference
[1] Blinding of outcome assessor(s) is unclear
[2] OIS not met (N<400)
[3] Funding from pharmaceutical company
[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm
[5] 95% CI crosses both line of no effect and threshold for clinically important benefit

Pregabalin (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin (augmentation of routine medications)	Placebo (augmentation of routine medications)	Relative (95% CI)	Absolute		
PTSD symptomatology self-rated (follow-up mean 6 weeks; measured with: PCL change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	18	19	-	SMD 0.71 lower (1.38 to 0.04 lower)	MODERATE	CRITICAL
Anxiety symptoms (follow-up mean 6 weeks; measured with: HAM-A change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	18	19	-	SMD 0.39 lower (1.04 lower to 0.26 higher)	MODERATE	IMPORTANT
Depression symptoms (follow-up mean 6 weeks; measured with: HAM-D change score; Better indicated by lower values)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pregabalin (augmentation of routine medications)**	**Placebo (augmentation of routine medications)**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	18	19	-	SMD 0.1 lower (0.74 lower to 0.55 higher)	LOW	IMPORTANT
Quality of life (follow-up mean 6 weeks; measured with: Spitzer Quality of Life Index change score; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	18	19	-	SMD 0.21 lower (0.86 lower to 0.44 higher)	MODERATE	IMPORTANT
Discontinuation due to any reason (follow-up mean 6 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	0/18 (0%)	0/19 (0%)	not pooled	not pooled	MODERATE	CRITICAL
Discontinuation due to adverse events (follow-up mean 6 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	0/18 (0%)	0/19 (0%)	not pooled	not pooled	MODERATE	CRITICAL

CI, confidence interval; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; PCL, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standardised mean difference

[1] OIS not met (N<400)

[2] 95% CI crosses both line of no effect and threshold for clinically important benefit

[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

[4] 95% CI crosses both line of no effect and threshold for clinically important harm

[5] OIS not met (events<300)

Antipsychotics

Antipsychotic monotherapy versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antipsychotic monotherapy	Placebo	Relative (95% CI)	Absolute		
PTSD symptomatology self-rated (follow-up 8-12 weeks; measured with: DTS change score; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	56	52	-	SMD 0.84 lower (1.23 to 0.44 lower)	VERY LOW	CRITICAL
PTSD symptomatology clinician-rated (follow-up 8-24 weeks; measured with: CAPS change score; Better indicated by lower values)												
3	randomised trials	no serious risk of bias	very serious[4]	no serious indirectness	serious[2]	reporting bias[3]	179	176	-	SMD 0.75 lower (1.38 to 0.11 lower)	VERY LOW	CRITICAL
Remission (follow-up mean 8 weeks; assessed with: Number of people scoring <50 on CAPS)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	10/14 (71.4%)	3/14 (21.4%)	RR 3.33 (1.16 to 9.59)	499 more per 1000 (from 34 more to 1000 more)	VERY LOW	CRITICAL
Response (follow-up mean 8 weeks; assessed with: Number of people showing >50% improvement on CAPS)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	10/14 (71.4%)	3/14 (21.4%)	RR 3.33 (1.16 to 9.59)	499 more per 1000 (from 34 more to 1000 more)	VERY LOW	CRITICAL
Anxiety symptoms (follow-up 12-24 weeks; measured with: HAM-A change score; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	serious[7]	reporting bias[3]	165	162	-	SMD 0.54 lower (1.11 lower to 0.04 higher)	VERY LOW	IMPORTANT
Depression symptoms (follow-up 8-24 weeks; measured with: MADRS/HAM-D change score; Better indicated by lower values)												
3	randomised trials	no serious	serious[6]	no serious indirectness	serious[2]	reporting bias[3]	179	176	-	SMD 0.75 lower (1.19 to	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antipsychotic monotherapy	Placebo	Relative (95% CI)	Absolute		
		risk of bias								0.31 lower)		
Functional impairment (follow-up mean 8 weeks; measured with: SDS change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	14	14	-	SMD 0.81 lower (1.59 to 0.04 lower)	LOW	IMPORTANT
Quality of life (follow-up mean 24 weeks; measured with: BLSI change score; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	123	124	-	SMD 0.14 higher (0.11 lower to 0.39 higher)	LOW	IMPORTANT
Sleeping difficulties (follow-up 12-24 weeks; measured with: PSQI change score; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	165	162	-	SMD 0.3 lower (0.52 to 0.08 lower)	LOW	IMPORTANT
Discontinuation due to any reason (follow-up 12-24 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	reporting bias[3]	35/189 (18.5%)	43/187 (23%)	RR 0.76 (0.46 to 1.24)	55 fewer per 1000 (from 124 fewer to 55 more)	LOW	CRITICAL
Discontinuation due to adverse events (follow-up 12-24 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	reporting bias[3]	10/189 (5.3%)	4/187 (2.1%)	RR 2.31 (0.75 to 7.1)	28 more per 1000 (from 5 fewer to 130 more)	VERY LOW	CRITICAL

BLSI, Boston Life Satisfaction Inventory; CAPS, Clinician Administered PTSD Scale; CI, confidence interval; DTS, Davidson Trauma Scale; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; MADRS, Montgomery-Asberg Depression Rating Scale; PSQI, Sleep Quality Assessment; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference

[1] Risk of bias is high or unclear across multiple domains

[2] OIS not met (N<400)

[3] Funding from pharmaceutical company

[4] Considerable heterogeneity (I2>80%)

[5] *OIS not met (events<300)*
[6] *Substantial heterogeneity (I2=50-80%)*
[7] *95% CI crosses both line of no effect and threshold for clinically important benefit*
[8] *95% CI crosses line of no effect and thresholds for both clinically important benefit and harm*

Antipsychotic (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antipsychotic (augmentation of routine medications)**	**Placebo (augmentation of routine medications)**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
PTSD symptomatology clinician-rated (follow-up 9-16 weeks; measured with: CAPS change score; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	34	38	-	SMD 0.51 lower (0.98 to 0.04 lower)	VERY LOW	CRITICAL
Response (follow-up 9-16 weeks; assessed with: Number of people showing ≥20/50% improvement on CAPS)												
2	randomised trials	serious[1]	serious[4]	no serious indirectness	very serious[5]	reporting bias[3]	12/48 (25%)	4/47 (8.5%)	RR 2.66 (0.28 to 24.82)	141 more per 1000 (from 61 fewer to 1000 more)	VERY LOW	CRITICAL
Anxiety symptoms (follow-up 9-16 weeks; measured with: HAM-A change score; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	30	36	-	SMD 0.66 lower (1.17 to 0.16 lower)	VERY LOW	IMPORTANT
Depression symptoms (follow-up 9-16 weeks; measured with: HAM-D change score; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[3]	30	36	-	SMD 0.35 lower (0.84 lower to 0.14 higher)	VERY LOW	IMPORTANT
Discontinuation due to any reason (follow-up mean 16 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antipsychotic (augmentation of routine medications)	Placebo (augmentation of routine medications)	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[3]	11/33 (33.3%)	6/32 (18.8%)	RR 1.78 (0.75 to 4.23)	146 more per 1000 (from 47 fewer to 606 more)	VERY LOW	CRITICAL
Discontinuation due to adverse events (follow-up 9-16 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[3]	6/48 (12.5%)	6/47 (12.8%)	RR 0.96 (0.34 to 2.72)	5 fewer per 1000 (from 84 fewer to 220 more)	VERY LOW	CRITICAL

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] OIS not met (N<400)
[3] Funding from pharmaceutical company
[4] Substantial heterogeneity (I2>50%)
[5] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm
[6] 95% CI crosses both line of no effect and threshold for clinically important benefit

Benzodiazepines

Alprazolam (+virtual reality exposure therapy) versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alprazolam (+ virtual reality exposure therapy)	Placebo (+ virtual reality exposure therapy)	Relative (95% CI)	Absolute		
PTSD symptomatology self-report at endpoint (follow-up mean 6 weeks; measured with: PSS-SR change score; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alprazolam (+ virtual reality exposure therapy)	Placebo (+ virtual reality exposure therapy)	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	53	-	SMD 0.11 higher (0.28 lower to 0.49 higher)	MODERATE	CRITICAL
PTSD symptomatology self-report at 3-month follow-up (follow-up mean 13 weeks; measured with: PSS-SR change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	50	53	-	SMD 0.35 higher (0.04 lower to 0.74 higher)	MODERATE	CRITICAL
PTSD symptomatology self-report at 6-month follow-up (follow-up mean 26 weeks; measured with: PSS-SR change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	53	-	SMD 0.49 higher (0.09 to 0.88 higher)	MODERATE	CRITICAL
PTSD symptomatology self-report at 1-year follow-up (follow-up mean 52 weeks; measured with: PSS-SR change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	50	53	-	SMD 0.19 higher (0.19 lower to 0.58 higher)	MODERATE	CRITICAL
PTSD symptomatology clinician-rated at endpoint (follow-up mean 6 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	50	53	-	SMD 0.02 higher (0.37 lower to 0.41 higher)	LOW	
PTSD symptomatology clinician-rated at 3-month follow-up (follow-up mean 13 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	50	53	-	SMD 0.54 higher (0.15 to 0.94 higher)	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alprazolam (+ virtual reality exposure therapy)	Placebo (+ virtual reality exposure therapy)	Relative (95% CI)	Absolute	Quality	Importance
PTSD symptomatology clinician-rated at 6-month follow-up (follow-up mean 26 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	50	53	-	SMD 0.57 higher (0.18 to 0.97 higher)	LOW	CRITICAL
PTSD symptomatology clinician-rated at 1-year follow-up (follow-up mean 52 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	50	53	-	SMD 0.2 higher (0.19 lower to 0.59 higher)	LOW	CRITICAL
Remission at endpoint (follow-up mean 6 weeks; assessed with: Number of people no longer meeting diagnostic criteria for PTSD)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	9/50 (18%)	9/53 (17%)	RR 1.06 (0.46 to 2.45)	10 more per 1000 (from 92 fewer to 246 more)	VERY LOW	CRITICAL
Remission at 3-month follow-up (follow-up mean 13 weeks; assessed with: Number of people no longer meeting diagnostic criteria for PTSD)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	5/50 (10%)	12/53 (22.6%)	RR 0.44 (0.17 to 1.16)	127 fewer per 1000 (from 188 fewer to 36 more)	LOW	CRITICAL
Remission at 6-month follow-up (follow-up mean 26 weeks; assessed with: Number of people no longer meeting diagnostic criteria for PTSD)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	6/50 (12%)	13/53 (24.5%)	RR 0.49 (0.2 to 1.19)	125 fewer per 1000 (from 196 fewer to 47 more)	LOW	CRITICAL
Remission at 1-year follow-up (follow-up mean 52 weeks; assessed with: Number of people no longer meeting diagnostic criteria for PTSD)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	8/50 (16%)	9/53 (17%)	RR 0.94 (0.39 to 2.25)	10 fewer per 1000 (from 104 fewer to 212 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 6 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alprazolam (+ virtual reality exposure therapy)	Placebo (+ virtual reality exposure therapy)	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	15/50 (30%)	19/53 (35.8%)	RR 0.84 (0.48 to 1.46)	57 fewer per 1000 (from 186 fewer to 165 more)	LOW	CRITICAL

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; PSS-SR, PTSD Symptom Scale-Self Report; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] OIS not met (N<400)
[2] 95% CI crosses both line of no effect and threshold for clinically important harm
[3] Blinding of outcome assessor(s) is unclear
[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Alprazolam (+ virtual reality exposure therapy) versus d-cycloserine (+ virtual reality exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alprazolam (+ virtual reality exposure therapy)	D-cycloserine (+ virtual reality exposure therapy)	Relative (95% CI)	Absolute		
PTSD symptomatology self-report at endpoint (follow-up mean 6 weeks; measured with: PSS-SR change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	53	-	SMD 0.08 lower (0.47 lower to 0.31 higher)	MODERATE	CRITICAL
PTSD symptomatology self-report at 3-month follow-up (follow-up mean 13 weeks; measured with: PSS-SR change score; Better indicated by lower values)												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[2]	none	50	53	-	SMD 0.11 higher	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alprazolam (+ virtual reality exposure therapy)	D-cycloserine (+ virtual reality exposure therapy)	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias								(0.28 lower to 0.5 higher)		
PTSD symptomatology self-report at 6-month follow-up (follow-up mean 26 weeks; measured with: PSS-SR change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	50	53	-	SMD 0.21 higher (0.17 lower to 0.6 higher)	MODERATE	CRITICAL
PTSD symptomatology self-report at 1-year follow-up (follow-up mean 52 weeks; measured with: PSS-SR change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	50	53	-	SMD 0.16 higher (0.22 lower to 0.55 higher)	MODERATE	CRITICAL
PTSD symptomatology clinician-rated at endpoint (follow-up mean 6 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	50	53	-	SMD 0.07 higher (0.32 lower to 0.45 higher)	LOW	CRITICAL
PTSD symptomatology clinician-rated at 3-month follow-up (follow-up mean 13 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	50	53	-	SMD 0.23 higher (0.16 lower to 0.62 higher)	LOW	CRITICAL
PTSD symptomatology clinician-rated at 6-month follow-up (follow-up mean 26 weeks; measured with: CAPS change score; Better indicated by lower values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alprazolam (+ virtual reality exposure therapy)	D-cycloserine (+ virtual reality exposure therapy)	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	50	53	-	SMD 0.27 higher (0.12 lower to 0.66 higher)	LOW	CRITICAL
PTSD symptomatology clinician-rated at 1-year follow-up (follow-up mean 52 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	50	53	-	SMD 0.39 higher (0 to 0.78 higher)	LOW	CRITICAL
Remission at endpoint (follow-up mean 6 weeks; assessed with: Number of people no longer meeting diagnostic criteria for PTSD)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	9/50 (18%)	6/53 (11.3%)	RR 1.59 (0.61 to 4.14)	67 more per 1000 (from 44 fewer to 355 more)	VERY LOW	CRITICAL
Remission at 3-month follow-up (follow-up mean 13 weeks; assessed with: Number of people no longer meeting diagnostic criteria for PTSD)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/50 (10%)	7/53 (13.2%)	RR 0.76 (0.26 to 2.23)	32 fewer per 1000 (from 98 fewer to 162 more)	VERY LOW	CRITICAL
Remission at 6-month follow-up (follow-up mean 26 weeks; assessed with: Number of people no longer meeting diagnostic criteria for PTSD)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/50 (12%)	7/53 (13.2%)	RR 0.91 (0.33 to 2.52)	12 fewer per 1000 (from 88 fewer to 201 more)	VERY LOW	CRITICAL
Remission at 1-year follow-up (follow-up mean 52 weeks; assessed with: Number of people no longer meeting diagnostic criteria for PTSD)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	8/50 (16%)	9/53 (17%)	RR 0.94 (0.39 to 2.25)	10 fewer per 1000 (from	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alprazolam (+ virtual reality exposure therapy)	D-cycloserine (+ virtual reality exposure therapy)	Relative (95% CI)	Absolute		
										104 fewer to 212 more)		
Discontinuation due to any reason (follow-up mean 6 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	15/50 (30%)	25/53 (47.2%)	RR 0.64 (0.38 to 1.06)	170 fewer per 1000 (from 292 fewer to 28 more)	MODERATE	CRITICAL

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; PSS-SR, Post-traumatic Symptom Scale-Self-Report; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] OIS not met (N<400)
[2] 95% CI crosses both line of no effect and threshold for clinically important effect
[3] Blinding of outcome assessor(s) is unclear
[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Other drugs: Prazosin

Prazosin (±TAU) versus placebo (±TAU) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prazosin (+/- TAU)	Placebo (+/- TAU)	Relative (95% CI)	Absolute		
PTSD symptomatology self-rated at endpoint (follow-up mean 26 weeks; measured with: PCL change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	141	143	-	SMD 0.11 higher (0.13 lower to 0.34 higher)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prazosin (+/- TAU)	Placebo (+/- TAU)	Relative (95% CI)	Absolute	Quality	Importance
PTSD symptomatology clinician-rated (follow-up 8-26 weeks; measured with: CAPS/MINI change score; Better indicated by lower values)												
4	randomised trials	serious[2]	very serious[3]	no serious indirectness	serious[4]	none	241	239	-	SMD 0.81 lower (1.71 lower to 0.1 higher)	VERY LOW	CRITICAL
Response (follow-up mean 16 weeks; assessed with: Number of people rated as 'much' or 'very much' improved on CGI-I)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	12/17 (70.6%)	2/17 (11.8%)	RR 6 (1.58 to 22.86)	588 more per 1000 (from 68 more to 1000 more)	MODERATE	CRITICAL
Depression symptoms (follow-up 16-26 weeks; measured with: HAM-D/PHQ-9 change score; Better indicated by lower values)												
2	randomised trials	serious[2]	very serious[3]	no serious indirectness	very serious[6]	none	158	160	-	SMD 0.4 lower (1.56 lower to 0.76 higher)	VERY LOW	IMPORTANT
Alcohol use (follow-up mean 12 weeks; assessed with: TLFB: Number of participants abstinent from alcohol during the trial)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	23/50 (46%)	16/46 (34.8%)	RR 1.32 (0.8 to 2.17)	111 more per 1000 (from 70 fewer to 407 more)	MODERATE	IMPORTANT
Alcohol craving/consumption (follow-up 12-26 weeks; measured with: OCDS/AUDIT-C change score; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	very serious[3]	no serious indirectness	very serious[6]	none	191	189	-	SMD 2.4 higher (2.33 lower to 7.13 higher)	VERY LOW	IMPORTANT
Sleeping difficulties (follow-up 8-26 weeks; measured with: PSQI change score; Better indicated by lower values)												
4	randomised trials	no serious risk of bias	very serious[3]	no serious indirectness	very serious[6]	none	241	239	-	SMD 0.48 lower (2.06 lower to 1.09 higher)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prazosin (+/- TAU)	Placebo (+/- TAU)	Relative (95% CI)	Absolute		
Quality of life (follow-up mean 26 weeks; measured with: QOLI change score; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	141	143	-	SMD 0 higher (0.23 lower to 0.23 higher)	MODERATE	IMPORTANT
Discontinuation due to any reason (follow-up 8-26 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	42/257 (16.3%)	46/251 (18.3%)	RR 0.85 (0.49 to 1.48)	27 fewer per 1000 (from 93 fewer to 88 more)	LOW	CRITICAL
Discontinuation due to adverse events (follow-up 8-26 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	13/257 (5.1%)	8/251 (3.2%)	RR 1.47 (0.62 to 3.51)	15 more per 1000 (from 12 fewer to 80 more)	LOW	CRITICAL

AUDIT-C, Alcohol Use Disorders Identification Test; CAPS, Clinician Administered PTSD Scale; CGI-I, Clinical Global Impression scale-Global Improvement; CI, confidence interval; HAM-A/D, Hamilton Anxiety Rating scale-Anxiety/Depression; MINI, Mini-International Neuropsychiatric Interview; OCDS, Obsessive Compulsive Drinking Scale; PCL, PTSD checklist; PHQ-9, Patient Health Questionnaire; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference; TAU, treatment as usual; TLFB, Timeline Follow back Method

[1] OIS not met (N<400)

[2] Blinding of outcome assessor(s) is unclear

[3] Considerable heterogeneity (I2>80%)

[4] 95% CI crosses both line of no effect and threshold for clinically important benefit

[5] OIS not met (events<300)

[6] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Prazosin versus hydroxyzine for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Prazosin**	**Hydroxyzine**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
PTSD symptomatology clinician-rated (follow-up mean 8 weeks; measured with: MINI change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33	34	-	SMD 0.3 lower (0.78 lower to 0.18 higher)	LOW	CRITICAL
Sleeping difficulties (follow-up mean 8 weeks; measured with: PSQI change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	33	34	-	SMD 1.26 lower (1.79 to 0.74 lower)	MODERATE	IMPORTANT
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	2/35 (5.7%)	0/34 (0%)	RR 4.86 (0.24 to 97.69)	-	LOW	CRITICAL
Discontinuation due to adverse events (follow-up mean 8 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	2/35 (5.7%)	0/34 (0%)	RR 4.86 (0.24 to 97.69)	-	LOW	CRITICAL

CI, confidence interval; MINI, Mini-International Neuropsychiatric Interview; PSQI, Pittsburgh Sleep Quality Index; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference

[1] Blinding of outcome assessor(s) is unclear

[2] 95% CI crosses both line of no effect and threshold for clinically important benefit

[3] OIS not met (N<400)

[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Other drugs: Hydroxyzine

Hydroxyzine versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hydroxyzine**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
PTSD symptomatology clinician-rated (follow-up mean 8 weeks; measured with: MINI change score; Better indicated by lower values)												
1	randomised trials	serious1	no serious inconsistency	no serious indirectness	serious[2]	none	34	33	-	SMD 2.05 lower (2.65 to 1.46 lower)	LOW	CRITICAL
Sleeping difficulties (follow-up mean 8 weeks; measured with: PSQI change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	34	33	-	SMD 2.01 lower (2.6 to 1.41 lower)	MODERATE	IMPORTANT
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	0/34 (0%)	0/33 (0%)	not pooled	not pooled	MODERATE	CRITICAL
Discontinuation due to adverse events (follow-up mean 8 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	0/34 (0%)	0/33 (0%)	not pooled	not pooled	MODERATE	CRITICAL

CI, confidence interval; MINI, Mini-International Neuropsychiatric Interview; PSQI, Pittsburgh Sleep Quality Index; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference

[1] Blinding of outcome assessor(s) is unclear

[2] OIS not met (N<400)

[3] OIS not met (events<300)

Other drugs: Eszopiclone

Eszopiclone versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Eszopiclone**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
PTSD symptomatology clinician-rated (follow-up mean 3 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	12	12	-	SMD 1.49 lower (2.41 to 0.57 lower)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 3 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	1/13 (7.7%)	2/14 (14.3%)	RR 0.54 (0.06 to 5.26)	66 fewer per 1000 (from 134 fewer to 609 more)	VERY LOW	CRITICAL

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference
[1] Blinding of outcome assessor(s) is not reported
[2] OIS not met (N<400)
[3] Funding from pharmaceutical company
[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Other drugs: Propranolol

Propranolol (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propranolol (augmentation of routine medications)	Placebo (augmentation of routine medications)	Relative (95% CI)	Absolute		
PTSD symptomatology self-rated (follow-up mean 0.1 weeks; measured with: IES-R change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	19	21	-	SMD 0.1 lower (0.72 lower to 0.52 higher)	LOW	CRITICAL

CI, confidence interval; IES-R, Impact of Event Scale-Revised; PTSD, post-traumatic stress disorder; SMD, standard mean difference
[1] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Other drugs: Rivastigmine

Rivastigmine (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rivastigmine (augmentation of routine medications)	Placebo (augmentation of routine medications)	Relative (95% CI)	Absolute		
PTSD symptomatology self-rated (follow-up mean 12 weeks; measured with: PCL change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	12	12	-	SMD 0.08 higher (0.72	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rivastigmine (augmentation of routine medications)	Placebo (augmentation of routine medications)	Relative (95% CI)	Absolute		
										lower to 0.88 higher)		

CI, confidence interval; PCL, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; SMD, standard mean difference
[1] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Other drugs: Guanfacine

Guanfacine (augmentation of routine medications) versus placebo (augmentation of routine medications) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Guanfacine (augmentation of routine medications)	Placebo (augmentation of routine medications)	Relative (95% CI)	Absolute		
PTSD symptomatology self-rated (follow-up mean 8 weeks; measured with: IES-R change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	23	30	-	SMD 0.39 higher (0.16 lower to 0.94 higher)	MODERATE	CRITICAL
PTSD symptomatology clinician-rated (follow-up mean 8 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	23	30	-	SMD 0.11 higher (0.43 lower to 0.66 higher)	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Guanfacine (augmentation of routine medications)	Placebo (augmentation of routine medications)	Relative (95% CI)	Absolute		
Depression symptoms (follow-up mean 8 weeks; measured with: HAM-D change score; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	23	30	-	SMD 0.27 higher (0.28 lower to 0.82 higher)	LOW	IMPORTANT
Quality of life (follow-up mean 8 weeks; measured with: QOLI change score; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	23	30	-	SMD 0.32 higher (0.23 lower to 0.86 higher)	MODERATE	IMPORTANT
Sleeping difficulties (follow-up mean 8 weeks; measured with: Sleep Quality Index change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	23	30	-	SMD 0.14 higher (0.41 lower to 0.68 higher)	MODERATE	IMPORTANT
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	6/29 (20.7%)	4/34 (11.8%)	RR 1.76 (0.55 to 5.63)	89 more per 1000 (from 53 fewer to 545 more)	LOW	CRITICAL
Discontinuation due to adverse events (follow-up mean 8 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	3/29 (10.3%)	0/34 (0%)	RR 8.17 (0.44 to 151.84)	-	LOW	CRITICAL

CAPS, Clinician Administered PTSD Scale; CI, confidence interval; HAM-D, Hamilton Anxiety Rating scale- Depression; IES-R, Impact of Event Scale-Revised; PTSD, post-traumatic stress disorder; QOLI, Quality of Life Inventory; RR, risk-ratio; SMD, standard mean difference
[1] 95% CI crosses both line of no effect and threshold for clinically important harm
[2] Blinding of outcome assessor(s) is unclear
[3] 95% CI crosses both line of no effect and threshold for clinically important benefit
[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Other drugs: D-cycloserine

D-cycloserine (+exposure therapy) versus placebo (+exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms in adults

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**D-cycloserine (+ exposure therapy)**	**Placebo (+ exposure therapy)**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
PTSD symptomatology self-rated at endpoint (follow-up 3-10 weeks; measured with: PCL/PSS-SR change score; Better indicated by lower values)												
3	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	99	100	-	SMD 0.17 higher (0.45 lower to 0.78 higher)	LOW	CRITICAL
PTSD symptomatology self-rated at 3-month follow-up (follow-up mean 13 weeks; measured with: PSS-SR change score; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	86	87	-	SMD 0.17 higher (0.22 lower to 0.57 higher)	MODERATE	CRITICAL
PTSD symptomatology self-rated at 6-month follow-up (follow-up mean 26 weeks; measured with: PSS-SR change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	53	53	-	SMD 0.38 higher (0 to 0.77 higher)	MODERATE	CRITICAL
PTSD symptomatology self-rated at 1-year follow-up (follow-up mean 52 weeks; measured with: PSS-SR change score; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**D-cycloserine (+ exposure therapy)**	**Placebo (+ exposure therapy)**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	53	53	-	SMD 0.04 higher (0.34 lower to 0.43 higher)	MODERATE	CRITICAL
PTSD symptomatology clinician-rated at endpoint (follow-up 3-10 weeks; measured with: CAPS change score; Better indicated by lower values)												
4	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	very serious[4]	none	112	112	-	SMD 0.03 lower (0.64 lower to 0.58 higher)	VERY LOW	CRITICAL
PTSD symptomatology clinician-rated at 3-month follow-up (follow-up mean 13 weeks; measured with: CAPS change score; Better indicated by lower values)												
2	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[2]	none	86	87	-	SMD 0.18 higher (0.2 lower to 0.55 higher)	LOW	CRITICAL
PTSD symptomatology clinician-rated at 6-month follow-up (follow-up mean 26 weeks; measured with: CAPS change score; Better indicated by lower values)												
2	randomised trials	serious[5]	very serious[6]	no serious indirectness	very serious[4]	none	66	65	-	SMD 0.55 lower (2.42 lower to 1.32 higher)	VERY LOW	CRITICAL
PTSD symptomatology clinician-rated at 1-year follow-up (follow-up mean 52 weeks; measured with: CAPS change score; Better indicated by lower values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[7]	none	53	53	-	SMD 0.17 lower (0.55 lower to 0.21 higher)	LOW	CRITICAL
Remission at endpoint (follow-up 6-10 weeks; assessed with: Number of people scoring <20 on CAPS/no longer meeting diagnostic criteria)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D-cycloserine (+ exposure therapy)	Placebo (+ exposure therapy)	Relative (95% CI)	Absolute		
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	23/99 (23.2%)	19/99 (19.2%)	RR 1.24 (0.52 to 2.93)	46 more per 1000 (from 92 fewer to 370 more)	LOW	CRITICAL
Remission at 3-month follow-up (follow-up mean 13 weeks; assessed with: Number of people scoring <20 on CAPS/no longer meeting diagnostic criteria)												
2	randomised trials	no serious risk of bias	very serious[6]	no serious indirectness	very serious[4]	none	22/86 (25.6%)	19/87 (21.8%)	RR 1.15 (0.31 to 4.25)	33 more per 1000 (from 151 fewer to 710 more)	VERY LOW	CRITICAL
Remission at 6-month follow-up (follow-up mean 26 weeks; assessed with: Number of people scoring <20 on CAPS/no longer meeting diagnostic criteria)												
2	randomised trials	serious[5]	very serious[6]	no serious indirectness	very serious[4]	none	16/66 (24.2%)	15/65 (23.1%)	RR 1.4 (0.19 to 10.39)	92 more per 1000 (from 187 fewer to 1000 more)	VERY LOW	CRITICAL
Remission at 1-year follow-up (follow-up mean 52 weeks; assessed with: Number of people no longer meeting diagnostic criteria)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[4]	none	9/53 (17%)	9/53 (17%)	RR 1 (0.43 to 2.32)	0 fewer per 1000 (from 97 fewer to 224 more)	VERY LOW	CRITICAL
Response at endpoint (follow-up mean 10 weeks; assessed with: Number of people showing improvement of at least 10 points on CAPS)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	21/33 (63.6%)	13/34 (38.2%)	RR 1.66 (1.01 to 2.74)	252 more per 1000 (from 4 more to 665 more)	MODERATE	CRITICAL
Response at 3-month follow-up (follow-up mean 13 weeks; assessed with: Number of people showing improvement of at least 10 points on CAPS)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	23/33 (69.7%)	17/34 (50%)	RR 1.39 (0.93 to 2.09)	195 more per 1000 (from 35 fewer to	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D-cycloserine (+ exposure therapy)	Placebo (+ exposure therapy)	Relative (95% CI)	Absolute		
										545 more)		
Anxiety symptoms at endpoint (follow-up mean 10 weeks; measured with: STAI State change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	33	34	-	SMD 0.55 lower (1.04 to 0.07 lower)	MODERATE	IMPORTANT
Anxiety symptoms at 3-month follow-up (follow-up mean 13 weeks; measured with: STAI State change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	33	34	-	SMD 0.06 lower (0.53 lower to 0.42 higher)	MODERATE	IMPORTANT
Depression symptoms at endpoint (follow-up 3-10 weeks; measured with: BDI/BDI-II change score; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	very serious[6]	no serious indirectness	very serious[4]	none	46	47	-	SMD 0.42 higher (0.89 lower to 1.72 higher)	VERY LOW	IMPORTANT
Depression symptoms at 3-month follow-up (follow-up mean 13 weeks; measured with: BDI change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	33	34	-	SMD 0.02 lower (0.5 lower to 0.45 higher)	MODERATE	IMPORTANT
Discontinuation due to any reason (follow-up 3-10 weeks; assessed with: Number of people who dropped out of the study for any reason, including adverse events)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	38/112 (33.9%)	37/112 (33%)	RR 1.02 (0.57 to 1.84)	7 more per 1000 (from 142 fewer to 277 more)	LOW	CRITICAL
Discontinuation due to adverse events (follow-up mean 10 weeks; assessed with: Number of people who dropped out of the study due to adverse events)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D-cycloserine (+ exposure therapy)	Placebo (+ exposure therapy)	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	1/33 (3%)	1/34 (2.9%)	RR 1.03 (0.07 to 15.8)	1 more per 1000 (from 27 fewer to 435 more)	LOW	CRITICAL

BDI, Beck Depression Inventory; CAPS, Clinician Administered PTSD Scale; CI, confidence interval; PCL, PTSD Checklist for DSM-5; PSS-SR, PTSD Symptom Scale-Self-Report; PTSD, post-traumatic stress disorder; RR, risk ratio; SMD, standard mean difference; STAI, State-Trait Anxiety Inventory

[1] Substantial heterogeneity (I2=50-80%)

[2] 95% CI crosses both line of no effect and threshold for clinically important harm

[3] OIS not met (N<400)

[4] 95% CI crosses both line of no effect and threshold for both clinically important benefit and harm

[5] Blinding of outcome assessor(s) is unclear

[6] Considerable heterogeneity (I2>80%)

[7] 95% CI crosses both line of no effect and threshold for clinically important benefit

[8] OIS not met (events<300)

Appendix G – Economic evidence study selection

Economic evidence study selection for "For adults at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?

Economic evidence study selection for "For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions? "

A global health economics search was undertaken for all areas covered in the guideline. The flow diagram of economic article selection across all reviews is provided in Appendix A of Supplement 1 – Methods Chapter'.

Appendix H – Economic evidence tables

Economic evidence tables for "For adults at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?

No economic evidence was identified for this review.

Economic evidence tables for "For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

Antidepressants: Selective serotonin reuptake inhibitors (SSRIs)

Mihalopoulos C, Magnus A, Lal A (2015) Is implementation of the 2013 Australian treatment guidelines for posttraumatic stress disorder cost-effective compared to current practice? A cost-utility analysis using QALYs and DALYs. Australian and New Zealand Journal of Psychiatry 49(4), 360-76

Study Country Study type	Intervention details	Study population Study design Data sources	Costs and outcomes: description and values	Results: Cost-effectiveness	Comments
Mihalopoulos 2015 Australia Cost-utility analysis	Interventions: Selective serotonin reuptake inhibitors (SSRIs) over 9 months; SSRIs replaced other currently prescribed antidepressants or were added to current medication as appropriate; number of medical visits and mix of providers was assumed to be the same as in TAU Treatment as usual (TAU): non-evidence-based care	Prevalent cases of adults with PTSD in Australia in 2012, who sought care and had consulted a health professional for a mental health problem during the previous 12 months, but did not receive evidence-based care Decision-analytic economic modelling Source of efficacy data: meta-analyses of SSRI trials Source of resource use data: published trial and epidemiological	Costs: intervention (medication) Mean incremental cost (million) per eligible population (95% CI): SSRIs vs TAU $1.2 (-$4.0 to $6.7) Primary outcome measure: QALY based on the Assessment of Quality of Life measure (AQoL-4D), Australian values used [DALY also considered] Mean incremental number of QALYs per eligible population	ICER of SSRIs vs TAU: $200/QALY 0.27 probability of intervention being dominant Results most sensitive to utility scores and participation rates	Perspective: health sector (government & service user (intervention costs only) Currency: Aus$ Cost year: 2012 Time horizon: in practice 9 months [5 years stated but costs and benefits measured over treatment duration] Discounting: NA Applicability:

Study Country Study type	Intervention details	Study population Study design Data sources	Costs and outcomes: description and values	Results: Cost-effectiveness	Comments
	comprising consultation with healthcare professionals plus other medication	data; expert opinion Source of unit costs: national sources	(x1,000) (95% CI): SSRIs vs TAU 3.7 (-2.6 to 12)		partially applicable Quality: potentially serious limitations

Appendix I – Health economic evidence profiles

Economic evidence tables for "For adults at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?

No economic evidence was identified for this review.

Economic evidence tables for "For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions? "

Economic evidence profile: SSRIs versus other medication for the treatment of adults with PTSD							
Study and country	**Limitations**	**Applicability**	**Other comments**	**Incremental cost (£)[1]**	**Incremental effect**	**ICER (£/effect)[1]**	**Uncertainty[1]**
Mihalopoulos 2015 Australia	Potentially serious limitations[2]	Partially applicable[3]	Population: prevalent cases of adults with PTSD in Australia in 2012, in receipt of non-evidence-based pharmacological care Outcome: QALY [and DALY]	£0.5 million	3,700	£89	ICER range from dominant to £2,177 Probability of SSRIs being dominant 0.27 Results most sensitive to utility scores and participation rates
1. Costs converted and uplifted to 2016 UK pounds using purchasing power parity (PPP) exchange rates and the UK HCHS index (Curtis & Burns, 2016). 2. Time horizon stated as 5 years, but costs and outcomes were measured until end of treatment; analysis based on economic modelling; effectiveness based on meta-analyses of SSRIs vs other drugs; resource use based on trial and epidemiological data and expert opinion; national unit costs used; PSA conducted; consideration of intervention costs only 3. Australian study; health sector perspective; QALY estimates based on the Assessment of Quality of Life measure (AQoL-4D, Australian values used)							

The economic evidence profile for the guideline economic analysis of psychological interventions for the treatment of adults with clinically important PTSD symptoms 3 months post-trauma, which includes SSRIs as one of the interventions assessed, is provided in Appendix I of Evidence Report D.

Appendix J – Health economic analysis

Health economic analysis for "For adults at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Health economic analysis for "For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions? "

No separate health economic analysis was conducted for these reviews. The cost effectiveness of SSRIs relative to other psychological interventions for the treatment of adults with clinically important PTSD symptoms more than 3 months after trauma was assessed in de novo economic modelling that is described in Appendix J of Evidence Report D.

Appendix K – Excluded studies

Clinical studies

Excluded studies for "For adults at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Antidepressants: Selective serotonin reuptake inhibitors (SSRIs)

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Fletcher 2010	RQ 4.1-4.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Fletcher S, Creamer M, Forbes D. Preventing post traumatic stress disorder: are drugs the answer?. Australian and New Zealand Journal of Psychiatry. 2010 Dec 1;44(12):1064-71.	
Marx 2007	RQ 4.1-4.2 (maximizing sensitivity)	Sample size (N<10/arm)	NCT00560612. Secondary Prevention With Paroxetine vs. Placebo in Subthreshold Posttraumatic Stress Disorder (PTSD). Available from: https://clinicaltrials.gov/ct2/show/NCT00560612 [accessed 22.12.16]	
NCT00114374	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00114374. SSRI Administration to Reduce Acute Stress Disorder Symptoms and Prevent Depression and Posttraumatic Stress Disorder in Physical Trauma Victims in the Medical Setting. Available from: https://clinicaltrials.gov/ct2/show/NCT00114374 [accessed 22.12.16]	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Shalev 2012	RQ 4.1-4.2 (maximizing sensitivity)	Non-randomised group assignment	Shalev AY, Ankri Y, Israeli-Shalev Y, Peleg T, Adessky R, Freedman S. Prevention of posttraumatic stress disorder by early treatment: results from the Jerusalem Trauma Outreach And Prevention study. Archives of general psychiatry. 2012 Feb 6;69(2):166-76.	
Shalev 2016	RQ 4.1-4.2 (maximizing sensitivity) AND Cochrane allRQ update	Non-randomised group assignment	Shalev AY, Ankri Y, Gilad M, Israeli-Shalev Y, Adessky R, Qian M, Freedman S. Long-term outcome of early interventions to prevent posttraumatic stress disorder. The Journal of clinical psychiatry. 2016 May 25;77(5):580-7.	
Simon 2005	RQ 1.1-1.2 & 2.1-2.2 (searches combined)	Paper unavailable	Simon, N. M. (2005) NCT00114374 SSRI Administration to Reduce Acute Stress Disorder Symptoms and Prevent Depression and PTSD in Physical Trauma Victims	
Stoddard 2005	RQ 4.1-4.2 (maximizing sensitivity)	Population not relevant for this review (to be considered for other relevant RQ)	NCT00182078. A Study of Sertraline to Prevent PTSD. Available from: https://clinicaltrials.gov/ct2/show/NCT00182078 [accessed 05.01.2017]	

Benzodiazepines

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
NCT01221883	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT01221883. Early Pharmacological Intervention With Diazepam in the Emergency Room Setting to Prevent Posttraumatic Stress Disorder (PTSD). Available from: https://clinicaltrials.gov/ct2/show/NCT01221883 [accessed 22.12.16]	

Other drugs

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Amos 2014	RQ 4.1-4.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Amos T, Stein DJ, Ipser JC. Pharmacological interventions for preventing post-traumatic stress disorder (PTSD). Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD006239. DOI: 10.1002/14651858.CD006239.pub2.	
Argolo 2015	RQ 4.1-4.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Argolo FC, Cavalcanti-Ribeiro P, Netto LR, Quarantini LC. Prevention of posttraumatic stress disorder with propranolol: A meta-analytic review. Journal of psychosomatic research. 2015 Aug 31;79(2):89-93.	
Birur 2017a	RQ 3.1-3.2,4.1-4.2 update	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Birur B, Moore NC, Davis LL. An evidence-based review of early intervention and prevention of posttraumatic stress disorder.	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			Community mental health journal. 2017 Feb 1;53(2):183-201.	
Birur 2017b	RQ 3.1-3.2,4.1-4.2 update	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Birur B, Math SB, Fargason RE. A review of psychopharmacological interventions post-disaster to prevent psychiatric sequelae. Psychopharmacology bulletin. 2017 Jan 26;47(1):8.	
Forneris 2013	RQ 4.1-4.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Forneris CA, Gartlehner G, Brownley KA, Gaynes BN, Sonis J, Coker-Schwimmer E, Jonas DE, Greenblatt A, Wilkins TM, Woodell CL, Lohr KN. Interventions to prevent post-traumatic stress disorder: a systematic review. American journal of preventive medicine. 2013 Jun 30;44(6):635-50.	
Hruska 2014	RQ 4.1-4.2 (maximizing sensitivity)	Non-systematic review	Hruska B, Cullen PK, Delahanty DL. Pharmacological modulation of acute trauma memories to prevent PTSD: considerations from a developmental perspective. Neurobiology of learning and memory. 2014 Jul 31;112:122-9.	
Kaplan 2015	RQ 1.1-1.2 & 2.1-2.2 (searches combined)	Comparison outside protocol	Kaplan, B. J., Rucklidge, J. J., Romijn, A. R., Dolph, M. (2015) A randomised trial of nutrient supplements to minimise psychological stress after a	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			natural disaster, Psychiatry research, 228, 373-379	
Linares 2017	RQ 3.1-3.2,4.1-4.2 update	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Linares IM, Corchs FD, Chagas MH, Zuardi AW, Martin-Santos R, Crippa JA. Early interventions for the prevention of PTSD in adults: a systematic literature review. Archives of Clinical Psychiatry (São Paulo). 2017 Feb;44(1):23-9.	
MacLaren 2015	RQ 4.1-4.2 (maximizing sensitivity)	Intervention outside protocol	MacLaren R, Preslaski CR, Mueller SW, Kiser TH, Fish DN, Lavelle JC, Malkoski SP. A Randomized, Double-Blind Pilot Study of Dexmedetomidine Versus Midazolam for Intensive Care Unit Sedation Patient Recall of Their Experiences and Short-Term Psychological Outcomes. Journal of intensive care medicine. 2015 Mar 1;30(3):167-75.	
Matsumura 2017	Cochrane allRQ update	Intervention not targeted at PTSD symptoms	Matsumura K, Noguchi H, Nishi D, Hamazaki K, Hamazaki T, Matsuoka YJ. Effects of omega-3 polyunsaturated fatty acids on psychophysiological symptoms of post-traumatic stress disorder in accident survivors: A randomized, double-blind, placebo-controlled trial. Journal of affective disorders. 2017 Dec 15;224:27-31.	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Matsuoka 2008/2015	RQ 1.1-1.2 & 2.1-2.2 (searches combined)	Intervention outside protocol	Matsuoka, Y., Nishi, D., Hamazaki, K., Yonemoto, N., Matsumura, K., Noguchi, H., Hashimoto, K., Hamazaki, T. (2015) Docosahexaenoic acid for selective prevention of posttraumatic stress disorder among severely injured patients: A randomized, placebo-controlled trial, Journal of clinical psychiatry, 76, e1015-1022	Matsuoka, Y. Tachikawa Project for Prevention of Posttraumatic Stress Disorder With Polyunsaturated Fatty Acid (TPOP): TPOP-02 Study [NCT00671099]. Available from: https://clinicaltrials.gov/ct2/show/NCT00671099
McAllister 2016	RQ 1.1-1.2 & 2.1-2.2 (searches combined)	Efficacy or safety data cannot be extracted	McAllister, T. W., Zafonte, R., Jain, S., Flashman, L. A., George, M. S., Grant, G. A., He, F., Lohr, J. B., Andaluz, N., Summerall, L., Paulus, M. P., Raman, R., Stein, M. B. (2016) Randomized Placebo-Controlled Trial of Methylphenidate or Galantamine for Persistent Emotional and Cognitive Symptoms Associated with PTSD and/or Traumatic Brain Injury, Neuropsychopharmacology, 41, 1191-1198	
Meng 2012	RQ 1.1-1.2 & 2.1-2.2 (searches combined)	Intervention not targeted at PTSD symptoms	Meng, X. Z., Wu, F., Wei, P. K., Xiu, L. J., Shi, J., Pang, B. (2012) A Chinese herbal formula to improve general psychological status in posttraumatic stress disorder: A randomized placebo-controlled trial on Sichuan earthquake	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			survivors, Evidence-based complementary and alternative medicine,	
Mistraletti 2015	Handsearch	Intervention outside protocol	Mistraletti G, Umbrello M, Sabbatini G, Miori S, Taverna M, Cerri B, Mantovani ES, Formenti P, Spanu P, D'agostino A, Salini S. Melatonin reduces the need for sedation in ICU patients: a randomized controlled trial. Minerva Anestesiol. 2015 Dec 1;81(12):1298-310.	
NCT01707680	Handsearch	Non-RCT (no control group)	NCT01707680. Non-interventional Comparison of Sedatives on Weaning From Mechanical Ventilation in Intensive Care Patients. Available from: https://clinicaltrials.gov/ct2/show/NCT01707680 [accessed 22.12.16]	
Nishi 2012	RQ 1.1-1.2 & 2.1-2.2 (searches combined)	Intervention outside protocol	Nishi, D., Koido, Y., Nakaya, N., Sone, T., Noguchi, H., Hamazaki, K., Hamazaki, T., Matsuoka, Y. (2012) Fish oil for attenuating posttraumatic stress symptoms among rescue workers after the Great East Japan Earthquake: A randomized controlled trial, Psychotherapy and Psychosomatics, 81, 315-317	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Pitman 2004	RQ 4.1-4.2 (maximizing sensitivity)	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00158262. Prophylaxis of Post-Traumatic Stress Disorder With Post-Trauma Propranolol. Available from: https://www.clinicaltrials.gov/ct2/show/NCT00158262 [accessed 22.12.16]	
Pitman 2005	RQ 4.1-4.2 (maximizing sensitivity)	Non-systematic review	Pitman RK, Delahanty DL. Conceptually driven pharmacologic approaches to acute trauma. CNS spectrums. 2005 Feb 1;10(02):99-106.	
Roque 2015	RQ 4.1-4.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Roque AP. Pharmacotherapy as prophylactic treatment of post-traumatic stress disorder: a review of the literature. Issues in mental health nursing. 2015 Sep 2;36(9):740-51.	
Schelling 2001	2004 GL (included)	Sample size (N<10/arm)	Schelling, G. (2001) The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. Biological Psychiatry, 50, 978-985	
Schelling 2004	RQ 4.1-4.2 (maximizing sensitivity)	Efficacy or safety data cannot be extracted	Schelling G, Kilger E, Roozendaal B, Dominique JF, Briegel J, Dagge A, Rothenhäusler HB, Krauseneck T, Nollert G, Kapfhammer HP. Stress doses of hydrocortisone, traumatic memories, and symptoms of posttraumatic stress disorder in patients after cardiac surgery: a randomized study. Biological Psychiatry. 2004 Mar 15;55(6):627-33.	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Searcy 2012	RQ 4.1-4.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Searcy CP, Bobadilla L, Gordon WA, Jacques S, Elliott L. Pharmacological prevention of combat-related PTSD: a literature review. Military medicine. 2012 Jun;177(6):649-54.	
Sijbrandij 2015	RQ 4.1-4.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Sijbrandij M, Kleiboer A, Bisson JI, Barbui C, Cuijpers P. Pharmacological prevention of post-traumatic stress disorder and acute stress disorder: A systematic review and meta-analysis. The Lancet Psychiatry. 2015 May 31;2(5):413-21.	
Strom 2011	RQ 1.1-1.2 & 2.1-2.2 (searches combined)	Intervention outside protocol	Strom, T., Stylsvig, M., Toft, P. (2011) Long-term psychological effects of a no-sedation protocol in critically ill patients, Critical Care, 15, R293	
Treggiari 2009	Handsearch	Intervention outside protocol	Treggiari MM, Romand JA, Yanez ND, Deem SA, Goldberg J, Hudson L, Heidegger CP, Weiss NS. Randomized trial of light versus deep sedation on mental health after critical illness. Critical care medicine. 2009 Sep 1;37(9):2527-34.	Forneris CA, Gartlehner G, Brownley KA, Gaynes BN, Sonis J, Coker-Schwimmer E, Jonas DE, Greenblatt A, Wilkins TM, Woodell CL, Lohr KN. Interventions to prevent post-traumatic stress disorder: a systematic review. American journal of preventive medicine. 2013 Jun 30;44(6):635-50.
Vaiva 2003	Handsearch	Non-randomised group assignment	Vaiva G, Ducrocq F, Jezequel K, Averland B, Lestavel P, Brunet A, Marmar CR. Immediate	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			treatment with propranolol decreases posttraumatic stress disorder two months after trauma. Biol Psychiatry. 2003 Nov 1;54(9):947-9. Erratum in: Biol Psychiatry. 2003 Dec 15;54(12):1471.	
Weis 2006	RQ 4.1-4.2 (maximizing sensitivity)	Efficacy or safety data cannot be extracted	Weis F, Kilger E, Roozendaal B, Dominique JF, Lamm P, Schmidt M, Schmölz M, Briegel J, Schelling G. Stress doses of hydrocortisone reduce chronic stress symptoms and improve health-related quality of life in high-risk patients after cardiac surgery: a randomized study. The Journal of Thoracic and Cardiovascular Surgery. 2006 Feb 28;131(2):277-82.	
Zohar 2009/2011	RQ 4.1-4.2 (maximizing sensitivity)	Sample size (N<10/arm)	NCT00855270. The Efficacy of a Single Dose IV Hydrocortisone Given Within 6 Hours of Exposure to a Traumatic Event in PTSD Prevention. Available from: https://clinicaltrials.gov/ct2/show/NCT00855270 [accessed 05.01.17]	Zohar J, Yahalom H, Kozlovsky N, Cwikel-Hamzany S, Matar MA, Kaplan Z, Yehuda R, Cohen H. High dose hydrocortisone immediately after trauma may alter the trajectory of PTSD: interplay between clinical and animal studies. European Neuropsychopharmacology. 2011 Nov 30;21(11):796-809.

Excluded studies for "For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions? "

Antidepressants: Selective serotonin reuptake inhibitors (SSRIs)

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Back 2006	RQ 4.1- 4.2 (maximizing sensitivity)	Efficacy or safety data cannot be extracted	Back SE, Brady KT, Sonne SC, Verduin ML. Symptom improvement in co-occurring PTSD and alcohol dependence. The Journal of nervous and mental disease. 2006 Sep 1;194(9):690-6.	
Barnett 2002	2004 GL (excluded)	Intervention not targeted at PTSD symptoms	Barnett, S. D., Tharwani, H. M., Hertzberg, M. A., Sutherland, S. M., Connor, K. M., & Davidson, J. R. (2002). Tolerability of fluoxetine in posttraumatic stress disorder. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 26, 363-367.	
Brady 2003	2004 GL (excluded)	Secondary analysis of data that has already been included	Brady, K. T. & Clary, C. M. (2003). Affective and anxiety comorbidity in post-traumatic stress disorder treatment trials of sertraline. Compr.Psychiatry, 44, 360-369.	
Davidson 2002	2004 GL (excluded)	Non-randomised group assignment	Davidson, J. R., Landerman, L. R., Farfel, G. M., & Clary, C. M. (2002). Characterizing the effects of sertraline in post-traumatic stress disorder. Psychological Medicine, 32, 661-670.	
Davidson 2004b	RQ 4.1-4.2 (maximizing sensitivity)	Subgroup/secondary analysis of RCT already included	Davidson J, Landerman LR, Clary CM. Improvement of anger	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			at one week predicts the effects of sertraline and placebo in PTSD. Journal of psychiatric research. 2004 Oct 31;38(5):497-502.	
Davidson 2005b	RQ 4.1-4.2 (maximizing sensitivity)	Non-systematic review	Davidson JR, Payne VM, Connor KM, Foa EB, Rothbaum BO, Hertzberg MA, Weisler RH. Trauma, resilience and saliostasis: effects of treatment in post-traumatic stress disorder. International clinical psychopharmacology. 2005 Jan 1;20(1):43-8.	
Eli Lilly (unpublished)	2004 GL (included)	Completion data <50%/Drop out >50%	Eli lilly (unpublished). Brief trial report (B1Y-MC-HCJL)	
Hertzberg 2000	2004 GL (included)	Sample size (N<10/arm)	Hertzberg, M.A.; Feldman, M.E.; Beckham, J.C.; Kudler, H.S. & Davidson, J.R.T. (2000) Lack of efficacy for fluoxetine in PTSD: A placebo controlled trial in combat veterens. Annals of Clinical Psychiatry, 12, 2, 101-105	
Hicks 2013	Handsearch	Sample size (N<10/arm)	Hicks PB. Predictors of Treatment Response to Fluoxetine in PTSD Following a Recent History of War Zone Stress Exposure. TEMPVA RESEARCH GROUP INC TEMPLE TX; 2013 Jul. Available from: http://oai.dtic.mil/oai/oai?verb=getRecord&metadataPrefix=html&id	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			entifier=ADA583752 [accessed 05.01.17]	
Hurst 2000	RQ 3.1-3.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Hurst, M. & Lamb, H. (2000) Fluoxetine: A review of its use in anxiety disorders and mixed anxiety and depression, CNS Drugs, 14, 51-80	
Jerud 2016	RQ 4.1-4.2 (maximizing sensitivity)	Outcomes reported are outside the scope	Jerud AB, Pruitt LD, Zoellner LA, Feeny NC. The effects of prolonged exposure and sertraline on emotion regulation in individuals with posttraumatic stress disorder. Behaviour research and therapy. 2016 Feb 29;77:62-7.	
Jun 2013	RQ 4.1-4.2 (maximizing sensitivity)	Interventions not relevant to this review (to be considered for other relevant RQ)	Jun JJ, Zoellner LA, Feeny NC. Sudden gains in prolonged exposure and sertraline for chronic PTSD. Depression and anxiety. 2013 Jul 1;30(7):607-13.	
Labbate 2004	RQ 4.1-4.2 (maximizing sensitivity)	Comparison outside scope	Labbate LA, Sonne SC, Randal CL, Anton RF, Brady KT. Does comorbid anxiety or depression affect clinical outcomes in patients with post-traumatic stress disorder and alcohol use disorders?. Comprehensive Psychiatry. 2004 Aug 31;45(4):304-10.	
Lawford 2003	2004 GL (excluded)	Non-randomised group assignment	Lawford, B.R.; Young, R; Noble, E.P. Kann, B.; Arnold, L.; Rowell, J. & Ritchie, T.L. (2003) D2 dopamine receptor gene polymorphism: paroxetine and	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			social functioning in posttraumatic stress disorder. European Nueropsychopharmacology, 13, 313-320	
Le 2013/2014	RQ 4.1-4.2 (maximizing sensitivity)	Efficacy or safety data cannot be extracted	Le QA, Doctor JN, Zoellner LA, Feeny NC. Minimal clinically important differences for the EQ-5D and QWB-SA in Post-traumatic Stress Disorder (PTSD): results from a Doubly Randomized Preference Trial (DRPT). Health and quality of life outcomes. 2013 Apr 12;11(1):1.	Le QA, Doctor JN, Zoellner LA, Feeny NC. Cost-effectiveness of prolonged exposure therapy versus pharmacotherapy and treatment choice in posttraumatic stress disorder (the Optimizing PTSD Treatment Trial): a doubly randomized preference trial. The Journal of clinical psychiatry. 2014 Mar 15;75(3):222-30.
Londborg 2001	2004 GL (excluded)	Non-randomised group assignment	Londborg, P. D., Hegel, M. T., Goldstein, S., Goldstein, D., Himmelhoch, J. M., Maddock, R. (2001). Sertraline treatment of posttraumatic stress disorder: results of 24 weeks of openlabel continuation treatment. Journal of Clinical Psychiatry, 62, 325-331.	
Malik 1999	2004 GL (excluded)	Secondary analysis of data that has already been included	Malik, M. L., Connor, K. M., Sutherland, S. M., Smith, R. D., Davison, R. M., & Davidson, J. R. (1999). Quality of life and posttraumatic stress disorder: a pilot study assessing changes in SF- 36 scores before and after treatment in a placebo-controlled trial of fluoxetine. Journal of Traumatic Stress, 12, 387-393.	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Marmar 1996	2004 GL (excluded)	Non-randomised group assignment	Marmar, C.R. (1996) Open trial of fluvoxamine treatment for combat-related posttraumatic stress disorder. Journal of Cinical Psychiatry, 57 (suppl 8), 66-72	
Marshall 1998b	2004 GL (excluded)	Non-randomised group assignment	Marshall, R. D., Schneier, F. R., Fallon, B. A., Knight, C. B., Abbate, L. A., Goetz, D. (1998). An open trial of paroxetine in patients with noncombat-related, chronic posttraumatic stress disorder. Journal of Clinical Psychopharmacology, 18, 10-18.	
Marshall 2004	Handsearch	Completion data <50%/Drop out >50%	Marshall, R., Blanco, C., Lewis-Fernandez, R., Simpson, B., Lin, S., Garcia, W. (2002) Randomsided controlled trial of paroxetine in adults with chronic PTSD, 18th Annual meeting, International Society for Traumatic Stress Studies, November 7-10, Baltimore MD.	Stein D., Ipser J., Seedat, S., Sager, C. & Amos, T. (2006) Pharmacotherapy for post traumatic stress disorder (PTSD), Cochrane Database of Systematic Reviews
Marshall 2007	RQ 4.1-4.2 (maximizing sensitivity)	Completion data <50%/Drop out >50%	Marshall RD, Lewis-Fernandez R, Blanco C, Simpson HB, Lin SH, Vermes D, Garcia W, Schneier F, Neria Y, Sanchez-Lacay A, Liebowitz MR. A controlled trial of paroxetine for chronic PTSD, dissociation, and interpersonal problems in mostly minority adults. Depression and anxiety. 2007 Jan 1;24(2):77-84.	
Martenyi 2006	RQ 4.1-4.2 (maximizing sensitivity)	Subgroup/secondary analysis of RCT already included	Martenyi F, Soldatenkova V. Fluoxetine in the acute treatment	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			and relapse prevention of combat-related post-traumatic stress disorder: Analysis of the veteran group of a placebo-controlled, randomized clinical trial. European Neuropsychopharmacology. 2006 Jul 31;16(5):340-9.	
Meltzerbrody 2000	2004 GL (excluded)	Secondary analysis of data that has already been included	Meltzer-Brody, S., Connor, K. M., Churchill, E., & Davidson, J. R. (2000). Symptom-specific effects of fluoxetine in post-traumatic stress disorder. International Clinical Psychopharmacology, 15, 227-231.	
NCT00665678	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00665678. Neural Correlates of Early Intervention for Posttraumatic Stress Disorder (PTSD). Available from: https://clinicaltrials.gov/ct2/show/NCT00665678 [accessed 22.12.16]	
Neylan 2001	Handsearch	Non-randomised group assignment	Neylan TC, Metzler TJ, Schoenfeld FB, Weiss DS, Lenoci M, Best SR, Lipsey TL, Marmar CR. Fluvoxamine and sleep disturbances in posttraumatic stress disorder. J Trauma Stress. 2001;14(3):461–67.	Schoenfeld, F., DeViva, J. and Manber, R. (2012) Treatment of sleep disturbances in posttraumatic stress disorder: a review, JRRD, 49, 729-752
Pacella 2014	RQ 4.1-4.2 (maximizing sensitivity)	Interventions not relevant to this review (to be considered for other relevant RQ)	Pacella ML, Feeny N, Zoellner L, Delahanty DL. The impact of PTSD treatment on the cortisol awakening response. Depression	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			and anxiety. 2014 Oct 1;31(10):862-9.	
Seedat 2002	2004 GL (excluded)	Non-randomised group assignment	Seedat, S., Stein, D. J., Ziervogel, C., Middleton, T., Kaminer, D., Emsley, R. A. (2002). Comparison of response to a selective serotonin reuptake inhibitor in children, adolescents, and adults with posttraumatic stress disorder. Journal of Child & Adolescent Psychopharmacology, 12, 37-46.	
Simon 2008	Handsearch	Sample size (N<10/arm)	Simon NM, Connor KM, Lang AJ, Rauch S, Krulewicz S, LeBeau RT, Davidson JR, Stein MB, Otto MW, Foa EB. Paroxetine CR augmentation for posttraumatic stress disorder refractory to prolonged exposure therapy. The Journal of clinical psychiatry. 2008 Mar 14;69(3):400-5.	
Smajic 2001	Handsearch	Efficacy or safety data cannot be extracted	Smajkic A, Weine S, Djuric-Bijedic Z, Boskailo E, Lewis J, Pavkovic I. Sertraline, paroxetine, and venlafaxine in refugee posttraumatic stress disorder with depression symptoms. Journal of Traumatic Stress 2001;14(3):445–52.	Stein D., Ipser J., Seedat, S., Sager, C. & Amos, T. (2006) Pharmacotherapy for post traumatic stress disorder (PTSD), Cochrane Database of Systematic Reviews
Sonne 2006	RQ 4.1-4.2 (maximizing sensitivity)	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00330239. Paroxetine Treatment in Outpatients With Comorbid PTSD and Substance Dependence. Available from: https://clinicaltrials.gov/ct2/show/	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			NCT00330239 [accessed 22.12.16]	
Stein 2003a	2004 GL (excluded)	Secondary analysis of data that has already been included	Stein, D.J.; Davidson, J.; Seedat, S. & Beebe, K. (2003) Paroxetine in the treatment of post-traumatic stress disorder: pooled analysis of placebo-controlled studies. Expert Opinion on Pharmactherapy, 4, 10, 1829-1838	
Stein 2006	RQ 4.1-4.2 (maximizing sensitivity)	Non-systematic review	Stein DJ, van der Kolk BA, Austin C, Fayyad R, Clary C. Efficacy of sertraline in posttraumatic stress disorder secondary to interpersonal trauma or childhood abuse. Annals of clinical psychiatry. 2006 Jan 1;18(4):243-9.	
Tucker 2000	2004 GL (excluded)	Non-randomised group assignment	Tucker, P.; Smith, K.L.; Marx, B.; Jones, D.; Miranda, R. & Lensgraf, J. (2000) Fluvoxamine reduces physiologic reactivity to trauma scripts in posttraumatic stress disorder. Journal of Clinical Psychopharmacology, 20, 3, 367-372	
Wang 2012	RQ 4.1-4.2 (maximizing sensitivity)	Population not relevant for this review (to be considered for other relevant RQ)	Wang Y, Hu YP, Wang WC, Pang RZ, Zhang AR. Clinical studies on treatment of earthquake-caused posttraumatic stress disorder using electroacupuncture. Evidence-Based Complementary and Alternative Medicine. 2012 Sep 25;2012	

Antidepressants: Serotonin-norepinephrine reuptake inhibitors (SNRIs)

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Bahk 2002	2004 GL (excluded)	Non-randomised group assignment	Bahk, W. M., Pae, C. U., Tsoh, J., Chae, J. H., Jun, T. Y., Chul, L. (2002). Effects of mirtazapine in patients with post-traumatic stress disorder in Korea: a pilot study. Human Psychopharmacology, 17, 341-344.	
Connor 1999	2004 GL (excluded)	Non-randomised group assignment	Connor, K.M.; Davidson, J.R.T.; Weisler, R.H. & Ahearn, E. (1999) A pilot study of mirtazapine in post-traumatic stres disorder. International Clinical Psychopharmacology. 14, 29-31	
Davidson 2004c	RQ 4.1-4.2 (maximizing sensitivity)	Conference abstract	Davidson J, Baldwin D, Stein D, Kuper E, Benattia I, Ahmed S, Yan B, Pedersen R, Musgnung J. Venlafaxine XR in the treatment of posttraumatic stress disorder: A 6-month placebo-controlled study. InNEUROPSYCHOPHARMACOLOGY 2004 Dec 1 (Vol. 29, pp. S97-S97). MACMILLAN BUILDING, 4 CRINAN ST, LONDON N1 9XW, ENGLAND: NATURE PUBLISHING GROUP.	

Antidepressants: Tricyclic antidepressants (TCAs)

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Davidson 1993	2004 GL (excluded)	Secondary analysis of data that has already been included	Davidson, J. R., Kudler, H. S., Saunders, W. B., Erickson, L., Smith, R. D., Stein, R. M. (1993). Predicting response to amitriptyline in posttraumatic stress disorder. American Journal of Psychiatry, 150, 1024-1029.	
Reist 1989a	2004 GL (excluded)	Sample size (N<10/arm)	Reist, C., Kauffmann, C. D., Haier, R. J., Sangdahl, C., DeMet, E. M., Chicz-DeMet, A. (1989). A controlled trial of desipramine in 18 men with posttraumatic stress disorder.[comment]. American Journal of Psychiatry, 146, 513-516.	

Antidepressants: Monoamine-oxidase inhibitors (MAOIs)

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Shestatzky 1988	2004 GL (excluded)	Completion data <50%/Drop out >50%	Shestatzky, M., Greenberg, D., & Lerer, B. (1988). A controlled trial of phenelzine in posttraumatic stress disorder. Psychiatry Research, 24, 149-155.	

Antidepressants: Other antidepressants

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Cankurtaran 2008	RQ 4.1-4.2 (maximizing sensitivity)	Population outside scope: Trials of people without PTSD	Cankurtaran ES, Ozalp E, Soygur H, Akbiyik DI, Turhan L, Alkis N. Mirtazapine improves sleep and lowers anxiety and depression in cancer patients: superiority over imipramine. Supportive care in	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			cancer. 2008 Nov 1;16(11):1291-8.	
Dow 1997	2004 GL (excluded)	Non-randomised group assignment	Dow, B. & Kline, N. (1997) Antidepressant treatment of posttraumatic stress disorder and major depression in veterens. Annals of Clinical Psychiatry, 9, 1, 1-5	
NCT00302107	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00302107. A Placebo-Controlled Study of Mirtazapine for PTSD in OIF/OEF Veterans. Available from: https://clinicaltrials.gov/ct2/show/NCT00302107 [accessed 22.12.16]	
NCT00449189	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00449189. A Placebo-Controlled Study of Mirtazapine for PTSD in OIF/OEF Veterans and Veterans From All Other Southwest Asia Conditions. Available from: https://www.clinicaltrials.gov/ct2/show/NCT00449189 [accessed 22.12.16]	
Schneier 2015/Hernandez 2010	RQ 4.1-4.2 (maximizing sensitivity)	Completion data <50%/Drop out >50%	Schneier FR, Campeas R, Carcamo J, Glass A, Lewis-Fernandez R, Neria Y, Sanchez-Lacay A, Vermes D, Wall MM. COMBINED MIRTAZAPINE AND SSRI TREATMENT OF PTSD: A PLACEBO-CONTROLLED TRIAL. Depression and anxiety. 2015 Aug 1;32(8):570-9.	NCT01178671. Combined Mirtazapine and Selective Serotonin Reuptake Inhibitor (SSRI) Treatment of Post-traumatic Stress Disorder (PTSD). Available from: https://clinicaltrials.gov/ct2/show/NCT01178671 [accessed 06.01.17]

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Schnier 2015	Handsearch	Completion data <50%/Drop out >50%	Schneier, F.R., Campeas, R., Carcamo, J., Glass, A., Lewis-Fernandez, R., Neria, Y., Sanchez- Lacay, A., Vermes, D., Wall, M.M., 2015. Combined mirtazapine and SSRI treatment of PTSD: a placebo-controlled trial. Depress. Anxiety http://dx.doi.org/10.1002/da.22384 ([Epub ahead of print] PMID: 26115513, Jun 26).	Koek, R., Schwartz, H., Scully, S., Langevin, J-P., Spangler, S., Korotinsky, A., Joua, K. and Leuchter, A. (2016) Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework for the future, Progress in Neuro-Psychopharmacology & Biological Psychiatry, 70, 170–218
Warner 2001	Handsearch	Non-randomised group assignment	Warner MD, Dorn MR, Peabody CA. Survey on the usefulness of trazodone in patients with PTSD with insomnia or nightmares. Pharmacopsychiatry. 2001;34(4):128–31.	Schoenfeld, F., DeViva, J. and Manber, R. (2012) Treatment of sleep disturbances in posttraumatic stress disorder: a review, JRRD, 49, 729-752

Anticonvulsants

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Afshar 2009	RQ 4.1-4.2 (maximizing sensitivity)	Paper unavailable	Afshar H, Amanat S. Efficacy of lamotrigine in the treatment of avoidance/numbing in post-traumatic stress disorder. World psychiatry. 2009; 8 (Suppl 1):218.	
Alderman 2009	Handsearch	Non-randomised group assignment	Alderman, C.P., McCarthy, L.C., Condon, J.T., Marwood, A.C., Fuller, J.R., 2009b. Topiramate in combat-related posttraumatic stress disorder. Ann.	Koek, R., Schwartz, H., Scully, S., Langevin, J-P., Spangler, S., Korotinsky, A., Joua, K. and Leuchter, A. (2016) Treatment-refractory

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			Pharmacother. 43 (4), 635–641 (Apr).	posttraumatic stress disorder (TRPTSD): a review and framework for the future, Progress in Neuro-Psychopharmacology & Biological Psychiatry, 70, 170–218
Batki 2012	RQ 4.1-4.2 (maximizing sensitivity)	Protocol	NCT01749215. A Controlled Trial of Topiramate Treatment for Alcohol Dependence in Veterans With PTSD. Available from: https://clinicaltrials.gov/ct2/show/NCT01749215 [accessed 05.01.17]	
Berlant 2002	2004 GL (excluded)	Non-randomised group assignment	Berlant, J. & van Kammen, D. P. (2002). Open-label topiramate as primary or adjunctive therapy in chronic civilian posttraumatic stress disorder: a preliminary report. Journal of Clinical Psychiatry, 63, 15-20.	
Cates 2004	Handsearch	Non-randomised group assignment	Cates ME, Bishop MH, Davis LL, Lowe JS, Woolley TW. Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. Ann Pharmacother. 2004;38(9):1395–99.	Schoenfeld, F., DeViva, J. and Manber, R. (2012) Treatment of sleep disturbances in posttraumatic stress disorder: a review, JRRD, 49, 729-752
Clark 1999	Handsearch	Non-randomised group assignment	Clark, R., Cañive, J., Calais, L., Qualls, C., Tuason, V. (1999) Divalproex in posttraumatic stress diorder: an open-label clinical trial, Journal of Traumatic Stress, 12, 395-401	Ahearn, E., Krohn, A., Connor, K. & Davidson, J. (2003) Pharmacologic Treatment of Posttraumatic Stress Disorder: A Focus on Antipsychotic Use,

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
				Annals of Clinical Psychiatry, 15, 193-201
Davis 2005	RQ 4.1-4.2 (maximizing sensitivity)	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00203463. Topiramate in the Treatment of Post Traumatic Stress Disorder (PTSD). Available from: https://www.clinicaltrials.gov/ct2/show/NCT00203463 [accessed 05.01.17]	
Fesler 1991	2004 GL (excluded)	Non-randomised group assignment	Fesler, F.A (1991) Valproate in combat-related posttraumatic stress disorder. Journal of Clinical Psychiatry, 52, 9, 361-364	
Fischer 2012	RQ 4.1-4.2 (maximizing sensitivity)	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT01408641. A 14-week Randomized, Placebo-controlled Study of Topiramate for Alcohol Use Disorders in Veterans With Posttraumatic Stress Disorder. Available from: https://clinicaltrials.gov/show/NCT01408641 [accessed 06.01.17]	
Frank 1988	2004 GL (excluded)	Secondary analysis of data that has already been included	Frank, J. B., Kosten, T. R., Giller, E. L., Jr., & Dan, E. (1988). A randomized clinical trial of phenelzine and imipramine for posttraumatic stress disorder. American Journal of Psychiatry, 145, 1289- 1291.	
Goldberg 2003	2004 GL (excluded)	Non-randomised group assignment	Goldberg, J.F.; Cloitre, M.; Whiteside, J.E.; & Han, H. (2003) An open-label pilot study of divalproex sodium for posttraumatic stress disorder	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			related to child abuse. Current Therapeutic Research, 64, 1, 45-54	
Hamner 2003a	2004 GL (excluded)	Non-randomised group assignment	Hamner, M.B. (2003) Quetiapine treatment in patients with posttraumatic stress disorder: an open trial of adjunctive therapy. Journal of Clinical Psychopharmacology, 23, 1, 15-20	
Hamner 2003b	2004 GL (included)	Population outside scope: Trials of people with psychosis as a coexisting condition	Hamner, M. B., Faldowski, R. A., Ulmer, H. G., Frueh, B. C., Huber, M. G., & Arana, G. W. (2003). Adjunctive risperidone treatment in post-traumatic stress disorder: A preliminary controlled trial of effects on comorbid psychotic symptoms. International Clinical Psychopharmacology, 18, 1-8.	
Hamner 2009	RQ 4.1-4.2 (maximizing sensitivity)	Paper unavailable	Hamner MB, Faldowski RA, Robert S, Ulmer HG, Horner MD, Lorberbaum JP. A preliminary controlled trial of divalproex in posttraumatic stress disorder. Annals of Clinical Psychiatry. 2009;21(2):89-94.	
Hertzberg 1999	2004 GL (excluded)	Completion data <50%/Drop out >50%	Hertzberg, M. A., Butterfield, M. I., Feldman, M. E., Beckham, J. C., Sutherland, S. M., Connor, K. M. (1999). A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. Biological Psychiatry, 45, 1226-1229.	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Lasher 2010	RQ 4.1-4.2 (maximizing sensitivity)	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT01087736. Topiramate Treatment of Alcohol Use Disorders in Veterans With Post Traumatic Stress Disorder (PTSD): A Pilot Controlled Trial of Augmentation Therapy. Available from: https://clinicaltrials.gov/ct2/show/NCT01087736 [accessed 06.01.17]	
Lindley 2007	Handsearch	Completion data <50%/Drop out >50%	Lindley SE, Carlson EB, Hill K. A randomized, double-blind, placebo-controlled trial of augmentation topiramate for chronic combat-related posttraumatic stress disorder. J Clin Psychopharmacol 2007;27:677–81.	Berger, W., Mendlowicz, M., Marques-Portella, C., Kinrys, G., Fontenelle, L., Marmar, C., Figueira, I. (2009) Pharmacologic alternatives to antidepressants in posttraumatic stress disorder: a systematic reviews, Progress in Neuro-psychopharmacology and biological psychiatry, 33, 169-180
Lipper 1986	2004 GL (excluded)	Non-randomised group assignment	Liper, S. (1986) Preliminary study of carbamazepine in post-traumatic stress disorder. Psychosomatics, 27, 12, 849-854	
Mello 2008	RQ 4.1-4.2 (maximizing sensitivity)	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00725920. Randomized Clinical Trial to Study the Topiramate Efficacy for Posttraumatic Disorder Treatment. Available from: https://clinicaltrials.gov/ct2/show/NCT00725920 [accessed 06.01.17]	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Petty 2005	RQ 4.1-4.2 (maximizing sensitivity)	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00208130. A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Determine the Efficacy and Safety of Topiramate in the Treatment of Posttraumatic Stress Disorder in Civilians. Available from: https://clinicaltrials.gov/ct2/show/NCT00208130 [accessed 06.01.17]	
Tucker 2005	RQ 4.1-4.2 (maximizing sensitivity)	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00204386. A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Determine the Efficacy and Safety of Topiramate in the Treatment of Posttraumatic Stress Disorder. Available from: https://clinicaltrials.gov/ct2/show/NCT00204386 [accessed 06.01.17]	
Wolf 1988	2004 GL (excluded)	Non-randomised group assignment	Wolf, M.E.; Alavi, A. & Mosnaim, A.D. (1988) Posttraumatic stress disorder in Vietnam veterens clinical and EEG findings; possible therapeutic effects of carbamazepine. Biological Psychiatry, 23, 642-644	

Antipsychotics

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Ahearn 2003	RQ 3.1-3.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Ahearn, E., Krohn, A., Connor, K. & Davidson, J. (2003) Pharmacologic Treatment of Posttraumatic Stress Disorder: A Focus on Antipsychotic Use, Annals of Clinical Psychiatry, 15, 193-204	
Butterfield 2001	2004 GL (included)	Sample size (N<10/arm)	Butterfield, M. I., Becker, M. E., Connor, K. M., Sutherland, S., Churchill, L. E., & Davidson, J. R. (2001). Olanzapine in the treatment of post-traumatic stress disorder: a pilot study. International Clinical Psychopharmacology, 16, 197-203.	
Kellner 2010	RQ 4.1-4.2 (maximizing sensitivity)	Letter	Kellner M, Muhtz C, Wiedemann K. Primary add-on of ziprasidone in sertraline treatment of posttraumatic stress disorder: lessons from a stopped trial?. Journal of clinical psychopharmacology. 2010 Aug 1;30(4):471-3.	
Liu 2014	RQ 1.1-1.2 & 2.1-2.2 (searches combined)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Liu, X. H., Xie, X. H., Wang, K. Y., Cui, H. (2014) Efficacy and acceptability of atypical antipsychotics for the treatment of post-traumatic stress disorder: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials, Database of Abstracts of Reviews of Effects, 543-549	
Monnelly 2003	2004 GL (excluded)	Sample size (N<10/arm)	Monnelly, E.P.; Ciraulo, D.A.; Knapp, C. & Keane, T. (2003) Low-dose risperidone as adjunctive therapy for irritable aggression in posttraumatic stress disorder. Journal of Clinical Psychopharmacology, 23, 2, 193-196.	
Naylor 2015	Handsearch	Sample size (N<10/arm)	Naylor, J.C., Kilts, J.D., Bradford, D.W., Strauss, J.L., Capehart, B.P., Szabo, S.T., Smith, K.D., Dunn, C.E., Conner, K.M., Davidson, J.R., Wagner, H.R., Hamer, R.M., Marx, C.E., 2015. A pilot randomized placebo-controlled trial of adjunctive aripiprazole for chronic PTSD in US military Veterans resistant to antidepressant treatment. Int. Clin. Psychopharmacol. 30 (3), 167–174 (May).	Koek, R., Schwartz, H., Scully, S., Langevin, J-P., Spangler, S., Korotinsky, A., Joua, K. and Leuchter, A. (2016) Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
				for the future, Progress in Neuro-Psychopharmacology & Biological Psychiatry, 70, 170–218
NCT00208182	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00208182. Risperidone Monotherapy in the Treatment of PTSD in Women Survivors of Domestic Abuse and Rape Trauma: a Double-Blind, Placebo Controlled, Randomized Clinical Trial. Available from: https://www.clinicaltrials.gov/ct2/show/NCT00208182 [accessed 22.12.16]	
NCT00208208	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00208208. Geodon (Ziprasidone) for Posttraumatic Stress Disorder. Available from: https://clinicaltrials.gov/ct2/show/NCT00208208 [accessed 22.12.16]	
NCT00292370	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00292370. A Placebo-controlled Trial of Adjunctive Quetiapine for Refractory PTSD. Available from: https://clinicaltrials.gov/ct2/show/NCT00292370 [accessed 22.12.16]	
Padala 2006	RQ 4.1-4.2 (maximizing sensitivity)	Sample size (N<10/arm)	Padala PR, Madison J, Monnahan M, MarcilW, Price P, Ramaswamy S. Risperidone monotherapy for post-traumatic stress disorder related to sexual assault and domestic abuse in women. Int Clin Psychopharmacol 2006;21:275–80.	
Ravindran 2007	RQ 3.1-3.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Ravindran, A., Bradbury, C., McKay, M. & da Silva, T. (2007) Novel uses for risperidone: Focus on depressive, anxiety and behavioral disorders, Expert Opinion on Pharmacotherapy, 8, 1693-1710	
Reich 2004	2004 GL (excluded)	Sample size (N<10/arm)	Reich, D.B.; Winternitz, S.; Hennen, J.; Watts, T.; Stanculescu, C. Mclean study of risperidone. Treatment of noncombat-related posttraumatic stress disorder related to childhood abuse in	Reich, D., Winternitz, s., Hennen, J., Watts, T., and Stanculescu, C. (2004) A Preliminary Study of

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			women. Presented at the 24th Annual Conference of the Anxiety Disorders Association of America, March 11-14, 2004, Miami, Florida.	Risperidone in the Treatment of Posttraumatic Stress Disorder Related to Childhood Abuse in Women, J Clin Psychiatry 2004;65(12):1601-1606
Rothbaum 2008	RQ 4.1-4.2 (maximizing sensitivity)	Sample size (N<10/arm)	Rothbaum BO, Killeen TK, Davidson JR, Brady KT, Connor KM, Heekin MH. Placebo-controlled trial of risperidone augmentation for selective serotonin reuptake inhibitor-resistant civilian posttraumatic stress disorder. The Journal of clinical psychiatry. 2008 Mar 18;69(4):520-5.	

Benzodiazepines

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Braun 1990	2004 GL (excluded)	Sample size (N<10/arm)	Braun, P., Greenberg, D., Dasberg, H., & Lerer, B. (1990). Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. Journal of Clinical Psychiatry, 51, 236-238.	
Gelpin 1996	2004 GL (excluded)	Non-randomised group assignment	Gelpin, E., Bonne, O., Peri, T., Brandes, D., & Shalev, A. Y. (1996). Treatment of recent trauma survivors with benzodiazepines: a prospective study. J Clin.Psychiatry, 57, 390-394.	
NCT01221883	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT01221883. Early Pharmacological Intervention With Diazepam in the Emergency Room Setting to Prevent Posttraumatic Stress Disorder (PTSD). Available from: https://clinicaltrials.gov/ct2/show/NCT01221883 [accessed 22.12.16]	

Other drugs

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Abramowitz 2008	RQ 4.1-4.2 (maximizing sensitivity)	Interventions not relevant to this review (to be considered for other relevant RQ)	Abramowitz EG, Barak Y, Ben-Avi I, Knobler HY. Hypnotherapy in the treatment of chronic combat-related PTSD patients suffering from insomnia: a randomized, zolpidem-controlled clinical trial. Intl. Journal of Clinical and Experimental Hypnosis. 2008 May 29;56(3):270-80.	
Aerni 2004	2004 GL (excluded)	Sample size (N<10/arm)	Aerni, A., Traber, R., Hock, C., Roozendaal, B., Schelling, G., Papassotiropoulos, A. (2004). Low-dose cortisol for symptoms of posttraumatic stress disorder. Am.J.Psychiatry, 161, 1488-1490.	
Aerni 2004	Handsearch	Sample size (N<10/arm)	Aerni, A., Traber, R., Hock, C., Roozendaal, B., Schelling, G., Papassotiropoulos, A., Nitsch, R.M., Schnyder, U., de Quervain, D.J., 2004. Low-dose cortisol for symptoms of posttraumatic stress disorder. Am. J. Psychiatry 161 (8), 1488–1490 (Aug).	Koek, R., Schwartz, H., Scully, S., Langevin, J-P., Spangler, S., Korotinsky, A., Joua, K. and Leuchter, A. (2016) Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework for the future, Progress in Neuro-Psychopharmacology & Biological Psychiatry, 70, 170–218
Albucher 2002	2004 GL (excluded)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Albucher, R. C. & Liberzon, I. (2002). Psychopharmacological treatment in PTSD: A critical review. Journal of Psychiatric Research, 36, 355-367.	
Attari 2014/Rajabi 2013	RQ 4.1-4.2 (maximizing sensitivity)	Outcomes reported are outside the scope	Attari A, Rajabi F, Maracy MR. D-cycloserine for treatment of numbing and avoidance in chronic post traumatic stress disorder: A randomized, double blind, clinical trial. Journal of research in medical	IRCT2013121015741N1. Efficacy of D-Cycloserine for Treatment of Numbing and Avoidance in patients with Chronic PTSD - D-

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			sciences: the official journal of Isfahan University of Medical Sciences. 2014 Jul;19(7):592.	Cycloserine for Numbing and Avoidance in Chronic PTSD. Available from: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=IRCT2013121015741N1 [accessed 06.01.17]
Berlant 2001	Handsearch	Non-randomised group assignment	Berlant, J. (2001) Topiramate in posttraumatic stress disorder: preliminary clinical observations, Journal of Clinical Psychiatry, 62, 60-63	Ahearn, E., Krohn, A., Connor, K. & Davidson, J. (2003) Pharmacologic Treatment of Posttraumatic Stress Disorder: A Focus on Antipsychotic Use, Annals of Clinical Psychiatry, 15, 193-203
Berlant 2003	2004 GL (excluded)	Non-systematic review	Berlant, J. (2003). New drug development for post-traumatic stress disorder. Current Opinion in Investigational Drugs, 4, 37-41.	
Bouso 2008	Handsearch	Sample size (N<10/arm)	Bouso, J.C., Doblin, R., Farré,M., Alcázar,M.A., 2008. Gómez-Jarabo G.MDMA-assisted psychotherapy using low doses in a small sample of women with chronic posttraumatic stress disorder. J. Psychoactive Drugs 40 (3), 225–236 (Sep).	Koek, R., Schwartz, H., Scully, S., Langevin, J-P., Spangler, S., Korotinsky, A., Joua, K. and Leuchter, A. (2016) Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework for the future, Progress in Neuro-Psychopharmacology & Biological Psychiatry, 70, 170–218
Cohen 2004b	2004 GL (included)	Sample size (N<10/arm)	Cohen, H., Kaplan, Z., Kotler, M., Kouperman, I., Moisa, R., & Grisaru, N. (2004). Repetitive	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: a double-blind, placebo-controlled study. Am.J.Psychiatry, 161, 515-524.	
Connor 2006	RQ 4.1-4.2 (maximizing sensitivity)	Sample size (N<10/arm)	Connor, K.M., Davidson, J.R., Weisler, R.H., Zhang, W., Abraham, K., 2006. Tiagabine for posttraumatic stress disorder: effects of open-label and double-blind discontinuation treatment. Psychopharmacology 184 (1), 21–25 (Jan).	
Coupland 1997	2004 GL (excluded)	Intervention not targeted at PTSD symptoms	Coupland, N.J. (1997) A pilot controlled study of the effects of Flumazenil in posttraumatic stress disorder. Biological Psychiatry, 41, 988-990	
Cyr 2000	RQ 3.1-3.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Cyr, M. & Farrar, M. (2000) Treatment for posttraumatic stress disorder, Annals of Pharmacotherapy, 34, 366-376	
Davidson 1998	2004 GL (excluded)	Non-randomised group assignment	Davidson, J.R.T.; Weisler, R.H.; Malik, M.L. & Connor (1998) Treatment of posttraumatic stress disorder with nefazodone. International Clinical Psychopharmacology. 13, 111-113	
Davidson 2003	2004 GL (excluded)	Sample size (N<10/arm)	Davidson, J. R. T., Weisler, R. H., Butterfield, M. I., Casat, C. D., Connor, K. M., Barnett, S. (2003). Mirtazapine vs. placebo in posttraumatic stress disorder: A pilot trial. Biological Psychiatry, 53, 188-191.	
Davis 2008b	RQ 4.1-4.2 (maximizing sensitivity)	Paper unavailable	Davis LL, Ward C, Rasmusson A, Newell JM, Frazier E, Southwick SM. A placebo-controlled trial of guanfacine for the treatment of posttraumatic stress disorder in veterans. Psychopharmacology bulletin. 2007 Dec;41(1):8-18.	
d'Otalora 2013	RQ 4.1-4.2 (maximizing sensitivity)	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT01793610. A Randomized, Double-Blind, Dose Response Phase 2 Pilot Study of Manualized MDMA-Assisted Psychotherapy in Subjects With Chronic, Treatment-Resistant Posttraumatic Stress Disorder	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			(PTSD). Available from: https://clinicaltrials.gov/ct2/show/NCT01793610 [accessed 06.01.17]	
Drake 2003	2004 GL (excluded)	Non-randomised group assignment	Drake, R.G. (2003) Baclofen treatment for chronic posttraumatic stress disorder. The Annals of Pharmacotherapy,37, 1177-1181	
Duffy 1994	2004 GL (excluded)	Non-randomised group assignment	Duffy, J.D. & Malloy, P.F. (1994) Efficacy of buspirone in the treatment of posttraumatic stress disorder: an open trial. Annals of Clinical Psychiatry, 6, 1, 33-37	
EudraCT 2007-000030-39	RQ 4.1-4.2 (maximizing sensitivity)	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	EudraCT 2007-000030-39. Prazosin as add-on therapy in the pharmacological treatment of sleep disturbances in post traumatic stress disorder, a placebo-controlled study using polysomnography. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-000030-39/NL [accessed 05.01.17]	
Feder 2014	RQ 4.1-4.2 (maximizing sensitivity)	Cross-over study and first phase data not available	Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, Saxena S, Kirkwood K, Aan Het Rot M, Lapidus KA, Wan LB, Iosifescu D. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. JAMA psychiatry. 2014 Jun 1;71(6):681-8.	
Feeny 2004	RQ 4.1-4.2 (maximizing sensitivity)	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00127673. Effectiveness of PTSD Treatment: CBT Versus Sertraline. Available from: https://clinicaltrials.gov/show/NCT00127673 [accessed 06.01.17]	
Friedman 2000	Handsearch	Book Section	Friedman MJ, Davidson JRT, Mellman TA, Southwick SM. Pharmacotherapy. In: Foa EB, Keane TM, Friedman MJ, eds. Effective treatments for PTSD: practice guidelines from the International Society for Traumatic Stress Studies. New York: Guilford, 2000:326–329.	Cooper, J., Carty, J. & Creamer, M. (2005) Pharmacotherapy for posttraumatic stress disorder: empirical review and clinical recommendations,

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
				Australian and New Zealand Journal of Psychiatry 2005; 39:674–682
Frommberger 2004	RQ 4.1-4.2 (maximizing sensitivity)	Interventions not relevant to this review (to be considered for other relevant RQ)	Frommberger U, Stieglitz RD, Nyberg E, Richter H, Novelli-Fischer U, Angenendt J, Zaninelli R, Berger M. Comparison between paroxetine and behaviour therapy in patients with posttraumatic stress disorder (PTSD): a pilot study. International Journal of Psychiatry in Clinical Practice. 2004 Jan 1;8(1):19-23.	
Gaffney 2003	2004 GL (excluded)	Secondary analysis of data that has already been included	Gaffney, M. (2003). Factor analysis of treatment response in posttraumatic stress disorder. J Trauma Stress, 16, 77-80.	
Golier 2012	Handsearch	Sample size (N<10/arm)	Golier, J.A., Caramanica, K., Demaria, R., Yehuda, R., 2012. A pilot study of mifepristone in combat-related PTSD. Depress. Res. Treat. 2012, 393251.	Koek, R., Schwartz, H., Scully, S., Langevin, J-P., Spangler, S., Korotinsky, A., Joua, K. and Leuchter, A. (2016) Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework for the future, Progress in Neuro-Psychopharmacology & Biological Psychiatry, 70, 170–218
Golier 2016	RQ 4.1-4.2 (maximizing sensitivity)	Outcomes are not of interest	Golier JA, Caramanica K, Michaelides AC, Makotkine I, Schmeidler J, Harvey PD, Yehuda R. A randomized, double-blind, placebo-controlled, crossover trial of mifepristone in Gulf War veterans with chronic multisymptom illness. Psychoneuroendocrinology. 2016 Feb 29;64:22-30.	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Green 2006	RQ 4.1-4.2 (maximizing sensitivity)	Interventions not relevant to this review (to be considered for other relevant RQ)	Green BL, Krupnick JL, Chung J, Siddique J, Krause ED, Revicki D, Frank L, Miranda J. Impact of PTSD comorbidity on one-year outcomes in a depression trial. Journal of clinical psychology. 2006 Jul 1;62(7):815-35.	
Guay 2007	RQ 4.1-4.2 (maximizing sensitivity)	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00452231. Comparative Study of the Efficacy of a Cognitive-Behavioral Therapy for Post-Traumatic Stress Disorder With or Without D-Cycloserine. Available from: https://clinicaltrials.gov/ct2/show/NCT00452231 [accessed 06.01.17]	
Heresco-Levy 2002	2004 GL (excluded)	Sample size (N<10/arm)	Heresco-Levy, U., Kremer, I., Javitt, D. C., Goichman, R., Reshef, A., Blanaru, M. (2002). Pilot-controlled trial of D-cycloserine for the treatment of post-traumatic stress disorder. International Journal of Neuropsychopharmacology, 5, 301-307.	
Heresco-Levy 2009	Handsearch	Cross-over study and first phase data not available	Heresco-Levy, U., Vass, A., Bloch, B., Wolosker, H., Dumin, E., Balan, L., Deutsch, L. and Kremer, I. (2009) Pilot controlled trial of D-serine for the treatment of post-traumatic stress disorder,International Journal of Neuropsychopharmacology,12, 1275–1282	
Hertzberg 2001	2004 GL (excluded)	Intervention not targeted at PTSD symptoms	Hertzberg, M. A., Moore, S. D., Feldman, M. E., & Beckham, J. C. (2001). A preliminary study of bupropion sustained-release for smoking cessation in patients with chronic posttraumatic stress disorder. J Clin.Psychopharmacol., 21, 94-98.	
Hertzberg 2002	2004 GL (excluded)	Non-randomised group assignment	Hertzberg, M.A.; Feldman, M.E.; Beckham, J.C.; Moore, S.D. & Davidson, J.R.T (2002) Three- to four-year follow-up to an open trial of nefazodone for combat-related posttraumatic stress disorder. Annals of Clinical Psychiatry, 14, 4, 215-221	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Jacobs-Rebhun	2004 GL (excluded)	Efficacy or safety data cannot be extracted	Jacobs-Rebhun, S. & Schnurr, P. (US). Posttraumatic stress disorder and sleep difficulty. American Journal of Psychiatry, 157, Sep-1526.	
Jetly 2015	Handsearch	Sample size (N<10/arm)	Jetly, R., Heber, A., Fraser, G., 2015. Boisvert D Psychoneuroendocrinology 51, 585–588 (Jan).	Koek, R., Schwartz, H., Scully, S., Langevin, J-P., Spangler, S., Korotinsky, A., Joua, K. and Leuchter, A. (2016) Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework for the future, Progress in Neuro-Psychopharmacology & Biological Psychiatry, 70, 170–218
Kaplan 1996	2004 GL (excluded)	Sample size (N<10/arm)	Kaplan Z, Amir M, Swartz M, Levine J. Inositol treatment of post-traumatic stress disorder. Anxiety. 1996 Jan 1;2(1):51-2.	
Kellner 2000	2004 GL (included)	Intervention not targeted at PTSD symptoms	Kellner, M., Wiedemann, K., Yassouridis, A., Levengood, R., Guo, L. S., Holsboer, F. (2000). Behavioral and endocrine response to cholecystokinin tetrapeptide in patients with posttraumatic stress disorder. Biological Psychiatry, 47, 107-111.	
Khan 2017	Handsearch	Non-randomised group assignment	Khan, A., Khan, S., Hobus, J., Faucett, J. and Davidson, J. (2017) Response to adrenergic blockade for post-traumatic stress disorder: data from a randomised, placebo-controlled, double-blind proof of concept trial with carvedilol. Unpublished manuscript.	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Kitchener 1985	Handsearch	Non-randomised group assignment	Kitchener, I., Greenstein, R. (1985) Low dose lithium carbonate in the treatment of posttarumatic stress disrder: brief communication, Mil Med, 150, 378-381	Ahearn, E., Krohn, A., Connor, K. & Davidson, J. (2003) Pharmacologic Treatment of Posttraumatic Stress Disorder: A Focus on Antipsychotic Use, Annals of Clinical Psychiatry, 15, 193-202
Koch 2016	RQ 4.1-4.2 (maximizing sensitivity)	Efficacy or safety data cannot be extracted	Koch SB, van Zuiden M, Nawijn L, Frijling JL, Veltman DJ, Olff M. Intranasal Oxytocin Normalizes Amygdala Functional Connectivity in Posttraumatic Stress Disorder. Neuropsychopharmacology. 2016 Jan 7.	
Kotler 2013	RQ 4.1-4.2 (maximizing sensitivity)	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT01689740. A Randomized, Double-Blind, Active Placebo-Controlled Phase 2 Pilot Study of MDMA-assisted Psychotherapy in People With Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD). Available from: https://clinicaltrials.gov/show/NCT01689740 [accessed 06.01.17]	
Kozaravic-Kovacic 2008	RQ 3.1-3.2 (maximizing sensitivity)	Non-systematic review	Kozaric-Kovacic, D. (2008) Psychopharmacotherapy of posttraumatic stress disorder, Croatian Medical Journal, 49, 459-475	
Kwako 2015	Handsearch	Efficacy or safety data cannot be extracted	Kwako, L.E., George, D.T., Schwandt, M.L., Spagnolo, P.A., Momenan, R., Hommer, D.W., Diamond, C.A., Sinha, R., Shaham, Y., Hellig, M., 2015. The neurokinin-1 receptor antagonist aprepitant in co-morbid alcohol dependence and posttraumatic stress disorder: a human experimental study. Psychopharmacology 232 (1), 295–304.	Koek, R., Schwartz, H., Scully, S., Langevin, J-P., Spangler, S., Korotinsky, A., Joua, K. and Leuchter, A. (2016) Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework for the future, Progress in

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
				Neuro-Psychopharmacology & Biological Psychiatry, 70, 170–218
Lerer 1987	2004 GL (excluded)	Non-randomised group assignment	Lerer, B.; Bleich, A.; Kotler, M.; Garb, R.; Hertzberg, M. & Levin, B. (1987) Posttraumatic stress disorder in Israeli combat veterens. Archives of General Psychiatry, 44, 976-981	
Ludäscher 2015	RQ 4.1-4.2 (maximizing sensitivity)	Cross-over study and first phase data not available	Ludäscher P, Schmahl C, Feldmann RE, Kleindienst N, Schneider M, Bohus M. No evidence for differential dose effects of hydrocortisone on intrusive memories in female patients with complex post-traumatic stress disorder–a randomized, double-blind, placebo-controlled, crossover study. Journal of Psychopharmacology. 2015; 29(10): 1077-1084	
Mathew 2011	Handsearch	Intervention outside scope	Mathew, S.J., Vythilingam, M., Murrough, J.W., Zarate Jr., C.A., Feder, A., Luckenbaugh, D.A., Kinkead, B., Parides, M.K., Trist, D.G., Bani, M.S., Bettica, P.U., Ratti, E.M., Charney, D.S., 2011. A selective neurokinin-1 receptor antagonist in chronic PTSD: a randomized, double-blind, placebo-controlled, proof-of-concept trial. Eur. Neuropsychopharmacol. 21 (3), 221–229 (Mar).	Koek, R., Schwartz, H., Scully, S., Langevin, J-P., Spangler, S., Korotinsky, A., Joua, K. and Leuchter, A. (2016) Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework for the future, Progress in Neuro-Psychopharmacology & Biological Psychiatry, 70, 170–218
Mellman 1999	2004 GL (excluded)	Non-randomised group assignment	Mellman, T.A.; David, D. & Barza, L. (1999) Nefazodone treatment and dream reports in chronic PTSD. Depression and Anxiety, 9: 146-148	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Mithoefer 2004	RQ 4.1-4.2 (maximizing sensitivity)	Protocol	NCT00090064. Phase II Clinical Trial Testing the Safety and Efficacy of 3,4-Methylenedioxymethamphetamine (MDMA)-Assisted Psychotherapy in Subjects With Chronic Posttraumatic Stress Disorder. Available from: https://clinicaltrials.gov/ct2/show/NCT00090064 [accessed 06.01.17]	
Mithoefer 2011	Handsearch	Sample size (N<10/arm)	Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. The safety and efficacy of±3, 4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. Journal of Psychopharmacology. 2011 Apr 1;25(4):439-52.	
Mithoefer 2013	Handsearch	Sample size (N<10/arm)	Mithoefer, M.C., Wagner, M.T., Mithoefer, A.T., Jerome, L., Martin, S.F., Yazar- Klosinski, B., Michel, Y., Brewerton, T.D., Doblin, R., 2013. Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. J. Psychopharmacol. 27 (1), 28–39 (Jan).	Koek, R., Schwartz, H., Scully, S., Langevin, J-P., Spangler, S., Korotinsky, A., Joua, K. and Leuchter, A. (2016) Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework for the future, Progress in Neuro-Psychopharmacology & Biological Psychiatry, 70, 170–218
Murrough 2015	RQ 4.1-4.2 (maximizing sensitivity)	Population outside scope: <80% of the study's participants are eligible for the review and disaggregated data cannot be obtained	Murrough JW, Soleimani L, DeWilde KE, Collins KA, Lapidus KA, Iacoviello BM, Lener M, Kautz M, Kim J, Stern JB, Price RB. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. Psychological medicine. 2015 Dec 1;45(16):3571-80.	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
NCT00018603	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00018603. Guanfacine for the Treatment of Post Traumatic Stress Disorder (PTSD). Available from: https://clinicaltrials.gov/ct2/show/NCT00018603 [accessed 22.12.16]	
NCT00025740	Handsearch	Paper unavailable	NCT00025740. Combined Treatment With a Benzodiazepine (Clonazepam) and a Selective Serotonin Reuptake Inhibitor (Paroxetine) for Rapid Treatment of Posttraumatic Stress Disorder (PTSD). Available from: https://clinicaltrials.gov/ct2/show/NCT00025740 [accessed 22.12.16]	
NCT00108420	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00108420. Prazosin Treatment for Combat Trauma PTSD (Post-Traumatic Stress Disorder) Nightmares and Sleep Disturbance. Available from: https://clinicaltrials.gov/ct2/show/NCT00108420 [accessed 22.12.16]	
NCT00167687	Handsearch	Population outside scope: Trials of people without PTSD	NCT00167687. A Double-Blind Placebo-Controlled Trial of Prazosin for the Treatment of Alcohol Dependence. Available from: https://clinicaltrials.gov/ct2/show/NCT00167687 [accessed 22.12.16]	
NCT00174551	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00174551. The Effect of Prazosin for Nighttime Symptoms of Civilian PTSD. Available from: https://clinicaltrials.gov/ct2/show/NCT00174551 [accessed 22.12.16]	
NCT00744055	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00744055. The Use of Prazosin for Treatment of Patients With Alcohol Dependence (AD) and Post Traumatic Stress Disorder (PTSD). Available from: https://clinicaltrials.gov/ct2/show/NCT00744055 [accessed 22.12.16]	
NCT00965809	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT00965809. Double Blind, Placebo-Controlled Trial of THC as add-on Therapy for PTSD. Availble from: https://clinicaltrials.gov/ct2/show/NCT00965809 [accessed 22.12.16]	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
NCT01000493	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT01000493. A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-Dose Study Evaluating the Efficacy and Safety of the Neurokinin-1 Receptor Antagonist Orvepitant (GW823296) in Post Traumatic Stress Disorder (PTSD). Available from: https://clinicaltrials.gov/ct2/show/NCT01000493 [accessed 22.12.16]	
NCT01336413	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT01336413. Neuroactive Steroids and Traumatic Brain Injury (TBI) in OEF/OIF Veterans. Available from: https://clinicaltrials.gov/ct2/show/NCT01336413 [accessed 22.12.16]	
NCT01715519	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT01715519. A Double-blind, Placebo-controlled Randomized Trial of Vilazodone in the Treatment of Posttraumatic Stress Disorder. Available from: https://clinicaltrials.gov/ct2/show/NCT01715519 [accessed 22.12.16]	
NCT01726088	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT01726088. A Double-Blind, Placebo-Controlled Trial of Modafinil in OEF/OIF Combat Veterans With PTSD. Available from: https://clinicaltrials.gov/ct2/show/NCT01726088 [accessed 22.12.16]	
NCT01739335	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT01739335. Novel Therapeutics in Posttraumatic Stress Disorder (PTSD): A Randomized Clinical Trial of Mifepristone. Available from: https://clinicaltrials.gov/ct2/show/NCT01739335 [accessed 22.12.16]	
NCT01946685	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT01946685. Novel Therapeutics in PTSD: A Randomized Clinical Trial of Mifepristone. Available from: https://clinicaltrials.gov/ct2/show/NCT01946685 [accessed 22.12.16]	
NCT02155829	Handsearch	Unpublished (registered on clinical trials.gov and author	NCT02155829. Riluzole for PTSD: Efficacy of a Glutamatergic Modulator as Augmentation Treatment for Posttraumatic Stress Disorder. Available from:	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
		contacted for full trial report but not provided)	https://clinicaltrials.gov/ct2/show/NCT02155829 [accessed 22.12.16]	
NCT02577250	Handsearch	Non-RCT (no control group)	NCT02577250. Efficacy and Safety of Repeated Intravenous Subanesthetic Ketamine Infusions Among Veterans With Treatment Resistant Depression Comorbid With Chronic Post-Traumatic Stress Disorder: A Proof-of-concept Study. Available from: https://clinicaltrials.gov/ct2/show/NCT02577250 [accessed 22.12.16]	
Neylan 2003	2004 GL (excluded)	Non-randomised group assignment	Neylan, T.C. (2003) The effect of nefazodone on subjective and objective sleep quality in posttraumatic stress disorder. Journal of Clinical Psychiatry, 64, 4, 445-450	
Oehen 2013	Handsearch	Sample size (N<10/arm)	Oehen, P., Traber, R.,Widmer, V., Schnyder, U., 2013. A randomized, controlled pilot study of MDMA (± 3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). J. Psychopharmacol. 27 (1), 40–52 (Jan).	Koek, R., Schwartz, H., Scully, S., Langevin, J-P., Spangler, S., Korotinsky, A., Joua, K. and Leuchter, A. (2016) Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework for the future, Progress in Neuro-Psychopharmacology & Biological Psychiatry, 70, 170–218
Pitman 1990	2004 GL (excluded)	Intervention not targeted at PTSD symptoms	Pitman, R.K. (1990) Naloxone-reversable analgesic response to combat-related stimuli in posttraumatic stress disorder. Archives of General Psychiatry, 47, 541-544	
Raskind 2003	2004 GL (excluded)	Sample size (N<10/arm)	Raskind, M. A., Peskind, E. R., Kanter, E. D., Petrie, E. C., Radant, A., Thompson, C. E. (2003). Reduction of nightmares and other PTSD symptoms	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			in combat veterans by prazosin: a placebocontrolled study. American Journal of Psychiatry, 160, 371-373.	
Raskind 2009/2013	RQ 4.1-4.2 (maximizing sensitivity)	Setting outside scope: Treatment provided to troops on operational deployment or exercise	Raskind, M.A., Peterson, K., Williams, T., Hoff, D.J., Hart, K., Holmes, H., Homas, D., Hill, J., Daniels, C., Calohan, J., Millard, S.P., Rohde, K., O'Connell, J., Pritzl, D., Feiszli, K., Petrie, E.C., Gross, C., Mayer, C.L., Freed, M.C., Engel, C., Peskind, E.R., 2013. A trial of prazosin for combat trauma PTSD with nightmares in activeduty soldiers returned from Iraq and Afghanistan. Am. J. Psychiatry 170 (9), 1003–1010 (Sep).	
Raskind 2014	RQ 4.1-4.2 (maximizing sensitivity)	Protocol	NCT02226367. Prazosin Augmentation of Outpatient Treatment of Alcohol Use Disorders in Active Duty Soldiers With and Without PTSD. Available from: https://clinicaltrials.gov/show/NCT02226367 [accessed 06.01.17]	
Reznik 2002	2004 GL (excluded)	Intervention not targeted at PTSD symptoms	Reznik, I., Zemishlany, Z., Kotler, M., Spivak, B., Weizman, A., & Mester, R. (2002). Sildenafil citrate for the sexual dysfunction in antidepressant-treated male patients with posttraumatic stress disorder: A preliminary pilot open-label study. Psychotherapy & Psychosomatics, 71, 173-176.	
Risse 1990	Handsearch	Non-randomised group assignment	Risse, S., Whitters, A., Burke, J., Chen, S., Scurfield, R., Raskind, M. (1990) Severe withdrawal symptoms after discontinuation of alprazolam in eight patients with combat-induced post-traumatic stress disorder, Journal of Clinical psychiatry, 51, 206-209	Ahearn, E., Krohn, A., Connor, K. & Davidson, J. (2003) Pharmacologic Treatment of Posttraumatic Stress Disorder: A Focus on Antipsychotic Use, Annals of Clinical Psychiatry, 15, 193-204
Schelling 1999	2004 GL (excluded)	Non-randomised group assignment	Schelling, G. (1999) The effect of stress doses of hydrocortisone during septic shock on posttraumatic	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			stress disorder and health-related quality of life in survivors. Critical Care Medicine, 27, 12, 2678-2683	
Schoenfeld 2012	RQ 3.1-3.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Schoenfeld, F., DeViva, J. and Manber, R. (2012) Treatment of sleep disturbances in posttraumatic stress disorder: a review, JRRD, 49, 729-752	
Shalev 1996	RQ 3.1-3.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Shalev, A., Bonne, O. & Eth, S. (1996) Treatment of posttraumatic stress disorder: A review, Psychosomatic Medicine, 58, 165-182	
Silver 1995	2004 GL (excluded)	Non-randomised group assignment	Sillver, S.M.; Brooks, A.; Obenchain, J. (1995) Treatment of Vietnam War veterans with PTSD: a comparison of eye movement desensitization and reprocessing, biofeedback, and relaxation training. J Trauma Stress. 1995 Apr;8(2):337-42.	
Stein 2002	2004 GL (included)	Sample size (N<10/arm)	Stein, M. B., Kline, N. A., & Matloff, J. L. (2002). Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. American Journal of Psychiatry, 159, 1777-1779.	
Suris 2010	RQ 4.1-4.2 (maximizing sensitivity)	Efficacy or safety data cannot be extracted	Surís A, North C, Adinoff B, Powell CM, Greene R. Effects of exogenous glucocorticoid on combat-related PTSD symptoms. Annals of Clinical Psychiatry. 2010 Nov 1;22(4):274-9.	
Taylor 2008a	RQ 3.1-3.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Taylor, H., Freeman, M. & Cates, M. (2008) Prazosin for treatment of nightmares related to posttraumatic stress disorder, American Journal of Health System Pharmacy, 65, 716-722	
Taylor 2008b	Handsearch	Sample size (N<10/arm)	Taylor FB, Martin P, Thompson C, Williams J, Mellman TA, Gross C, Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. Biol Psychiatry 2008;63:629–32.	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Yehuda 2011	RQ 4.1-4.2 (maximizing sensitivity)	Sample size (N<10/arm)	Yehuda R, Harvey PD, Golier JA, Newmark RE, Bowie CR, Wohltmann JJ, Grossman RA, Schmeidler J, Hazlett EA, Buchsbaum MS. Changes in relative glucose metabolic rate following cortisol administration in aging veterans with posttraumatic stress disorder: an FDG-PET neuroimaging study. The Journal of neuropsychiatry and clinical neurosciences. 2009 Apr;21(2):132-43.	
Yehuda 2015	RQ 4.1-4.2 (maximizing sensitivity)	Efficacy or safety data cannot be extracted	Yehuda R, Bierer LM, Pratchett LC, Lehrner A, Koch EC, Van Manen JA, Flory JD, Makotkine I, Hildebrandt T. Cortisol augmentation of a psychological treatment for warfighters with posttraumatic stress disorder: Randomized trial showing improved treatment retention and outcome. Psychoneuroendocrinology. 2015 Jan 31;51:589-97.	

Economic studies

No economic studies were reviewed at full text and excluded from these reviews.

Appendix L – Research recommendations

Research recommendation for "For adults at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?

Research recommendation for "For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions? "

No research recommendations were made for these review questions.