National Institute for Health and Care Excellence

Final

Medicines associated with dependence or withdrawal symptoms: safe prescribing and withdrawal management for adults

[B] Evidence review: Optimum prescribing strategies or interventions delivered alongside prescribing

NICE guideline NG215

Evidence reviews underpinning recommendations 1.2.7, 1.3.4, 1.3.5, 1.3.7, 1.3.8, 1.3.9, 1.3.10, 1.3.11, 1.3.12, 1.3.13, 1.3.14 in the NICE guideline

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Final

These evidence reviews were developed by the National Guideline Centre

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1.1 Review question: What are the optimum prescribing strategies or interventions delivered alongside prescribing, to limit the risk of dependence or withdrawal symptoms?

1.1.1 Introduction

It is not possible to predict which individuals will develop dependence on prescribed medicines or who will experience withdrawal symptoms if the medicine is reduced and stopped. Prescribers also vary in their confidence to manage these issues in clinical practice, often depending on previous experience to guide their actions. There may, however, be general strategies which could be applied when prescribing medicines associated with increased risk of dependence and withdrawal. Approaches to ensure safe use of medicines, especially when extended periods of use are necessary or the medicine needs to be stopped, will be considered for this review.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: adults (≥18 years) being initiated on or currently being prescribed medicines associated with dependence or withdrawal symptoms (opioids for chronic pain, benzodiazepines, gabapentinoids, Z-drugs, antidepressants). This will include people being prescribed these medicines either at initiation or being re-prescribed. However, if the population are already taking the medicine, the majority (at least 80%) should be shown not to have behaviours related to dependence at the start of the study (if it is unclear, the study will be excluded). **Stratification** • Opioids • Benzodiazepines, • Gabapentinoids • Z-drugs • Antidepressants (further stratified by SSRIs, MAOIs, tricyclics, others).
Interventions	Any prescribing strategy or intervention aimed at reducing the risk of dependence or preventing dependence. The interventions listed in the full protocol in Appendix A are examples and not an extensive list.
Comparisons	Any prescribing strategy compared to another, or to usual care
Outcomes	• HRQOL • Mortality • Dependence on the prescribed medicine • Withdrawal symptoms including rebound symptoms / intensity or duration of withdrawal syndrome • Non-fatal overdose • Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs • Patient Satisfaction • Self-harm or harm to others • Increase in symptoms for which the medication was originally prescribed

Study design	Randomised controlled trials Comparative non-randomised or cohort studies Systematic review of randomised controlled trials or non-randomised comparative studies.

1.1.3 Methods and process

This evidence review was developed using the methods and processes described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

This guideline and this review question relate to the stage in the treatment pathway after a decision has been made to prescribe one of the relevant medicines. This review question looks at the evidence for what the best prescribing strategy is in terms of reducing the risk of or preventing dependence or withdrawal symptoms. This is highlighted in the aims and interventions of the review protocol. Determining which is the most effective treatment for the underlying condition was outside the scope of this guideline. Therefore, this review did not include efficacy and safety studies, unless the aim of the study was also to assess whether one of the prescribing strategies reduced the risk of dependence. Some studies were identified in the literature assessing 2 different prescribing strategies and then a subsequent withdrawal (with the withdrawal schedule being the same in both arms of the study), and reports withdrawal symptoms within the outcomes. These studies did not necessarily have an aim of reducing dependence. However, such studies were included, as they are involving a withdrawal stage, and therefore are more than just efficacy studies. Antidepressants are not considered to be dependence forming, but can cause withdrawal symptoms on withdrawal. The committee agreed if any studies were identified that did report dependence for antidepressants, they would be included.

1.1.4.1 Included studies

Ten studies were included in the review;[36, 47, 52, 74, 76, 90, 92, 98, 105, 108] these are summarised by drug class in Table 2 to Table 5 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 8 to Table 18).

Evidence was identified in people prescribed opioids (n=4[36, 52, 90, 98]), gabapentinoids (n=2[47, 74]), Z-drugs (n=1[105]) and antidepressants (n=3[76, 92, 108]). No evidence was identified in people prescribed benzodiazepines.

Prescribing strategies or interventions used to reduce the risk of dependence or withdrawal symptoms included: different dosage regimens (gabapentinoids, n=2; antidepressants, n=2; Z-drugs, n=1),[47, 74, 76, 92, 105] providing patient or physician information and education (opioids, n=1),[98] adding an extra drug to the prescription (opioids, n=1),[36] varying the rate of upward titration (escalating versus stable dose, opioids, n=1),[90] the use of mindfulness alongside the prescription (opioids, n=1),[52] and class comparison (antidepressants, n=1).[108]

Three studies assessed the effectiveness of a prescribing strategy or intervention on the risk of dependence.[52, 90, 98] All of these studies were in people taking opioids. For the studies assessing dependence as the outcome, and the effect of a prescribing strategy or intervention on the risk of dependence, it was noted as important that the population did not have dependence at baseline. Therefore, the protocol stated that ideally the population should be initiating the prescribed medicines, or if currently taking it, the majority (at least 80%) shown not to have behaviours related to dependence at baseline. As all of these studies included participants who were already receiving the medication at baseline, the

exclusion criteria was checked to ensure that people with behaviours related to dependence were excluded (this is noted in the summary of included studies listed below, see Table 2).

When agreeing the protocol, the committee acknowledged that dependence might not be commonly reported as an outcome, as it is difficult to measure. Therefore, any definition of dependence as described by the study authors was accepted, this could include measures indicating problems with dependence, such as early refill requests, shopping behaviour, or measures of medicine misuse

The seven other studies included in the review were studies assessing the effectiveness of a prescribing strategy or intervention on the risk of withdrawal symptoms: opioids;[36] gabapentinoids;[47, 74] antidepressants[76, 92, 108] and Z-drugs.[105]

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

1.1.4.2 Excluded studies

One Cochrane review was identified as potentially relevant to this review.[5] The aim of the Cochrane review was to determine the effect of interventions to optimise overall prescribing for older people living in care homes, rather than reducing dependence or withdrawal symptoms. The population of the Cochrane review was also not limited to people being prescribed one of the five medicines associated with dependence or withdrawal symptoms in the current review protocol. Therefore, this review was not relevant to include.

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

1.1.5.1 Opioids

Table 2: Summary of studies included in the evidence review: opioids

Study	Intervention and comparison	Population	Outcomes	Comments
Chu 2018[36] Withdrawal study	**Additional drug** **Morphine plus ondansetron** Vs **Morphine plus placebo** 10 days taper on, 20 days maintenance and 10 days taper off	Low back pain Status at start of study: mixture of existing opioid and initiating medicine (7 had current chronic opioid use) Dependence at baseline: n/a In the past 5 years 21/48 were opioid naïve 7 had current chronic opioid use N= 76 Age: Mean (SD): 39.3 (11.2). USA	Objective Opioid Withdrawal Scale (OOWS) Subjective Opioid Withdrawal Scale (SOWS) At 40 days	Taper: IV naloxone was used to induce acute withdrawal Baseline data only available for study completers (n=48). Baseline opioid dosage (7 patients) shows marked difference between groups- likely to affect findings.
Garland 2019[52] Dependence study	**Mindfulness- Orientated Recovery Enhancement (MORE)** Vs	Chronic non-cancer pain Status at start of study: all were taking opioids for analgesia daily or nearly	Dependence on the prescribed medicine: misuse (Current Opioid Misuse Measure- COMM) At 3 months	Attempt made by the study to avoid dependence on the prescribed medicine at baseline by only including people with COMM score <13 (i.e., people without opioid misuse, as this is a validated cut- off point to identify

Study	Intervention and comparison	Population	Outcomes	Comments
	Support group 14 weeks	every day for at least the past 90 days Dependence at baseline: COMM score <13 only included N= 95 Age: - Mean (SD): 56.8 (11.7) USA		opioid misuse among chronic pain patients).
Naliboff 2011[90] Dependence study	**Escalating dose** Vs **Stable dose** 12–13-month follow-up	Chronic non-cancer pain. Status at start of study: all participants were using opioids Dependence at baseline: Addiction Behaviours Checklist (ABC) 1.6 and 1.5 (scale of 0-20) at baseline Excluded current diagnosis of, or history of, substance abuse N= 140 Age 52.6 (7.48) years 94% male	Dependence on the prescribed medicine (Opioid medication discontinuation for non-compliance) At 12-13 months	Unclear whether <20% had dependence at baseline, but baseline values for the Addiction Behaviours Checklist (ABC) score are provided, and the mean score is below the threshold of 3 for flagging possible opioid misuse. ABC baseline scores: stable dose: 1.6 (2.1); escalating dose: 1.5 (2.0). 47% had a history of substance-related (excluding alcohol) disorder 65% history of alcohol related disorder 40% history of both substance-related and alcohol related disorder

Study	Intervention and comparison	Population	Outcomes	Comments
		USA		
Pasquale 2017[98] Dependence study	**Physician received patient specific information** (opioid utilization, pain diagnoses etc.) Vs **Physicians given links to educational materials** (diagnosis and management of pain) Vs **Physician given patient information and education** Vs **Usual care** Follow up: 91-270 days post intervention	Physician/patient clusters Status at start of study: Enrolment in MAPD plan with ≥1 claim for opioid prescription (July 2012-April 2014), ≥180 days continuous enrolment pre index Dependence at baseline: Excluded patients diagnosed with opioid abuse dependence (ICD codes) or if diagnosed with opioid abuse or dependence during 180 days prior to intervention N=2391 (Patients were grouped into mutually exclusive patient-physician clusters, stratified by size and geographic region.) Age, range of means 57.3 (10.6) to 58.7 (11.8) years USA	•Uncoordinated opioid use (>3 opioid prescription fills of any ingredient written by ≥3 prescribers within any 90-day period) •Diagnosis of opioid abuse At 91-270 days follow-up	Attempt made by the study to avoid dependence on opioids at baseline by excluding people with a diagnosis of opioid abuse or dependence. Unclear if this would only include abuse or dependence on illicit opioids, and therefore unclear if there may have been some undiagnosed dependence on the prescribed medicine at baseline. Risk that some participants were using opioids for acute pain conditions may have been included No adequate adjustment for cluster differences within intervention groups only differences between intervention arms.

1.1.5.2 Gabapentinoids

Table 3: Summary of studies included in the evidence review: gabapentinoids

Study	Intervention and comparison	Population	Outcomes	Comments
Feltner 2003[47] Withdrawal study	**High dose pregabalin (200mg tid (600mg/day))** Vs **Low dose pregabalin (50mg tid (150mg/day))** 4 weeks treatment (short term), 1 week taper	Generalised Anxiety Disorder (GAD) Status at start of study: no details on existing medication therefore no information about whether any of the participants had previously used pregabalin. Dependence at baseline: n/a N= 271 total, 136 included in this review (4-arm trial, of which only 2 arms were relevant for the current review) Age: Mean (SD): Pregabalin 50mg group: 37.9 (10.9); Pregabalin 200mg group: 36.3 (10.9). USA	Withdrawal symptoms: (Physician's Withdrawal Checklist (PWC) At 5 weeks	Taper details: 1 week Z-drug allowed if required during study, but not on night before assessments.
Kasper 2014[74] Withdrawal study	**High dose pregabalin 450-600mg/d** (short/long term) Vs	Primary diagnosis of GAD Status at start of study: initiating medication (people with prior exposure to pregabalin were excluded.)	PWC Discontinuation- Emergent Signs and Symptoms (DESS)	Taper details: 1-week double-blind taper schedule; if a patient experienced severe discontinuation symptoms during the taper periods and up to 7 days afterwards could be provided with

Study	Intervention and comparison	Population	Outcomes	Comments
	Low dose pregabalin 150-300mg/d (short/ long term) Initiation and withdrawal of medication (flexible dose for 6 weeks, followed by fixed dose) 12 (short term) and 24 (long term) weeks	Dependence at baseline: n/a N= 139 Age: mean 59 (11.4) years 60 centres in 16 countries	Rebound anxiety (increase in symptoms for which the medication was originally prescribed)	a more gradual 'rescue' taper, extending the taper to 4 weeks while maintaining the blind. The same taper was used for all patients, regardless of when treatment was discontinued.

1.1.5.3 Z-drugs

Table 4: Summary of studies included in the evidence review: Z-drugs

Study	Intervention and comparison	Population	Outcomes	Comments
Shaw 1992[105] Withdrawal study	**High dose: 20mg Zolpidem** Vs **Low dose: 10mg Zolpidem** 3–14-day washout, 7-day placebo, 21 days treatment, 7 days placebo (withdrawal)	Older people (65-85 years) with insomnia Status at start of study: initiating treatment. 84.9% had prior treatment for insomnia, the most frequent was temazepam Dependence at baseline: n/a N=119 (n=80 in 2 arms, placebo arm excluded) Age 74.9 (1.0) & 72.9 (1.0) years	Mortality Withdrawal symptoms During the 7-day withdrawal period	Taper: 7 days placebo (abrupt discontinuation of z-drug) Majority of participants had been hospitalised for a number of years. Majority of patients were taking concomitant drugs likely to have an effect on sleep.

Study	Intervention and comparison	Population	Outcomes	Comments
		Unknown country		

1.1.5.4 Antidepressants

Table 5: Summary of studies included in the evidence review: antidepressants

Study	Intervention and comparison	Population	Outcomes	Comments
Krystal 2011[76] Class: antidepressants (TCA) Withdrawal study	**6 mg doxepin**. Vs **3 mg doxepin** Initiation and withdrawal of medication 5 weeks treatment and abrupt discontinuation	Primary insomnia. Status at start of study: initiating medication Dependence at baseline: n/a N=229 age: Mean (SD): Doxepin 3mg: 45.5 (10.6), Doxepin 6mg: 44.2 (11.1) USA	Increase in symptoms for which the medicine was originally prescribed -rebound insomnia. Withdrawal symptoms (≥3 new symptoms on Benzodiazepine Withdrawal Symptom Questionnaire-BWSQ.	Taper: Abrupt discontinuation with placebo for 2 days. Mean BWSQ was reported by the study without variance, unable to analyse.
Nishimura 2018[92] Class: Antidepressants (SSRI) Withdrawal study	**5mg Vortioxetine** Vs **10mg Vortioxetine** Vs **20mg Vortioxetine**	Primary diagnosis of Major Depressive Disorder (MDD), Status at start of study: unclear previous medication but this did not include Vortioxetine Dependence at baseline: n/a	•Withdrawal symptoms (DESS) At week 10	Unclear method of scoring used for the DESS

Study	Intervention and comparison	Population	Outcomes	Comments
	8-week intervention, 2-week discontinuation period	N=600 (n=448 in 3 arms, placebo arm excluded) Age 44.4 (11.54) years Multiple countries		
Sir 2005[108] Class: Antidepressants (SSRI and SNRI) Withdrawal study	**Sertraline (50-150mg/ day)** Vs **Venlafaxine XR (75-225mg/day)** 8-week intervention, 2-week taper	Major depression (diagnosis made using the Mini International Neuropsychiatric Interview (MINI) 5.0.0) Status at start of study: initiation of medication (excluded those with a history of non-response to either study drug) Dependence at baseline: n/a N=163 Age - Mean (SD): 37.0 (12.9). Turkey and Australia	Deterioration during taper period (Antidepressant Discontinuation Scale, ADDS). Worst severity of discontinuation symptoms (investigator global assessment) rated none, minimal, mild, moderate, severe or very severe). At weeks 8-10 (taper period)	Taper: 2 weeks ADDS is an unvalidated scale Unclear if the investigators rating is added to the total intensity score (risk of double counting)

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

1.1.6.1 Opioids

Table 6: Clinical evidence summary: Risk of Withdrawal Symptoms: Morphine plus Ondansetron vs Morphine plus placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Morphine+ placebo	Risk difference with Morphine+ Ondansetron
Withdrawal Symptoms (OOWS) assessed with: Objective Opioid Withdrawal Scale Scale from: 0 to 13 follow up: 40 days	48 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The mean OOWS score was 4.2	MD 0.3 higher (1.09 lower to 1.69 higher)
Withdrawal Symptoms (SOWS) assessed with: Subjective Opioid Withdrawal Scale Scale from: 0 to 64 follow up: 40 days	48 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The mean SOWS score was 12	MD 4.4 higher (2.24 lower to 11.04 higher)

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.

b. Downgraded by 2 increments as the confidence interval crossed 2 MIDs. MID for OOWS was 0.325 and MID for SOWS was 0.9 (0.5* median baseline SDs of intervention and control groups).

Table 7: Clinical evidence summary: Risk of Dependence: MORE vs support group

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Support group	Risk difference with MORE
Dependence on the prescribed drug assessed with: Opioid misuse (Current Opioid Misuse Measure: COMM; 17 items rated on a 5-point Likert scale 0-4; higher values = worse outcome) follow up: 3 months	95 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The mean dependence on the prescribed drug was 9.08	MD 1.36 lower (3.5 lower to 0.78 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Support group	Risk difference with MORE
a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias. b. Downgraded by 1 increment as the CI crossed 1 MID. MID calculated by 0.5x median of baseline SD for intervention and control groups. Calculated MID was 1.36					

Table 8: Clinical evidence summary: Risk of Dependence: Escalating vs stable dose

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with stable dose	Risk difference with Escalating dose
Dependence on the prescribed drug assessed with: Opioid medication discontinuation for non-compliance follow up: 12 months	140 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 0.79 (0.46 to 1.38)	301 per 1,000	63 fewer per 1,000 (163 fewer to 115 more)
a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias. b. Downgraded by 2 increments as the confidence interval crossed 2 MIDs. The MID for dichotomous outcomes was 0.8 and 1.25.					

Table 9: Clinical evidence summary: Risk of Dependence: Physician education vs physician patient information (opioids)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with physician patient information	Risk difference with Physician education
Dependence on the prescribed medicine assessed with: uncoordinated opioid use (>3 opioid prescription fills of any ingredient written by ≥3 prescribers within any 90-day period) follow up: 91-270 days	790 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.08 (0.81 to 1.43)	185 per 1,000	15 more per 1,000 (35 fewer to 80 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with physician patient information	Risk difference with Physician education
Dependence on the prescribed medicine assessed with: diagnosis of opioid abuse follow up: 91-270 days	726 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.90 (0.58 to 1.39)	106 per 1,000	11 fewer per 1,000 (45 fewer to 41 more)

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25.

Table 10: Clinical evidence summary: Risk of Dependence: Physician education vs usual care

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with Physician education
Dependence on the prescribed medicine assessed with: Uncoordinated opioid use follow up: 91-270 days	1212 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.04 (0.81 to 1.32)	192 per 1,000	8 more per 1,000 (37 fewer to 62 more)
Dependence on the prescribed medicine assessed with: Diagnosis of opioid abuse follow up: 91-270 days	1090 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	OR 0.83 (0.55 to 1.26)	Unable to calculate[c]	Unable to calculate[c]

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25.

c. Unable to calculate control group risk and absolute effect as adjusted OR reported by study.

Table 11: Clinical evidence summary: Risk of Dependence: Physician patient information and education vs physician patient information

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with physician patient information	Risk difference with Physician patient information and education
Dependence on the prescribed medicine assessed with: uncoordinated opioid use follow up: 91-270 days	807 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.07 (0.81 to 1.42)	185 per 1,000	13 more per 1,000 (35 fewer to 78 more)
Dependence on the prescribed medicine assessed with: diagnosis of opioid abuse follow up: 91-270 days	731 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 0.78 (0.50 to 1.23)	106 per 1,000	23 fewer per 1,000 (53 fewer to 24 more)

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25.

Table 12: Clinical evidence summary: Risk of Dependence: Physician patient information and education vs physician education

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Physician education	Risk difference with Physician patient information and education
Dependence on the prescribed medicine assessed with: uncoordinated opioid use follow up: 91-270 days	799 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.00 (0.75 to 1.31)	199 per 1,000	0 fewer per 1,000 (50 fewer to 62 more)
Dependence on the prescribed medicine assessed with: diagnosis of opioid abuse follow up: 91-270 days	721 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 0.87 (0.54 to 1.39)	95 per 1,000	12 fewer per 1,000 (44 fewer to 37 more)

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25.

Table 13: Clinical evidence summary: Risk of Dependence: Physician patient information vs usual care

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with Physician patient information
Dependence on the prescribed medicine assessed with: uncoordinated opioid use follow up: 91-270 days	1220 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.96 (0.75 to 1.24)	192 per 1,000	8 fewer per 1,000 (48 fewer to 46 more)
Dependence on the prescribed medicine assessed with: diagnosis of opioid abuse follow up: 91-270 days	1100 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	OR 0.95 (0.63 to 1.43)	Unable to calculate[c]	Unable to calculate[c]

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25.

c. Unable to calculate control group risk and absolute effect as adjusted OR reported by study.

Table 14: Clinical evidence summary: Risk of Dependence: Physician patient information and education vs usual care

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with Physician patient information and education
Dependence on the prescribed medicine assessed with: Uncoordinated opioid use follow up: 91-270 days	1229 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.03 (0.81 to 1.31)	192 per 1,000	6 more per 1,000 (37 fewer to 60 more)
Dependence on the prescribed medicine assessed with: Diagnosis of opioid abuse follow up: 91-270 days	1100 (1 RCT)	⊕⊕◯◯ LOW [a,b]	OR 0.72 (0.46 to 1.13)	Unable to calculate[c]	Unable to calculate[c]

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25.

c. Unable to calculate control group risk and absolute effect as adjusted OR reported by study.

1.1.6.2 Gabapentinoids

Table 15: Clinical evidence summary: high vs low dose short-term treatment (gabapentinoids)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with low dose pregabalin (short-term)	Risk difference with High dose pregabalin (short-term)
Withdrawal symptoms (PWC) week 1 after taper assessed with: Physician Withdrawal Checklist Scale from: 0 to 60 follow up: 5 weeks (post-taper)	95 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	-	The mean PWC score was 2.306	MD 0.54 higher (1.89 lower to 2.98 higher)
Withdrawal symptoms- week 2 after initiating taper (PWC) assessed with: Physician Withdrawal Checklist Scale from: 0 to 60 follow up: 14 weeks (follow-up)	103 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	-	The mean PWC score was 2.0	MD 0.1 higher (2.17 lower to 2.37 higher)
Withdrawal Symptoms (DESS) assessed with: Number of people with Discontinuation-Emergent Signs and Symptoms follow up: 14 weeks	110 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.11 (0.66 to 1.86)	327 per 1,000	36 more per 1,000 (111 fewer to 281 more)
Withdrawal Symptoms-number of people with anxiety (DESS) assessed with: Discontinuation- Emergent Signs and Symptoms follow up: 14 weeks	110 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	Peto OR 6.90 (0.70 to 68.01)	0 per 1,000	50 more per 1,000 (from 10 fewer to 120 more)[c]
Withdrawal Symptoms-number of people with dizziness (DESS)	110 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	Peto OR 6.90 (0.70 to 68.01)	0 per 1,000	50 more per 1,000

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with low dose pregabalin (short-term)	Risk difference with High dose pregabalin (short-term)
assessed with: Discontinuation- Emergent Signs and Symptoms follow up: 14 weeks					(from 10 fewer to 120 more)[c]
Withdrawal Symptoms- number of people with headache (DESS) assessed with: Discontinuation- Emergent Signs and Symptoms follow up: 14 weeks	110 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 0.67 (0.16 to 2.86)	77 per 1,000	25 fewer per 1,000 (65 fewer to 143 more)
Withdrawal Symptoms- number of people with insomnia (DESS) assessed with: Discontinuation- Emergent Signs and Symptoms follow up: 14 weeks	110 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.34 (0.40 to 4.50)	77 per 1,000	26 more per 1,000 (46 fewer to 269 more)
Withdrawal Symptoms- number of people with nausea (DESS) assessed with: Discontinuation- Emergent Signs and Symptoms follow up: 14 weeks	110 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.20 (0.28 to 5.09)	58 per 1,000	12 more per 1,000 (42 fewer to 236 more)
Withdrawal symptoms (Rebound anxiety) assessed with: Hamilton Anxiety Rating Scale follow up: 14 weeks	110 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 2.69 (0.29 to 25.06)	19 per 1,000	33 more per 1,000 (14 fewer to 463 more)

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with low dose pregabalin (short-term)	Risk difference with High dose pregabalin (short-term)
b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25. The MID for PWC was 0.5 x the control group SD as they were change scores. This was 2.98 for the outcome at 5 weeks, and 2.61 for the outcome at 14 weeks. c. Calculated from risk difference due to zero events in control arm.					

Table 16: Clinical evidence summary: High vs low dose (long-term) gabapentinoids

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with low dose pregabalin (long-term)	Risk difference with High dose pregabalin (long-term)
Withdrawal Symptoms - week 2 after initiating taper (PWC) assessed with: Physician Withdrawal Checklist Scale from: 0 to 60 follow up: 26 weeks	190 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The mean PWC score was 1.7	MD 1.1 higher (0.46 lower to 2.66 higher)
Withdrawal Symptoms (DESS) assessed with: Discontinuation Signs and Symptoms follow up: 26 weeks	203 (1 RCT)	⨁⨁◯◯ LOW [a,b]	RR 1.40 (0.87 to 2.23)	223 per 1,000	89 more per 1,000 (29 fewer to 275 more)
Withdrawal Symptoms- anxiety (DESS) assessed with:	203 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.51 (0.46 to 5.00)	43 per 1,000	22 more per 1,000 (23 fewer to 170 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with low dose pregabalin (long-term)	Risk difference with High dose pregabalin (long-term)
Discontinuation Signs and Symptoms follow up: 26 weeks					
Withdrawal symptoms- headache (DESS) assessed with: Discontinuation Signs and Symptoms follow up: 26 weeks	203 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.44 (0.35 to 5.85)	32 per 1,000	14 more per 1,000 (21 fewer to 155 more)
Withdrawal symptoms- insomnia (DESS) assessed with: Discontinuation Signs and Symptoms follow up: 26 weeks	203 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.40 (0.61 to 3.23)	85 per 1,000	34 more per 1,000 (33 fewer to 190 more)
Withdrawal symptoms (Rebound anxiety) assessed with: Hamilton Anxiety Rating Scale follow up: 26 weeks	203 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	Peto OR 6.62 (0.91 to 47.97)	0 per 1,000	40 more per 1,000 (0 fewer to 80 more)[c]

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25. The MID for the PWC outcome was 0.5* control group SD as they were change scores. This was 2.46 for the 14-week outcome.

c. Calculated from risk difference due to zero events in control arm.

1.1.6.3 Z-drugs

Table 17: Clinical evidence summary: 20mg zolpidem vs 10mg zolpidem

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 10mg Zolpidem	Risk difference with 20mg Zolpidem
Mortality follow up: 22-28 days	80 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	Peto OR 7.29 (0.15 to 372.38)	0 per 1,000	30 more per 1,000 (40 fewer to 90 more)[c]
Withdrawal symptoms assessed with: Narrative report of "no withdrawal symptoms during the second 7-day placebo treatment period". follow up: 22-28 days	74 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	not estimable	0 per 1,000	0 fewer per 1,000 (50 fewer to 50 more)

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25.

c. Calculated from risk difference due to zero events in control arm.

1.1.6.4 Antidepressants

Table 18: Clinical evidence summary: 6mg doxepin vs 3mg doxepin (tricyclic antidepressants)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 3mg Doxepin	Risk difference with 6mg Doxepin
Withdrawal symptoms (Withdrawal signs) assessed with: 3 or more new symptoms in the BWSQ Follow-up: 5 weeks	148 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	Peto OR 0.14 (0.00 to 7.01)	13 per 1,000	10 fewer per 1,000 (50 fewer to 20 more)[c]
Withdrawal symptoms assessed with: Rebound insomnia based on wake time after sleep onset (WASO) criteria experienced over the 2 nights after discontinuation	148 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 3.08 (0.33 to 28.96)	13 per 1,000	28 more per 1,000 (9 fewer to 373 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 3mg Doxepin	Risk difference with 6mg Doxepin
Follow-up: 5 weeks					

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25.

c. Calculated from risk difference due to zero events in intervention arm.

Table 19: Clinical evidence summary: 20mg vortioxetine vs 10mg vortioxetine (other antidepressants)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 10mg Vortioxetine qd	Risk difference with 20mg Vortioxetine qd
Withdrawal symptoms (DESS) assessed with: Discontinuation -Emergent Signs and Symptoms Range of values unclear follow up: 10 weeks	254 (1 RCT)	⊕⊕◯◯ LOW [a b]	-	The mean DESS score was 1.1	MD 0.4 lower (0.92 lower to 0.12 higher)

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.

b. Not downgraded for imprecision as the confidence interval did not cross the MID. The MID for DESS was 1.26 (0.5*control group SD for DESS score)

Table 20: Clinical evidence summary: 10mg vortioxetine vs 5mg vortioxetine (other antidepressants)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 5mg Vortioxetine qd	Risk difference with 10mg Vortioxetine qd
Withdrawal symptoms (DESS) assessed with: Discontinuation-Emergent Signs and Symptoms	250 (1 RCT)	⊕⊕◯◯ LOW [a,b]	-	The mean DESS score was 0.8	MD 0.3 higher (0.28 lower to 0.88 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 5mg Vortioxetine qd	Risk difference with 10mg Vortioxetine qd
Range of values unclear follow up: 10 weeks					

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Not downgraded for imprecision as the confidence interval did not cross the MID. The MID for DESS was 1.11 (0.5*control group SD for DESS score)

Table 21: Clinical evidence summary: 20mg vortioxetine vs 5mg vortioxetine (other antidepressants)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 5mg Vortioxetine qd	Risk difference with 20mg Vortioxetine qd
Withdrawal Symptoms (DESS) assessed with: Discontinuation -Emergent Signs and Symptoms Range of values unclear follow up: 10 weeks	248 (1 RCT)	⨁⨁◯◯ LOW [a b]	-	The mean DESS score was 0.8	MD 0.1 lower (0.59 lower to 0.39 higher)

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Not downgraded for imprecision as the confidence interval did not cross the MID. The MID for DESS was 1.11 (0.5*control group SD for DESS score)

Table 22: Clinical evidence summary: Sertraline vs Venlafaxine (SSRI / other antidepressants)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with venlafaxine SR	Risk difference with Sertraline
Withdrawal symptoms (Deterioration during taper) (ADDS) assessed with: Antidepressant discontinuation scale (unvalidated) Scale from: 0 to 210 follow up: 8-10 weeks	136 (1 RCT)	⨁⨁◯◯ LOW [a]	-	The mean ADDS score was 10.2	MD 2.4 lower (2.79 lower to 2.01 lower)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with venlafaxine SR	Risk difference with Sertraline
Withdrawal symptoms assessed with: Worst severity of discontinuation symptoms (Investigator global assessment); none follow up: 8-10 weeks	129 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.59 (0.67 to 3.77)	113 per 1,000	67 more per 1,000 (37 fewer to 313 more)
Withdrawal symptoms assessed with: Worst severity of discontinuation symptoms (Investigator global assessment); minimal follow up: 8-10 weeks	129 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.35 (0.68 to 2.67)	177 per 1,000	62 more per 1,000 (57 fewer to 296 more)
Withdrawal symptoms assessed with: (Worst severity of discontinuation symptoms (Investigator global assessment); mild) follow up: 8-10 weeks	129 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.87 (0.48 to 1.57)	274 per 1,000	36 fewer per 1,000 (143 fewer to 156 more)
Withdrawal symptoms assessed with: Worst severity of discontinuation symptoms (Investigator global assessment); moderate follow up: 8-10 weeks	129 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.89 (0.56 to 1.40)	387 per 1,000	43 fewer per 1,000 (170 fewer to 155 more)
Withdrawal symptoms assessed with: Worst severity of discontinuation symptoms (Investigator global assessment); severe follow up: 8-10 weeks	129 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	Peto OR 0.12 (0.01 to 1.99)	32 per 1,000	30 fewer per 1,000 (80 fewer to 20 more)[c]
Withdrawal symptoms assessed with: Worst severity of discontinuation symptoms (Investigator global assessment); very severe follow up: 8-10 weeks	129 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	Peto OR 0.12 (0.00 to 6.31)	16 per 1,000	20 fewer per 1,000 (60 fewer to 30 more)[c]

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25. For continuous outcomes the MID was calculated as 0.6 for deterioration during taper (0.5 x SD for change score in control group).

c. Calculated from risk difference due to zero events in intervention arm.

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.1.8 Summary of included economic evidence

None.

1.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.10 Evidence statements

1.1.10.1 Economic

- No relevant economic evaluations were identified.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1 The outcomes that matter most

Dependence

This review aimed to assess the effectiveness of different prescribing strategies (such as the initial prescribing dose or duration), or interventions delivered alongside prescribing, to reduce the risk of the person developing dependence on the prescribed medicine. Therefore, dependence was agreed as a critical outcome. When agreeing the protocol, the committee acknowledged that dependence might not be commonly reported as an outcome, as it is difficult to measure. Therefore, any definition as defined by the study authors was accepted, which could also include measures indicating problems with dependence or addiction, such as early refill requests, shopping behaviour, or measures of medicine misuse.

The medicines of interest also included antidepressants, which are not considered to be dependence forming, unlike the other included medicines. However, any studies reporting dependence on antidepressants were reported, if identified.

Withdrawal

Antidepressants are known to cause withdrawal symptoms, therefore the committee were also interested in the effectiveness of the prescribing strategies or interventions on withdrawal symptoms, as a critical outcome. The committee acknowledged that this would also be influenced by other factors such as the withdrawal strategy, as well as the risk from the initial prescribing strategy.

The other critical outcomes for this review were mortality and health related quality of life. Important outcomes for this review were: use of illicit drugs or alcohol as a replacement to prescribed drugs, non-fatal overdose, patient satisfaction, self-harm or harm to others and symptoms for which the medication was originally prescribed.

Evidence was identified in people prescribed opioids, gabapentinoids, Z-drugs and antidepressants. No evidence was identified in people prescribed benzodiazepines.

Opioids

Dependence was reported as opioid medication discontinuation for non-compliance, opioid misuse (on the current opioid misuse measure score, COMM), uncoordinated opioid use and a diagnosis of opioid abuse. Evidence was also available on withdrawal symptoms in people prescribed and withdrawing from opioids plus ondansetron versus opioids plus placebo. None of the other protocol outcomes were reported.

Gabapentinoids

The only outcome reported was withdrawal symptoms in people prescribed and withdrawing from a higher versus a lower dose.

Z-drugs

Withdrawal symptoms and mortality were reported in people prescribed and withdrawing from a higher versus a lower dose. None of the other protocol outcomes were reported.

Antidepressants

The only outcome reported was withdrawal symptoms in people prescribed and withdrawing from either a higher versus a lower dose, or from sertraline versus venlafaxine.

1.1.11.2 The quality of the evidence

Overall, there was a lack of evidence across all drug classes, with a limited number of prescribing strategies or interventions identified in the literature, and only 1 or 2 outcomes reported for each comparison.

Opioids

The quality of evidence for all of the comparisons and outcomes for opioids were of very low or low quality due to risk of bias and imprecision. The main reason for high or very high risk of bias was due to incomplete outcome reporting (a high number of people who dropped out), along with some comparisons and outcomes also being rated as high risk of bias for selection bias or blinding.

Gabapentinoids

The quality of evidence for a higher versus lower dose, when given for short-term treatment before withdrawal, was of moderate quality for withdrawal symptoms assessed using the physician withdrawal checklist (PWC). The evidence was very low quality for a number of withdrawal symptoms when assessed with the Discontinuation- Emergent Signs and Symptoms checklist (DESS). This was due to evidence being downgraded for risk of bias for all outcomes, and additionally downgraded for imprecision for the DESS withdrawal symptom outcomes.

For a higher versus lower dose, long term before withdrawal, all of the withdrawal symptoms outcomes were downgraded for both risk of bias and imprecision, and were of low or very

low quality. The main reason for high or very high risk of bias was due to selection bias, along with some comparisons and outcomes also being rated as high risk of bias for incomplete outcome reporting.

Z-drugs

The quality of evidence for the comparison of 20mg or 10mg zolpidem, with subsequent withdrawal, was of moderate quality for the occurrence of withdrawal symptoms, due to risk of bias. For mortality, the evidence was of very low quality due to risk of bias and imprecision. The main reason for high or very high risk of bias was due to selection bias, along with some outcomes also being rated as high risk of bias for blinding and outcome reporting.

Antidepressants

The quality of evidence for the comparison of 20mg, 10mg, or 5mg vortioxetine was of low quality, due to risk of bias and imprecision for the occurrence of withdrawal symptoms. For the comparison of sertraline versus venlafaxine, a number of withdrawal symptom measures were reported, with the quality of the evidence being low or very low quality, due to risk of bias and imprecision. The quality of evidence for the comparison of 6mg or 3mg doxepin was of very low quality, due to risk of bias and imprecision for withdrawal symptoms. The main reason for high or very high risk of bias was due to selection bias, along with some comparisons and outcomes also being rated as high risk of bias for incomplete outcome reporting or blinding.

1.1.11.3 Benefits and harms

Opioids

The committee acknowledged that all the studies reported problems associated with dependence, but that these were signs of misuse or abuse rather than dependence per se. They noted that people can be dependent on medicines without showing any problems of dependence such as misuse. Therefore, the committee interpreted this evidence with caution.

One study compared morphine plus ondansetron versus morphine plus placebo. The outcomes reported were withdrawal symptoms after a naloxone-induced withdrawal. Therefore, this study differed from the others in that it was an experimentally induced withdrawal. The committee agreed that it was not usual practice in the UK for ondansetron to be prescribed alongside opioids, and that this study was probably testing the hypothesis that 5HT-3 receptor antagonists (such as ondansetron) may help decrease withdrawal symptoms. There was no clinical difference demonstrated between the groups in terms of withdrawal symptoms when assessed with the objective opioid withdrawal scale. There was, however, a clinical benefit of placebo for withdrawal symptoms when assessed with the subjective opioid withdrawal scale. From the available evidence, the committee found no reason to recommend the use of ondansetron alongside prescribing, to reduce the risk of subsequent withdrawal symptoms.

One study compared MORE (a mindfulness-based intervention) versus the support group. There was no clinical difference in terms of dependence when assessed by the study as opioid misuse (COMM score). This intervention consisted of group mindfulness sessions over 8 weeks. The committee noted the active control condition of the support group in this study which also received 8 weekly group sessions, covering similar themes to the MORE intervention group. The committee agreed that it was likely the control group were receiving benefit from this support group and this may contribute to the lack of difference in effect seen, when compared to the mindfulness intervention in preventing opioid misuse. This was

the only study providing evidence for a psychological intervention alongside prescribing. The committee agreed that this was insufficient evidence to inform a recommendation for psychological interventions to be offered alongside prescribing to limit the risk of dependence. However, the committee discussed the importance of providing the person with support and information at the time of prescribing. From committee experience, this is important in setting expectations with the person about what the medicine can and cannot do, but also can help prevent problems with dependence later down the line.

One study compared escalating versus stable dose. Escalating dose was associated with a clinical benefit in terms of dependence, when assessed by 'opioid medication discontinuation for non-compliance'. The committee discussed that this was counter-intuitive if the assumption is that the escalating dose group end up on higher doses, as from the committee's experience, higher doses tend to lead to more problems with dependence. The data from the study suggested that the final morphine equivalent doses only differed by around 10mg between groups at the end of the study, which the committee agreed was not a clinically meaningful difference in dose, and therefore cast doubt on the reliability of comparisons between these two groups. The committee also noted that it would depend on when dose escalations occurred, during the treatment period, and by how much. Starting at a lower dose and slowly increasing the dose may be better than starting on a dose that is too high for the person. One explanation for the benefit of the escalating dose group is about the control the person has over the medicine. If a person has more control over their dose, then they may feel more comfortable staying at a lower dose, as they know the option to increase is available. The committee also noted that increasing opioid doses too fast can have a cumulative effect and cause respiratory depression. Therefore, in addition to the considerations around the best prescribing strategy to reduce the risk of dependence, there may be considerations within condition-specific guidance around the most efficacious doses that reduce the chance of side effects or adverse effects.

One study compared interventions aimed at the physician responsible for prescribing. The interventions were, providing the physician with patient-specific information, providing the physician with links to education materials, providing the physician with both of these, or usual care. For the majority of these when compared to each other, there was no clinical difference between the groups in terms of development of dependence as assessed by 'uncoordinated opioid use' or 'diagnosis of opioid abuse'. The exception was when providing the physician with both educational materials and patient-specific information, versus usual care. For this comparison there was potentially a clinical benefit from the physician intervention on the subsequent diagnosis of opioid abuse. The committee questioned what the aim of the interventions was, and whether the study was aiming to reduce overall prescribing or influence prescribing behaviour, but that this was not necessarily an intervention to give alongside prescribing intended to limit the individual's risk of dependence. The committee noted they did not have enough evidence to make a recommendation on education for prescribers. However, the committee agreed that it is important that healthcare professionals prescribe within the limits of their competence and expertise, and that the GMC has guidance on good practice in prescribing which highlights this point.

No specific recommendations were made on the basis of the evidence for opioids.

Gabapentinoids

Two studies compared lower (150-300mg/day) versus higher dose (450-600mg/day) pregabalin, for both short-term (6 weeks flexible dose followed by 12 weeks fixed dose) or longer-term treatment (6 weeks flexible dose followed by 24 weeks fixed dose), both followed by a 1-week taper period.

For the short-term treatment study, there was a clinical benefit of the lower dose for withdrawal symptoms when assessed by the number of people with anxiety on the DESS

checklist and the number of people with dizziness on the DESS checklist. There was no clinical difference for the other withdrawal symptoms outcomes including the PWC score, the number of people with symptoms on the DESS checklist, the number of people with rebound anxiety, or the number of people with headache, insomnia or nausea on the DESS checklist.

For the evidence of longer-term treatment, there was a clinical benefit of the lower dose for withdrawal symptoms when assessed by the number of people with symptoms on the DESS checklist and the number of people with rebound anxiety. However, there was no clinical difference for the other withdrawal symptoms outcomes including the PWC score, or the number of people with headache, insomnia or anxiety on the DESS checklist. The committee agreed this suggests that lower doses could result in a lower risk of withdrawal symptoms and agreed this reflected their experience of risk of both dependence and withdrawal with gabapentinoids. The committee noted that, as with other medicines considered in this review, withdrawal symptoms will be influenced by factors other than the initial prescribing strategy alone, and this evidence should be interpreted with caution. See discussion below for the recommendation on prescribing low doses.

Z-drugs

One study compared different doses of zolpidem (20mg and 10mg) given for 3 weeks followed by a subsequent withdrawal. There was no clinical difference between groups for withdrawal symptoms. However, it was noted that the study only reported narratively the number of people with ‘no withdrawal symptoms’, which was no one in either group. Indicating that all the participants in both groups experienced at least one withdrawal symptom, but conclusions could not be drawn on whether one group experienced more or less than the other. There was a clinical benefit of the group receiving 10mg of zolpidem for mortality, due to one death from pneumonia (post-treatment) in the 20mg group. The committee agreed they could not draw any firm conclusions on the use of different Z-drug doses from this study and no recommendations were made from this evidence.

Antidepressants

Three antidepressant studies reported withdrawal symptoms from antidepressants, each was a different comparison and reported a different measure of withdrawal symptom occurrence or severity (for example, total DESS score, BWSQ, rebound insomnia, and the antidepressant discontinuation scale) and therefore these could not be pooled. The committee noted that the antidepressant discontinuation scale was not validated, but that other withdrawal symptom outcomes were available for the relevant comparison. One compared different doses of vortioxetine (20mg, 10mg and 5mg) given for 8 weeks followed by a subsequent 2-week withdrawal period. One compared doxepin 6mg versus 3mg, given for 5 weeks followed by an abrupt withdrawal. Finally, one study compared sertraline with venlafaxine, given for 8 weeks followed by a 2-week taper period. There was no clinical difference in withdrawal symptoms in any of these included studies or comparisons, with one exception; a clinical benefit of sertraline for the number of people experiencing no or minimal discontinuation symptoms as assessed using investigator global assessment when compared to withdrawal from venlafaxine.

The committee noted that in each of these studies antidepressants were prescribed for a relatively short time period which did not reflect clinical practice where antidepressants would be given for much longer before being withdrawn. Therefore, it was thought likely that the withdrawal symptoms measured in these studies could underestimate occurrence in practice. The committee also acknowledged that other factors would influence withdrawal symptoms, not only the initial prescribing strategy. In particular, the withdrawal or dose reduction strategy would influence the risk of withdrawal symptoms. The committee agreed the withdrawal strategies used in the studies were not reflective of clinical practice, as antidepressants were either withdrawn abruptly or over a short 2-week period. Therefore, the

committee did not base any recommendations on the evidence from withdrawal symptoms outcomes alone.

Considerations across all medicine classes

The committee agreed that it was difficult to base recommendations on the available evidence due to the limited evidence base and the concerns in interpretation. Furthermore, all dependence outcomes were reported by the studies as misuse or abuse outcomes. Therefore, it was difficult to determine which prescribing strategies or interventions may be effective in limiting the risk of dependence. They also noted that the majority of the studies reporting these outcomes of misuse are from the US where there are different prescribing practices and so the evidence was not necessarily generalisable to the UK setting.

For withdrawal symptoms, the committee also discussed that, at the stage of initial prescribing, the focus is more likely to be on the efficacy of the particular medicine and prescribing strategy, for the given indication. At this stage, the committee agreed it is important to also consider the risk of dependence of that prescribing strategy, but that withdrawal symptoms may be less impacted by the initial prescribing strategy, because if the medicine is reduced and withdrawn safely, this will decrease the risk of withdrawal symptoms. However, it was also noted from committee experience, that prescribing strategies that have a lower risk of dependence (such as prescribing at a lower dose for shorter periods) may also result in less problems with withdrawal. There was also an indication from some of the evidence that prescribing with lower doses was associated with a benefit on withdrawal symptoms outcomes upon subsequent withdrawal.

There was no evidence identified in the literature on interventions such as educational or support interventions that could be given to the person alongside prescribing, to limit the risks of dependence. The committee agreed that one of the most important aspects in terms of safe prescribing and avoiding future problems with dependence, is to give the person information and support before prescribing, in order to structure expectations. Therefore, the committee made recommendations on the information that should be given before starting treatment, including a management plan that should be given to the person prior to starting treatment. This was based both on the experience and consensus opinion of the committee and supported by evidence review A, the Patient Information and Support chapter of this guideline. For more detail, see the section on Patient Information and Support.

The committee agreed that although the evidence was limited, there was some indication from the evidence on gabapentinoids that prescribing at a lower dose may reduce the risk of withdrawal symptoms, albeit with the caveats of the limitations in this evidence as described above. Evidence was not available for the effect of prescribed dose on subsequent dependence to the medicine. However, there was some evidence from review E, the Risk Factors evidence review for this guideline demonstrating that higher opioid doses may increase the risk of problems associated with dependence. The committee agreed that this was consistent with their clinical experience that a person should be prescribed the lowest effective dose in order to reduce the risk of developing dependence. This would involve starting at the lowest dose likely to be safe and effective, and having a period of titration and observation to find the person's lowest effective dose. The committee agreed (by consensus) that there was no reason that this recommendation should not apply to all the medicine classes.

No evidence was identified in the literature on comparisons of different prescribing durations. From their clinical experience, the committee agreed that longer duration of use of these medicines is more likely to result in dependence. The committee discussed that some people may be on these medicines longer than they need to be. There was also evidence from review E, the Risk Factors chapter of this guideline, that long-term opioid therapy is a risk factor for dependence and abuse related behaviours to opioids (see section on Risk Factors), and that being on a higher daily dose long-term increased the risk further. Based on

this evidence and the committee's consensus, it was agreed that a recommendation should be made for regular reviews, to ensure that the benefits of the medicine continue to outweigh the potential harms, to avoid medicines being used for longer than they are needed and in order to avoid risks of dependence from long-term use. The committee agreed based on consensus that it was important to take particular care during dose adjustments and not to automatically increase dose due to lack of response. They noted that although pharmacological tolerance is a property of the medicines considered, if a person has an initially favourable response which then diminishes, it is rarely helpful to increase the dose to try to restore the clinical benefit. They considered such an approach increases the risk of harms, and the loss of benefit is rarely due to pharmacological tolerance, but due to other factors.

It was highlighted that for some people long-term use at safe doses can be appropriate if they are beneficial. The committee agreed the trade-off between the risks associated with problematic use or dependence and the clinical benefit the person derives from the medication should determine prescribing decisions and it may be clinically appropriate for medicines to continue being prescribed for as long as they continue to be helpful. It was also noted that within the content of the management plan, regular reviews should pick up when it might be an appropriate time to stop a medicine. Discussions about the continued effectiveness of the medicine should be initiated at the point of initial prescribing and again at each encounter. This should be captured within the management plan. The point was raised that people may assume their prescriber will tell them when a medicine is no longer needed and may not necessarily know themselves. The information given along with the management plan may give people more awareness of this.

In addition, it was noted that someone should not be given multiple repeat prescriptions or be given a long duration of prescription without review, as this could lead to people remaining on medicines longer than necessary. There was also some qualitative evidence within the Patient Information and Support chapter (Evidence review A) showing that health care professionals emphasised the importance of setting short-term timeframes for the prescription of benzodiazepines. The committee discussed that when there are concerns around a person's risk of dependence, it would be best practice to give shorter prescriptions. In addition, a shorter duration of prescription may also allow for an early assessment of whether the medicine is effective. However, the committee agreed it wasn't possible to recommend a minimum length as it would vary according to medicine and condition being treated, therefore, the committee recommended that the duration of each prescription should be given for a duration reflecting the plan for review. Some of the medicines of interest are controlled drugs and the committee discussed that it is also important to highlight that the length of each prescription should be in line with relevant legislation.

1.1.11.4 Cost effectiveness and resource use

No economic evidence was found for this question.

The committee decided to make recommendations reflecting best practice when prescribing medicines and emphasised the need for determining the lowest effective dose to minimise the risk of dependence and harms. Higher doses at initial prescription was found in the clinical review to be related to increased withdrawal symptoms for gabapentinoids. This was supported by evidence in the risk factors review, demonstrating dose to be a risk factor for problems associated with dependence.

The committee noted that there is currently heterogeneity in prescribing strategies across different Trusts and these recommendations should encourage prescribers to adopt best practice. Longer consultations or additional follow-up may be needed to allow for a full discussion of treatments and treatment options when starting or reviewing a medicine. However, encouraging effective discussions, at the time of prescriptions, about risk and benefits could reduce unnecessary prescribing for people who could potentially experience

harms, dependence or withdrawal symptoms in the future. This, in turn, should reduce costs to the NHS and ultimately improve its efficiency.

1.1.11.5 Other factors the committee took into account

The committee strongly agreed that every effort should be made to reach a shared decision with the person, however there are instances when agreement cannot be reached, and the healthcare professional believes the prescribing is particularly unsafe and is not in the person's best interest. The committee noted that the prescriber has a professional obligation to not continue something which is unsafe. It was agreed that guidance should be in line with advice on 'handling patient requests for medicines you don't think will benefit them' in the General Medical Council guidance: good practice in prescribing and managing medicines and devices. The reasons for the decision should be explained to the person and documented, and the person should be offered a second opinion.

The committee discussed situations that can occur in clinical practice, such as prescribing at the suggestion of another health care professional, taking over care for or becoming the prescriber of a person already taking a medicine. The committee agreed that the new prescriber should decide if the current medicine and dose are in the best interest of the person. For this decision to be made, it is essential that the health care professional has sufficient knowledge of the person's health and personal circumstances. This is in line with good practice in prescribing guidance set out by the GMC. Even in cases where continued prescribing is deemed not to be in the person's best interest, it would not be appropriate to abruptly withdraw the medicine, but rather that careful withdrawal would be advised in line with the recommendations in section 1.5 of this guideline: Withdrawing Medicines associated with dependence and withdrawal symptoms. There were concerns around the anxiety a person could feel if a healthcare professional takes over their prescribing and decides that the medicine should be stopped. To avoid this anxiety, it is important when prescribing is inherited that the person is seen promptly, and the information provided when starting treatment is reiterated to help establish the new therapeutic relationship and employ the principles of shared decision making. It was highlighted that there would be additional considerations if a person was going into prison, and therefore their care was being transferred to a new prescriber.

The committee emphasised the importance of continuity of care when prescribing recommendations are made in different settings, for example in secondary care with the recommendation to be prescribed in primary care. To facilitate this, they agreed that it is important for prescribers to provide clear information on the management plan and how to follow up. They also agreed that the person should be informed that this is only a recommendation to their primary care prescriber, as their primary care provider may wish to make a decision about whether the prescribed medicine is the best option for the person, potentially based on more in-depth information about the patient from a primary care perspective. In some situations, a medicine may be prescribed in secondary care to be reviewed in primary care. In these cases, it should be explained to the person that the medicine will be reviewed in primary care and may not be prescribed long term. Where primary care prescribers do not agree that a prescription recommended by a specialist is appropriate for prescription in primary care, then this should be discussed with the specialist to agree how the prescribing will be managed. They should involve the person in these discussions and ensure they are made aware if prescribing needs to be delayed while discussions continue.

The committee discussed that ensuring one person has overall responsibility for the prescribing could be difficult in a fast-flowing environment when people don't always see the same GP or healthcare professional each time. In cases when the prescriber is unable to review the person, continuity of care is extremely important and there should be a consistent line of communication. The management plan should also be clearly documented in the person's medical record, setting out aims and directions that everyone can follow as part of a

multidisciplinary team. They noted that pharmacists are likely to play a key role in leading prescribing and can help ensure continuity of care in medicines reviews. It was noted that this is discussed in recommendations for structured medicines reviews in the NICE Medicines Optimisation guideline and so the committee agreed to cross refer to this section of that guideline.

The committee discussed that take home naloxone was commonly used in people with known current or history or substance misuse and discussed whether this might be a strategy that could be used when prescribing opioids to help prevent problems associated with dependence and withdrawal. However, it was noted that there is no evidence that this is an effective strategy for dependence on prescribed medicines, and although it is a strategy that is beginning to be used in the US, there is much more cross over in the US setting of people with prescription drug dependence and substance misuse problems. Therefore, this is likely to be a context-dependent strategy that is less likely to be relevant in the UK setting. The committee therefore agreed not to include a research recommendation on this topic.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.2.7, 1.3.4, 1.3.5, 1.3.7, 1.3.8, 1.3.9, 1.3.10, 1.3.11, 1.3.12, 1.3.13 and 1.3.14. No research recommendations were made from this evidence review. Other evidence supporting these recommendations can be found in the evidence reviews on E Risk Factors for Dependence or Withdrawal; F Monitoring.

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Appendices

Appendix A Review protocols

A.1 Review protocol for optimum prescribing strategies or interventions delivered alongside prescribing

Field	Content
PROSPERO registration number	CRD42020188353
Review title	Optimum prescribing strategies or interventions delivered alongside prescribing, to limit the risk of dependence on opioids, benzodiazepines, gabapentinoids and Z-drugs or withdrawal symptoms associated with antidepressants
Review question	What are the optimum prescribing strategies or interventions delivered alongside prescribing, to limit the risk of dependence or withdrawal symptoms?
Objective	To identify the optimum prescribing strategies or interventions delivered alongside prescribing, to limit the risk of dependence on opioids, benzodiazepines, gabapentinoids and Z-drugs or withdrawal symptoms associated with antidepressants.
Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos • Health and Evidence • HTA Searches will be restricted by: • English language studies

	• Human studies • Letters and comments are excluded **Other searches**: Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before the final committee meeting, and further studies retrieved for inclusion if relevant. For full search strategies see A.2.
Condition or domain being studied	Dependence on prescribed opioids, benzodiazepines, Z-drugs and gabapentinoids or withdrawal symptoms associated with antidepressants.
Population	Inclusion: adults (≥18 years) being initiated on or currently being prescribed medicines associated with dependence or withdrawal symptoms (opioids for chronic pain, benzodiazepines, Z-drugs, gabapentinoids, antidepressants). This will include people being prescribed these medicines either at initiation or being re-prescribed. However, if the population are already taking the medicine, the majority (at least 80%) should be shown not to have behaviours related to dependence at the start of the study (if it is unclear, the study will be excluded). **Stratification** Drug class • Opioids • Benzodiazepines, • Z-drugs • Gabapentinoids • Antidepressants (further stratified by SSRIs, MAOIs, tricyclics, others). No other population strata **Exclusions:** Children and young people (<18 years) People being prescribed opioids for end-of-life care, acute pain, cancer pain. Use of gabapentinoids when prescribed for epilepsy.

	People taking the above drugs that have not been prescribed for their own use. **Decision rules for inclusion of primary studies** If study includes prescribed medicines and non-prescribed / OTC medicines, the study will only be included if at least 80% were prescribed. If the study includes people <18 years old, the study will only be included if at least 80% of people were ≥18 years old.
Intervention	The following interventions are examples, and other interventions will be included if they are prescribing strategies or interventions aimed at reducing the risk of dependence or preventing dependence. • Starting dose principles (e.g., lower initial dose), • initial prescribing duration (e.g., trial for short duration), • initial prescription quantity or duration, • rate of upward titration, • trials of efficacy and stopping rules if lack of efficacy, • polydrug use principles (e.g., sequencing – stopping one drug due to lack of efficacy before adding another), • providing patient information, education or support when prescribing, around the management of potentially dependence forming medicines, as an intervention to limit dependence (including comparisons of different forms the information is given in), • a medication contract / agreement, • different formulation and/or route of medication: e.g., immediate release, slow release (including slow-release routes such as transdermal patches), • half-life (for benzodiazepines, e.g., long or short half-life), • use of different drugs within a class
Comparator	Any prescribing strategy compared to another, or to usual care
Types of study to be included	Randomised controlled trials Comparative non-randomised or cohort studies Systematic review of randomised controlled trials or non-randomised comparative studies. For a systematic review to be included it must be conducted to the same methodological standard as NICE guideline reviews.

	If sufficient details are not provided to include a relevant systematic review, the review will be used for citation searching. **Exclusions:** Before and after studies Non-comparative cohort studies Other non-comparative evidence
Other exclusion criteria	Non-NHS prescribed medicines (for the full list of medicines to be included in the guideline see Appendix K) Medicines prescribed for end-of-life care, cancer pain or acute pain Over-the-counter medicines Use of gabapentinoids when prescribed for epilepsy Antipsychotic and stimulant medicines. Medicines to treat drug misuse disorders (e.g., methadone and buprenorphine when prescribed for withdrawal from illicit drugs). Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
Context	This will cover any setting in which one of the above-mentioned medicines are being prescribed. As this is an overarching guideline covering many different conditions, it needs to cover all settings.
Primary outcomes (critical outcomes)	Validated HRQOL (continuous outcome), including: • Physical health • Psychological health • Social functioning Mortality (dichotomous or time-to-event outcome, all-cause mortality and breakdown of overdose or suicide related mortality) Dependence on the prescribed medicine (dichotomous outcome, accept any definition as defined by the study (may also include measures suggesting dependence or addiction, examples to include: early refill requests, loss of prescriptions, drug shopping behaviour, prescription misuse)) Withdrawal symptoms including rebound symptoms / intensity or duration of withdrawal syndrome (dichotomous or continuous outcome, as defined by the study)

	Report outcomes at post-intervention and longest follow-up
Secondary outcomes (important outcomes)	Non-fatal overdose (dichotomous outcome) Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs (dichotomous outcome) Patient Satisfaction (dichotomous or continuous outcome) Self-harm or harm to others (dichotomous outcome) Increase in symptoms for which the medication was originally prescribed (dichotomous or continuous outcome, as reported by the study e.g., numerical rating scale or visual analogue scale for pain) ***Report outcomes at post-intervention and longest follow-up***
Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. An in-house developed database; EviBase, will be used for data extraction. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately

	• a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.	
Strategy for data synthesis	Drugs will be pooled within classes stated in the population and antidepressants pooled by sub-class of type of antidepressant. Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.	
Analysis of sub-groups	**Subgroups that will be investigated if heterogeneity is present:** Gabapentin and pregabalin will be pooled in the analysis as ‘gabapentinoids’ unless heterogeneity is observed.	
Type and method of review	☒	Intervention

	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	
Review team members	From the National Guideline Centre: Serena Carville, Guideline lead Emily Terrazas-Cruz, Senior systematic reviewer Melina Vasileiou, Senior systematic reviewer Alfredo Mariani, Health economist Elizabeth Pearton, Information specialist Tamara Diaz, Project Manager	
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	

Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10141
Other registration details	n/a
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020188353
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Details of existing review of same topic by same authors	None
Additional information	None
Details of final publication	www.nice.org.uk

A.2 Review protocol for health economics

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[91] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

	• OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later but that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

This literature search strategy was used for the following review:

- Optimum prescribing strategies or interventions delivered alongside prescribing, to limit the risk of dependence on opioids, benzodiazepines, gabapentinoids and Z-drugs or withdrawal symptoms associated with antidepressants

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[91] For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate and where possible English language limits

Table 23: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 15 June 2021	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments)
Embase (OVID)	1974 – 15 June 2021	Randomised controlled trials Systematic review studies Observational studies

Database	Dates searched	Search filter used
		Exclusions (animal studies, letters, comments)
The Cochrane Library (Wiley)	Cochrane Reviews to 2021 Issue 6 of 12 CENTRAL to 2021 Issue 6 of 12	None
Epistemonikos (The Epistemonikos Foundation)	Inception - 15 June 2021	English
Health and Evidence	Inception – 15 June 2021	None

Medline (Ovid) search terms

1.	*substance-related disorders/ or *narcotic-related disorders/
2.	*Substance Withdrawal Syndrome/
3.	exp Inappropriate Prescribing/
4.	*Medical Overuse/
5.	exp Prescription Drug Misuse/
6.	exp Deprescriptions/
7.	Medication Therapy Management/
8.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) adj2 (drug* or medicine* or medicat* or medical* or pharm*)).ti,ab.
9.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw*) adj3 (prescription* or prescrib*)).ti,ab.
10.	(addict* adj3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)).ti,ab.
11.	(deprescription* or de-prescription* or deprescrib* or de-prescrib*).ti,ab.
12.	((therap* or treat*) adj2 (manag* or substit*)).ti,ab.
13.	((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) adj2 symptom*).ti,ab.
14.	((drug* or medic*) adj2 (prescription* or prescrib*)).ti,ab.
15.	or/1-14
16.	((withdraw* or prescription* or prescrib*) adj2 opi*).ti,ab.
17.	Opiate Substitution Treatment/ or *Opioid-related disorders/
18.	or/16-17
19.	letter/
20.	editorial/
21.	news/
22.	exp historical article/
23.	Anecdotes as Topic/
24.	comment/
25.	case report/
26.	(letter or comment*).ti.
27.	or/19-26
28.	randomized controlled trial/ or random*.ti,ab.

29.	27 not 28
30.	animals/ not humans/
31.	exp Animals, Laboratory/
32.	exp Animal Experimentation/
33.	exp Models, Animal/
34.	exp Rodentia/
35.	(rat or rats or mouse or mice or rodent*).ti.
36.	or/29-35
37.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
38.	15 not (36 or 37)
39.	limit 38 to English language
40.	18 not (36 or 37)
41.	limit 40 to English language
42.	exp Narcotics/
43.	((analgesic* adj3 narcotic) or (opioid* or opiate*)).ti,ab.
44.	(alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*).ti,ab.
45.	(z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon).ti,ab.
46.	Zolpidem/ or Eszopiclone/
47.	(generation adj3 hypnotic*).ti,ab.
48.	exp Benzodiazepines/
49.	(benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam).ti,ab.
50.	exp Antidepressive Agents/
51.	(antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*).ti,ab.
52.	exp Flupenthixol/
53.	(Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine).ti,ab.
54.	(5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine).ti,ab.
55.	(Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine).ti,ab.

56.	gabapentin/ or pregabalin/
57.	(gabapentin* or pregabalin*).ti,ab.
58.	or/42-57
59.	39 and 58
60.	41 or 59
61.	randomized controlled trial.pt.
62.	controlled clinical trial.pt.
63.	randomi#ed.ab.
64.	placebo.ab.
65.	randomly.ab.
66.	clinical trials as topic.sh.
67.	trial.ti.
68.	or/61-67
69.	Meta-Analysis/
70.	Meta-Analysis as Topic/
71.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
72.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
73.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
74.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
75.	(search* adj4 literature).ab.
76.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
77.	cochrane.jw.
78.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
79.	or/69-78
80.	Epidemiologic studies/
81.	Observational study/
82.	exp Cohort studies/
83.	(cohort adj (study or studies or analys* or data)).ti,ab.
84.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
85.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
86.	Controlled Before-After Studies/
87.	Historically Controlled Study/
88.	Interrupted Time Series Analysis/
89.	(before adj2 after adj2 (study or studies or data)).ti,ab.
90.	exp case control study/
91.	case control*.ti,ab.
92.	Cross-sectional studies/
93.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
94.	or/80-93
95.	60 and (68 or 79 or 94)

Embase (Ovid) search terms

1.	*drug dependence/
2.	*withdrawal syndrome/
3.	exp inappropriate prescribing/
4.	deprescription/
5.	exp prescription drug misuse/
6.	medication therapy management/
7.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) adj2 (drug* or medicine* or medicat* or medical* or pharm*)).ti,ab.
8.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw*) adj3 (prescription* or prescrib*)).ti,ab.
9.	(addict* adj3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)).ti,ab.
10.	(deprescription* or de-prescription* or deprescrib* or de-prescrib*).ti,ab.
11.	((therap* or treat*) adj2 (manag* or substit*)).ti,ab.
12.	((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) adj2 symptom*).ti,ab.
13.	((drug* or medic*) adj2 (prescription* or prescrib*)).ti,ab.
14.	or/1-13
15.	((withdraw* or prescription* or prescrib*) adj2 (opioid* or opiate*)).ti,ab.
16.	*benzodiazepine dependence/
17.	Opiate Substitution Treatment/
18.	or/15-17
19.	letter.pt. or letter/
20.	note.pt.
21.	editorial.pt.
22.	case report/ or case study/
23.	(letter or comment*).ti.
24.	or/19-23
25.	randomized controlled trial/ or random*.ti,ab.
26.	24 not 25
27.	animal/ not human/
28.	nonhuman/
29.	exp Animal Experiment/
30.	exp Experimental Animal/
31.	animal model/
32.	exp Rodent/
33.	(rat or rats or mouse or mice or rodent*).ti.
34.	or/26-33
35.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
36.	14 not (34 or 35)
37.	limit 36 to English language
38.	18 not (34 or 35)
39.	limit 38 to English language

40.	*narcotic agent/
41.	*alphaprodine/ or *buprenorphine/ or *codeine/ or *dextromoramide/ or *dextropropoxyphene/ or *diamorphine/ or *dihydrocodeine/ or *dihydromorphine/ or *dipipanone/ or *ethylmorphine/ or *hydrocodone/ or *hydromorphone/ or *levorphanol/ or *methadone/ or *morphine/ or *oxycodone/ or *pethidine/ or *tapentadol/ or *tilidine/
42.	*alfentanil/ or *butorphanol/ or *cocodamol/ or *fentanyl/ or *meptazinol/ or *oxymorphone/ or *opiate/ or *pentazocine/ or *phenazocine/ or *remifentanil/ or *sufentanil/ or *tramadol/ or *trimeperidine/
43.	((analgesic* adj3 narcotic) or (opioid* or opiate*)).ti,ab.
44.	(alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*).ti,ab.
45.	(z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon).ti,ab.
46.	*zolpidem/ or *zopiclone/ or *eszopiclone/ or *zaleplon/
47.	(generation adj3 hypnotic*).ti,ab.
48.	*benzodiazepine derivative/ or *alprazolam/ or *benzodiazepine/ or *chlordiazepoxide/ or *clobazam/ or *clonazepam/ or *diazepam/ or *flurazepam/ or *loprazolam/ or *lorazepam/ or *lormetazepam/ or *midazolam/ or *nitrazepam/ or *olanzapine/ or *oxazepam/ or *temazepam/
49.	(benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam).ti,ab.
50.	exp *antidepressant agent/
51.	(antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*).ti,ab.
52.	*flupentixol/
53.	(Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine).ti,ab.
54.	(5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine).ti,ab.
55.	(Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine).ti,ab.
56.	*pregabalin/ or *gabapentin/
57.	(gabapentin* or pregabalin*).ti,ab.
58.	or/40-57
59.	37 and 58
60.	39 or 59
61.	random*.ti,ab.

62.	factorial*.ti,ab.
63.	(crossover* or cross over*).ti,ab.
64.	((doubl* or singl*) adj blind*).ti,ab.
65.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
66.	crossover procedure/
67.	single blind procedure/
68.	randomized controlled trial/
69.	double blind procedure/
70.	or/63-71
71.	systematic review/
72.	Meta-Analysis/
73.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
74.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
75.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
76.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
77.	(search* adj4 literature).ab.
78.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
79.	cochrane.jw.
80.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
81.	or/73-82
82.	Clinical study/
83.	Observational study/
84.	family study/
85.	longitudinal study/
86.	retrospective study/
87.	prospective study/
88.	cohort analysis/
89.	follow-up/
90.	cohort*.ti,ab.
91.	89 and 90
92.	(cohort adj (study or studies or analys* or data)).ti,ab.
93.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
94.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
95.	(before adj2 after adj2 (study or studies or data)).ti,ab.
96.	exp case control study/
97.	case control*.ti,ab.
98.	cross-sectional study/
99.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
100.	or/82-88,91-99
101.	60 and (70 or 81 or 100)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Substance-Related Disorders] this term only
#2.	MeSH descriptor: [Narcotic-Related Disorders] this term only
#3.	MeSH descriptor: [Substance Withdrawal Syndrome] this term only
#4.	MeSH descriptor: [Inappropriate Prescribing] explode all trees
#5.	MeSH descriptor: [Medical Overuse] this term only
#6.	MeSH descriptor: [Deprescriptions] 1 tree(s) exploded
#7.	MeSH descriptor: [Prescription Drug Misuse] explode all trees
#8.	MeSH descriptor: [Medication Therapy Management] this term only
#9.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) NEAR/2 (drug* or medicine* or medicat* or medical* or pharm*)):ti,ab
#10.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw*) NEAR/3 (prescription* or prescrib*)):ti,ab
#11.	(addict* NEAR/3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)):ti,ab
#12.	(deprescription* or de-prescription* or deprescrib* or de-prescrib*):ti,ab
#13.	((therap* or treat*) NEAR/2 (manag* or substit*)):ti,ab
#14.	((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) NEAR/2 symptom*):ti,ab
#15.	((drug* or medic*) NEAR/2 (prescription* or prescrib*)):ti,ab
#16.	(OR #1-#15)
#17.	((withdraw* or prescription* or prescrib*) near/2 (opioid* or opiate*)):ti,ab
#18.	MeSH descriptor: [Opiate Substitution Treatment] this term only
#19.	MeSH descriptor: [Opioid-Related Disorders] this term only
#20.	MeSH descriptor: [Narcotics] explode all trees
#21.	(OR #17-#20)
#22.	((analgesic* NEAR/3 narcotic NEAR/3 agent*) or (opioid* or opiate*)):ti,ab
#23.	(alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*):ti,ab
#24.	(z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon):ti,ab
#25.	MeSH descriptor: [Zolpidem] this term only
#26.	MeSH descriptor: [Eszopiclone] this term only
#27.	(generation NEAR/3 hypnotic*):ti,ab
#28.	MeSH descriptor: [Benzodiazepines] explode all trees
#29.	(benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam):ti,ab
#30.	MeSH descriptor: [Antidepressive Agents] explode all trees
#31.	(antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and

	norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*):ti,ab
#32.	MeSH descriptor: [Flupenthixol] explode all trees
#33.	(Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine):ti,ab
#34.	(5 Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine):ti,ab
#35.	(Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine):ti,ab
#36.	MeSH descriptor: [Gabapentin] this term only
#37.	MeSH descriptor: [Pregabalin] this term only
#38.	(gabapentin* or pregabalin*):ti,ab
#39.	(OR #22-#38)
#40.	#16 AND #39
#41.	#21 or #40

Epistemonikos search terms

1.	(advanced_title_en:((advanced_title_en:(("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses)) OR advanced_abstract_en:(("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses)))) OR advanced_abstract_en:((advanced_title_en:(("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses)) OR advanced_abstract_en:(("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses))))) AND (advanced_title_en:((opioid* OR opiate* OR narcotic* OR alfentanil* OR alphaprodine* OR buprenorphine* OR butorphanol* OR codeine* OR co-codamol* OR dextromoramide* OR dextropropoxyphene* OR diamorphine* OR dihydrocodeine* OR dihydromorphine* OR dipipanone* OR ethylmorphine* OR fentanyl* OR heroin* OR hydrocodone* OR hydromorphone* OR levorphanol* OR meperidine* OR meptazinol* OR methadone* OR morphine* OR oxycodone* OR oxymorphone* OR papaveretum* OR pentazocine* OR pethidine* OR phenazocine* OR promedol* OR remifentanil* OR sufentanil* OR tapentadol* OR tilidine* OR tramadol* OR z drug* OR z hypnotic* OR non-benzodiazepin* OR nonbenzodiazepin* OR imidazopyridines OR cyclopyrrolones OR pyrazolopyrimidines OR zolpidem OR zopiclone OR eszopiclone OR zaleplon OR benzodiazepin* OR bzd OR Alprazolam OR Chlordiazepoxide OR Clobazam OR Clonazepam OR Diazepam OR Flurazepam OR Loprazolam OR Lorazepam OR Lormetazepam OR Midazolam OR Nitrazepam OR Olanzapine OR Oxazepam OR Temazepam OR antidepress* OR anti depress* OR thymoanaleptic* OR thymoleptic* OR MAOI* OR NDRI* OR SSRI* OR SNRI* OR SNORI* OR SARI* OR RIMA* OR tricyclic* OR TCA* OR tetracyclic* OR TeCA* OR Agomelatine OR Aripiprazole OR Benactyzine OR Clorgyline OR Deanol OR Desvenlafaxine* OR Duloxetine* OR Flupentixol OR Iproniazid OR Isocarboxazid OR Levomilnacipran OR Lithium* OR Mirtazapine OR Moclobemide OR Nialamide OR Phenelzine OR Pizotyline OR Quetiapine* OR Reboxetine OR Rolipram OR Selegiline OR Sertraline OR Tranylcypromine OR Vilazodone* OR Vortioxetine OR 5-Hydroxytryptophan OR

	Amisulpride OR Bupropion OR Citalopram OR Escitalopram OR Fluoxetine OR Fluvoxamine OR Maprotiline OR Mianserin OR Paroxetine OR Quipazine OR Ritanserin OR Sulpiride OR Trazodone OR Tryptophan OR Venlafaxine OR Viloxazine OR Amitriptyline OR Amoxapine OR Clomipramine OR Desipramine OR Dothiepin OR Dosulepin OR Doxepin OR Imipramine OR Iprindole OR Lofepramine OR Nefazodone OR Nortriptyline OR Opipramol OR Protriptyline OR Trimipramine OR gabapentin* OR pregabalin*)) OR advanced_abstract_en:((opioid* OR opiate* OR narcotic* OR alfentanil* OR alphaprodine* OR buprenorphine* OR butorphanol* OR codeine* OR co-codamol* OR dextromoramide* OR dextropropoxyphene* OR diamorphine* OR dihydrocodeine* OR dihydromorphine* OR dipipanone* OR ethylmorphine* OR fentanyl* OR heroin* OR hydrocodone* OR hydromorphone* OR levorphanol* OR meperidine* OR meptazinol* OR methadone* OR morphine* OR oxycodone* OR oxymorphone* OR papaveretum* OR pentazocine* OR pethidine* OR phenazocine* OR promedol* OR remifentanil* OR sufentanil* OR tapentadol* OR tilidine* OR tramadol* OR z drug* OR z hypnotic* OR non-benzodiazepin* OR nonbenzodiazepin* OR imidazopyridines OR cyclopyrrolones OR pyrazolopyrimidines OR zolpidem OR zopiclone OR eszopiclone OR zaleplon OR benzodiazepin* OR bzd OR Alprazolam OR Chlordiazepoxide OR Clobazam OR Clonazepam OR Diazepam OR Flurazepam OR Loprazolam OR Lorazepam OR Lormetazepam OR Midazolam OR Nitrazepam OR Olanzapine OR Oxazepam OR Temazepam OR antidepress* OR anti depress* OR thymoanaleptic* OR thymoleptic* OR MAOI* OR NDRI* OR SSRI* OR SNRI* OR SNORI* OR SARI* OR RIMA* OR tricyclic* OR TCA* OR tetracyclic* OR TeCA* OR Agomelatine OR Aripiprazole OR Benactyzine OR Clorgyline OR Deanol OR Desvenlafaxine* OR Duloxetine* OR Flupentixol OR Iproniazid OR Isocarboxazid OR Levomilnacipran OR Lithium* OR Mirtazapine OR Moclobemide OR Nialamide OR Phenelzine OR Pizotyline OR Quetiapine* OR Reboxetine OR Rolipram OR Selegiline OR Sertraline OR Tranylcypromine OR Vilazodone* OR Vortioxetine OR 5-Hydroxytryptophan OR Amisulpride OR Bupropion OR Citalopram OR Escitalopram OR Fluoxetine OR Fluvoxamine OR Maprotiline OR Mianserin OR Paroxetine OR Quipazine OR Ritanserin OR Sulpiride OR Trazodone OR Tryptophan OR Venlafaxine OR Viloxazine OR Amitriptyline OR Amoxapine OR Clomipramine OR Desipramine OR Dothiepin OR Dosulepin OR Doxepin OR Imipramine OR Iprindole OR Lofepramine OR Nefazodone OR Nortriptyline OR Opipramol OR Protriptyline OR Trimipramine OR gabapentin* OR pregabalin*)))

Health and evidence

1.	[(("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses) OR abstract:("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses)) AND ((opioid* OR opiate* OR narcotic* OR alfentanil* OR alphaprodine* OR buprenorphine* OR butorphanol* OR codeine* OR co-codamol* OR dextromoramide* OR dextropropoxyphene* OR diamorphine* OR dihydrocodeine* OR dihydromorphine* OR dipipanone* OR ethylmorphine* OR fentanyl* OR heroin* OR hydrocodone* OR hydromorphone* OR levorphanol* OR meperidine* OR meptazinol* OR methadone* OR morphine* OR oxycodone* OR oxymorphone* OR papaveretum* OR pentazocine* OR pethidine* OR phenazocine* OR promedol* OR remifentanil* OR sufentanil* OR tapentadol* OR tilidine* OR tramadol* OR z drug* OR z hypnotic* OR non-benzodiazepin* OR nonbenzodiazepin* OR imidazopyridines OR cyclopyrrolones OR pyrazolopyrimidines OR zolpidem OR zopiclone OR eszopiclone OR zaleplon OR benzodiazepin* OR bzd OR Alprazolam OR Chlordiazepoxide OR Clobazam OR Clonazepam OR Diazepam OR Flurazepam OR Loprazolam OR Lorazepam OR Lormetazepam OR Midazolam OR Nitrazepam OR Olanzapine OR Oxazepam OR Temazepam OR antidepress* OR anti depress* OR thymoanaleptic* OR thymoleptic* OR MAOI* OR NDRI* OR SSRI* OR SNRI* OR SNORI* OR SARI* OR RIMA* OR tricyclic* OR TCA* OR tetracyclic* OR TeCA* OR Agomelatine OR Aripiprazole OR Benactyzine OR Clorgyline OR Deanol OR Desvenlafaxine* OR Duloxetine* OR Flupentixol OR Iproniazid OR Isocarboxazid OR Levomilnacipran OR Lithium* OR Mirtazapine OR Moclobemide OR Nialamide OR Phenelzine OR Pizotyline OR

	Quetiapine* OR Reboxetine OR Rolipram OR Selegiline OR Sertraline OR Tranylcypromine OR Vilazodone* OR Vortioxetine OR 5-Hydroxytryptophan OR Amisulpride OR Bupropion OR Citalopram OR Escitalopram OR Fluoxetine OR Fluvoxamine OR Maprotiline OR Mianserin OR Paroxetine OR Quipazine OR Ritanserin OR Sulpiride OR Trazodone OR Tryptophan OR Venlafaxine OR Viloxazine OR Amitriptyline OR Amoxapine OR Clomipramine OR Desipramine OR Dothiepin OR Dosulepin OR Doxepin OR Imipramine OR Iprindole OR Lofepramine OR Nefazodone OR Nortriptyline OR Opipramol OR Protriptyline OR Trimipramine OR gabapentin* OR pregabalin*))]

Health Economics literature search strategy

Health economic evidence was identified by conducting searches with the terms used in the clinical search for prescription withdrawal and drug types. The NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015) and the Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) were searched via the Centre for Research and Dissemination (CRD). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for economic modelling and quality of life studies.

Table 24: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 17 June 2021	Health economics studies Quality of life studies Modelling studies Exclusions (animal studies, letters, comments)
	Quality of Life 1946 – 17 June 2021	
	Modelling 1946 – 17 June 2021	
Embase	Health Economics 1 January 2014 – 17 June 2021	Health economics studies Quality of life studies Modelling studies Exclusions (animal studies, letters, comments)
	Quality of Life 1974 – 17 June 2021	
	Modelling 1974 – 17 June 2021	
Centre for Research and Dissemination (CRD)	NHSEED Inception –31 March 2015	None
	HTA Inception – 31 March 2018	

Medline (Ovid) search terms

1.	*substance-related disorders/ or *narcotic-related disorders/
2.	*Substance Withdrawal Syndrome/
3.	exp Inappropriate Prescribing/
4.	*Medical Overuse/
5.	exp Prescription Drug Misuse/
6.	exp Deprescriptions/

7.	Medication Therapy Management/
8.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) adj2 (drug* or medicine* or medicat* or medical* or pharm*)).ti,ab.
9.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw*) adj3 (prescription* or prescrib*)).ti,ab.
10.	(addict* adj3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)).ti,ab.
11.	(deprescription* or de-prescription* or deprescrib* or de-prescrib*).ti,ab.
12.	((therap* or treat*) adj2 (manag* or substit*)).ti,ab.
13.	((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) adj2 symptom*).ti,ab.
14.	((drug* or medic*) adj2 (prescription* or prescrib*)).ti,ab.
15.	or/1-14
16.	((withdraw* or prescription* or prescrib*) adj2 opi*).ti,ab.
17.	Opiate Substitution Treatment/ or *Opioid-related disorders/
18.	or/16-17
19.	letter/
20.	editorial/
21.	news/
22.	exp historical article/
23.	Anecdotes as Topic/
24.	comment/
25.	case report/
26.	(letter or comment*).ti.
27.	or/19-26
28.	randomized controlled trial/ or random*.ti,ab.
29.	27 not 28
30.	animals/ not humans/
31.	exp Animals, Laboratory/
32.	exp Animal Experimentation/
33.	exp Models, Animal/
34.	exp Rodentia/
35.	(rat or rats or mouse or mice or rodent*).ti.
36.	or/29-35
37.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
38.	15 not (36 or 37)
39.	limit 38 to English language
40.	18 not (36 or 37)
41.	limit 40 to English language
42.	exp Narcotics/
43.	((analgesic* adj3 narcotic) or (opioid* or opiate*)).ti,ab.

44.	(alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*).ti,ab.
45.	(z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon).ti,ab.
46.	Zolpidem/ or Eszopiclone/
47.	(generation adj3 hypnotic*).ti,ab.
48.	exp Benzodiazepines/
49.	(benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam).ti,ab.
50.	exp Antidepressive Agents/
51.	(antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*).ti,ab.
52.	exp Flupenthixol/
53.	(Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine).ti,ab.
54.	(5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine).ti,ab.
55.	(Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine).ti,ab.
56.	gabapentin/ or pregabalin/
57.	(gabapentin* or pregabalin*).ti,ab.
58.	or/42-57
59.	39 and 58
60.	41 or 59
61.	quality-adjusted life years/
62.	sickness impact profile/
63.	(quality adj2 (wellbeing or well being)).ti,ab.
64.	sickness impact profile.ti,ab.
65.	disability adjusted life.ti,ab.
66.	(qal* or qtime* or qwb* or daly*).ti,ab.
67.	(euroqol* or eq5d* or eq 5*).ti,ab.
68.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
69.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
70.	(hui or hui1 or hui2 or hui3).ti,ab.

71.	(health* year* equivalent* or hye or hyes).ti,ab.
72.	discrete choice*.ti,ab.
73.	rosser.ti,ab.
74.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
75.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
76.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
77.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
78.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
79.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
80.	or/61-79
81.	exp models, economic/
82.	*Models, Theoretical/
83.	*Models, Organizational/
84.	markov chains/
85.	monte carlo method/
86.	exp Decision Theory/
87.	(markov* or monte carlo).ti,ab.
88.	econom* model*.ti,ab.
89.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
90.	or/81-89
91.	economics/
92.	value of life/
93.	exp "costs and cost analysis"/
94.	exp Economics, Hospital/
95.	exp Economics, medical/
96.	Economics, nursing/
97.	economics, pharmaceutical/
98.	exp "Fees and Charges"/
99.	exp budgets/
100.	budget*.ti,ab.
101.	cost*.ti.
102.	(economic* or pharmaco?economic*).ti.
103.	(price* or pricing*).ti,ab.
104.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
105.	(financ* or fee or fees).ti,ab.
106.	(value adj2 (money or monetary)).ti,ab.
107.	or/91-106
108.	60 and (80 or 90 or 107)

Embase (Ovid) search terms

1.	*drug dependence/
2.	*withdrawal syndrome/
3.	exp inappropriate prescribing/
4.	deprescription/
5.	exp prescription drug misuse/

6.	medication therapy management/
7.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) adj2 (drug* or medicine* or medicat* or medical* or pharm*)).ti,ab.
8.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw*) adj3 (prescription* or prescrib*)).ti,ab.
9.	(addict* adj3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)).ti,ab.
10.	(deprescription* or de-prescription* or deprescrib* or de-prescrib*).ti,ab.
11.	((therap* or treat*) adj2 (manag* or substit*)).ti,ab.
12.	((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) adj2 symptom*).ti,ab.
13.	((drug* or medic*) adj2 (prescription* or prescrib*)).ti,ab.
14.	or/1-13
15.	((withdraw* or prescription* or prescrib*) adj2 (opioid* or opiate*)).ti,ab.
16.	*benzodiazepine dependence/
17.	Opiate Substitution Treatment/
18.	or/15-17
19.	letter.pt. or letter/
20.	note.pt.
21.	editorial.pt.
22.	case report/ or case study/
23.	(letter or comment*).ti.
24.	or/19-23
25.	randomized controlled trial/ or random*.ti,ab.
26.	24 not 25
27.	animal/ not human/
28.	nonhuman/
29.	exp Animal Experiment/
30.	exp Experimental Animal/
31.	animal model/
32.	exp Rodent/
33.	(rat or rats or mouse or mice or rodent*).ti.
34.	or/26-33
35.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
36.	14 not (34 or 35)
37.	limit 36 to English language
38.	18 not (34 or 35)
39.	limit 38 to English language
40.	*narcotic agent/
41.	*alphaprodine/ or *buprenorphine/ or *codeine/ or *dextromoramide/ or *dextropropoxyphene/ or *diamorphine/ or *dihydrocodeine/ or *dihydromorphine/ or *dipipanone/ or *ethylmorphine/ or *hydrocodone/ or *hydromorphone/ or *levorphanol/ or *methadone/ or *morphine/ or *oxycodone/ or *pethidine/ or *tapentadol/ or *tilidine/

42.	*alfentanil/ or *butorphanol/ or *cocodamol/ or *fentanyl/ or *meptazinol/ or *oxymorphone/ or *opiate/ or *pentazocine/ or *phenazocine/ or *remifentanil/ or *sufentanil/ or *tramadol/ or *trimeperidine/
43.	((analgesic* adj3 narcotic) or (opioid* or opiate*)).ti,ab.
44.	(alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*).ti,ab.
45.	(z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon).ti,ab.
46.	*zolpidem/ or *zopiclone/ or *eszopiclone/ or *zaleplon/
47.	(generation adj3 hypnotic*).ti,ab.
48.	*benzodiazepine derivative/ or *alprazolam/ or *benzodiazepine/ or *chlordiazepoxide/ or *clobazam/ or *clonazepam/ or *diazepam/ or *flurazepam/ or *loprazolam/ or *lorazepam/ or *lormetazepam/ or *midazolam/ or *nitrazepam/ or *olanzapine/ or *oxazepam/ or *temazepam/
49.	(benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam).ti,ab.
50.	exp *antidepressant agent/
51.	(antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*).ti,ab.
52.	*flupentixol/
53.	(Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine).ti,ab.
54.	(5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine).ti,ab.
55.	(Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine).ti,ab.
56.	*pregabalin/ or *gabapentin/
57.	(gabapentin* or pregabalin*).ti,ab.
58.	or/40-57
59.	37 and 58
60.	39 or 59
61.	quality-adjusted life years/
62.	"quality of life index"/
63.	short form 12/ or short form 20/ or short form 36/ or short form 8/
64.	sickness impact profile/
65.	(quality adj2 (wellbeing or well being)).ti,ab.

66.	sickness impact profile.ti,ab.
67.	disability adjusted life.ti,ab.
68.	(qal* or qtime* or qwb* or daly*).ti,ab.
69.	(euroqol* or eq5d* or eq 5*).ti,ab.
70.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
71.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
72.	(hui or hui1 or hui2 or hui3).ti,ab.
73.	(health* year* equivalent* or hye or hyes).ti,ab.
74.	discrete choice*.ti,ab.
75.	rosser.ti,ab.
76.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
77.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
78.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
79.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
80.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
81.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
82.	or/61-81
83.	statistical model/
84.	exp economic aspect/
85.	83 and 84
86.	*theoretical model/
87.	*nonbiological model/
88.	stochastic model/
89.	decision theory/
90.	decision tree/
91.	monte carlo method/
92.	(markov* or monte carlo).ti,ab.
93.	econom* model*.ti,ab.
94.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
95.	or/85-94
96.	health economics/
97.	exp economic evaluation/
98.	exp health care cost/
99.	exp fee/
100.	budget/
101.	funding/
102.	budget*.ti,ab.
103.	cost*.ti.
104.	(economic* or pharmaco?economic*).ti.
105.	(price* or pricing*).ti,ab.
106.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
107.	(financ* or fee or fees).ti,ab.
108.	(value adj2 (money or monetary)).ti,ab.
109.	or/96-108
110.	60 and (82 or 95 or 109)

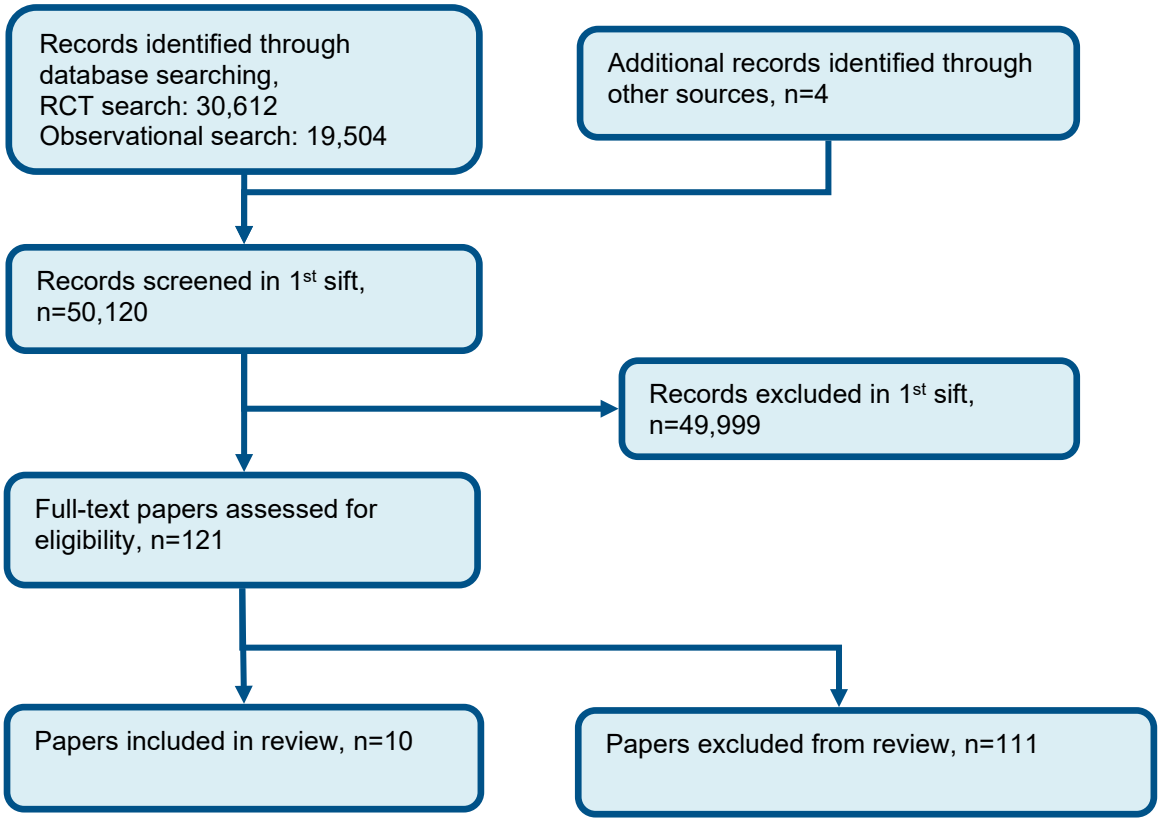
NHS EED and HTA (CRD) search terms

#1.	(MeSH DESCRIPTOR Substance-Related Disorders)
#2.	(MeSH DESCRIPTOR Substance Withdrawal Syndrome)
#3.	(MeSH DESCRIPTOR Inappropriate Prescribing EXPLODE ALL TREES)
#4.	(MeSH DESCRIPTOR Medical Overuse)
#5.	(MeSH DESCRIPTOR Deprescriptions EXPLODE ALL TREES)
#6.	(MeSH DESCRIPTOR Prescription Drug Misuse EXPLODE ALL TREES)
#7.	(MeSH DESCRIPTOR Medication Therapy Management)
#8.	(((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) adj2 (drug* or medicine* or medicat* or medical* or pharm*)))
#9.	(((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw*) adj3 (prescription* or prescrib*)))
#10.	((addict* adj3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)))
#11.	((deprescription* or de-prescription* or deprescrib* or de-prescrib*))
#12.	(((therap* or treat*) adj2 (manag* or substit*)))
#13.	(((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) adj2 symptom*))
#14.	MeSH DESCRIPTOR Narcotic-Related Disorders
#15.	(((drug* or medic*) adj2 (prescription* or prescrib*)))
#16.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17.	(MeSH DESCRIPTOR narcotics EXPLODE ALL TREES)
#18.	(((analgesic* adj3 narcotic adj3 agent*) or (opioid* or opiate*)))
#19.	((alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*))
#20.	((z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon))
#21.	(MeSH DESCRIPTOR Eszopiclone)
#22.	((generation adj3 hypnotic*))
#23.	(MeSH DESCRIPTOR Benzodiazepines EXPLODE ALL TREES)
#24.	((benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam))
#25.	(MeSH DESCRIPTOR Antidepressive Agents EXPLODE ALL TREES)
#26.	((antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or NDRI* or SSRI* or SNRI* or SNORI* SARI* or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*))
#27.	(("monoamine oxidase inhibit*"))
#28.	((Norepinephrine adj2 dopamine))

#29.	(("Selective serotonin reuptake inhibit*"))
#30.	((Serotonin adj2 norepinephrine))
#31.	((Serotonin antagonist))
#32.	(("Reversible Monoamine Oxidase Inhibit*"))
#33.	(MeSH DESCRIPTOR Flupenthixol EXPLODE ALL TREES)
#34.	((Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine))
#35.	((5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine))
#36.	((Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine))
#37.	(MeSH DESCRIPTOR pregabalin)
#38.	((gabapentin* or pregabalin*))
#39.	(#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38)
#40.	#16 AND #39
#41.	(((withdraw* or prescription* or prescrib*) adj2 (opioid* or opiate*)))
#42.	MeSH DESCRIPTOR Opiate Substitution Treatment
#43.	MeSH DESCRIPTOR Opioid-Related Disorders
#44.	#41 OR #42 OR #43
#45.	#40 OR #44

Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of optimum prescribing strategies or interventions delivered alongside prescribing



Appendix D Effectiveness evidence

Study	**Chu 2018[36]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=48)
Countries and setting	Conducted in USA; Setting: Unclear
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 40 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: baseline average pain determined by VAS scale
Stratum	Opioids
Subgroup analysis within study	Not applicable
Inclusion criteria	diagnosis of low back pain, 18-50 years of age, eligibility to escalate opioid therapy dose, as determined by the treating physician and study PI and low risk for addiction as determined by the PI, an individual with expertise in opioid addiction aided by the use of the Opioid Risk Tool at the patient intake exam.
Exclusion criteria	History of cardiac disease, history of peripheral neuropathic pain, scleroderma, or other condition that would preclude cold water forearm immersion, history of addiction or chronic pain conditions other than low back pain, history of cardiac arrhythmia, history of hepatic disease, use of steroid or nerve-stimulating medications, any condition precluding opioid use or pregnancy.
Recruitment/selection of patients	Advertisements and referrals from ResearchMatch and the Stanford Pain Clinic.
Age, gender and ethnicity	Age - Mean (SD): 39.3 (11.2). Gender (M:F): 26M, 22F (completers). Ethnicity: Caucasian: 33, African American: 4, Asian: 4, Hispanic: 6, other: 1
Further population details	1. Gabapentinoids: Not applicable

Extra comments	The participant sample included patients with and without existing opioid use. Opioid naive in past 5 years: 21, some opioid exposure in past 5 years: 17, chronic/ intermittent opioid exposure in past 5 years: 0, chronic opioid use in past 5 years: 1, current chronic opioid use: 7. Baseline participant details only provided for the patients who completed the study (48 people). However, 76 were randomised.
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Morphine + ondansetron. During the first session, baseline data were obtained. Following this, patients were titrated onto sustained-release oral morphine (Purdue Pharma, Stamford, CT 2007) following a 40-day schedule of 10 days taper on, 20 days maintenance and 10 days taper off. Titration: participants began with 30mg/day and increased by 15mg every two days or as dictated by side effects until (1) adequate analgesia was achieved;(2) side effects inhibited further titration or (3) the maximum dose of 120mg/day was reached. Research personnel contacted patients daily until a stable dose was achieved and all side effects were controlled. If patients experienced persistent nausea or constipation, their dose of opioid medication was reduced and they were given metoclopramide (Schward Pharma Mgf., Inc. Seymour, IN, 2004) for nausea or ducusate sodium 100mg soft gel capsules for constipation and were instructed to increase water intake. 30 days after the first session, participants received IV naloxone (Hospira Inc., Lake Forest, IL, 2004) 0.4mg/70kg to precipitate opioid withdrawal. If significant withdrawal (OOWS<6) was not observed and the participant consented, another larger dose of IV naloxone (0.8mg/70kg) was administered. Naloxone dosing was calculated with Robinson's ideal bodyweight for participants with BMI>40. Duration 40 days. Concurrent medication/care: 8mg ondansetron (Hospira Inc., Lake Forest, IL, 2004) three times daily during the titration period. Indirectness: No indirectness (n=36) Intervention 2: Morphine + placebo. During the first session, baseline data were obtained. Following this, patients were titrated onto sustained-release oral morphine (Purdue Pharma, Stamford, CT 2007) following a 40-day schedule of 10 days taper on, 20 days maintenance and 10 days taper off. Titration: participants began with 30mg/day and increased by 15mg every two days or as dictated by side effects until (1) adequate analgesia was achieved;(2) side effects inhibited further titration or (3) the maximum dose of 120mg/day was reached. Research personnel contacted patients daily until a stable dose was achieved and all side effects were controlled. If patients experienced persistent nausea or constipation, their dose of opioid medication was reduced and they were given metoclopramide (Schward Pharma Mgf., Inc. Seymour, IN, 2004) for nausea or ducusate sodium 100mg soft gel capsules for constipation and were instructed to increase water intake. 30 days after the first session, participants received IV naloxone (Hospira Inc., Lake Forest, IL, 2004) 0.4mg/70kg to precipitate opioid withdrawal. If significant withdrawal (OOWS<6) was not observed and the participant consented, another larger dose of IV naloxone (0.8mg/70kg) was administered. Naloxone dosing was calculated with Robinson's ideal bodyweight for participants with BMI>40. Duration 40 days. Concurrent medication/care: 8mg placebo three times

	daily during the titration period. Indirectness: No indirectness
Funding	Academic or government funding (Stanford Center for Clinical Informatics (Stanford CTSA award number UL1RR025744 from NIH/NCRR), National Institutes for Health (nIH, 1 R01DA029078-01A1), Stanford University School of Medicine Department of Anaesthesiology. Clinical trials registration NCT01549652, protocol ID 5HT3 19821.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MORPHINE+ONDANSETRON versus MORPHINE+PLACEBO Protocol outcome 1: Dependence on the prescribed medicine (accept study definition) - Actual outcome for Opioids: Objective Opioid Withdrawal Scale (OOWS) at 40 days; Group 1: mean 4.5 (SD 2.5); n=23, Group 2: mean 4.2 (SD 2.4); n=25; Objective Opioid Withdrawal Scale 0-13 Top=High is poor outcome; Comments: OOWS consists of 13 observable physical signs that are surveyed over a five minute observation period and scored as present (score of 1) or absent (score of 0). 11 participants did not display sufficient signs of withdrawal (OOWS score <6) after the first dose of naloxone (0.4mg/70kg). These 11 participants consented to receive a second dose of naloxone (0.8mg/70kg) which then produced an OOWS score of >6 indicating sufficient withdrawal for study purposes. Replacing the first OOWS score with the second OOWS score after the second naloxone dose, where applicable, did not change study results. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Baseline details for all randomised participants not provided; only completers.; Indirectness of outcome: No indirectness ; Baseline details: ? Large difference in pre-existing opioid dose (7 patients). Ondansetron group average dose: 4.2, placebo: 32.5; Group 1 Number missing: 17, Reason: Did not receive intervention: 2, non-compliance: 4, side effects during titration: 6, death in family: 1, withdrawal due to unrelated illness: 2, anxious about IV: 1, sinus infection: 1; Group 2 Number missing: 11, Reason: Non-compliance: 5, IV difficulty: 1, side effects during titration: 3, conflicting medication: 1, allergic reaction: 1 - Actual outcome for Opioids: Subjective Opioid Withdrawal Scale (SOWS) at 40 days; Group 1: mean 16.4 (SD 13.1); n=23, Group 2: mean 12 (SD 10); n=25; Subjective Opioid Withdrawal Scale 0-16 Top=High is poor outcome; Comments: The SOWS scale consists of 16 physical and emotional symptoms that are rated by the participant on a scale from 0 (not at all) to 4 (extremely) to indicate the degree to which the participant is feeling that emotion or physical symptom. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: ? Large difference in pre-existing opioid dose; Group 1 Number missing: 17, Reason: Did not receive intervention: 2, non-compliance: 4, side effects during titration: 6, death in family: 1, withdrawal due to unrelated illness: 2, anxious about IV: 1, sinus infection: 1; Group 2 Number missing: 11, Reason: Non-compliance: 5, IV difficulty: 1, side effects during titration: 3, conflicting medication: 1, allergic reaction: 1	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms / intensity or duration of withdrawal syndrome; Non-fatal overdose; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed

Study	**Feltner 2003[47]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=(271 total, including lorazepam and placebo groups). Pregabalin 50mg group: 70, Pregabalin 200mg group: 66)
Countries and setting	Conducted in Unknown multicentre; Setting: Outpatient
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks, plus 1 week taper
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV criteria used to diagnose GAD. In patients with comorbid psychiatric diagnoses, GAD was required to be the primary disorder, as judged by the psychiatrist/ investigator, considering relative severity and time of onset.
Stratum	Gabapentinoids
Subgroup analysis within study	Not applicable
Inclusion criteria	Outpatients aged 18 years or older meeting DSM-IV criteria for diagnosis of GAD.
Exclusion criteria	Patients were excluded if they suffered from another axis I disorder except dysthymia, simple phobia, social phobia, somatization disorder, or a history of major depressive disorder (current major depressive disorder was excluded). In addition, patients with severe personality disorders (antisocial or borderline); drug or alcohol abuse/ dependence (active within preceding 6 months); and suicide risk, as judged by the clinician (based on history and examination) or according to current severity of suicidal ideation (a HAM-D item 3 score ≥2) were excluded.
Recruitment/selection of patients	Clinic referrals or advertisements.
Age, gender and ethnicity	Age - Mean (SD): Pregabalin 50mg group: 37.9 (10.9); Pregabalin 200mg group: 36.3 (10.9). Gender (M:F): Pregabalin 50mg group: 34M/36F; Pregabalin 200mg group: 33M/33F. Ethnicity: Pregabalin 50mg group: White 71.4%, Black 14.3%, Hispanic 8.6%, Other 5.7% Pregabalin 200mg group: White 74.2%, Black 13.6%, Hispanic 6.1%, Other 6.1%
Further population details	1. Gabapentinoids: People on pregabalin

Extra comments	Patients were required to be free of psychotropic medications for 2 weeks (5 weeks for fluoxetine) prior to enrolment. No psychotropic medications were allowed during the study, except for zolpidem (5mg, <2 nights per week and not the night before a clinic visit).
Indirectness of population	No indirectness
Interventions	(n=70) Intervention 1: Pregabalin 50mg tid (150mg/day). Lead-in phase (1 week) was intended to establish the stability of GAD symptoms and to eliminate the effects of prior treatments. No drug was given. Treatment phase: study medication was titrated during the first 6 days of double-blind treatment, maintaining a constant number of capsules to preserve the blind, until the targeted dose was reached. Following these 4 weeks of treatment, the final efficacy assessments were made. Study medication dose was then tapered over 1 week, and the follow-up visit was conducted. Duration 4 weeks. Concurrent medication/care: No psychotropic medications were allowed during the study, except for zolpidem (5mg, <2 nights per week and not the night before a clinic visit). Indirectness: No indirectness. (n=66) Intervention 2: Pregabalin 200mg tid (600mg/day). Lead-in phase (1 week) was intended to establish the stability of GAD symptoms and to eliminate the effects of prior treatments. No drug was given. Treatment phase: study medication was titrated during the first 6 days of double-blind treatment, maintaining a constant number of capsules to preserve the blind, until the targeted dose was reached. Following these 4 weeks of treatment, the final efficacy assessments were made. Study medication dose was then tapered over 1 week, and the follow-up visit was conducted. Duration 4 weeks. Concurrent medication/care: No psychotropic medications were allowed during the study, except for zolpidem (5mg, <2 nights per week and not the night before a clinic visit). Indirectness: No indirectness.
Funding	Study funded by industry (Parke-Davis Pharmaceutical Research, a Division of the Warner-Lambert Company (now Pfizer, Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN 200MG TID versus PREGABALIN 50MG TID

Protocol outcome 1: Withdrawal symptoms including rebound symptoms / intensity or duration of withdrawal syndrome
- Actual outcome for Gabapentinoids: Physician's Withdrawal Checklist at Week 5; Group 1: mean 2.851 (SD 6.07); n=42, Group 2: mean 2.306 (SD 5.95); n=53; PWC. Based on 20 common symptoms of medication discontinuation on a scale ranging from 0 (not present) to 3 (severe) for each. Scores on the 20 individual items were summed to obtain a PWC total score (possible scores range from 0-60). PWC change scores were calculated by subtracting PWC score at end of treatment (wk4) from follow-up (wk5). Top=High is poor outcome; Comments: SDs calculated from SEs reported

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: Checklist is for BZD withdrawal; Group 1 Number missing: 20, Reason: adverse event: 13, lack of compliance: 1, other/administrative reason: 6; Group 2 Number missing: 17, Reason: adverse event: 5, lack of compliance: 6, other/administrative reason: 6	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Dependence on the prescribed medicine (accept study definition); Non-fatal overdose; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Patient Satisfaction; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed

Study	**Garland 2019[52]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=95)
Countries and setting	Conducted in USA; Setting: Primary care and pain clinics, Salt Lake City, Utah
Line of therapy	Unclear
Duration of study	Intervention + follow up: 8 weeks + 3-month follow up
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Participants underwent screening at first authors' laboratory
Stratum	Opioids
Subgroup analysis within study	Not applicable
Inclusion criteria	Participants met study inclusion criteria if they reported frequent recurrent pain (i.e., pain on more days than not) stemming from chronic, noncancer pain conditions and had been prescribed and taken opioids for analgesia daily or nearly every day for at least the past 90 days. Patients with COMM scores <13 were included (validated cut- off point to identify opioid misuse among chronic pain patients).
Exclusion criteria	Patients were assessed for comorbid psychiatric disorders with the Mini-international Neuropsychiatric Interview 6.0 and excluded if they were actively suicidal or psychotic or had engaged in a prior mindfulness-based intervention.

Recruitment/selection of patients	From primary care and pain clinics in Salt Lake City, Utah, through electronic health record view, opt-out letters, flyers and radio advertisements. Advertisements recruited individuals who suffered from, and were prescribed medicine for, chronic pain to participate in a study investigating ways to better address problems with chronic pain and prescription pain medication.
Age, gender and ethnicity	Age - Mean (SD): 56.8 (11.7. Gender (M:F): Define. Ethnicity: MORE: 88% white/Caucasian, 4% Hispanic/Latino, 0% Asian, 0% Pacific Islander, 6% >1 race. Support group: 91% white/Caucasian, 2% Hispanic/Latino, 2% Asian, 2% Pacific Islander, 2% >1 race.
Further population details	1. Gabapentinoids: Not applicable
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Mindfulness based approaches. The manualised MORE intervention was delivered over eight weekly 2-hour sessions to groups of 8-12 participants. Sessions involved mindfulness training to promote self-awareness, self-regulation and self-transcendence; reappraisal training to engender meaning and psychological growth in the face of adversity; and training in savouring pleasant events and emotions to enhance natural reward processing and positive affectivity. Session topics focused on applying mindfulness and other therapeutic skills to promote positive psychological health, gaining awareness of automaticity and coping habits in chronic pain; disrupting the link between negative emotions, catastrophising and pain experience through reappraisal: refocusing attention from pain and life stressors to savour pleasant experiences, regulating addictive tendencies toward opioids through mindful stress reduction; cultivating self-transcendence and meaning in life; and developing a mindful recovery plan. Mindfulness training involved mindful breathing and body scan techniques, with instructions to deepen meta-awareness into non-dual states of consciousness imbued with qualities of self-transcendence- that is a fading of the sense of self and/or an experiential oneness of self and world with attendant positive affective qualities of bliss, awe or peace. Participants were asked to engage in daily 15-minute mindfulness practice sessions at home guided by an audio recording. They were also asked to engage in 3 min of mindful breathing prior to making a decision about whether to take their opioid medication. This exercise was intended to clarify whether opioid use was driven by appetitive motivations (i.e., urges) versus a legitimate need for pain relief, prevent unnecessary opioid dosing by providing a nonpharmacologic means of pain management and synergistically increase the analgesic efficacy of opioid medication. Therapists engaged in an array of general therapeutic behaviours including building a rapport, setting goal and providing positive reinforcement. Therapists modulated vocal tone and pacing to induce a sense of calm while providing mindfulness instruction which involved a period of focused attention to and acceptance of present moment experience, followed by a period of open monitoring designed to evoke a state of self-transcendent awareness that ultimately culminated in a period of

	savouring positive experiences arising during medication practice. In each session, debriefing of in-session mindfulness meditation practice involved: inquiring into phenomenology of the meditative experience, utilizing participant experience as a means of emphasizing concepts presented didactically reframing participant reports of meditation experience into the terminology and concepts in the MORE therapeutic model, educating about and normalizing meditative phenomena; and providing positive reinforcement for engaging in mindfulness practice attempts. Behavioural change theory principles of selective reinforcement and successive approximation were used to shape participant responses to meditation practice toward achievement of the state of mindfulness and deeper self-transcendent states of awareness, as well as their application to reduce pain and opioid misuse. Debriefing tactics and behavioural change principles were also used to process participant homework practice of mindfulness, reappraisal and savouring skills after which homework assignments for the following week were provided. Duration 8 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness Comments: 74% completed treatment (n=45) Intervention 2: Patient support. The active control condition in this study consisted of 8 weekly, 2-hour conventional SG sessions comprised of 8 to 12 participants, which a Master's level clinical social worker led discussions on topics pertinent to chronic pain and long-term opioid use that were selected to roughly match corresponding themes in the MORE intervention: the physical and psychological dimensions of pain experience; ways of coping with chronic pain; ways of coping with negative emotions; the impact of life events on pain; the stigma and experience of opioid craving; the relation between stress and craving; acceptance versus denial; and plans for the future. To match the MORE format, SG participants were asked to engage in 15 minutes of journaling a day on weekly session topics. This SG format was derived from the active, evidence-based treatment condition outlined in the Matrix Model intensive outpatient treatment manual. SG participants were guided via client-centred reflective listening techniques to disclose feelings and thoughts about group topics, as well as to provide advice and emotional support for their peers. Therapists engaged in an array of general therapeutic behaviours including building a rapport, presenting unconditional positive regard, active listening, empathic responding, elicitation of emotional expression and promoting mutual support between group members. No psychoeducation or specific recommendations for change were provided. The first author reviewed treatment session recordings weekly day to monitor fidelity and provide clinical supervision until a level of adequate or greater therapist competence and adherence had been achieved (mean score >4 on a scale of 1-7 on a Treatment fidelity measure). Duration 8 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness Comments: 86% completed treatment
Funding	Academic or government funding ((Fahs Beck Fund for Research and Experimentation; the National Institute of Drug Abuse; the National Centre for Complementary and Integrative Health)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINDFULNESS- ORIENTATED RECOVERY ENHANCEMENT (MORE) versus SUPPORT GROUP

Protocol outcome 1: Dependence on the prescribed medicine (accept study definition)
- Actual outcome for Opioids: Opioid misuse at 3 months (assessed with Current Opioid Misuse Measure); Group 1: mean 7.72 (SD 4.75); n=50, Group 2: mean 9.08 (SD 5.77); n=45; Comments: Participants responded to 17 items rated on a 5 point Likert scale from 0 (never) to 4 (very often) regarding how often in the past 30 days they had engaged in aberrant drug-related behaviours linked with opioid misuse.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Maximum likelihood estimation was used to handle missing data in the ITT analysis.; Indirectness of outcome: No indirectness ; Baseline details: Months of opioid use: MORE: 111.24 (81.27), SG: 134.49 (105.93)
Morphine equivalent daily dose: MORE: 67.85 (78.33), SG: 71.07 (106.42); Group 1 Number missing: 28, Reason: did not receive allocated intervention: 13, lost to follow-up: 12 discontinued intervention: 3; Group 2 Number missing: 17, Reason: did not receive allocated intervention: 6 lost to follow-up: 7 discontinued intervention: 4

Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms / intensity or duration of withdrawal syndrome; Non-fatal overdose; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed

Study	**Kasper 2014[74]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=412 (615 including lorazepam arm))
Countries and setting	Conducted in Multiple countries; Setting:
Line of therapy	Unclear
Duration of study	Intervention + follow up: 24 weeks, followed by 1 week taper and 1 week follow-up.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Gabapentinoids

Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18-65 years, primary diagnosis of GAD, HAM-A total score ≥14, HAM-D item 1 score ≤2 at both screening and baseline visits (the baseline visit occurred about 4-10 days following screening.
Exclusion criteria	Patients with a current or past diagnosis of any other DSM-IV Axis I disorder besides GAD were excluded (except for current or past diagnosis of depression not otherwise specified, specific phobia, somatization disorder, nicotine or caffeine abuse/dependence or history of major depressive disorder, social phobia, panic disorder or eating disorder). Individuals were also excluded from the study if they reported daily (≥5d/wk.) use of benzodiazepines for treating GAD during the 3 months prior to screening, a history of failed treatment with any benzodiazepine (determined by a judgement of the clinical investigator who took into account reported dosage and duration) or any reported prior exposure to pregabalin. Those individuals taking a benzodiazepine for less than 5d/wk. could be included if they stopped taking the benzodiazepine 2 wk. prior to baseline. No benzodiazepine use was allowed during the study. Additional exclusion criteria were pregnancy/ lactation, suicide risk, current us of psychotropic medication that could not be discontinued prior to baseline, positive urine test results at screening for potential drug abuse or illegal drugs, positive alcohol breathalyser test at screening or any serious or unstable medical condition assessed at screening.
Recruitment/selection of patients	Recruited from the clinic population, clinic referrals or from advertisements.
Age, gender and ethnicity	Age - Mean (SD): Low dose group: 40.5 (12.3), High dose group: 42.4 (11.5). Gender (M:F): Low dose group: 35.4% male, High dose group: 42.2% male. Ethnicity: Low dose group: white 80.1%, black: 0%, Asian 10.7%, Other 9.2% High-dose group: white 85.4%, black: 0%, Asian 6.8%, Other 7.8%
Further population details	1. Gabapentinoids:
Indirectness of population	No indirectness
Interventions	(n=52) Intervention 1: 150-300mg/d 12 weeks. Treatment was initiated with a 150mg/d starting dose of pregabalin. Upward dose escalation occurred during the first 3 weeks. Following dose escalation, patients received pregabalin 150-300mg/d with flexible dose treatment within the specified ranges during the first 6 weeks based on tolerability and clinical improvement. Patients who showed a clinical response (CGI-I score of 1 or 2) at week 6 continued treatment; those who had a score >2 at week 6 were discontinued from the study. During the second half of treatment period 1, patients were maintained on a fixed-dose treatment at the final dosage achieved during the initial 6-week flexible dosage phase. Study drug was administered twice per day in equal doses and was blinded using a double dummy method. Patients entering treatment period 2 were tapered to placebo (25% of the original low dose group). Following the

	double-blind taper, patients received placebo in treatment period 2 (12 weeks). Any patients who were discontinued from active medication at any other point during the study also underwent a 1-week double blind taper. Duration 24 weeks. Concurrent medication/care: NR. Indirectness: No indirectness Comments: The 1-week, double-blind taper schedule was generally consistent with product labelling and was intended to minimise the risk that patients could potentially experience severe drug discontinuation symptoms. Any patients experiencing severe discontinuation symptoms during the taper periods and up to 7 days afterwards could be provided with a more gradual 'rescue' taper, extending the taper to 4 weeks while maintaining the blind. This same taper schedule and rescue taper protocol was used for all patients, regardless of when treatment was discontinued. (n=52) Intervention 2: 450-600mg/d 12 weeks. Treatment was initiated with a 150mg/d starting dose of pregabalin. Upward dose escalation occurred during the first 3 weeks. Following dose escalation, patients received pregabalin 450-600mg/d with flexible dose treatment within the specified ranges during the first 6 weeks based on tolerability and clinical improvement. Patients who showed a clinical response (CGI-I score of 1 or 2) at week 6 continued treatment; those who had a score >2 at week 6 were discontinued from the study. During the second half of treatment period 1, patients were maintained on a fixed-dose treatment at the final dosage achieved during the initial 6-week flexible dosage phase. Study drug was administered twice per day in equal doses and was blinded using a double dummy method. Patients entering treatment period 2 were tapered to placebo (25% of the original high dose group). Following the double-blind taper, patients received placebo in treatment period 2 (12 weeks). Any patients who were discontinued from active medication at any other point during the study also underwent a 1-week double blind taper. Duration 24 weeks. Concurrent medication/care: NR. Indirectness: No indirectness Comments: The 1-week, double-blind taper schedule was generally consistent with product labelling and was intended to minimise the risk that patients could potentially experience severe drug discontinuation symptoms. Any patients experiencing severe discontinuation symptoms during the taper periods and up to 7 days afterwards could be provided with a more gradual 'rescue' taper, extending the taper to 4 weeks while maintaining the blind. This same taper schedule and rescue taper protocol was used for all patients, regardless of when treatment was discontinued. (n=154) Intervention 3: 150-300mg/d 24 weeks. Treatment was initiated with a 150mg/d starting dose of pregabalin. Upward dose escalation occurred during the first 3 weeks. Following dose escalation, patients received pregabalin 150-300mg/d with flexible dose treatment within the specified ranges during the first 6 weeks based on tolerability and clinical improvement. Patients who showed a clinical response (CGI-I score of 1 or 2) at week 6 continued treatment; those who had a score >2 at week 6 were discontinued from the study. During the second half of treatment period 1, patients were maintained on a fixed-dose treatment at the final dosage achieved during the initial 6-week flexible dosage phase. Study drug was administered twice per day in equal doses and was blinded using a double dummy method. At the end of week 12, patients continued on to treatment period 2 on the same fixed dose for 12 weeks (75% of the

	original low dose group). The patients who continued with active medication during treatment period 2 underwent a 1-week double blind taper at the beginning of week 25. Any patients who were discontinued from active medication at any other point during the study also underwent a 1-week double blind taper. Duration 24 weeks. Concurrent medication/care: NR. Indirectness: No indirectness Comments: The 1-week, double-blind taper schedule was generally consistent with product labelling and was intended to minimise the risk that patients could potentially experience severe drug discontinuation symptoms. Any patients experiencing severe discontinuation symptoms during the taper periods and up to 7 days afterwards could be provided with a more gradual 'rescue' taper, extending the taper to 4 weeks while maintaining the blind. This same taper schedule and rescue taper protocol was used for all patients, regardless of when treatment was discontinued. (n=154) Intervention 4: 450-600mg/d 24 weeks. Treatment was initiated with a 150mg/d starting dose of pregabalin. Upward dose escalation occurred during the first 3 weeks. Following dose escalation, patients received pregabalin 450-600mg/d with flexible dose treatment within the specified ranges during the first 6 weeks based on tolerability and clinical improvement. Patients who showed a clinical response (CGI-I score of 1 or 2) at week 6 continued treatment; those who had a score >2 at week 6 were discontinued from the study. During the second half of treatment period 1, patients were maintained on a fixed-dose treatment at the final dosage achieved during the initial 6-week flexible dosage phase. Study drug was administered twice per day in equal doses and was blinded using a double dummy method. Patients entering treatment period 2 were tapered to placebo. At the end of week 12, patients continued on to treatment period 2 on the same fixed dose for 12 weeks (75% of the original high dose group). The patients who continued with active medication during treatment period 2 underwent a 1-week double blind taper at the beginning of week 25. Any patients who were discontinued from active medication at any other point during the study also underwent a 1-week double blind taper. Duration 24 weeks. Concurrent medication/care: NR. Indirectness: No indirectness Comments: The 1-week, double-blind taper schedule was generally consistent with product labelling and was intended to minimise the risk that patients could potentially experience severe drug discontinuation symptoms. Any patients experiencing severe discontinuation symptoms during the taper periods and up to 7 days afterwards could be provided with a more gradual 'rescue' taper, extending the taper to 4 weeks while maintaining the blind. This same taper schedule and rescue taper protocol was used for all patients, regardless of when treatment was discontinued.
Funding	Equipment / drugs provided by industry (Pfizer Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH DOSE, SHORT-TERM versus LOW DOSE, SHORT-TERM

Protocol outcome 1: Withdrawal symptoms including rebound symptoms / intensity or duration of withdrawal syndrome
- Actual outcome for Gabapentinoids: Physicians Withdrawal Checklist at Week 14 (week 2, after initiating taper); Group 1: mean 2.1 (SD 6.23); n=54, Group 2: mean 2 (SD 5.22); n=49; Physicians Withdrawal Checklist 0-60 Top=High is poor outcome; Comments: SDs calculated from 95% CI using Revman calculator

CI for high dose PGL: 0.4, 3.7
CI for low dose PGL: 0.5, 3.6

The taper period was 1 wk. long. Included all patients who discontinued between weeks 9-15 or who switched to placebo at the end of week 12. and had a corresponding assessment in the 2-wk. following taper initiation.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Limited number of baseline characteristics reported. Hamilton anxiety scale NR at baseline.; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: unclear

1 Number missing: 22, Reason: adverse event, lack of efficacy, miscellaneous; Group 2 Number missing: 23, Reason: adverse event, lack of efficacy, miscellaneous
- Actual outcome for Gabapentinoids: Number of people with a symptom on the DESS checklist at 12 weeks; Group 1: 21/58, Group 2: 17/52; Comments: Discontinuation emergent signs and symptoms (DESS) occurring in ≥5% of patients after 12 weeks of treatment. DESS are a subset of Treatment Emergent Signs and Symptoms and are defined as those spontaneously reported adverse events that developed or existed prior to but worsened during the 2-week following taper initiation (i.e., weeks 13 and 14). The taper period was 1 wk. long. Included all patients who discontinued between weeks 9-15 or who switched to placebo at the end of week 12. and had a corresponding assessment in the 2 wk. following taper initiation.

Anxiety, headache, insomnia and nausea were the only DESS that occurred in ≥55% of patients in any treatment group during treatment period 1.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Limited number of baseline characteristics reported. Hamilton anxiety scale NR at baseline.; Group 1 Number missing: 0, Reason: included 6 extra patients who stopped early (included all patients who discontinued between weeks 9-15, or who switched to placebo at the end of 122k 12, and had a corresponding discontinuation week assessment.); Group 2 Number missing: 0
- Actual outcome for Gabapentinoids: DESS-Anxiety at 12 weeks; Group 1: 3/58, Group 2: 0/52; Comments: Discontinuation emergent signs and symptoms (DESS) occurring in ≥5% of patients after 12 weeks of treatment. DESS are a subset of Treatment Emergent Signs and Symptoms and are defined as those spontaneously reported adverse events that developed or existed prior to but worsened during the 2-week following taper initiation (i.e., weeks 13 and 14). The taper period was 1 wk. long. Included all patients who discontinued between weeks 9-15 or who switched to placebo at the end of week 12. and had a corresponding assessment in the 2 wk. following taper initiation.

Anxiety, headache, insomnia and nausea were the only DESS that occurred in ≥55% of patients in any treatment group during treatment period 1.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Limited number of baseline characteristics reported. Hamilton anxiety scale NR at baseline.; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome for Gabapentinoids: DESS- Headache at 12 weeks; Group 1: 3/58, Group 2: 4/52; Comments: Discontinuation emergent signs and symptoms (DESS) occurring in ≥5% of patients after 12 weeks of treatment. DESS are a subset of Treatment Emergent Signs and Symptoms and are defined as those spontaneously reported adverse events that developed or existed prior to but worsened during the 2-week following taper initiation (i.e., weeks 13 and 14). The taper period was 1 wk. long. Included all patients who discontinued between weeks 9-15 or who switched to placebo at the end of week 12. and had a corresponding assessment in the 2 wk. following taper initiation.

Anxiety, headache, insomnia and nausea were the only DESS that occurred in ≥55% of patients in any treatment group during treatment period 1.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups

- Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Limited number of baseline characteristics reported. Hamilton anxiety scale NR at baseline.; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome for Gabapentinoids: DESS- Dizziness at 12 weeks; Group 1: 3/58, Group 2: 0/52; Comments: Discontinuation emergent signs and symptoms (DESS) occurring in ≥5% of patients after 12 weeks of treatment. DESS are a subset of Treatment Emergent Signs and Symptoms and are defined as those spontaneously reported adverse events that developed or existed prior to but worsened during the 2-week following taper initiation (i.e., weeks 13 and 14). The taper period was 1 wk. long. Included all patients who discontinued between weeks 9-15 or who switched to placebo at the end of week 12. and had a corresponding assessment in the 2 wk. following taper initiation.

Anxiety, headache, insomnia and nausea were the only DESS that occurred in ≥5% of patients in any treatment group during treatment period 1.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups

- Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Limited number of baseline characteristics reported. Hamilton anxiety scale NR at baseline.; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome for Gabapentinoids: DESS- Insomnia at 12 weeks; Group 1: 6/58, Group 2: 4/52; Comments: Discontinuation emergent signs and symptoms (DESS) occurring in ≥5% of patients after 12 weeks of treatment. DESS are a subset of Treatment Emergent Signs and Symptoms and are defined as those spontaneously reported adverse events that developed or existed prior to but worsened during the 2-week following taper initiation (i.e., weeks 13 and 14). The taper period was 1 wk. long. Included all patients who discontinued between weeks 9-15 or who switched to placebo at the end of week 12. and had a corresponding assessment in the 2 wk. following taper initiation.

Anxiety, headache, insomnia and nausea were the only DESS that occurred in ≥55% of patients in any treatment group during treatment period 1.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups

- Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Limited number of baseline characteristics reported. Hamilton anxiety scale NR at baseline.; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome for Gabapentinoids: DESS- Nausea at 12 weeks; Group 1: 4/58, Group 2: 3/52; Comments: Discontinuation emergent signs and symptoms (DESS) occurring in ≥5% of patients after 12 weeks of treatment. DESS are a subset of Treatment Emergent Signs and Symptoms and are defined as those spontaneously reported adverse events that developed or existed prior to but worsened during the 2-week following taper initiation (i.e., weeks 13 and 14). The taper period was 1 wk. long. Included all patients who discontinued between weeks 9-15 or who switched to placebo at the end of week 12. and had a corresponding assessment in the 2 wk. following taper initiation.

Anxiety, headache, insomnia and nausea were the only DESS that occurred in ≥5% of patients in any treatment group during treatment period 1.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups

- Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Limited number of baseline characteristics reported. Hamilton anxiety scale NR at baseline.; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome for Gabapentinoids: Rebound anxiety at 12 weeks; Group 1: 3/58, Group 2: 1/52; Comments: During 2 weeks following taper initiation (taper period was 1 weeklong). Included all patients who discontinued between weeks 9-15 or who switched to placebo at the end of week 12. and had a corresponding assessment in the 2 wk. following taper initiation.

Rebound anxiety was defined as a HAM-A rating scale total score >baseline score during either of the 2 wk. following taper initiation.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups

- Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Limited number of baseline characteristics reported. Hamilton anxiety scale NR at baseline.; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH DOSE, LONG-TERM versus LOW DOSE, LONG-TERM

Protocol outcome 1: Withdrawal symptoms including rebound symptoms / intensity or duration of withdrawal syndrome

- Actual outcome for Gabapentinoids: Physicians Withdrawal Checklist at Week 26 (week 2, after initiating taper); Group 1: mean 2.8 (SD 6.23); n=106, Group 2: mean 1.7 (SD 4.6); n=84; Physicians Withdrawal Checklist 0-60 Top=High is poor outcome; Comments: SDs calculated from 95% CI using Revman calculator
CI for high dose PGL: 1.6, 3.9
CI for low dose PGL: 0.7, 2.8

Included all patients who either completed the study or discontinued after week 15, and had a corresponding assessment in the 2 weeks following taper initiation.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups

- Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Limited number of baseline characteristics reported. Hamilton anxiety scale NR at baseline.; Group 1 Number missing: 48, Reason: Total number discontinued over the study: 52- adverse event (13),lack of efficacy (8), miscellaneous (31); Group 2 Number missing: 70, Reason: Total number discontinued over the study: 65- adverse event (22),lack of efficacy (12), miscellaneous (31)

- Actual outcome for Gabapentinoids: Number of patients with symptoms on the DESS checklist at 24 weeks; Group 1: 34/109, Group 2: 21/94; Comments: Discontinuation emergent signs and symptoms (DESS) occurring in ≥5% of patients after 24 weeks of treatment. DESS are a subset of Treatment Emergent Signs and Symptoms and are defined as those spontaneously reported adverse events that developed or existed prior to but worsened during the 2-week following taper initiation (i.e., weeks 25 and 26). The taper period was 1 wk. long. Included all patients who either completed the study or discontinued after week 15, and had a corresponding assessment in the 2 wk. following taper initiation.

Anxiety, headache and insomnia were the only DESS that occurred in ≥5% of patients in any of the treatment groups during treatment period 2.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups

- Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Limited number of baseline characteristics reported. Hamilton anxiety scale NR at baseline.; Group 1 Number missing: 45, Reason: discontinued, adverse event, lack of efficacy, miscellaneous; Group 2 Number missing: 60, Reason: discontinued, adverse event, lack of efficacy, miscellaneous

- Actual outcome for Gabapentinoids: DESS- Anxiety at 24 weeks; Group 1: 7/109, Group 2: 4/94; Comments: DESS occurring in ≥5% of patients
Discontinuation emergent signs and symptoms (DESS) occurring in ≥5% of patients after 24 weeks of treatment. DESS are a subset of Treatment Emergent Signs and Symptoms and are defined as those spontaneously reported adverse events that developed or existed prior to but worsened during the 2-week following taper initiation (i.e., weeks 25 and 26). The taper period was 1 wk. long. Included all patients who either completed the study or discontinued after week 15, and had a corresponding assessment in the 2 wk. following taper initiation.

Anxiety, headache and insomnia were the only DESS that occurred in ≥5% of patients in any of the treatment groups during treatment period 2.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups

- Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Limited number of baseline characteristics reported. Hamilton anxiety scale NR at baseline.; Group 1 Number missing: 45, Reason: Total discontinued 52: adverse event (13), lack of efficacy (8), miscellaneous (31); Group 2 Number missing: 60, Reason: Total discontinued 65: adverse event (22),lack of efficacy (12), miscellaneous (31)

- Actual outcome for Gabapentinoids: DESS- Headache at 24 weeks; Group 1: 5/109, Group 2: 3/94; Comments: Discontinuation emergent signs and symptoms (DESS) occurring in ≥5% of patients after 24 weeks of treatment. DESS are a subset of Treatment Emergent Signs and Symptoms and are defined as those spontaneously reported adverse events that developed or existed prior to but worsened during the 2-week following taper initiation (i.e., weeks 25 and 26). The taper period was 1 wk. long. Included all patients who either completed the study or discontinued after week 15, and had a corresponding assessment in the 2 wk. following taper initiation.
Anxiety, headache and insomnia were the only DESS that occurred in ≥5% of patients in any of the treatment groups during treatment period 2.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups

- Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Limited number of baseline characteristics reported. Hamilton anxiety scale NR at baseline.; Group 1 Number missing: 45, Reason: Total number discontinued over the study: 52- adverse event (13),lack of efficacy (8), miscellaneous (31); Group 2 Number missing: 60, Reason: Total number discontinued over the study: 65- adverse event (22),lack of efficacy (12), miscellaneous (31)

- Actual outcome for Gabapentinoids: DESS- Insomnia at 24 weeks; Group 1: 13/109, Group 2: 8/94; Comments: Discontinuation emergent signs and symptoms (DESS) occurring in ≥5% of patients after 24 weeks of treatment. DESS are a subset of Treatment Emergent Signs and Symptoms and are defined as those spontaneously reported adverse events that developed or existed prior to but worsened during the 2-week following taper initiation (i.e., weeks 25 and 26). The taper period was 1 wk. long. Included all patients who either completed the study or discontinued after week 15, and had a corresponding assessment in the 2 wk. following taper initiation.
Anxiety, headache and insomnia were the only DESS that occurred in ≥5% of patients in any of the treatment groups during treatment period 2.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups

- Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Limited number of baseline characteristics reported. Hamilton anxiety scale NR at baseline.; Group 1 Number missing: 45, Reason: Total number discontinued over the study: 52- adverse event (13), lack of efficacy (8), miscellaneous (31); Group 2 Number missing: 60, Reason: Total number discontinued over the study: 65- adverse event (22), lack of efficacy (12), miscellaneous (31)

- Actual outcome for Gabapentinoids: Rebound anxiety at 24 weeks; Group 1: 4/109, Group 2: 0/94; Comments: During 2 weeks following taper initiation (taper period was 1 weeklong). Included all patients who either completed the study or discontinued between after week 15 and had a corresponding assessment in the 2 wk. following taper initiation. Rebound anxiety was defined as a HAM-A rating scale total score >baseline score during either of the 2 wk. following taper initiation. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Limited number of baseline characteristics reported. Hamilton anxiety scale not reported at baseline.; Group 1 Number missing: 45, Reason: Total number discontinued over the study: 52- adverse event (13), lack of efficacy (8), miscellaneous (31); Group 2 Number missing: 60, Reason: Total number discontinued over the study: 65- adverse event (22), lack of efficacy (12), miscellaneous (31)	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Dependence on the prescribed medicine (accept study definition); Non-fatal overdose; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Patient Satisfaction; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed

Study	**Krystal 2011[76]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=229 randomised, including 73 in the placebo group which is not included); 8 patients discontinued after randomization but before receiving a dose of double-blind study drug and these patients were not included in ITT or safety analyses data sets).
Countries and setting	22 sleep centres in the US.
Duration of study	5-week sleep study.
Stratum	Antidepressants (TCAs)
Inclusion criteria	Men and women between the ages of 18 and 64 years with a DSM-IV-TR diagnosis of primary insomnia who reported sleep maintenance difficulty were eligible. Patient screening for general eligibility and sleep history was conducted during an initial clinical visit and involved a medical, sleep and psychiatric history; physical examination; vital sign measurements; clinical laboratory tests; and an electrocardiogram. Patients meeting genital screening criteria were asked to record their sleep patterns onto a daily sleep diary prior to PSG screening (≥7 days of assessment). The initial

	screening results and sleep diary data were used to verify a DSM-IV-TR diagnosis of insomnia for at least the last 3 months. During the first 2 nights of placebo the patients spent it in the sleep laboratory to determine whether they met the PSG screening criteria. Patients were required to meet the following polysomnographic entry criteria in order to be eligible for randomization: latency to persistent sleep (LPS) > 10 minutes on both PSG screening nights; mean wake time during sleep (WTDS) ≥ 60 min on both PSG screening nights, with no night < 45 minutes; and TST > 240 and ≤ 400 minutes on both screening nights. Patients were excluded from the study if the y had 10 or more apnea/hypopnea events or periodic leg movements with arousals/hour of sleep/
Exclusion criteria	Excessive use of alcohol, nicotine, or caffeinated beverages, intentional napping more than twice per week; having a variation in bedtime > 2 hours on 5 of 7 nights; or use of a hypnotic or any other medication known to affect sleep.
Recruitment/selection of patients	Primary insomnia patients from sleep centers.
Age, gender and ethnicity	Age, y, Mean (SD): Group 1: 45.5 (10.6), Group 2: 44.2 (11.1), Group 3: 43.6 (12.3) Female: Group 1: 77%, Group 2: 71%, Group 3: 70% Race/Ethnicity: Caucasian: Group 1: 44%, Group 2: 53% African American: Group 1: 35%, Group 2: 29% Hispanic: Group 1: 20%, Group 2: 14%, Other: Group 1: 1%, Group 2: 4% Authors reported that baseline characteristics were comparable across groups.
Extra comments	Sleep maintenance and duration reported.
Indirectness of population	No indirectness.
Interventions & comparators	Phase A: 2 weeks of single blind placebo dosing. Patients spent first 2 nights in a sleep laboratory to determine whether they met PSG screening criteria and then took the placebo for 5 nights at home. After completing this, patients participated in 2 consecutive nights of 8-h continuous PSG recordings in a sleep laboratory. (n=75) Group 1: Doxepin 3mg, 35 days of nightly treatment and two days of placebo to evaluate discontinuation effects. (n=73) Group 2: Doxepin 6mg, 35 days of nightly treatment and two days of placebo to evaluate discontinuation effects.

Funding	Provided by Somaxon Pharmaceuticals, Inc.

RESULTS (NUMBER ANALYSED) AND RISK OF BIAS FOR COMPARISON: Doxepin 3mg vs doxepin 6mg

Protocol outcome 1: Withdrawal symptoms including rebound symptoms / intensity or duration of withdrawal syndrome;

Actual outcome: Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) criteria of 3 more new symptoms in the BWSQ, the predetermined withdrawal criteria.

Group 1 (n=75): 1, Group 2 (n=73): 0, Group 3 (n=73): 1

Mean BWSQ scores from day 38:

Group 1 (n=75): 0.8, Group 2 (n=73): 0.4, Group 3 (n=73): 0.6

Risk of bias: All domain –High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement – Low, Crossover - Low; Indirectness of outcome: No indirectness; At end of study - Group 1 Number missing: 9; Group 2 Number missing: 8, Group 3 Number missing; 9. Reason*: Adverse event (7%), consent withdrawn (7%), protocol violation (1%), noncompliance (9%), other (11%).

Actual outcome: Rebound insomnia based on wake time after sleep onset (WASO) criteria experienced over the 2 nights after discontinuation:

Group 1: 1/75 (1%), Group 2: 3/73 (4%), and Group 3: 1 /73 (1%)

Note: actual numbers assumed by NGC calculations, % only provided in study.

Risk of bias: All domain –High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement – Low, Crossover - Low; Indirectness of outcome: No indirectness; At end of study - Group 1 Number missing: 9; Group 2 Number missing: 8, Group 3 Number missing; 9. Reason*: Adverse event (7%), consent withdrawn (7%), protocol violation (1%), noncompliance (9%), other (11%).

Narrative information: Overall there was a low incidence of AEs reported during the discontinuation period. Approximately 8% in each of the 3 groups experienced an AE during the discontinuation period. A review of these adverse events revealed no evidence of physical dependence, withdrawal syndrome, or worsening insomnia. Additionally, BWSQ data indicated no evidence of withdrawal syndrome.

Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Dependence on the prescribed medicine (accept study definition); Non-fatal overdose; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed

Study	**Naliboff 2011[90]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=140)
Countries and setting	Conducted in USA; Setting: The Chronic Pain Clinic consists of a multidisciplinary staff providing consultation and follow-up care for complex chronic pain cases and receives referrals from primary care physicians am a variety of subspecialty clinics.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12-13 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Opioids
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of non-malignant chronic pain for at least 6 months prior to enrolment, and a determination by the clinic team that the patient was eligible for long-term opioid treatment. This determination is made for all new patients entering the clinic with an opioid prescription or requesting one, and is based on an absence in the electronic chart and clinical exam of evidence of active or recent substance abuse, a willingness of the patient to agree to the clinic procedures for medication monitoring, and an indication from the patient's report that the opioid medications may or do provide some measure of pain relief.
Exclusion criteria	Anticipated surgery within the 1-year follow-up; participant still undergoing diagnostic testing to determine pain aetiology; patients with postoperative pain; patients with pulmonary disease or congestive heart failure; current diagnosis or history within past 2 years of substance abuse disorder (by chart review and psychiatric interview); and hospitalisation for a psychiatric condition within the past 2 years.
Recruitment/selection of patients	Participants were recruited from sequential referrals of patients to the Chronic Pain Clinic at the greater Los Angeles Veterans Affairs Healthcare System (August 2001-April 2004)
Age, gender and ethnicity	Age - Mean (SD): Stable dose group: 52.4 (7.1), Escalating dose group: 52.7 (7.9). Gender (M:F): Stable dose group: 1F/69M Escalating dose group: 7F/57M. Ethnicity: NR
Further population details	1. Gabapentinoids: Not applicable
Extra comments	Although not a requirement, all patients were already using opioid medications for pain management and were referred to the Chronic Pain Clinic for long-term management. 63 (46%) had a history of a substance-related (excluding alcohol) disorder, 87 (65%) had a history of alcohol-related disorder, and 53 (40%) had a history of both alcohol and substance-related disorders.

	Unclear whether <20% had dependence at baseline, but baseline values for the ABC score are provided, and the mean score is below the threshold of 3 for flagging possible opioid misuse. ABC baseline scores: stable dose: 1.6 (2.1); escalating dose: 1.5 (2.0).
Indirectness of population	No indirectness
Interventions	(n=67) Intervention 1: Rate of upward titration – escalating dose. During the course of monthly clinic visits, participants were assessed for pain severity as well as for any medication side effects, and behaviours related to potentially problematic medication use. Medication dosage adjustment decisions were made by the treatment team based on the patient's report of efficacy and in accordance with their assigned group protocol. Patients assigned to this group who reported inadequate pain relief were given a moderate opioid dose increase, possibly including a switch from short-acting to long-acting medications. Medications would not be increased in cases where it would be medically or ethically irresponsible based on side effects or presence of 'red flags' for possible substance abuse. Duration 12-13 months. Concurrent medication/care: Participants also received nonopioid interventions and similar nonpharmacological coping skills to maintain equivalence of treatment between groups. Medications for all participants were typically presented on a time-contingent schedule with specified times for each dose. Whereas decisions for opioid dosage changes were made by study protocol, all other decisions such as discontinuation from opioids, referral for other services or treatments, and changes in nonopioid medications were made based on usual clinic practice and were the same for both treatment groups. Indirectness: No indirectness (n=73) Intervention 2: Rate of upward titration – stable dose. During monthly clinic visits, participants were assessed for pain severity as well as for any medication side effects, and behaviours related to potentially problematic medication use. Medication dosage adjustment decisions were made by the treatment team based on the patient's report of efficacy and in accordance with their assigned group protocol. Medication increases were kept to a minimum with the target of a steady opioid dosage over the study period. In this condition, opioid medications were only increased when deemed medically necessary (clear indications of dosage tolerance or acute injury). For patients in this group the primary response to a report of inadequate pain relief involved maximising nonopioid interventions such as increasing adjuvant (e.g., antidepressant) medication or encouraging use of nonpharmacological coping skills (e.g., exercise, activity pacing). Duration 12-13 months. Concurrent medication/care: Participants also received nonopioid interventions and similar nonpharmacological coping skills to maintain equivalence of treatment between groups. Medications for all participants were typically presented on a time-contingent schedule with specified times for each dose. Whereas decisions for opioid dosage changes were made by study protocol, all other decisions such as discontinuation from opioids, referral for other services or treatments, and changes in nonopioid medications were made based on usual clinic practice and were the same for both treatment groups. Indirectness: No indirectness

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ESCALATING DOSE versus STABLE DOSE Protocol outcome 1: Dependence on the prescribed medicine (accept study definition) - Actual outcome for Opioids: Medication discontinuation due to opioid medication non-compliance or clinic non-compliance. at 12-13 months; Group 1: 16/67 Group 2: 22/73; Comments: Discontinuation decisions were made as a group by the multidisciplinary Pain Clinic treatment team based on results of urine toxicology screens, medication contract violations and other factors such as alcohol intoxication or inappropriate behaviours in clinic. The primary reasons for discontinuing opioid medications were as follows: 1) alcohol or illicit substance abuse; 2) noncompliance with clinic procedures (e.g., refusing to submit urine toxicology screens, repeatedly missing appointments and expecting medication refills via phone request). Particular attention was paid to ensure these behaviours did not primarily reflect inadequate pain control. Decisions for discontinuing opioid medications were done on an individual basis and not by a rigid algorithm. Of total sample, 13 (10%) discontinuations were due to alcohol or illicit substance abuse, 20 (15%) due to noncompliance with medications, 5 (4%) due to noncompliance with clinic procedures. Of those discontinued, 30% occurred in the first 2 months, another 30% by 6 months, and 5% in the last 2 months. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - ABC checklist specified to be collected monthly but results not reported. Baseline drug abuse not reported per group. Patient satisfaction with current treatment reported at baseline only.; Indirectness of outcome: No indirectness ; Baseline details: Details of substance abuse history not reported for groups separately.; Blinding details: States that patients were blinded, but this blinding would have been broken by the response by caregivers for more pain relief.; Group 1 Number missing: 17, Reason: did not receive allocated intervention (2), withdrew from treatment for other reasons (13), lost to follow-up (2), excluded from analysis (1); Group 2 Number missing: 19, Reason: did not receive allocated intervention (3), withdrew from treatment for other reasons (13), lost to follow-up (3)	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms / intensity or duration of withdrawal syndrome; Non-fatal overdose; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Patient Satisfaction; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed

Study	**NCT01255787 trial: Nishimura 2018[92]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=600 randomised to 4 arms). Placebo arm not relevant to current review and not included (n=152).
Countries and setting	Conducted in Multiple countries; Setting: Unclear setting. Enrolled in 90 sites in 14 countries; 44 in Europe, 31 in Japan and an additional 15 sites in Asia/Oceania.

Line of therapy	Not applicable
Duration of study	Intervention + follow up: 12 weeks (8-week intervention, 2-week discontinuation period, 2 week follow up period)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Primary diagnosis of MDD (Major Depressive disorder) according to the DSM-IV-TR criteria (codes 296.2x and 296.3x)
Stratum	Antidepressants: others: Vortioxetine 5, 10 and 20mg/ day
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion criteria: Primary diagnosis of MDD (DSM IV TR criteria), a MADRS total score ≥26, a Clinical Global Impression Scale-Severity (CGI-S) score ≥4, and had the current major depressive episode for ≥3 months at baseline, age ≥20 and ≤64 years, capacity to understand and comply with protocol requirements, signed informed consent form, agreement from female patients to routinely use adequate contraception throughout the duration of the study.
Exclusion criteria	Any current psychiatric or neurological disorder other than MDD as defined in the DSN-IV-TR, had a significant health-related issue, or an abnormal test results, or taken any disallowed medication, had current depressive symptoms resistant to two adequate antidepressant treatments of at least 6 weeks' duration each, had significant risk of suicide, a score ≥5 on Item 10 (suicidal thoughts) of the MADRS, or had attempted suicide within 6 months, and had received vortioxetine or a disallowed treatment. The patient was also excluded if he or she were in the investigator's opinion unsuitable for any reason.
Recruitment/selection of patients	Not stated.
Age, gender and ethnicity	Age - Mean (SD): 44.4 (11.54). Gender (M:F): 3:5 (225:375). Ethnicity: Caucasian 414 (69%), Asian 186 (31%), Japanese only 129 (21.5%)
Further population details	1. Gabapentinoids: Not applicable
Extra comments	Pharmacotherapy for current MDE n=277 (46.2%) - unclear what medication they were on, but this did not include Vortioxetine.
Indirectness of population	No indirectness

Interventions	(n=144) Intervention 1: 5mg vortioxetine q.d. 1 week screening period, 8-week double blind treatment period (5mg vortioxetine q.d.), 2-week single discontinuation period and a 2-week follow-up period. Patients were seen weekly during the first 2 weeks and then every 2 weeks up to the end of the 8-week treatment. A 2-week discontinuation period assessed withdrawal symptoms during which patients received placebo q.d. (single blind). Safety follow up 4 weeks after last dose of study medication. Duration 8 weeks. Concurrent medication/care: Not described. Baseline figures for Pharmacotherapy for current MDE n=60 (41.7%). Indirectness: No indirectness (n=150) Intervention 2: 10mg vortioxetine q.d. 1 week screening period, 8-week double blind treatment period (10mg vortioxetine q.d.), 2-week single discontinuation period and a 2-week follow-up period. Patients were seen weekly during the first 2 weeks and then every 2 weeks up to the end of the 8-week treatment. A 2-week discontinuation period assessed withdrawal symptoms during which patients received placebo q.d. (single blind). Safety follow up 4 weeks after last dose of study medication. Duration 8 weeks. Concurrent medication/care: Not described. Baseline figures for Pharmacotherapy for current MDE n=69 (46%). Indirectness: No indirectness (n=154) Intervention 3: 20mg vortioxetine q.d. 1 week screening period, 8-week double blind treatment period (20mg vortioxetine q.d.), 2-week single discontinuation period and a 2-week follow-up period. Patients were seen weekly during the first 2 weeks and then every 2 weeks up to the end of the 8-week treatment. A 2-week discontinuation period assessed withdrawal symptoms during which patients received placebo q.d. (single blind). Safety follow up 4 weeks after last dose of study medication. Patients who were assigned 20mg Vortioxetine q.d. received 10mg q.d. for the first week and were then titrated up to 20mg q.d. for the remaining 7 weeks of the treatment period. Duration 8 weeks. Concurrent medication/care: Not described. Baseline figures for Pharmacotherapy for current MDE n=75 (48.7%). Indirectness: No indirectness
Funding	Study funded by industry (Supported by Takeda Pharmaceuticals USA Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: 5MG VORTIOXETINE Q.D. versus 10MG VORTIOXETINE Q.D.

Protocol outcome 1: Withdrawal symptoms including rebound symptoms / intensity or duration of withdrawal syndrome
- Actual outcome for Antidepressants: others: Discontinuation-Emergent Signs and Symptoms (DESS) at Week 10; Group 1: mean 0.8 Total Score (SD 2.21); n=122, Group 2: mean 1.1 Total Score (SD 2.49); n=128; Discontinuation-Emergent Signs and Symptoms (DESS) Scale Unclear. Range of values unclear Top=Unclear; Comments: Patients are asked 'Since the last visit, have you experienced any changes in the following symptoms? (Please check only one response for each symptom). There are 43 items/ symptoms listed. The options for each symptoms are as follows: (1) New symptom (2) Old symptom but worse (3) Old symptom but improved (4) Old symptom but unchanged (5) Symptom not present.

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: MADRS total score, mean (SD); 31.6 (3.67) vs. 31.8 (4.02), Clinical Global Impression Scale- Severity mean (SD); 4.7 (0.65) vs. 4.7 (0.66); Blinding details: Stated to be double blind during the treatment but single blind during the discontinuation period. No description of blinding for outcome assessors.; Group 1 Number missing: 22, Reason: Unclear. Discontinuation reasons given for n=17: withdrawal of consent (n=9), pre-treatment event or AE (n=2), lack of efficacy (n=2), lost to follow up (n=2), major protocol deviation (n=1), noncompliance (n=1); Group 2 Number missing: 22, Reason: Unclear. Discontinuation reasons given for n=18: withdrawal of consent (n=3), pre-treatment event or AE (n=9), lack of efficacy (n=2), lost to follow up (n=4)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: 5MG VORTIOXETINE Q.D. versus 20MG VORTIOXETINE Q.D.

Protocol outcome 1: Withdrawal symptoms including rebound symptoms / intensity or duration of withdrawal syndrome
- Actual outcome for Antidepressants: others: Discontinuation-Emergent Signs and Symptoms (DESS) at Week 10; Group 1: mean 0.8 Total score (SD 2.21); n=122, Group 2: mean 0.7 Total score (SD 1.71); n=126; Discontinuation-Emergent Signs and Symptoms (DESS) Scale Unclear. Cumulative total score 43-215. Top=Unclear; Comments: Patients are asked 'Since the last visit, have you experienced any changes in the following symptoms? (Please check only one response for each symptom). There are 43 items/ symptoms listed. The options for each symptoms are as follows: (1) New symptom (2) Old symptom but worse (3) Old symptom but improved (4) Old symptom but unchanged (5) Symptom not present.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: MADRS total score, mean (SD); 31.6 (3.67) vs. 31.7 (3.73), Clinical Global Impression Scale- Severity mean (SD); 4.7 (0.65) vs. 4.7 (0.65); Blinding details: Stated to be double blind during the treatment but single blind during the discontinuation period. No description of blinding for outcome assessors.; Group 1 Number missing: 22, Reason: Unclear. Discontinuation reasons given for n=17: withdrawal of consent (n=9), pre-treatment event or AE (n=2), lack of efficacy (n=2), lost to follow up (n=2), major protocol deviation (n=1), noncompliance (n=1); Group 2 Number missing: 28, Reason: Unclear. Discontinuation reasons given for n=22: withdrawal of consent (n=4), pre-treatment event or AE (n=9), lack of efficacy (n=2), lost to follow up (n=2), major protocol deviation (n=4), pregnancy (n=1)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: 10MG VORTIOXETINE Q.D. versus 20MG VORTIOXETINE Q.D.

Protocol outcome 1: Withdrawal symptoms including rebound symptoms / intensity or duration of withdrawal syndrome
- Actual outcome for Antidepressants: others: Discontinuation-Emergent Signs and Symptoms (DESS) at Week 10; Group 1: mean 1.1 Total score (SD 2.49); n=128, Group 2: mean 0.7 Total score (SD 1.71); n=126; Discontinuation-Emergent Signs and Symptoms (DESS) Scale Unclear. Cumulative total score 43-215. Top=Unclear; Comments: Patients are asked 'Since the last visit, have you experienced any changes in the following symptoms? (Please check only one response for each symptom). There are 43 items/ symptoms listed. The options for each symptoms are as follows: (1) New symptom (2) Old symptom but worse (3) Old symptom but improved (4) Old symptom but unchanged (5) Symptom not present.

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: MADRS total score, mean (SD); 31.8 (4.02) vs. 31.7 (3.73), Clinical Global Impression Scale- Severity mean (SD); 4.7 (0.66) vs. 4.7 (0.65); Blinding details: Stated to be double blind during the treatment but single blind during the discontinuation period. No description of blinding for outcome assessors.; Group 1 Number missing: 22, Reason: Unclear. Discontinuation reasons given for n=18: withdrawal of consent (n=3),

pre-treatment event or AE (n=9), lack of efficacy (n=2), lost to follow up (n=4); Group 2 Number missing: 28, Reason: Unclear. Discontinuation reasons given for n=22: withdrawal of consent (n=4), pre-treatment event or AE (n=9), lack of efficacy (n=2), lost to follow up (n=2), major protocol deviation (n=4), pregnancy (n=1)	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Dependence on the prescribed medicine (accept study definition); Non-fatal overdose; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Patient Satisfaction ; Increase in symptoms for which the medication was originally prescribed

Study	**Pasquale 2017[98]**
Study type	RCT (Cluster randomised; Parallel)
Number of studies (number of participants)	1 (n=2391 randomised, 2019 analysed)
Countries and setting	Conducted in Unknown, USA; Setting: Not described
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 91-270 days post intervention
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Patients enrolled in a MAPD (Medicare Advantage and Prescription Drug) plan with ≥1 claim for an opioid prescription from July 1 2012 to April 30, 2014, ≥180 days of continuous enrolment pre-index. Patients were at risk of opioid abuse.
Stratum	Opioids
Subgroup analysis within study	Not applicable
Inclusion criteria	Enrolment in an MAPD plan with ≥1 claim for opioid prescription from July 1 2012 to April 30 2014 (most recent date of claim was assigned as the index date, age 18-89 as of the index date, ≥180 days of continuous enrolment pre index.

Exclusion criteria	Patients diagnosed with opioid abuse dependence (ICD-9-CM: 304.0x, 304.7x, 305.5x, 965.0x excluding 965.01) anytime between January 1, 2012 and April 30, 2014, <270 days of continuous enrolment post-intervention (November 7 2014-August 4, 2015), diagnosis of opioid abuse or dependence during the 180 days immediately preceding the intervention, patients affected by the health plan's drug utilization review program already in progress.
Recruitment/selection of patients	Patients enrolled in a Medicare Advantage and Prescription Drug (MDP) plan who were at risk of opioid abuse from July 1 2012 to April 30 2014 (based on a published predictive model of diagnosed opioid abuse). Patients were risk link to their most recent prescribing physician, then grouped into mutually exclusive patient-physician clusters. Clusters stratified by size and geographic region.
Age, gender and ethnicity	Age - Range of means: 57.3 (10.6) - 58.7 (11.8). Gender (M:F): 1125:1266. Ethnicity: White (%): 87.1
Further population details	1. Gabapentinoids: Not applicable
Extra comments	
Indirectness of population	No indirectness: Risk of inclusion of some acute pain conditions requiring opioids.
Interventions	(n=493) Intervention 1: Physicians of the patients received notification with patient-specific information, including opioid utilization (with multiple prescriptions from multiple prescribers) and pain diagnoses. Duration 180 days prior to the mailings and 270 days after the mailings. Concurrent medication/care: Not described. Indirectness: No indirectness (n=460) Intervention 2: Physicians were given links to educational materials for the diagnosis and management of pain. Duration 180 days prior to the mailings and 270 days after the mailings. Concurrent medication/care: None described. Indirectness: No indirectness (n=480) Intervention 3: Physicians were given both patient specific information, including opioid utilization (with multiple prescriptions from multiple prescribers) and pain diagnoses and links to educational materials for diagnosis and management of pain. Duration 180 days prior to the mailings and 270 days after the mailings. Concurrent medication/care: Not described. Indirectness: No indirectness

	(n=958) Intervention 4No communication. Duration 180 days prior to the mailings and 270 days after the mailings. Concurrent medication/care: Not described. Indirectness: No indirectness
Funding	Study funded by industry (Sponsored by Humana Inc. and Pfizer Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHYSICIAN PATIENT INFORMATION versus PHYSICIAN EDUCATION

Protocol outcome 1: Dependence on the prescribed medicine (accept study definition)

- Actual outcome for Opioids: Uncoordinated opioid use at 91-270 days post intervention; Group 1: 74/399, Group 2: 78/391
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster RCT. No adjustment for cluster differences in the analysis. Difference in Differences analysis and adjusted logistic regression is also carried out but this is for differences between the intervention groups, not the clusters within the groups.; Indirectness of outcome: No indirectness; Baseline details: Chronic high dose opioid use p=0.0796. Blinding details: No blinding described in the paper. Outcome definition: >3 opioid prescription fills of any ingredient written by ≥3 prescribers within any 90-day period.; Group 1 Number missing: 106, Reason: Loss to follow up due to disenrollment or death (specific figures not given).; Group 2 Number missing: 69, Reason: Loss to follow up due to disenrollment or death (specific figures not given).

- Actual outcome for Opioids: Diagnosis of opioid abuse at 91-270 days post intervention; Group 1: 39/368, Group 2: 34/358; Comments: Patients diagnosed with opioid abuse during preintervention were excluded from the diagnosed opioid abuse outcome.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster RCT. No adjustment for cluster differences in the analysis. Difference in Differences analysis and adjusted logistic regression is also carried out but this is for differences between the intervention groups, not the clusters within the groups.; Indirectness of outcome: No indirectness; Baseline details: Chronic high dose opioid use p=0.0796. Those who were diagnosed with opioid abuse during the pre-intervention were excluded from the opioid abuse outcome.; Blinding details: No blinding described in the paper.; Group 1 Number missing: 125, Reason: Loss to follow up due to disenrollment or death (specific figures not given). 31 excluded for being diagnosed during the pre-intervention period with opioid abuse.; Group 2 Number missing: 102, Reason: Loss to follow up due to disenrollment or death (specific figures not given). 33 excluded for being diagnosed during the pre-intervention period with opioid abuse.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHYSICIAN PATIENT INFORMATION versus PHYSICIAN PATIENT INFORMATION & EDUCATION

Protocol outcome 1: Dependence on the prescribed medicine (accept study definition)

- Actual outcome for Opioids: Uncoordinated opioid use at 91-270 days post intervention; Group 1: 74/399, Group 2: 81/408
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster RCT. No adjustment for cluster differences in the analysis. Difference in Differences analysis and adjusted logistic regression is also carried out but this is for differences between the intervention groups, not the clusters within the groups.; Indirectness of outcome: No indirectness; Baseline details: Chronic high dose opioid use p=0.0796. ; Blinding details: No blinding described in the paper. Outcome definition: >3 opioid prescription fills of any

ingredient written by ≥3 prescribers within any 90 day period.; Group 1 Number missing: 106, Reason: Loss to follow up due to disenrollment or death (specific figures not given).; Group 2 Number missing: 72, Reason: Loss to follow up due to disenrollment or death (specific figures not given).

- Actual outcome for Opioids: Diagnosis of opioid abuse at 91-270 days post intervention; Group 1: 39/368, Group 2: 30/363; Comments: Patients diagnosed with opioid abuse during preintervention were excluded from the diagnosed opioid abuse outcome.

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster RCT. No adjustment for cluster differences in the analysis. Difference in Differences analysis and adjusted logistic regression is also carried out but this is for differences between the intervention groups, not the clusters within the groups.; Indirectness of outcome: No indirectness; Baseline details: Chronic high dose opioid use p=0.0796. Those who were diagnosed with opioid abuse during the pre-intervention were excluded from the opioid abuse outcome.; Blinding details: No blinding described in the paper.; Group 1 Number missing: 125, Reason: Loss to follow up due to disenrollment or death (specific figures not given). 31 excluded for being diagnosed during the pre-intervention period with opioid abuse.; Group 2 Number missing: 117, Reason: Loss to follow up due to disenrollment or death (specific figures not given). 45 excluded for being diagnosed during the pre-intervention period with opioid abuse.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHYSICIAN PATIENT INFORMATION versus USUAL CARE

Protocol outcome 1: Dependence on the prescribed medicine (accept study definition)
- Actual outcome for Opioids: Uncoordinated opioid use at 91-270 days post intervention; Group 1: 74/399, Group 2: 158/821
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster RCT. No adjustment for cluster differences in the analysis. Difference in Differences analysis and adjusted logistic regression is also carried out but this is for differences between the intervention groups, not the clusters within the groups.; Indirectness of outcome: No indirectness ; Baseline details: Chronic high dose opioid use p=0.0796. ; Blinding details: No blinding described in the paper. Outcome definition: >3 opioid prescription fills of any ingredient written by ≥3 prescribers within any 90 day period.; Group 1 Number missing: 106, Reason: Loss to follow up due to disenrollment or death (specific figures not given).; Group 2 Number missing: 137, Reason: Loss to follow up due to disenrollment or death (specific figures not given).

- Actual outcome for Opioids: Diagnosis of opioid abuse at 91-270 days post intervention; OR; 0.95 (95%CI 0.63 to 1.42);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Cluster RCT. Multivariable logistic regression analysis used.; Indirectness of outcome: No indirectness ; Baseline details: Chronic high dose opioid use p=0.0796. Those who were diagnosed with opioid abuse during the pre-intervention were excluded from the opioid abuse outcome.; Blinding details: No blinding described in the paper.; Group 1 Number missing: 125, Reason: Loss to follow up due to disenrollment or death (specific figures not given). 31 excluded for being diagnosed during the pre-intervention period with opioid abuse.; Group 2 Number missing: 226, Reason: Loss to follow up due to disenrollment or death (specific figures not given). 89 excluded for being diagnosed during the pre-intervention period with opioid abuse.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHYSICIAN EDUCATION versus PHYSICIAN PATIENT INFORMATION & EDUCATION

Protocol outcome 1: Dependence on the prescribed medicine (accept study definition)

- Actual outcome for Opioids: Uncoordinated opioid use at 91-270 days post intervention; Group 1: 78/391, Group 2: 81/408
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster RCT. No adjustment for cluster differences in the analysis. Difference in Differences analysis and adjusted logistic regression is also carried out but this is for differences between the intervention groups, not the clusters within the groups.; Indirectness of outcome: No indirectness ; Baseline details: Chronic high dose opioid use p=0.0796. ; Blinding details: No blinding described in the paper. Outcome definition: >3 opioid prescription fills of any ingredient written by ≥3 prescribers within any 90 day period.; Group 1 Number missing: 69, Reason: Loss to follow up due to disenrollment or death (specific figures not given).; Group 2 Number missing: 72, Reason: Loss to follow up due to disenrollment or death (specific figures not given).
- Actual outcome for Opioids: Diagnosis of opioid abuse at 91-270 days post intervention; Group 1: 34/358, Group 2: 30/363; Comments: Patients diagnosed with opioid abuse during preintervention were excluded from the diagnosed opioid abuse outcome.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster RCT. No adjustment for cluster differences in the analysis. Difference in Differences analysis and adjusted logistic regression is also carried out but this is for differences between the intervention groups, not the clusters within the groups.; Indirectness of outcome: No indirectness ; Baseline details: Chronic high dose opioid use p=0.0796. Those who were diagnosed with opioid abuse during the pre-intervention were excluded from the opioid abuse outcome.; Blinding details: No blinding described in the paper.; Group 1 Number missing: 102, Reason: Loss to follow up due to disenrollment or death (specific figures not given). 33 excluded for being diagnosed during the pre-intervention period with opioid abuse.; Group 2 Number missing: 117, Reason: Loss to follow up due to disenrollment or death (specific figures not given). 45 excluded for being diagnosed during the pre-intervention period with opioid abuse.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHYSICIAN EDUCATION versus USUAL CARE

Protocol outcome 1: Dependence on the prescribed medicine (accept study definition)
- Actual outcome for Opioids: Uncoordinated opioid use at 91-270 days post intervention; Group 1: 78/391, Group 2: 158/821
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster RCT. No adjustment for cluster differences in the analysis. Difference in Differences analysis and adjusted logistic regression is also carried out but this is for differences between the intervention groups, not the clusters within the groups.; Indirectness of outcome: No indirectness ; Baseline details: Chronic high dose opioid use p=0.0796. ; Blinding details: No blinding described in the paper. Outcome definition: >3 opioid prescription fills of any ingredient written by ≥3 prescribers within any 90 day period.; Group 1 Number missing: 69, Reason: Loss to follow up due to disenrollment or death (specific figures not given).; Group 2 Number missing: 137, Reason: Loss to follow up due to disenrollment or death (specific figures not given).
- Actual outcome for Opioids: Diagnosis of opioid abuse at 91-270 days post intervention; OR; 0.83 (95%CI 0.55 to 1.27);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Cluster RCT. Multivariable logistic regression analysis used.; Indirectness of outcome: No indirectness ; Baseline details: Chronic high dose opioid use p=0.0796. Those who were diagnosed with opioid abuse during the pre-intervention were excluded from the opioid abuse outcome.; Blinding details: No blinding described in the paper.; Group 1 Number missing: 102, Reason: Loss to follow up due to disenrollment or death (specific figures not given). 33 excluded for being diagnosed during the pre-intervention period with opioid abuse.; Group 2 Number missing: 226, Reason: Loss to follow up due to disenrollment or death (specific figures not given). 89 excluded for being diagnosed during the pre-intervention period with opioid abuse.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHYSICIAN PATIENT INFORMATION & EDUCATION versus USUAL CARE

Protocol outcome 1: Dependence on the prescribed medicine (accept study definition)
- Actual outcome for Opioids: Uncoordinated opioid use at 91-270 days post intervention; Group 1: 81/408, Group 2: 158/821
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster RCT. No adjustment for cluster differences in the analysis. Difference in Differences analysis and adjusted logistic regression is also carried out but this is for differences between the intervention groups, not the clusters within the groups.; Indirectness of outcome: No indirectness ; Baseline details: Chronic high dose opioid use p=0.0796. ; Blinding details: No blinding described in the paper. Outcome definition: >3 opioid prescription fills of any ingredient written by ≥3 prescribers within any 90 day period.; Group 1 Number missing: 72, Reason: Loss to follow up due to disenrollment or death (specific figures not given).; Group 2 Number missing: 137, Reason: Loss to follow up due to disenrollment or death (specific figures not given).
- Actual outcome for Opioids: Diagnosis of opioid abuse at 91-270 days post intervention; OR; 0.72 (95%CI 0.46 to 1.13);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Cluster RCT. No adjustment for cluster differences in the analysis. Difference in Differences analysis and adjusted logistic regression is also carried out but this is for differences between the intervention groups, not the clusters within the groups.; Indirectness of outcome: No indirectness ; Baseline details: Chronic high dose opioid use p=0.0796. Those who were diagnosed with opioid abuse during the pre-intervention were excluded from the opioid abuse outcome.; Blinding details: No blinding described in the paper.; Group 1 Number missing: 117, Reason: Loss to follow up due to disenrollment or death (specific figures not given).45 excluded for being diagnosed during the pre-intervention period with opioid abuse.; Group 2 Number missing: 226, Reason: Loss to follow up due to disenrollment or death (specific figures not given). 89 excluded for being diagnosed during the pre-intervention period with opioid abuse.

Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms / intensity or duration of withdrawal syndrome; Non-fatal overdose; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Patient Satisfaction; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed

Study	**Shaw 1992[105]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=119 (80 are in relevant comparisons for our protocol))
Countries and setting	Conducted in Unknown; Setting: Hospitalized/ institutionalized.
Line of therapy	Unclear

Duration of study	Intervention + follow up: 7-day placebo washout, 21 days intervention, 7 days placebo (withdrawal)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Insomnia of at least 2 weeks duration and fulfilling at least two of the following conditions were included: latency of onset of sleep >30mins, awake for >1hr during the night, ≥2 waking periods during the night, total sleep time<6hrs
Stratum	Z-drugs:
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients of either sex, between the ages of 65-85 years, hospitalized for psychiatric conditions but who were without serious systemic medical conditions. Insomnia ≥2 weeks duration, fulfilling ≥2 of the following conditions: latency of onset of sleep >30minutes, awake >1hr during the night, ≥2 waking periods during the night, total sleep time <6hrs.
Exclusion criteria	Anaemia, significant cardiac, hepatic or renal dysfunction, or other serious medical condition, history of alcohol abuse, significant abnormalities in routine laboratory tests, concomitant use of benzodiazepines or hypnotic drugs. Transient or situational insomnia, insomnia associated with the use of drugs or alcohol, or related to respiratory impairment (Association of Sleep Disorders Center insomnia class A1a, A3 or A4) were also ineligible.
Recruitment/selection of patients	Unclear. Through the psychiatric hospitals/ institutions?
Age, gender and ethnicity	Age - Mean (SD): 10mg/day: 74.9 (1.0), 20mg/day: 72.9 (1.0). Gender (M:F): 26:54. Ethnicity: Not described.
Further population details	1. Gabapentinoids: Not applicable
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Starting dose - Low dose. Patients were withdrawn from any previous hypnotic or benzodiazepine medication and 3-14 days later (depending on the duration of action of the previous hypnotic) started a 7-day placebo treatment period. Patients received 10mg of zolpidem as a single capsule for 21 days, followed by a 7-day placebo treatment phase. The capsule was given 30 mins before bedtime and patients were allowed to sleep until they awoke spontaneously in the morning. Duration 21 days. Concurrent medication/care: Patients were allowed to continue treatment for their psychiatric condition providing a constant dosage regimen was maintained. 85% overall of the patients were taking concomitant medication; antipsychotics (62%), antidepressants (12%) and drugs for the treatment of movement disorders (22%) were the most frequent ones.

	Others included cardiovascular drugs, diuretics and other medications (figures not provided). Indirectness: No indirectness (n=40) Intervention 2: Starting dose - High dose. Patients were withdrawn from any previous hypnotic or benzodiazepine medication and 3-14 days later (depending on the duration of action of the previous hypnotic) started a 7-day placebo treatment period. Patients received 20mg of zolpidem as a single capsule for 21 days, followed by a 7-day placebo treatment phase. The capsule was given 30 mins before bedtime and patients were allowed to sleep until they awoke spontaneously in the morning. Duration 21 days. Concurrent medication/care: Patients were allowed to continue treatment for their psychiatric condition providing a constant dosage regimen was maintained. 85% overall of the patients were taking concomitant medication; antipsychotics (62%), antidepressants (12%) and drugs for the treatment of movement disorders (22%) were the most frequent ones. Others included cardiovascular drugs, diuretics and other medications (figures not provided). Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: 10MG ZOLPIDEM versus 20MG ZOLPIDEM

Protocol outcome 1: Mortality (all-cause mortality and breakdown of overdose or suicide related mortality)

- Actual outcome for Z-drugs: Mortality at During the 7 day withdrawal period (placebo); Group 1: 0/40, Group 2: 1/40; Comments: Death from pneumonia (post treatment)

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported not to be comparable for height and total sleep time. Insomnia mean (SE) duration in weeks 91.8 (16.21) vs. 11.4 (18.4). After placebo washout: sleep duration of ≤6hrs 63% vs. 82%.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Withdrawal symptoms including rebound symptoms / intensity or duration of withdrawal syndrome

- Actual outcome for Z-drugs: Withdrawal symptoms at During the 7 day withdrawal period (placebo); Group 1: 0/38, Group 2: 0/36; Comments: Narrative report of "no withdrawal symptoms during the second 7-day placebo treatment period".
Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low, Comments - Narrative description given only.; Indirectness of outcome: No indirectness ; Baseline details: Reported not to be comparable for height and total sleep time. Insomnia mean (SE) duration in weeks 91.8 (16.21) vs. 11.4 (18.4). After placebo washout: sleep duration of ≤6hrs 63% vs. 82%.; Group 1 Number missing: 2, Reason: Withdrew due to AEs (ataxia and drowsiness, death from pneumonia (post treatment)); Group 2 Number missing: 4, Reason: Withdrew due to AEs (irritability and aggression, excessive sedation, drowsiness and lethargy) and went on holiday (n=1)

Protocol outcomes not reported by the study	Quality of life; Dependence on the prescribed medicine (accept study definition); Non-fatal overdose; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed

Study	**Sir 2005[108]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=163)
Countries and setting	Conducted in Australia, Turkey; Setting: 7 sites in Turkey and 6 sites in Australia. Details of exact sites not given.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 8 weeks intervention followed by 2-week taper
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis was made using the Mini International Neuropsychiatric Interview (MINI) 5.0.0.
Stratum	Mixed (all drug classes): SSRI vs. Other
Subgroup analysis within study	Not applicable
Inclusion criteria	Outpatients ≥18 years, 17 item Hamilton Rating Scale for Depression (HAM-D) total score of ≥18 at screening visit (with HAM-D item 1 [depressed mood] score ≥2) and met criteria for MDD, single episode or recurrent, without psychotic features as defined by the DSM-IV. Women of childbearing age to have a negative serum β-hCG pregnancy test and practice an effective form of contraception.
Exclusion criteria	History of bipolar disorder, any psychotic disorder, delirium, dementia, alcohol/drug abuse/ dependence (in the past 6 months) or schizoid, schizotypal or borderline personality disorders. DSM-IV Axis I diagnoses not listed above were permitted only if they were identified as secondary diagnoses. History of nonresponse to sertraline (≥ 150mg/day for ≥4 weeks), venlafaxine or venlafaxine XR (≥150mg/day for ≥4 weeks) or nonresponse to an adequate trial of 2 antidepressants in the current episode.
Recruitment/selection of patients	Recruited between October 2002 and July 2003. The last subject's last visit was in September 2003.
Age, gender and ethnicity	Age - Mean (SD): 37.0 (12.9). Gender (M:F): 50:113. Ethnicity: White 96.2% Sertraline, 100% Venlafaxine XR
Further population details	1. Gabapentinoids: Not applicable
Indirectness of population	No indirectness

Interventions	(n=79) Intervention 1: Flexibly titrated Sertraline (50-150mg/day). Dosage could be increased in increments of 50mg at scheduled visits, at least 1 week apart, in the event that the subject did not exhibit a satisfactory treatment response and in the absence of dose-limiting side effects. Dose reductions of the same magnitude were allowed at weeks 2,3,4, and 6 to a minimum of 50mg/day. Starting at the week 8 visit tapering began at a rate not exceeding 50mg/day every 4 days, with the goal of having all subjects study drug free by the end of week 10. Mean dose at week 8 as 105.4 (29.51) mg/day, n=69. Duration 8 weeks of active treatment followed by a 2-week taper. Concurrent medication/care: Not described. Indirectness: No indirectness (n=84) Intervention 2: Flexibly titrated Venlafaxine XR (75-225mg/day). Dosage could be increased in increments of 75mg at scheduled visits, at least 1 week apart, in the event that the subject did not exhibit a satisfactory treatment response and in the absence of dose-limiting side effects. Dose reductions of the same magnitude were allowed at weeks 2,3,4, and 6 to a minimum of 75mg/day. Starting at the week 8 visit tapering began at a rate not exceeding 75mg/day every 4 days, with the goal of having all subjects study drug free by the end of week 10. Mean dose at week 8 was 161.4 (44.36) mg/day, n=62. Duration 8 weeks of active treatment followed by a 2-week taper. Concurrent medication/care: Not described. Indirectness: No indirectness
Funding	Study funded by industry (Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SERTRALINE versus VENLAFAXINE XR

Protocol outcome 1: Withdrawal symptoms including rebound symptoms / intensity or duration of withdrawal syndrome
- Actual outcome for Mixed (all drug classes): Deterioration during taper period at Weeks 8-10 (taper period); Group 1: mean 7.8 Total score (SD 1.14); n=72, Group 2: mean 10.2 Total score (SD 1.2); n=64; Antidepressant Discontinuation Scale (ADDS) 0-210 Top=High is poor outcome; Comments: Unvalidated scale. 30 items each scored on intensity (0-3, 3 being severe) and relationship to discontinuation (1-4, 4 being definite). The total intensity score can be up to 210. The Investigator also makes a rating from 0 (none) to 5 (very severe) discontinuation symptoms. It is unclear whether this score is added to the total intensity score or just reported separately.
Means reported are the least square means, with treatment and study site fitted as factors.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Randomised using permuted block method (with a block size of 4) stratified by centre. No information on the method of randomising. Unvalidated scale used (Antidepressant Discontinuation Scale). This has not been downgraded for as not specified on the protocol. Indirectness of outcome: No indirectness ; Blinding details: Double blind (double dummy) design. Patient subjective outcome so low risk of bias as blinded.; Group 1 Number missing: 7, Reason: Overall 13 dropped out. Unclear why 7 did not have LOCF.; Group 2 Number missing: 20, Reason: Overall 25 dropped out. Unclear why 20 did not have LOCF.
- Actual outcome for Mixed (all drug classes): Worst severity of discontinuation symptoms (investigator global assessment); None at Weeks 8-10 (taper period); Group 1: 12/67, Group 2: 7/62
Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low,

Comments - Randomised using permuted block method (with a block size of 4) stratified by centre. No information on the method of randomising. Unvalidated scale used (Antidepressant Discontinuation Scale). As the outcome is no discontinuation symptoms, it has been marked as low risk of bias.; Indirectness of outcome: No indirectness ; Blinding details: Double blind (double dummy) design. Investigator assessed subjective outcome, so it has been classed as high risk of bias as it was unclear/ not stated to be triple blind/ outcome assessor blinded.; Group 1 Number missing: 12, Reason: Overall 13 dropped out. Unclear why 12 did not have LOCF.; Group 2 Number missing: 22, Reason: Overall 25 dropped out. Unclear why 22 did not have LOCF.
- Actual outcome for Mixed (all drug classes): Worst severity of discontinuation symptoms (investigator global assessment); Minimal at Weeks 8-10 (taper period); Group 1: 16/67, Group 2: 11/62
Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Randomised using permuted block method (with a block size of 4) stratified by centre. No information on the method of randomising. Unvalidated scale used (Antidepressant Discontinuation Scale). The investigator assessed part of this scale is not clearly defined so assessed as a high risk of bias.; Indirectness of outcome: No indirectness; Blinding details: Double blind (double dummy) design. Investigator assessed subjective outcome, so it has been classed as high risk of bias as it was unclear/ not stated to be triple blind/ outcome assessor blinded.; Group 1 Number missing: 12, Reason: Overall 13 dropped out. Unclear why 12 did not have LOCF.; Group 2 Number missing: 22, Reason: Overall 25 dropped out. Unclear why 22 did not have LOCF.
- Actual outcome for Mixed (all drug classes): Worst severity of discontinuation symptoms (investigator global assessment); Mild at Weeks 8-10 (taper period); Group 1: 16/67, Group 2: 17/62
Risk of bias: All domain – Very High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Randomised using permuted block method (with a block size of 4) stratified by centre. No information on the method of randomising. Unvalidated scale used (Antidepressant Discontinuation Scale). The investigator assessed part of this scale is not clearly defined so assessed as a high risk of bias.; Indirectness of outcome: No indirectness; Blinding details: Double blind (double dummy) design. Investigator assessed subjective outcome, so it has been classed as high risk of bias as it was unclear/ not stated to be triple blind/ outcome assessor blinded.; Group 1 Number missing: 12, Reason: Overall 13 dropped out. Unclear why 12 did not have LOCF.; Group 2 Number missing: 22, Reason: Overall 25 dropped out. Unclear why 22 did not have LOCF.
- Actual outcome for Mixed (all drug classes): Worst severity of discontinuation symptoms (investigator global assessment); Moderate at Weeks 8-10 (taper period); Group 1: 23/67, Group 2: 24/62
Risk of bias: All domain - Very High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Randomised using permuted block method (with a block size of 4) stratified by centre. No information on the method of randomising. Unvalidated scale used (Antidepressant Discontinuation Scale). The investigator assessed part of this scale is not clearly defined so assessed as a high risk of bias.; Indirectness of outcome: No indirectness ; Blinding details: Double blind (double dummy) design. Investigator assessed subjective outcome, so it has been classed as high risk of bias as it was unclear/ not stated to be triple blind/ outcome assessor blinded.; Group 1 Number missing: 12, Reason: Overall 13 dropped out. Unclear why 12 did not have LOCF.; Group 2 Number missing: 22, Reason: Overall 25 dropped out. Unclear why 22 did not have LOCF.
- Actual outcome for Mixed (all drug classes): Worst severity of discontinuation symptoms (investigator global assessment); Severe at Weeks 8-10 (taper period); Group 1: 0/67, Group 2: 2/62
Risk of bias: All domain - Very High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Randomised using permuted block method (with a block size of 4) stratified by centre. No information on the method of randomising. Unvalidated scale used (Antidepressant Discontinuation Scale). The investigator assessed part of this scale is not clearly defined so assessed as a high risk of bias.; Indirectness of outcome: No indirectness ; Blinding details: Double blind (double dummy) design. Investigator assessed subjective outcome, so it has been classed as high risk of bias as it was unclear/

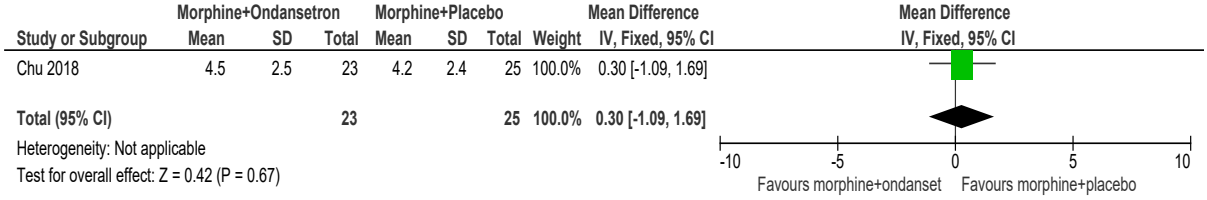
not stated to be triple blind/ outcome assessor blinded.; Group 1 Number missing: 12, Reason: Overall 13 dropped out. Unclear why 12 did not have LOCF.; Group 2 Number missing: 22, Reason: Overall 25 dropped out. Unclear why 22 did not have LOCF. - Actual outcome for Mixed (all drug classes): Worst severity of discontinuation symptoms (investigator global assessment); Very severe at Weeks 8-10 (taper period); Group 1: 0/67, Group 2: 1/62 Risk of bias: All domain - Very High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Randomised using permuted block method (with a block size of 4) stratified by centre. No information on the method of randomising. Unvalidated scale used (Antidepressant Discontinuation Scale). The investigator assessed part of this scale is not clearly defined so assessed as a high risk of bias.; Indirectness of outcome: No indirectness ; Blinding details: Double blind (double dummy) design. Investigator assessed subjective outcome, so it has been classed as high risk of bias as it was unclear/ not stated to be triple blind/ outcome assessor blinded.; Group 1 Number missing: 12, Reason: Overall 13 dropped out. Unclear why 12 did not have LOCF.; Group 2 Number missing: 22, Reason: Overall 25 dropped out. Unclear why 22 did not have LOCF.	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Dependence on the prescribed medicine (accept study definition); Non-fatal overdose; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed

Appendix E Forest plots

E.1 Opioids

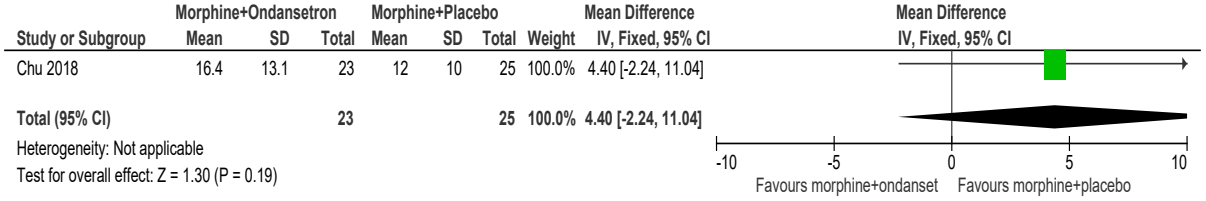
E.1.1 Morphine plus Ondansetron vs Morphine plus Placebo

Figure 2: Withdrawal symptoms (OOWS) at 12 months



Objective Opioid Withdrawal Scale score 0-13, higher is worse

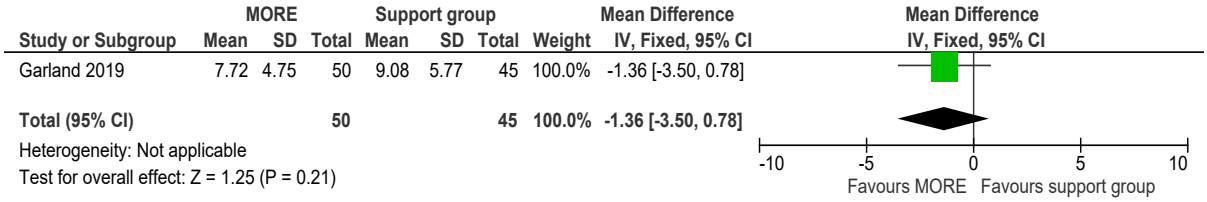
Figure 3: Withdrawal symptoms (SOWS) at 12 months



Subjective Opioid Withdrawal Scale score 0-64, higher is worse

E.1.2 MORE vs Support Group

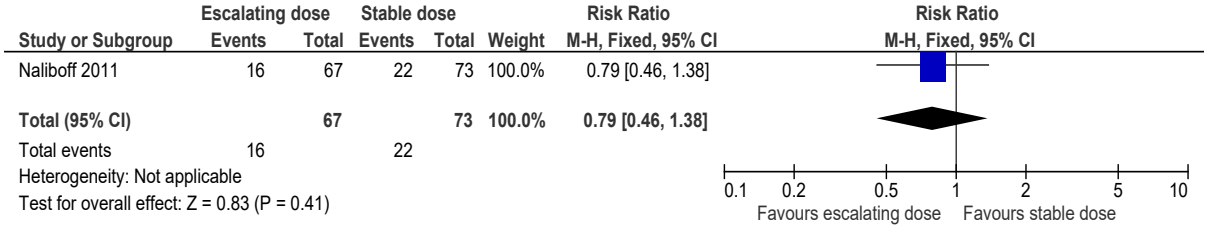
Figure 22: Dependence on the prescribed medicine (Opioid misuse- assessed with Current Opioid Misuse Measure) at 3-month follow-up



Participants responded to 17 items rated on a 5-point Likert scale from 0 (never) to 4 (very often) regarding how often in the past 30 days they had engaged in aberrant drug-related behaviours linked with opioid misuse

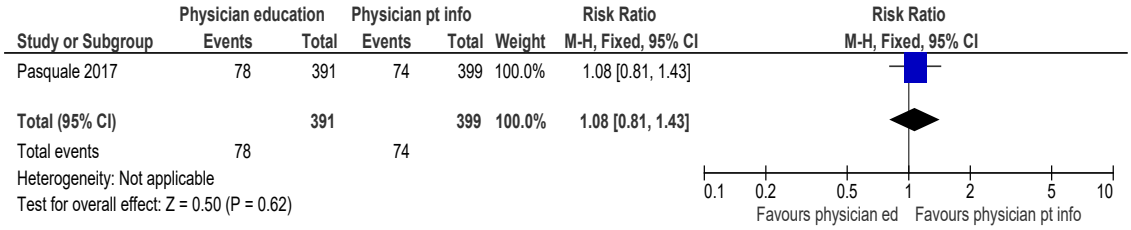
E.1.3 Escalating vs Stable dose

Figure 4: Dependence on the prescribed medicine (Medication discontinuation for non-compliance at 12 months)



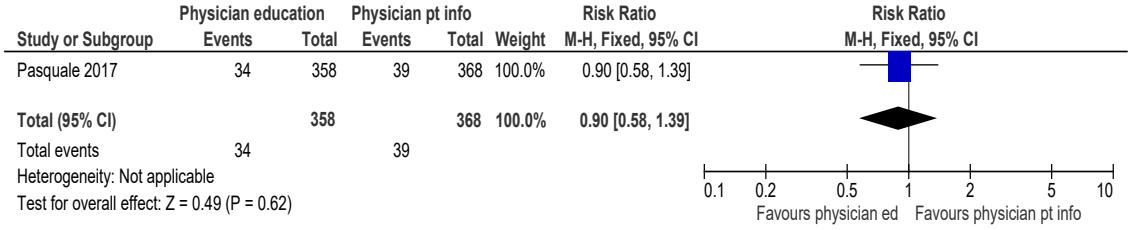
E.1.4 Physician education vs Physician patient information

Figure 5: Dependence on the prescribed medicine (Uncoordinated opioid use* at 91-270 days post intervention)



** >3 opioid prescription fills of any ingredient written by ≥3 prescribers within any 90-day period.*

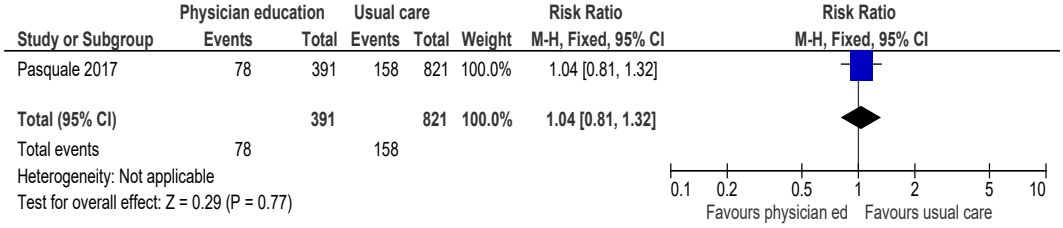
Figure 6: Dependence on the prescribed medicine (Diagnosis of opioid abuse at 91-270 days post intervention)



People diagnosed with opioid abuse during preintervention were excluded from the diagnosed opioid abuse outcome

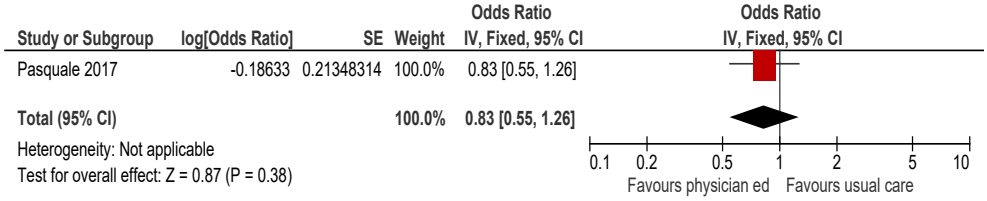
E.1.5 Physician education vs usual care (opioids)

Figure 7: Dependence on the prescribed medicine (Uncoordinated opioid use* at 91-270 days post intervention)



** >3 opioid prescription fills of any ingredient written by ≥3 prescribers within any 90-day period.*

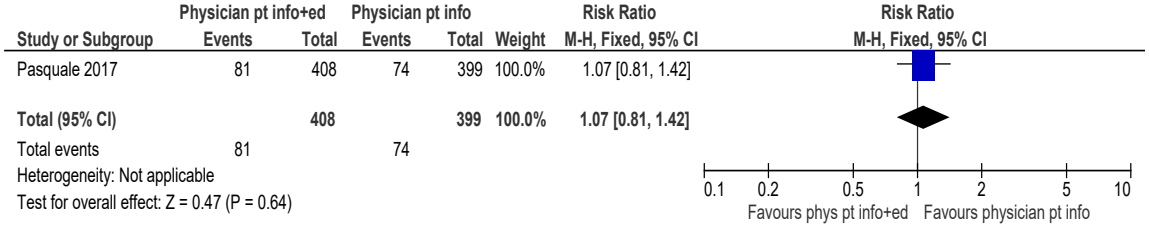
Figure 8: Dependence on the prescribed medicine (Diagnosis of opioid abuse at 91-270 days post intervention)



People diagnosed with opioid abuse during preintervention were excluded from the diagnosed opioid abuse outcome.

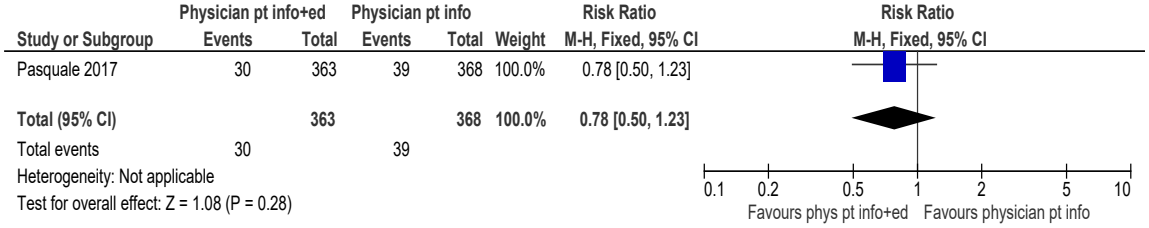
E.1.6 Physician patient information and education vs Physician patient information (opioids)

Figure 9: Dependence on the prescribed medicine (Uncoordinated opioid use* at 91-270 days post intervention)



** >3 opioid prescription fills of any ingredient written by ≥3 prescribers within any 90-day period.*

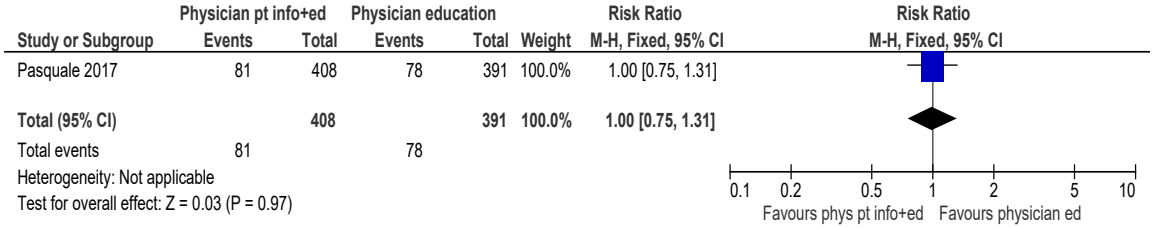
Figure 10: Dependence on the prescribed medicine (Diagnosis of opioid abuse at 91-270 days post intervention)



People diagnosed with opioid abuse during preintervention were excluded from the diagnosed opioid abuse outcome

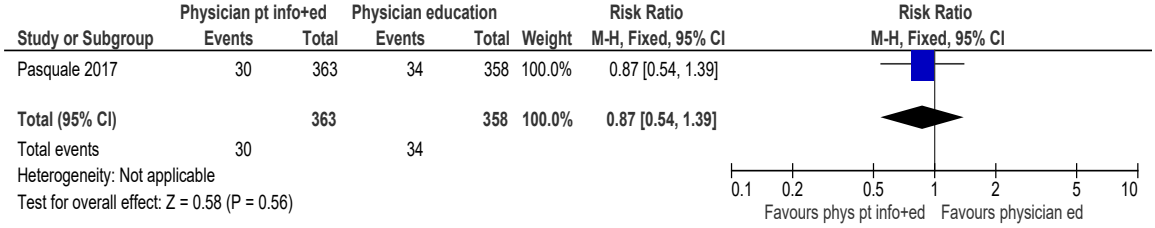
E.1.7 Physician patient information and education vs Physician education (opioids)

Figure 11: Dependence on the prescribed medicine (Uncoordinated opioid use* at 91-270 days post intervention)



** >3 opioid prescription fills of any ingredient written by ≥3 prescribers within any 90-day period.*

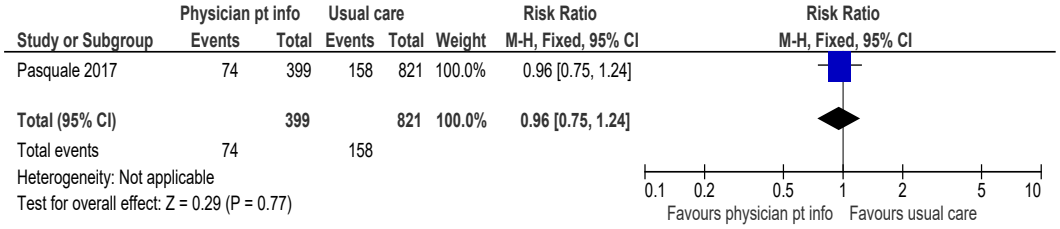
Figure 12: Dependence on the prescribed medicine (Diagnosis of opioid abuse at 91-270 days post intervention)



People diagnosed with opioid abuse during preintervention were excluded from the diagnosed opioid abuse outcome

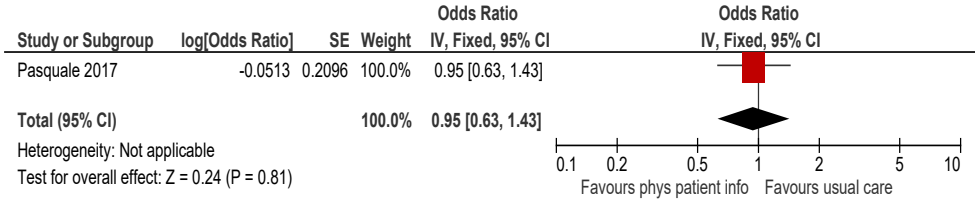
E.1.8 Physician patient information vs Usual care (opioids)

Figure 13: Dependence on the prescribed medicine (Uncoordinated opioid use* at 91-270 days post intervention)



** >3 opioid prescription fills of any ingredient written by ≥3 prescribers within any 90-day period.*

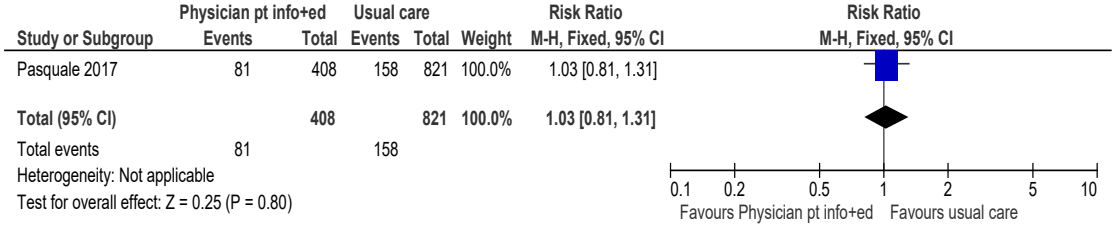
Figure 14: Dependence on the prescribed medicine (Diagnosis of opioid abuse at 91-270 days post intervention)



People diagnosed with opioid abuse during preintervention were excluded from the diagnosed opioid abuse outcome.

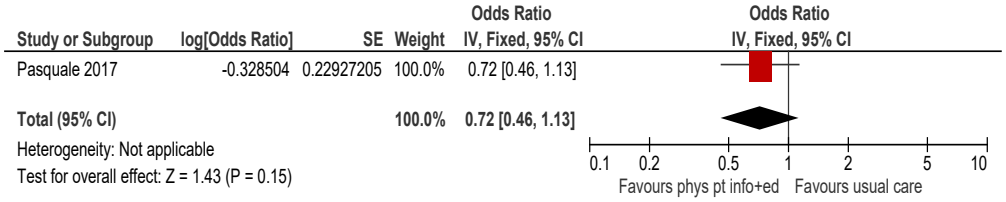
E.1.9 Physician patient information and education vs Usual care (opioids)

Figure 15: Dependence on the prescribed medicine (Uncoordinated opioid use* at 91-270 days post intervention)



** >3 opioid prescription fills of any ingredient written by ≥3 prescribers within any 90-day period.*

Figure 16: Dependence on the prescribed medicine (Diagnosis of opioid abuse at 91-270 days post intervention)

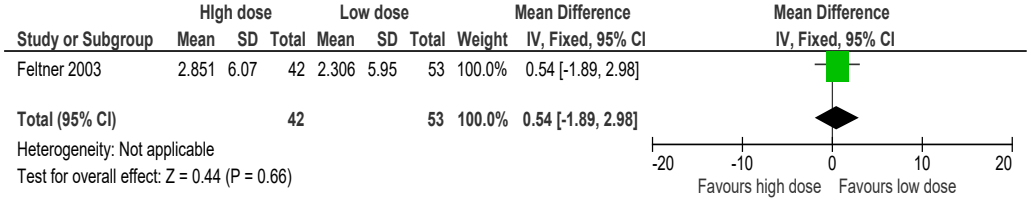


People diagnosed with opioid abuse during preintervention were excluded from the diagnosed opioid abuse outcome.

E.2 Gabapentinoids

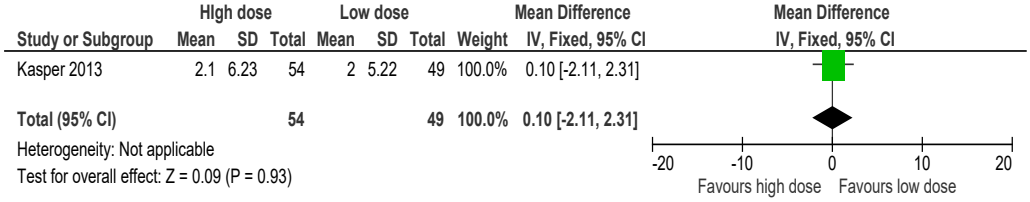
E.2.1 High vs low dose treatment, short-term (gabapentinoids)

Figure 2: Withdrawal symptoms (Physician Withdrawal Checklist) at week 5, 1 week after initiating taper



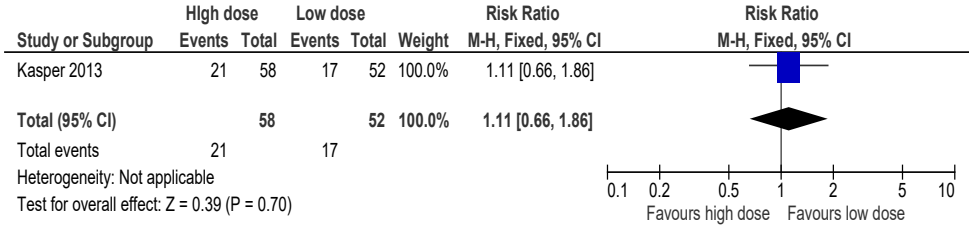
Physician Withdrawal Checklist score range 0-60, higher value is worse. Post- taper outcome.

Figure 3: Withdrawal symptoms (Physician Withdrawal Checklist) at week 14, week 2 after initiating taper



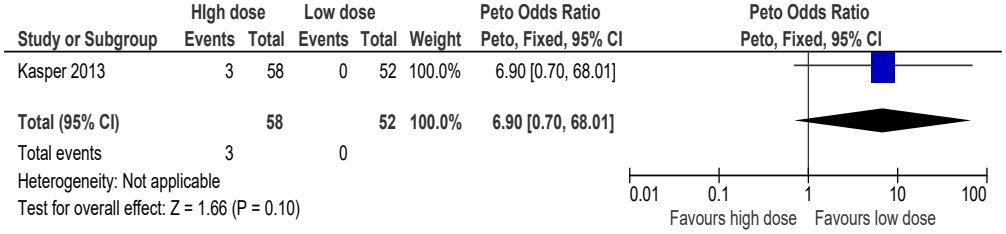
Physician Withdrawal Checklist score range 0-60, higher value is worse. Included all people who discontinued between weeks 9-15, or who switched to placebo at the end of week 12 and had a corresponding assessment in the 2 weeks following initiation of the taper. Longest follow-up after taper.

Figure 17: Withdrawal symptoms –People with DESS during the 2 week post taper period (weeks 13 and 14)



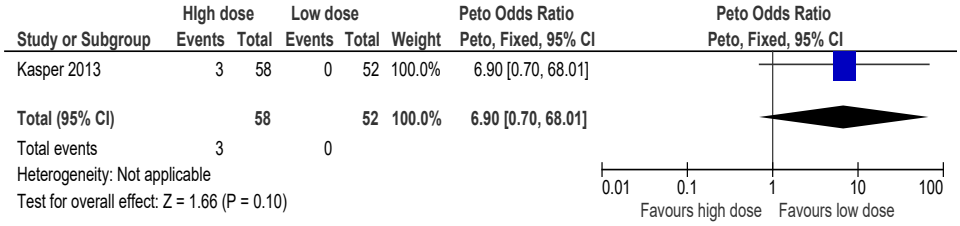
Discontinuation-Emergent Signs and Symptoms (DESS) adverse events are a subset of Treatment Emergent Signs and Symptoms and were defined as those spontaneously reported adverse events that developed or existed prior to but worsened during the 2 weeks following taper initiation.

Figure 18: Withdrawal symptoms – anxiety (DESS) during the 2 week post taper period (weeks 13 and 14)



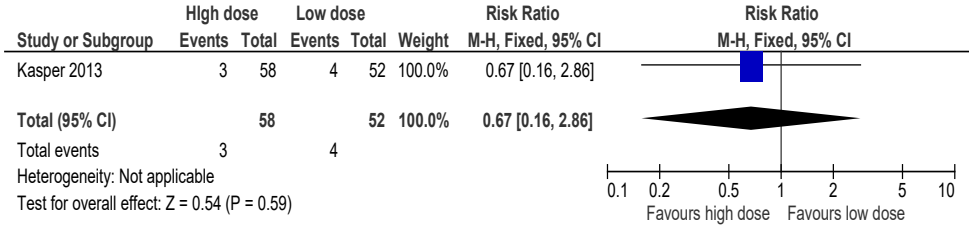
All people who discontinued between weeks 9-15, or who switched to placebo at the end of week 12, and had a corresponding discontinuation week assessment. Only DESS with an incidence of ≥5% were recorded.

Figure 19: Withdrawal symptoms- dizziness (DESS) during the 2 week post taper period (weeks 13 and 14)



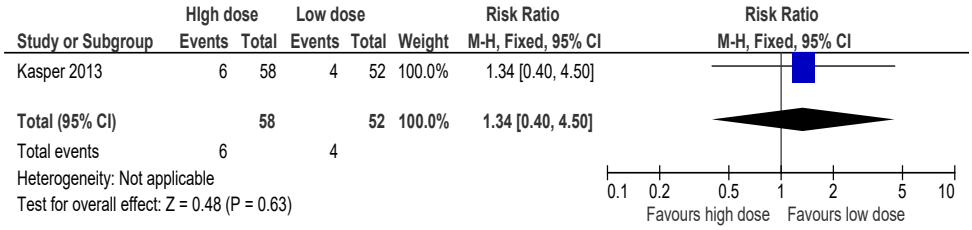
All people who discontinued between weeks 9-15, or who switched to placebo at the end of week 12, and had a corresponding discontinuation week assessment. Only DESS with an incidence of ≥5% were recorded.

Figure 20: Withdrawal symptoms- headache (DESS) during the 2-week post taper period (weeks 13 and 14)



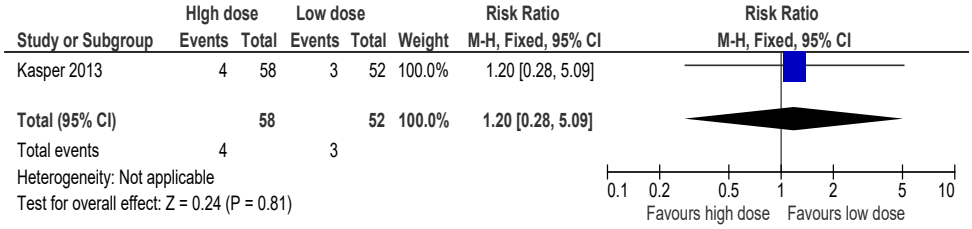
All people who discontinued between weeks 9-15, or who switched to placebo at the end of week 12, and had a corresponding discontinuation week assessment. Only DESS with an incidence of ≥5% were recorded.

Figure 21: Withdrawal symptoms- insomnia (DESS) during the 2-week post taper period (weeks 13 and 14)



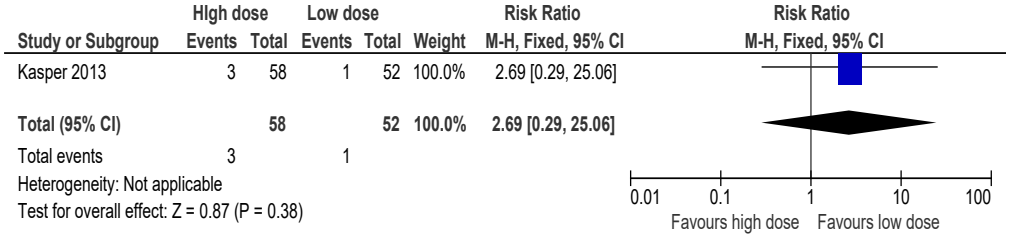
Source: All people who discontinued between weeks 9-15, or who switched to placebo at the end of week 12, and had a corresponding discontinuation week assessment. Only DESS with an incidence of ≥5% were recorded.

Figure 22: Withdrawal symptoms- nausea (DESS) during the 2 week post taper period (weeks 13 and 14)



Source: All people who discontinued between weeks 9-15, or who switched to placebo at the end of week 12, and had a corresponding discontinuation week assessment. Only DESS with an incidence of ≥5% were recorded.

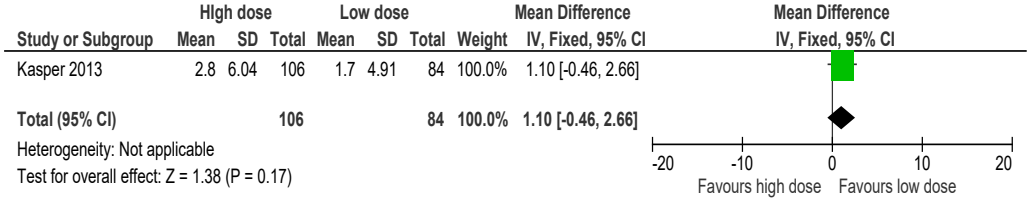
Figure 23: Withdrawal symptoms (Rebound anxiety) during the 2 week post taper period (weeks 13 and 14)



Rebound anxiety was defined as a Hamilton Anxiety Rating Scale total score greater than the baseline score during either of the 2 weeks following taper initiation.

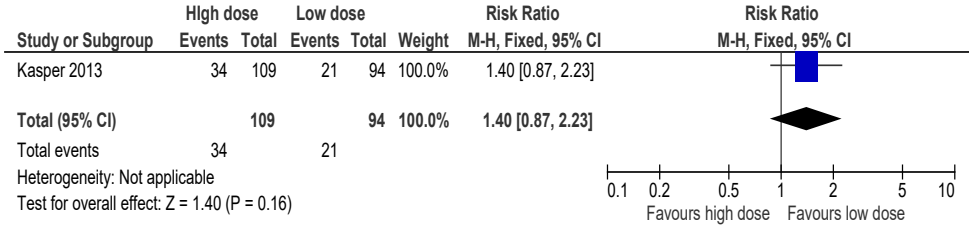
E.2.2 High vs low dose treatment, long-term (gabapentinoids)

Figure 24: Withdrawal symptoms (Physician Withdrawal Checklist) at week 26 (week 2 after initiating taper)



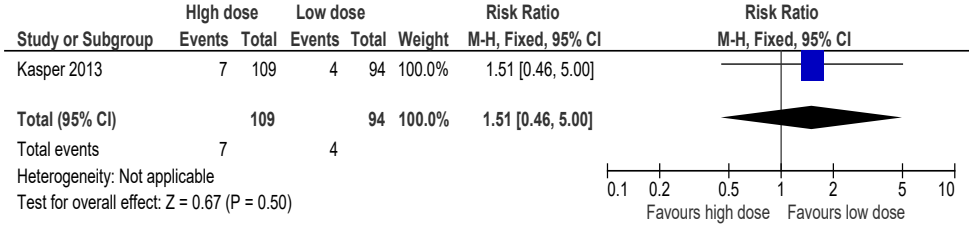
Physician Withdrawal Checklist score range 0-60, higher is worse. Included all people who either completed the study or discontinued after week 13, and had a corresponding assessment in the 2 weeks following taper initiation.

Figure 25: Withdrawal symptoms- People with DESS during the 2-week taper period (weeks 25 and 26)



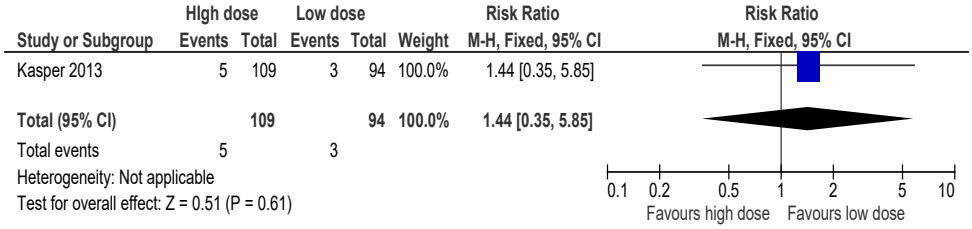
Discontinuation-Emergent Signs and Symptoms (DESS) adverse events are a subset of Treatment Emergent Signs and Symptoms and were defined as those spontaneously reported adverse events that developed or existed prior to but worsened during the 2 weeks following taper initiation.

Figure 26: Withdrawal symptoms- anxiety (DESS) during the 2 -week taper period (weeks 25 and 26)



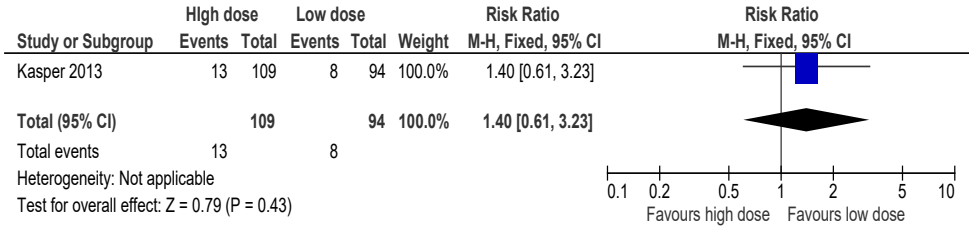
Source: All people who either completed the study or discontinued after week 15, and had a corresponding discontinuation week assessment. Only DESS with an incidence of ≥5% were recorded.

Figure 27: Withdrawal symptoms- headache (DESS) during the 2- week taper period (weeks 25 and 26)



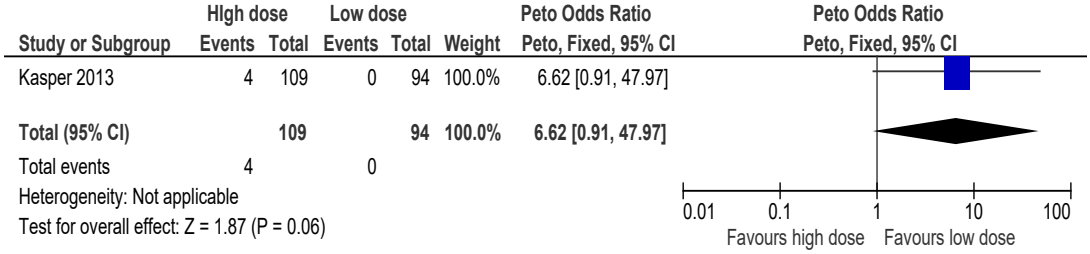
Source: All people who either completed the study or discontinued after week 15, and had a corresponding discontinuation week assessment. Only DESS with an incidence of ≥5% were recorded.

Figure 28: Withdrawal symptoms- insomnia (DESS) during the 2- week taper period (weeks 25 and 26)



Source: All people who either completed the study or discontinued after week 15, and had a corresponding discontinuation week assessment. Only DESS with an incidence of ≥5% were recorded.

Figure 29: Withdrawal symptoms (Rebound anxiety) during 2-week taper period (weeks 25 and 26)

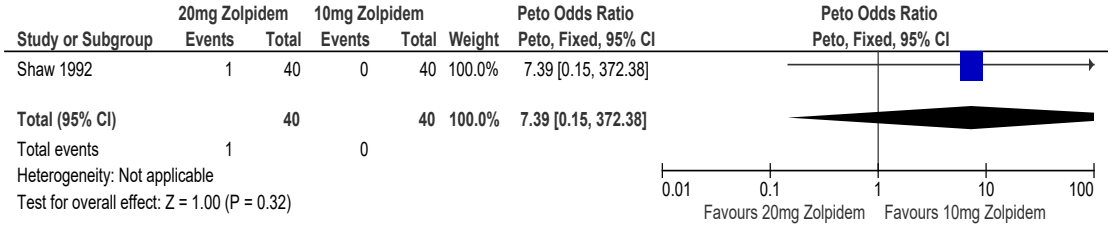


Rebound anxiety was defined as a Hamilton Anxiety Rating Scale total score greater than the baseline score during either of the 2 weeks following taper initiation.

E.3 Z-drugs

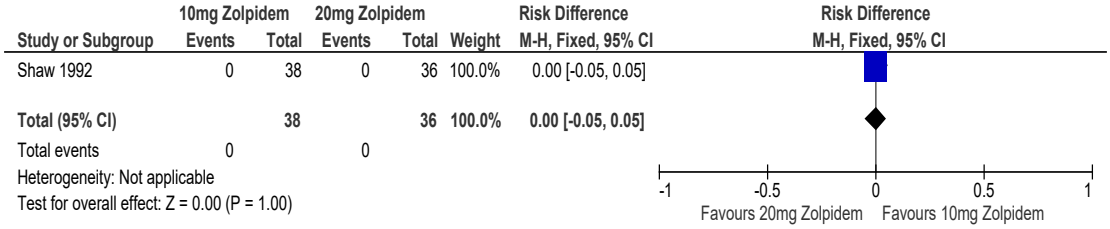
E.3.1 20mg Zolpidem vs 10mg Zolpidem (Z-drugs)

Figure 30: Mortality during the 7-day withdrawal period (22-28 days)



Death from pneumonia (post treatment)

Figure 31: Withdrawal symptoms during the 7-day withdrawal period (22-28 days)

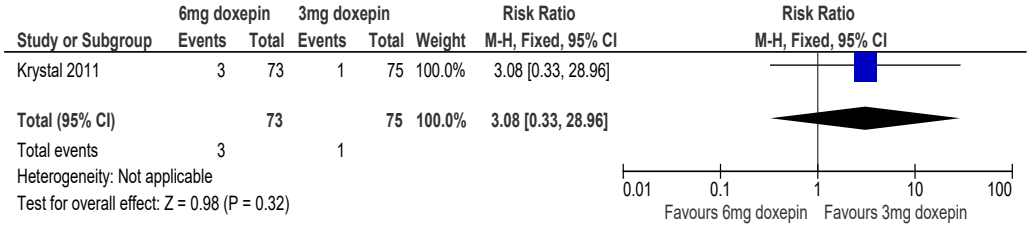


Narrative report of "no withdrawal symptoms during the second 7-day placebo treatment period".

E.4 Antidepressants

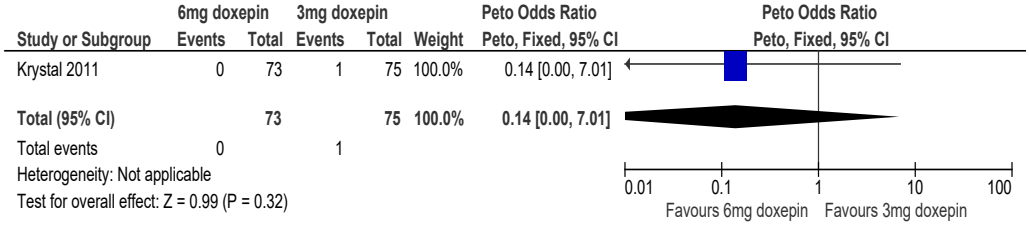
E.4.1 6mg doxepin vs 3mg doxepin (TCA antidepressants)

Figure 32: Withdrawal symptoms (rebound insomnia) at 5 weeks



actual numbers assumed by NGC calculations, % only provided in study. Rebound insomnia (based on wake time after sleep onset (WASO) criteria experienced over the 2 nights after discontinuation

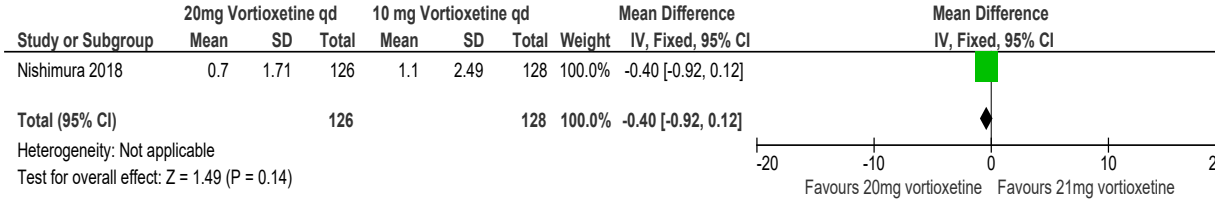
Figure 33: Withdrawal symptoms (BWSQ 3 or more new symptoms at 5 weeks)



Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) criteria of 3 more new symptoms

E.4.2 20 mg Vortioxetine qd vs 10 mg Vortioxetine qd (Other antidepressants)

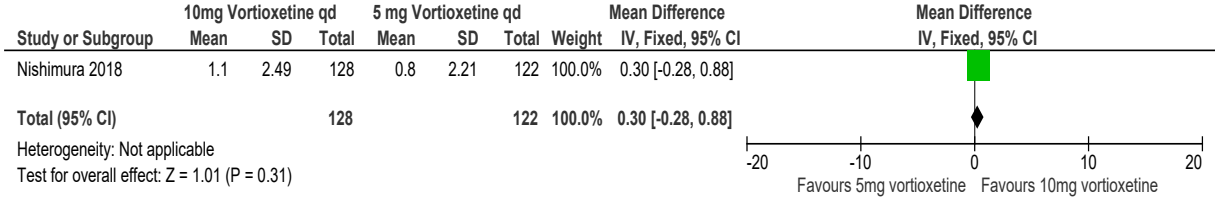
Figure 34: Withdrawal symptoms (DESS) at week 10



Discontinuation- Emergent Signs and Symptoms (DESS) scale unclear if higher or lower value is worse. Range of values unclear

E.4.3 10 mg Vortioxetine qd vs 5 mg Vortioxetine qd (Other antidepressants)

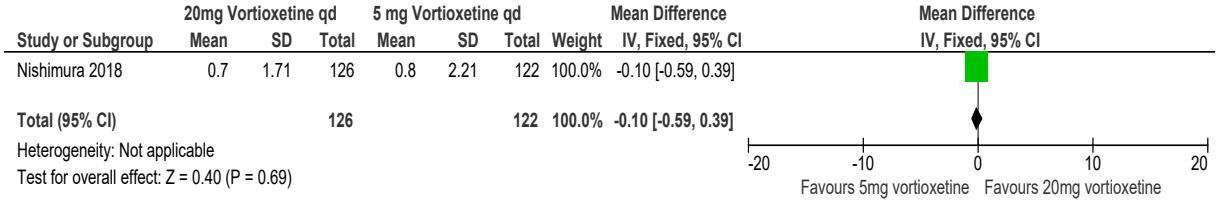
Figure 35: Withdrawal symptoms (DESS) at week 10



Discontinuation- Emergent Signs and Symptoms (DESS) scale unclear if higher or lower value is worse. Range of values unclear

E.4.4 20 mg Vortioxetine qd vs 5 mg Vortioxetine qd (Other antidepressants)

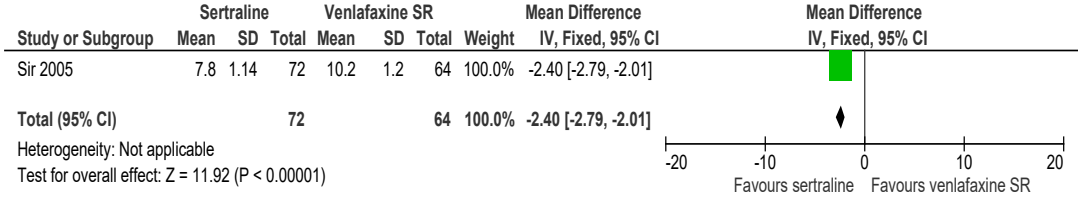
Figure 36: Withdrawal symptoms (DESS) at week 10



Discontinuation- Emergent Signs and Symptoms (DESS) scale higher values = worse outcome. Range of values unclear

E.4.5 Sertraline vs Venlafaxine SR (SSRI and other antidepressants)

Figure 37: Withdrawal symptoms: Deterioration during taper (weeks 8-10)



Antidepressant Discontinuation Scale (ADDS), score 0-210, higher is worse. Unvalidated scale. 30 items each scored on intensity (0-3, 3 being severe) and relationship to discontinuation (1-4, 4 being definite). The total intensity score can be up to 210. The Investigator also makes a rating from 0 (none) to 5 (very severe) discontinuation symptoms. It is unclear whether this score is added to the total intensity score or just reported separately.

Figure 38: Worst severity of discontinuation symptoms (investigator global assessment); none (weeks 8-10)

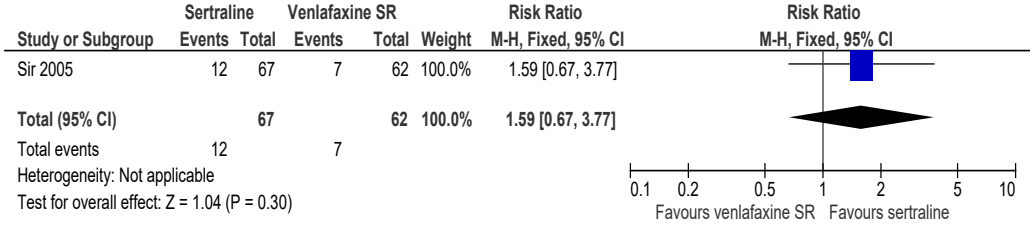


Figure 39: Worst severity of discontinuation symptoms (investigator global assessment); minimal (weeks 8-10)

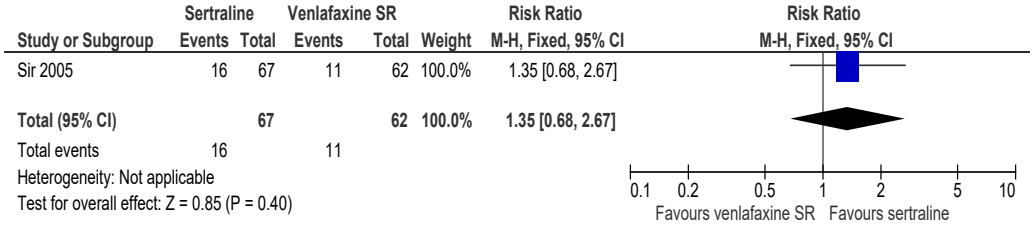


Figure 40: Worst severity of discontinuation symptoms (investigator global assessment); mild (weeks 8-10)

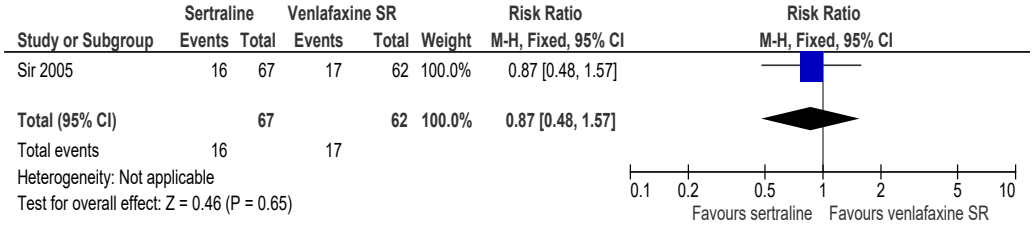


Figure 41: Worst severity of discontinuation symptoms (investigator global assessment); moderate (weeks 8-10)

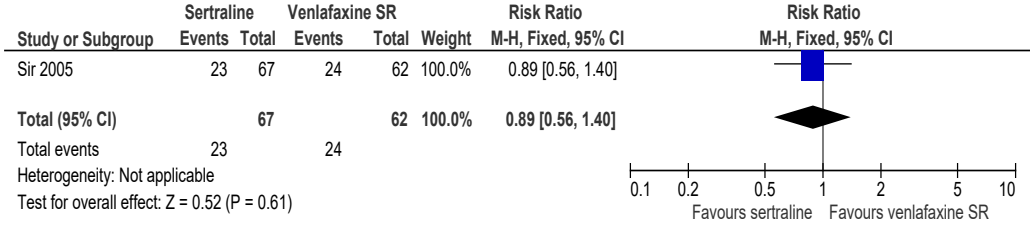


Figure 42: Worst severity of discontinuation symptoms (investigator global assessment); severe (weeks 8-10)

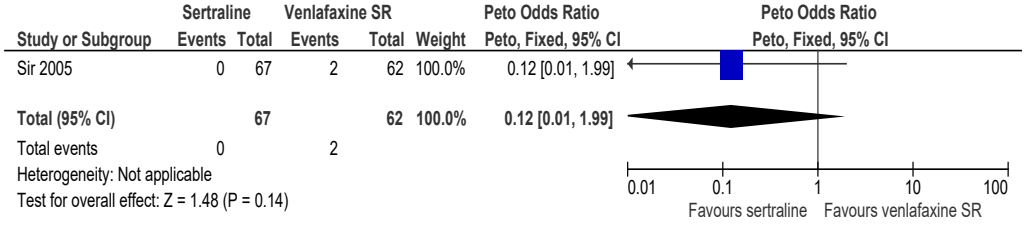
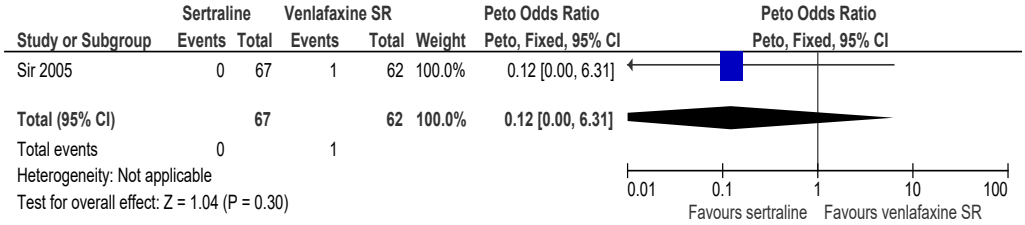


Figure 43: Worst severity of discontinuation symptoms (investigator global assessment); very severe (weeks 8-10)



Appendix F GRADE tables

F.1 Opioids

Table 25: Clinical evidence profile: Morphine plus Ondansetron vs Morphine plus placebo (opioids)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Morphine Ondansetron	Morphine placebo	Relative (95% CI)	Absolute (95% CI)		
Withdrawal Symptoms (follow up: 40 days; assessed with: Objective Opioid Withdrawal Scale; Scale from: 0 to 13)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	23	25	-	MD **0.3 higher** (1.09 lower to 1.69 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal Symptoms (follow up: 40 days; assessed with: Subjective Opioid Withdrawal Scale; Scale from: 0 to 64)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	23	25	-	MD **4.4 higher** (2.24 lower to 11.04 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 2 increments as the confidence interval crossed 2 MIDs. MID for OOWS was 0.325 and MID for SOWS was 0.9 (0.5 median baseline SDs of intervention and control groups).*

Table 26: Clinical evidence profile: MORE vs Support group (opioids)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MORE	Support group	Relative (95% CI)	Absolute (95% CI)		
Dependence on the prescribed drug (follow up: 3 months; assessed with: Opioid misuse)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	50	45	-	MD **1.36 lower** (3.5 lower to 0.78 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 1 increment as the CI crossed 1 MID. MID calculated by 0.5x median of baseline SD for intervention and control groups. Calculated MID was 1.36

Table 27: Clinical evidence profile: Escalating vs Stable dose (opioids)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Escalating dose	stable dose	Relative (95% CI)	Absolute (95% CI)		
Dependence on the prescribed drug (follow up: 12 months; assessed with: Opioid medication discontinuation for non-compliance)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	16/67 (23.9%)	22/73 (30.1%)	**RR 0.79** (0.46 to 1.38)	**63 fewer per 1,000** (from 163 fewer to 115 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 2 increments as the confidence interval crossed 2 MIDs. The MID for dichotomous outcomes was 0.8 and 1.25.

Table 28: Clinical evidence profile: Physician education vs physician patient information (opioids)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physician education	physician patient information	Relative (95% CI)	Absolute (95% CI)		
Dependence on the prescribed medicine (follow up: 91-270 days; assessed with: uncoordinated opioid use)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	78/391 (19.9%)	74/399 (18.5%)	**RR 1.08** (0.81 to 1.43)	**15 more per 1,000** (from 35 fewer to 80 more)	⨁◯◯◯ VERY LOW	CRITICAL
Dependence on the prescribed medicine (follow up: 91-270 days; assessed with: diagnosis of opioid abuse)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	34/358 (9.5%)	39/368 (10.6%)	**RR 0.90** (0.58 to 1.39)	**11 fewer per 1,000** (from 45 fewer to 41 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25.

Table 29: Clinical evidence profile: Physician education vs usual care (opioids)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physician education	usual care	Relative (95% CI)	Absolute (95% CI)		
Dependence on the prescribed medicine (follow up: 91-270 days; assessed with: Uncoordinated opioid use)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	78/391 (19.9%)	158/821 (19.2%)	**RR 1.04** (0.81 to 1.32)	**8 more per 1,000** (from 37 fewer to 62 more)	⨁◯◯◯ VERY LOW	CRITICAL
Diagnosis of opioid abuse												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physician education	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	391	821	**OR 0.83** (0.55 to 1.26)	**Unable to calculate**[c]	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25.
c. Unable to calculate absolute effect as adjusted OR reported by study.

Table 30: Clinical evidence profile: Physician patient information and education vs Physician patient information (opioids)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physician patient information and education	physician patient information	Relative (95% CI)	Absolute (95% CI)		
Dependence on the prescribed medicine (follow up: 91-270 days; assessed with: uncoordinated opioid use)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	81/408 (19.9%)	74/399 (18.5%)	**RR 1.07** (0.81 to 1.42)	**13 more per 1,000** (from 35 fewer to 78 more)	⨁◯◯◯ VERY LOW	CRITICAL
Dependence on the prescribed medicine (follow up: 91-270 days; assessed with: diagnosis of opioid abuse)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	30/363 (8.3%)	39/368 (10.6%)	**RR 0.78** (0.50 to 1.23)	**23 fewer per 1,000** (from 53 fewer to 24 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25.

Table 31: Clinical evidence profile: Physician patient information and education vs Physician education (opioids)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physician patient information and education	Physician education	Relative (95% CI)	Absolute (95% CI)		
Dependence on the prescribed medicine (follow up: 91-270 days; assessed with: uncoordinated opioid use)												
1	randomised trials	very serious [a]	not serious	not serious	Very serious [b]	none	81/408 (19.9%)	78/391 (19.9%)	**RR 1.00** (0.75 to 1.31)	**0 fewer per 1,000** (from 50 fewer to 62 more)	⨁◯◯◯ VERY LOW	CRITICAL
Dependence on the prescribed medicine (follow up: 91-270 days; assessed with: diagnosis of opioid abuse)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	30/363 (8.3%)	34/358 (10.6%)	**RR 0.87** (0.54 to 1.39)	**12 fewer per 1,000** (from 44 fewer to 37 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25.

Table 32: Clinical evidence profile: Physician patient information vs usual care (opioids)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physician patient information	usual care	Relative (95% CI)	Absolute (95% CI)		
Dependence on the prescribed medicine (follow up: 91-270 days; assessed with: uncoordinated opioid use)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	74/399 (18.5%)	158/821 (19.2%)	**RR 0.96** (0.75 to 1.24)	**8 fewer per 1,000** (from 48 fewer to 46 more)	⨁◯◯◯ VERY LOW	CRITICAL
Diagnosis of opioid abuse												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physician patient information	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	399	821	**OR 0.95** (0.63 to 1.43)	**Unable to calculate**[c]	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25.
c. Unable to calculate absolute effect as adjusted OR reported by study.

Table 33: Clinical evidence profile: Physician patient information and education vs Usual care (opioids)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physician patient information and education	usual care	Relative (95% CI)	Absolute (95% CI)		
Dependence on the prescribed medicine (follow up: 91-270 days; assessed with: Uncoordinated opioid use)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	81/408 (19.6%)	158/821 (19.2%)	**RR 1.03** (0.81to 1.31)	**6 more per 1,000** (from 37 fewer to 60 more)	⨁◯◯◯ VERY LOW	CRITICAL
Diagnosis of opioid abuse												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	408	821	**OR 0.72** (0.46 to 1.13)	**Unable to calculate**[c]	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25.
c. Unable to calculate absolute effect as adjusted OR reported by study.

F.2 Gabapentinoids

Table 34: Clinical evidence profile: High dose pregabalin (short-term) vs low dose pregabalin (short-term)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose pregabalin (short-term)	low dose pregabalin (short-term)	Relative (95% CI)	Absolute (95% CI)		
Withdrawal symptoms (follow up: 5 weeks; assessed with: Physician Withdrawal Checklist; Scale from: 0 to 60)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	42	53	-	MD **0.54 higher** (1.89 lower to 2.98 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Withdrawal symptoms (follow up: 14 weeks; assessed with: Physician Withdrawal Checklist; Scale from: 0 to 60)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	54	49	-	MD **0.1 higher** (2.17 lower to 2.37 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Withdrawal Symptoms: occurring in 5% or more patients (follow up: 14 weeks; assessed with: Discontinuation- Emergent Signs and Symptoms)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	21/58 (36.2%)	17/52 (32.7%)	**RR 1.11** (0.66 to 1.86)	**36 more per 1,000** (from 111 fewer to 281 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal Symptoms: number of people with anxiety (follow up: 14 weeks; assessed with: Discontinuation-Emergent Signs and Symptoms)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	3/58 (5.2%)	0/52 (0.0%)	**Peto OR 6.90** (0.70 to 68.01)	**50 more per 1,000** [c] (from 10 fewer to 120 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal Symptoms: number of people with dizziness (follow up: 14 weeks; assessed with: Discontinuation-Emergent Signs and Symptoms)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose pregabalin (short-term)	low dose pregabalin (short-term)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	not serious	none	3/58 (5.2%)	0/52 (0.0%)	**Peto OR 6.90** (0.70 to 68.01)	**50 more per 1,000** [c] (from 10 fewer to 120 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal Symptoms: number of people with headache (follow up: 14 weeks; assessed with: Discontinuation- Emergent Signs and Symptoms)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	3/58 (5.2%)	4/52 (7.7%)	**RR 0.67** (0.16 to 2.86)	**25 fewer per 1,000** (from 65 fewer to 143 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal Symptoms: number of people with insomnia (follow up: 14 weeks; assessed with: Discontinuation- Emergent Signs and Symptoms)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	6/58 (10.3%)	4/52 (7.7%)	**RR 1.34** (0.40 to 4.50)	**26 more per 1,000** (from 46 fewer to 269 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal Symptoms: number of people with nausea (follow up: 14 weeks; assessed with: Discontinuation- Emergent Signs and Symptoms)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	4/58 (6.9%)	3/52 (5.8%)	**RR 1.20** (0.28 to 5.09)	**12 more per 1,000** (from 42 fewer to 236 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms: rebound anxiety (follow up: 14 weeks; assessed with: Hamilton Anxiety Rating Scale)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	3/58 (5.2%)	1/52 (1.9%)	**RR 2.69** (0.29 to 25.06)	**33 more per 1,000** (from 14 fewer to 463 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25. The MID for PWC was 0.5 x control group SD as they were change scores. This was 2.98 for the outcome at 5 weeks, and 2.61 for the outcome at 14 weeks.
c. Calculated from risk difference due to zero events in control arm.

Table 35: Clinical evidence profile: High dose pregabalin (long-term) vs low dose pregabalin (long-term)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose pregabalin (long-term)	low dose pregabalin (long-term)	Relative (95% CI)	Absolute (95% CI)		
Withdrawal Symptoms - week 2 after initiating taper (follow up: 26 weeks; assessed with: Physician Withdrawal Checklist; Scale from: 0 to 60)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	106	84	-	MD **1.1 higher** (0.46 lower to 2.66 higher)	⨁⨁◯◯ LOW	CRITICAL
Withdrawal Symptoms: occurring in 5% or more people (follow up: 26 weeks; assessed with: Discontinuation Signs and Symptoms)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	34/109 (31.2%)	21/94 (22.3%)	**RR 1.40** (0.87 to 2.23)	**89 more per 1,000** (from 29 fewer to 275 more)	⨁⨁◯◯ LOW	CRITICAL
Withdrawal Symptoms: number of people with anxiety (follow up: 26 weeks; assessed with: Discontinuation Signs and Symptoms)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	7/109 (6.4%)	4/94 (4.3%)	**RR 1.51** (0.46 to 5.00)	**22 more per 1,000** (from 23 fewer to 170 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms: number of people with headache (follow up: 26 weeks; assessed with: Discontinuation Signs and Symptoms)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	5/109 (4.6%)	3/94 (3.2%)	**RR 1.44** (0.35 to 5.85)	**14 more per 1,000** (from 21 fewer to 155 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms: number of people with insomnia (follow up: 26 weeks; assessed with: Discontinuation Signs and Symptoms)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose pregabalin (long-term)	low dose pregabalin (long-term)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	13/109 (11.9%)	8/94 (8.5%)	**RR 1.40** (0.61 to 3.23)	**34 more per 1,000** (from 33 fewer to 190 more)	⨁◯◯◯ VERY LOW	CRITICAL

Withdrawal symptoms: rebound anxiety (follow up: 26 weeks; assessed with: Hamilton Anxiety Rating Scale)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	4/109 (3.7%)	0/94 (0.0%)	**Peto OR 6.62** (0.91 to 47.97	**40 more per 1,000** [c] (from 0 fewer to 80 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25. The MID for the PWC outcome was 0.5 x the control group SD as they were change scores. This was 2.46 for the 14 week outcome.
c. Calculated from risk difference due to zero events in control arm.

F.3 Z-drugs

Table 36: Clinical evidence profile: 20mg Zolpidem vs 10mg Zolpidem (Z-drugs)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	20mg Zolpidem	10mg Zolpidem	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/40 (2.5%)	0/40 (0.0%)	**Peto OR 7.39** (0.15 to 372.38)	**30 more per 1,000**[c] (from 40 fewer to 90 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Withdrawal symptoms (follow up: 22-28 days; assessed with: Narrative report of "no withdrawal symptoms during the second 7-day placebo treatment period".)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	20mg Zolpidem	10mg Zolpidem	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	not serious	none	0/38 (0.0%)	0/36 (0.0%)	not estimable	**0 fewer per 1,000** (from 50 fewer to 50 more)	⨁⨁⨁◯ MODERATE	CRITICAL

a Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25.
c. Calculated from risk difference due to zero events in control arm.

F.4 Antidepressants

Table 37: Clinical evidence profile: Doxepin 6mg vs Doxepin 3mg SR (TCA antidepressants)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6mg Doxepin	3mg Doxepin	Relative (95% CI)	Absolute (95% CI)		
Withdrawal symptoms (follow-up: 5 weeks; assessed with: 3 or more new symptoms in the BWSQ)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/73 (0.0%)	1/75 (1.3%)	**Peto OR 0.14** (0.00 to 7.01)	**10 fewer per 1,000**[c] (from 50 fewer to 20 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms (rebound insomnia) (follow-up: 5 weeks; assessed with: Rebound insomnia based on wake time after sleep onset (WASO) criteria experienced over the 2 nights after discontinuation)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	3/73 (4.1%)	1/75 (1.3%)	**RR 3.08** (0.33 to 28.96)	**28 more per 1,000** (from 9 fewer to 373 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25.

c. Calculated from risk difference due to zero events in intervention arm.

Table 38: Clinical evidence profile: 20 mg Vortioxetine qd vs 10 mg Vortioxetine qd (Other antidepressants)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	20mg Vortioxetine qd	10mg Vortioxetine qd	Relative (95% CI)	Absolute (95% CI)		
Withdrawal symptoms (follow up: 10 weeks; assessed with: Discontinuation -Emergent Signs and Symptoms; Range of values unclear)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [b]	none	126	128	-	MD **0.4 lower** (0.92 lower to 0.12 higher)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. The MID for this outcome was 1.26 (0.5 the control group SD)*

Table 39: Clinical evidence profile: 20 mg Vortioxetine qd vs 5 mg Vortioxetine qd (Other antidepressants)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	20mg Vortioxetine qd	5mg Vortioxetine qd	Relative (95% CI)	Absolute (95% CI)		
Withdrawal Symptoms (Discontinuation -Emergent Signs and Symptoms) (follow up: 10 weeks; assessed with: Discontinuation -Emergent Signs and Symptoms; Range of values unclear)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [b]	none	126	122	-	MD **0.1 lower** (0.59 lower to 0.39 higher)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. bThe MID for this outcome was 1.11 (0.5 the control group SD)*

Table 40: Clinical evidence profile: 10 mg Vortioxetine qd vs 5 mg Vortioxetine qd (Other antidepressants)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	10mg Vortioxetine qd	5mg Vortioxetine qd	Relative (95% CI)	Absolute (95% CI)		
Withdrawal symptoms (follow up: 10 weeks; assessed with: Discontinuation-Emergent Signs and Symptoms; Range of values unclear)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [b]	none	128	122	-	MD **0.3 higher** (0.28 lower to 0.88 higher)	⨁⨁◯◯ LOW	CRITICAL

a. *Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.*
b. *The MID for this outcome was 1.11 (0.5* the control group SD)*

Table 41: Clinical evidence profile: Sertraline vs Venlafaxine SR (SSRI and SNRI antidepressants)

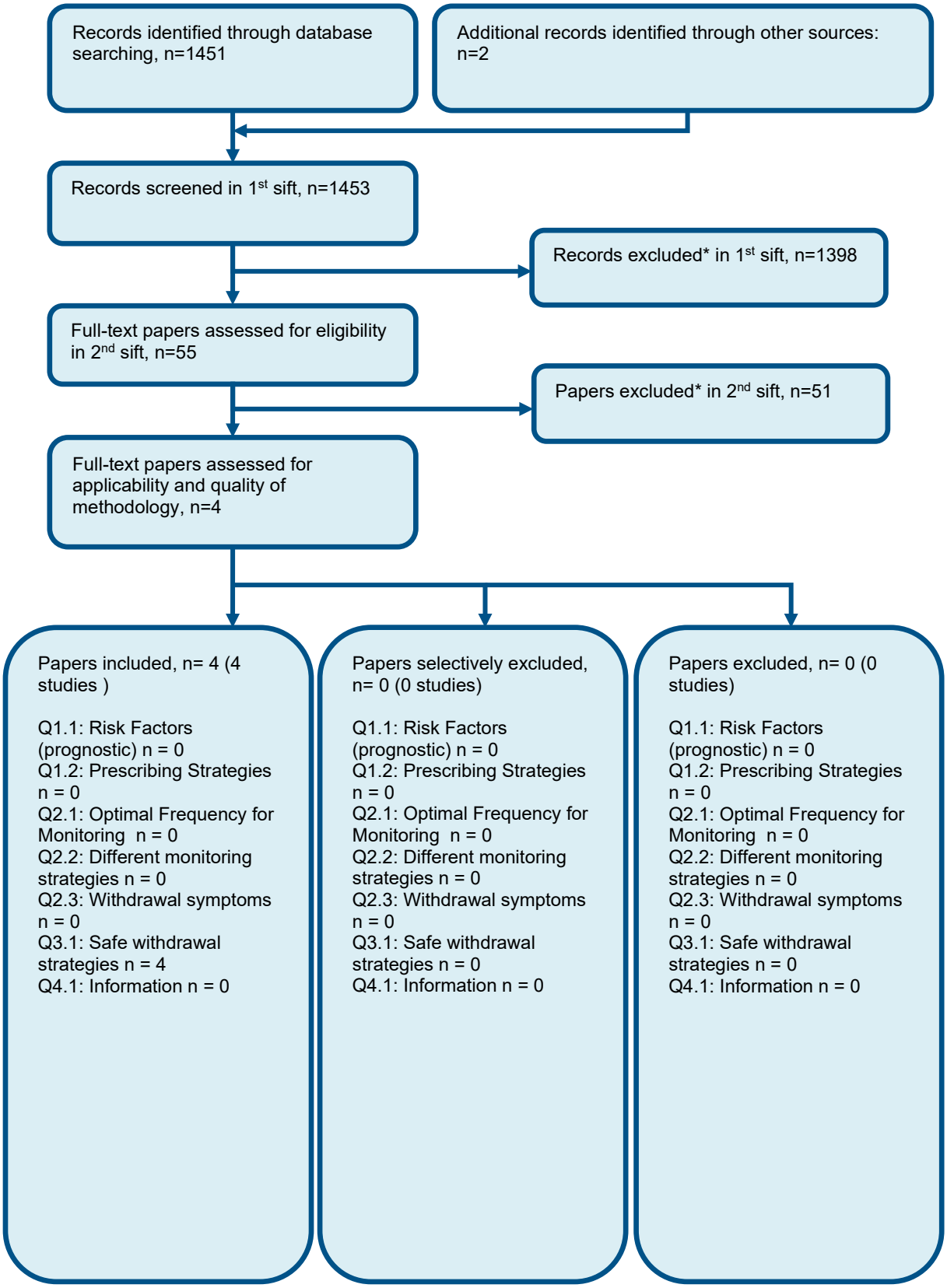
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline	venlafaxine SR	Relative (95% CI)	Absolute (95% CI)		
Withdrawal symptoms (Deterioration during taper) (follow up: 8-10 weeks; assessed with: Antidepressant discontinuation scale (unvalidated); Scale from: 0 to 210)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	72	64	-	MD **2.4 lower** (2.79 lower to 2.01 lower)	⨁⨁◯◯ LOW	CRITICAL
Withdrawal symptoms (follow up: 8-10 weeks; assessed with: Worst severity of discontinuation symptoms; none)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	12/67 (17.9%)	7/62 (11.3%)	**RR 1.59** (0.67 to 3.77)	**67 more per 1,000** (from 37 fewer to 313 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms (follow up: 8-10 weeks; assessed with: Worst severity of discontinuation symptoms; minimal)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline	venlafaxine SR	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	16/67 (23.9%)	11/62 (17.7%)	**RR 1.35** (0.68 to 2.67)	**62 more per 1,000** (from 57 fewer to 296 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms (follow up: 8-10 weeks; assessed with: (Worst severity of discontinuation symptoms; mild))												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	16/67 (23.9%)	17/62 (27.4%)	**RR 0.87** (0.48 to 1.57)	**36 fewer per 1,000** (from 143 fewer to 156 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms (follow up: 8-10 weeks; assessed with: Worst severity of discontinuation symptoms; moderate)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	23/67 (34.3%)	24/62 (38.7%)	**RR 0.89** (0.56 to 1.40)	**43 fewer per 1,000** (from 170 fewer to 155 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms (follow up: 8-10 weeks; assessed with: Worst severity of discontinuation symptoms; severe)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	0/67 (0.0%)	2/62 (3.2%)	**Peto OR 0.12** (0.01 to 1.99)	**30 fewer per 1,000**[c] (from 80 fewer to 20 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms (follow up: 8-10 weeks; assessed with: Worst severity of discontinuation symptoms; very severe)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	0/67 (0.0%)	1/62 (1.6%)	**Peto OR 0.12** (0.00 to 6.31)	**20 fewer per 1,000**[c] (from 60 fewer to 30 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. MID for dichotomous outcomes was 0.8 and 1.25. For continuous outcomes the MID was calculated as 0.6 for deterioration during taper (0.5 x SD for change score in control group).

c. Calculated from risk difference due to zero events in intervention arm.

Appendix G Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H Economic evidence tables

None.

Appendix I Health economic model

This question was not prioritised for health economic modelling.

Appendix J Excluded studies

J.1 Clinical studies

Table 42: Studies excluded from the clinical review

Study	Exclusion reason
Adams 2006[1]	No baseline comparability data. Switching permitted. Physicians could choose to enter a person into a tramadol only arm, and therefore not all participants were randomised. No baseline comparability data for those receiving tramadol and those receiving hydrocodone. Once the subject was enrolled, it became a natural history study, in that physicians could prescribe whatever medication was therapeutically appropriate based on response to initial medication.
Afilalo 2010[2]	Intervention does not match protocol: included population were on opioids or non-opioids for more than 3 months prior to inclusion (and it is not clear from baseline data how many were on opioids). There is also no measure of whether they showed dependence on prescribed opioids on recruitment.
Ahmed 2019[3]	Study design does not match protocol: retrospective review
Alenezi 2021[4]	Systematic review (quality assessment is not adequate/unclear)
Alldred 2016[5]	Systematic review (protocol does not match current review protocol)
Anderson 2016[6]	Study design does not match protocol: before and after intervention study
Arizmendez 2019[7]	Study design does not match protocol: before and after intervention study
Ashworth 2021[8]	Intervention does not match protocol: intervention to change prescriber behaviour, not a prescribing strategy or intervention to reduce the risk of dependence
Avdagic 2018[9]	Study design does not match protocol: before and after intervention study
Azermai 2017[10]	Study design does not match protocol: before and after intervention study
Azocar 2006[11]	Intervention does not match protocol: strategies to improve compliance with taking medication
Bachhuber 2018[12]	Population does not match protocol: acute pain
Bachhuber 2021[13]	Population does not match protocol: acute pain
Baird 2019[14]	Study design does not match protocol: before and after intervention study
Baldwin 2006[15]	No usable outcomes

Study	Exclusion reason
Bao 2009[16]	Population does not match protocol: Not all patients were started on antidepressants
Baron 2016[17]	Intervention does not match protocol: comparison of efficacy and tolerability of different drugs within a class – intervention not aimed at reducing the risk of dependence or preventing dependence
Baron 2016[18]	Intervention does not match protocol: comparison of efficacy of different drugs within a class – intervention not aimed at reducing the risk of dependence or preventing dependence
Beaulieu 2007[19]	Intervention does not match protocol: comparison of efficacy of different drug preparations – intervention not aimed at reducing the risk of dependence or preventing dependence
Berube 2019[20]	Protocol
Bi-Mohammed 2017[21]	Systematic review: protocol does not match current review protocol.
Bogetto 2002[22]	Intervention does not match protocol: taper strategy different between groups
Bohnert 2016[23]	Population does not match protocol: people with non-medical use of prescription opioids in the prior 3 months. Being initiated on or currently being prescribed medicines associated with dependence or withdrawal symptoms was not an inclusion criteria.
Borsari 2021[24]	Population does not match protocol: all had long-term opioid use and opioid misuse at baseline
Cadth 2014[26]	Systematic review protocol does not match current review protocol (population of systematic review protocol is opioids for non-cancer pain in the emergency department or in hospital, but not specified chronic pain only)
Callahan 1994[25]	Intervention does not match protocol: Not all participants were started on antidepressants
Chakravarthy 2018[27]	No usable outcomes
Cheatle 2018[28]	Study design does not match protocol: before and after intervention study
Cheesman 2020[29]	Population does not match protocol: post-operative opioids
Chelminski 2005[30]	Study design does not match protocol: before and after intervention study
Chen 2019[31]	Study design does not match protocol: before and after intervention study
Chiu 2020[32]	Protocol for a review on policies

Study	Exclusion reason
Chou 2014[33]	Systematic review protocol does not match current review protocol (population of systematic review includes cancer pain)
Chou 2015[34]	Systematic review protocol does not match current review protocol (comparison of systematic review protocol includes effectiveness studies opioids versus no opioids)
Chu 2012[35]	Comparator does not match protocol: placebo (comparator should be another intervention/strategy or usual care)
Clift 1972[37]	Intervention does not match protocol: Amylobarbitone is non-formulary.
Coyle 2018[38]	Narrative review: no relevant studies
Cutler 1993[39]	Intervention and comparison do not match protocol: 5HT agonist vs. benzodiazepine
Da 2014[40]	Intervention and comparison do not match protocol or non-relevant outcomes: oral or transdermal opioids vs. placebo or no intervention
deBurgh 1995[41]	Intervention does not match protocol: effect of educational visit on benzodiazepine prescribing
Doctor 2018[42]	No usable outcomes (prescriber related outcomes)
Donovan 2010[43]	No usable outcomes
Elie 1999[44]	Intervention does not match protocol (zaleplon no longer licensed in UK)
Evrard 2020[45]	Population does not match protocol: >50% already taking benzodiazepines at baseline. There is no measure of whether they showed dependence at baseline.
Fedoriw 2020[46]	Study design does not match protocol: before and after study
Firth 2015[48]	Systematic review: not all participants received medication, interventions do not match protocol
Fleischman 2019[49]	Population does not match protocol: post hip surgery
Franx 2014[50]	Intervention, comparison and outcome does not match protocol: prevent antidepressant prescription use, non-comparative, decrease in antidepressant prescriptions
Fry, 2000[51]	Intervention does not match protocol (zaleplon no longer licensed in UK)
Garland 2014[53]	Population does not match protocol (people with prescription opioid use disorder at the start of the study).
Gibson 2017[54]	Study design does not match protocol: non-comparative study

Study	Exclusion reason
Goldberg 2005[55]	No usable outcomes (pain rather than dependence)
Gonzalez 2012[56]	No usable outcomes (prescriber related outcomes)
Gould 2014[57]	Review: no relevant studies
Guarino 2018[58]	Population does not match protocol: people with aberrant drug related behaviours at the start of the study
Hale 2016[60]	Comparison does not match protocol: open label extension study, both arms received intervention
Hale 2009 [59]	Population does not match protocol: around 50% had had use of an opioid for more than 5 days/week during the 30 days prior to the screening visit, and dependence at baseline was not measured.
Hallfors 1993[61]	Systematic review: quality assessment is inadequate.
Harder 2021[62]	Study design does not match protocol: before and after study
Hartmann 1983[63]	Intervention and comparison do not match protocol: tryptophan, benzodiazepines, secobarbital
Hayes 2020[64]	Population does not match protocol: opioid users, unclear if had dependence at baseline
Hitzeman 2010[65]	Summary of Cochrane Systematic Reviews: no relevant papers
Hruschak 2021[66]	Population does not match protocol: population prescribed opioids and >20% had opioid misuse at baseline
Huhn 2018[67]	No usable outcomes
Jacobs 2016[68]	No comparison group
Jamison 1998[69]	Outcomes do not match protocol
Jamison 2010[70]	Population does not match protocol: unclear whether the population had dependence at baseline
John 2016[71]	No usable outcomes
Kales 1982[72]	No useable outcomes
Kalman 1998[73]	Unable to obtain paper
Katzman 2019[75]	No usable outcomes
Leas 2013[77]	Study design does not match protocol: narrative review
Leas 2010[78]	Update of systematic review already excluded from this review (Starrels 2010[110])
LeBlanc 2015[79]	Population does not match protocol

Study	Exclusion reason
Liebschutz 2017[80]	Population does not match protocol- unclear if <80% have dependence at baseline
Maguire 2021[81]	Systematic review (protocol does not match review protocol: efficacy and safety trials)
Mahableshwarkar 2015[82]	Intervention does not match protocol- groups received different tapers. No useable outcomes
Manchikanti 2005[84]	Study design does not match protocol: cross-sectional
Manchikanti 2006[83]	No comparison group.
McCracken 2012[85]	No usable outcomes
Mokhar 2018[86]	Systematic Review: protocol does not match review protocol. No relevant studies.
Montgomery 2004[87]	No useable data: mean DESS scores given for each group at the end of the run-out period, but no measure of variance (unable to estimate variance from P value, as the number of people in each arm with DESS scores is unclear).
Moride 2019[88]	Systematic review: different protocol criteria
Myers 1973[89]	No usable outcomes
Nolan 2020[93]	Study design does not match protocol: before and after study
Odineal 2020[94]	Population does not match protocol: not all population were being initiate on or currently prescribed opioids
Oehrberg 1995[95]	No usable data
Paljarvi 2021[96]	Population does not match protocol: supplementary material indicates >50% of the population were having surgery (presumed this means they were being prescribed opioids post-operatively)
Pande 2003[97]	No useable data
Perahia 2008[99]	No useable data
Pigott 1990[100]	No usable outcomes
Quadens 1982[102]	Intervention and comparison do not match protocol: Z-drug versus benzodiazepine
Quanbeck 2018[103]	Unclear if participants had behaviours related to dependence. No baseline data.
Rosenbaum 1997[104]	No useable data
Simon 2000[106]	No usable outcomes
Sindrup 1990[107]	No usable outcomes
Smith 2010[109]	Non-systematic review

Study	Exclusion reason
Starrels 2010[110]	Systematic Review: different protocol criteria
Stip 1999[111]	Comparison does not match protocol: Z-drug, placebo, temazepam
Tourian[112]	Intervention does not match protocol (desvenlafaxine not on guideline medicine list)
Unutzer 2001[113]	No usable outcomes
VonKorff 2017[115]	Population does not match protocol: opioid drug use disorder (~11%), >20% opioid excess days supplied (~23%), 22.1% prescription opioid use disorder
VonKorff 2019[114]	Population does not match protocol: unclear if had dependence at baseline
Ward 1988[116]	No usable outcomes
Wasan 2012[117]	Population does not match protocol: high risk misuse. No comparator for low-risk population.
Webster 2006[118]	Population does not match protocol: taking opioids at baseline with a short wash-out period, but unclear if people still had dependence before randomisation.
Weddle 2017[119]	Population does not match protocol: people aged 65 years or older with use of high-risk medications or potentially harmful drug-disease interactions.
Wild 2010[120]	Population does not match protocol: around 50% were taking opioids during the 3 months prior to the screening, and they do not measure dependence at baseline.
Wilson 2015[121]	Population does not match protocol: high opioid misuse scoring at baseline
Yeo 1994[122]	Comparison and outcomes do not match protocol: non comparative education arm only, no usable outcomes
Zandifar 2021[123]	Intervention does not match protocol: comparison of efficacy – intervention not aimed at reducing the risk of dependence or preventing dependence

J.2 Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.

Appendix K List of medicines to be included

This list refers to codes from BNF version 68.

Drug class (for this analysis)	BNF chapter	Drugs included
Opioids	4.7.2	Buprenorphine
		Codeine*
		Dextromoramide
		Diamorphine
		Dihydrocodeine**
		Dipipanone (including with cyclizine)
		Fentanyl
		Hydromorphone
		Meptazinol
		Methadone
		Morphine (including with cyclizine)
		Oxycodone (including with naloxone)
		Papaveretum
		Pentazocine
		Pentazocine
		Pethidine
		Tapentadol
		Tramadol (including with paracetamol)
	4.7.1	Codeine with paracetamol = co-codamol*
		Dihydrocodeine with paracetamol = co-dydramol**
Z-drugs	4.1.1	Zaleplon[$]
		Zopiclone
		Zolpidem
Benzodiazepines[£]	4.1.1 (insomnia)	Flurazepam
		Loprazolam
		Lormetazepam
		Nitrazepam
		Temazepam

Drug class (for this analysis)	BNF chapter	Drugs included
	4.1.2 (anxiety)	Diazepam
		Chlordiazepoxide
		Lorazepam
		Oxazepam
		Clonazepam
Gabapentinoids	4.7.3	Gabapentin
	4.8.1	Pregabalin
Antidepressants	4.3.1 (Tricyclics)	Amitriptyline (including with perphenazine)
		Amoxapine
		Clomipramine
		Dosulepin
		Doxepin
		Imipramine
		Lofepramine
		Maprotiline
		Mianserin
		Nortriptyline
		Protriptyline
		Trazodone
		Trimipramine
	4.3.2 (MAOIs)	Isocarboxazid
		Moclobemide
		Phenelzine
		Tranylcypromine
	4.3.3 (SSRIs)	Citalopram
		Escitalopram
		Fluoxetine
		Fluvoxamine
		Paroxetine
		Sertraline

Drug class (for this analysis)	BNF chapter	Drugs included
	4.3.4 (Other antidepressants)	Agomelatine
		Duloxetine
		Flupentixol
		Mirtazapine
		Nefazodone
		Oxitriptan
		Reboxetine
		Tryptophan
		Venlafaxine
		Vortioxetine

List of medicines taken from the 2019 Public Health England review of prescribed medicines, and adapted where necessary[101].

* Although they are captured within different BNF chapters, codeine and co-codamol will be regarded as a single drug when considering co-prescribing within the opioid class.

** Although they are captured within different BNF chapters, dihydrocodeine and co-dydramol will be regarded as a single drug when considering co-prescribing within the opioid class.

$ Zaleplon was initially included for consistency with the Public Health England (PHE) report on prescribed drug dependence and withdrawal. Subsequent to starting guideline development, Zaleplon was discovered to no longer have a marketing authorisation in the UK. Therefore, it was excluded from evidence reviews.

£ Alprazolam and clobazam are listed within the BNF, however they are not prescribable in NHS primary care. Therefore, they were not included in this guideline. This is consistent with the Public Health England (PHE) report on prescribed drug dependence and withdrawal.