National Institute for Health and Care Excellence

Final

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

[D] Evidence review: Withdrawal symptoms

NICE guideline NG215

Evidence reviews underpinning recommendations 1.5.3, 1.5.9, 1.5.13, 1.5.14, 1.5.17, 1.5.18, 1.5.19, 1.5.20 in the NICE guideline

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These evidence reviews were developed by the National Guideline Centre

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1 Withdrawal Symptoms

1.1 Review question

What are the withdrawal symptoms associated with prescribed medicines?

1.1.1 Introduction

Some prescribed medicines may cause withdrawal symptoms when stopped abruptly. These symptoms can be distressing for the person withdrawing and may mimic symptoms of the underlying condition for which the medicine was originally prescribed. Patterns of withdrawal symptoms have been clearly identified for some drug classes, but for others, there is less evidence available.

This review seeks to identify and highlight the common withdrawal symptoms associated with opioids, benzodiazepines, Z-drugs, gabapentinoids, and antidepressants, in order to better inform both prescriber and patient, to encourage shared decision-making, and to facilitate effective monitoring and safe tapering of medicines that are no longer beneficial.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question: mixed methods review

Population	Inclusion: adults (≥18 years) taking prescribed medicines that are associated with dependence or withdrawal symptoms (opioids, benzodiazepines, Z-drugs, gabapentinoids, or antidepressants; including prescription medicines which can also be bought over the counter) Stratification Drug class • Opioids • Benzodiazepines, • Z-drugs • Gabapentinoids (further stratified by gabapentin and pregabalin) • Antidepressants (further stratified by SSRIs, MAOIs, tricyclics, others).
Intervention / Phenomena of interest	**Intervention data:** Withdrawal from/stopping use of one of the prescribed medicines **Qualitative data:** Perceptions and experiences of patients of the withdrawal symptoms experienced from stopping one of these prescribed medicines
Comparisons	**Intervention data:** • Withdrawal from one of the prescribed medicines vs no withdrawal, OR • Withdrawal from one of the prescribed medicines vs withdrawal from placebo **Qualitative data:** n/a
Outcomes	**Intervention data:** • Specific withdrawal symptoms including rebound symptoms (dichotomous outcome)

	• Any withdrawal symptom, i.e., all symptoms lumped together (dichotomous outcome) • Intensity of withdrawal symptoms (validated scales only, continuous outcome) • Duration of withdrawal syndrome (continuous outcome) **Qualitative data:** Themes emerging from qualitative data (themes will be derived from the evidence identified for this review and not pre-specified)
Study design	**Intervention studies:** Randomised controlled trials Systematic reviews of randomised controlled trials. **Qualitative studies:** Qualitative studies (e.g., transcript data collected from focus groups/semi-structured interviews)

1.1.3 Methods and process

This evidence review was developed using the methods and process 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 Quantitative evidence

1.1.4.1 Included studies

Two comparisons were reported separately, as per the protocol for this review: withdrawal from one of the prescribed medicines vs withdrawal from placebo; and withdrawal from one of the prescribed medicines vs no withdrawal (i.e., continuation on the prescribed medicine).

For opioids, 3 RCTs comparing withdrawal from opioids versus withdrawal from placebo were included[10, 372, 775]. These included withdrawal from tapentadol, oxycodone, transdermal fentanyl and buprenorphine. No evidence was identified for withdrawal from opioids versus continuation.

For benzodiazepines, 4 RCTs comparing withdrawal from benzodiazepines versus withdrawal from placebo were included[200, 320, 472, 506]. Three RCTs were identified comparing withdrawal from benzodiazepines with continuation[133, 149, 266]. The studies included a mixture of short and long-acting benzodiazepines: diazepam, lorazepam, clonazepam and in one study[149] the benzodiazepines were not identified but were used as 'sleeping tablets'.

For gabapentinoids, 3 RCTs comparing withdrawal from gabapentinoids versus withdrawal from placebo were included[200, 320, 506]. All evidence found related to pregabalin only. No evidence was identified for withdrawal from gabapentinoids versus continuation.

For Z-drugs, one RCT comparing withdrawal from zopiclone versus withdrawal from placebo was included[254]. No evidence was identified for withdrawal from Z-drugs versus continuation.

For antidepressants, 10 studies were identified; 7 compared to withdrawal from placebo[197, 296, 527, 561, 562, 584, 612] and 3 compared to continuing on the medicine[334, 442, 443].

Studies are summarised in Table 2 to Table 6 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 7 to Table 14).

In Khan 2014 and Rickels 2010, the antidepressant used was desvenlafaxine. This is not licenced for use in the UK and was not on the guideline medicine list for included medicines (see Appendix K). However, in the context of evidence for withdrawal symptoms it was considered that desvenlafaxine was sufficiently similar to venlafaxine as it is the active metabolite of venlafaxine; and therefore, these studies were included in the evidence.

See also the study selection flow chart in Appendix C section C.1, study evidence tables in Appendix E section E.1, forest plots in Appendix D and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

A number of papers were identified in the literature assessing the effectiveness of continuation (versus discontinuation) of antidepressants for the prevention of relapse of the original condition. These 'continuation studies' usually consist of an open-label period, where all the population are treated with antidepressants. Responders (people who are considered to have successful treatment of their condition and be in remission) are then randomised to continue the antidepressant or to discontinue (either abruptly or with a taper) to placebo. The primary outcome is relapse or recurrence of the condition. Many of these studies were excluded from the current review as they did not report withdrawal or rebound symptoms. It has been suggested that some of the reported cases of relapse in the placebo arms of such trials may in fact, be due to withdrawal symptoms or rebound symptoms[270]. Withdrawal symptoms can overlap with the symptoms of depression or anxiety, making it difficult to distinguish withdrawal or rebound from relapse. Therefore, if the study authors only report relapse, or do not differentiate between relapse and withdrawal/rebound, then they have not been included in the current review. Occasionally these studies report adverse events or side effects occurring in the continuation versus discontinuation arms. Some of these symptoms may be considered to have overlap with withdrawal symptoms, such as dizziness or headache. However, these may also be investigated in order to assess the side effects and safety of the antidepressant in the continuation arm, and not with the aim of identifying withdrawal symptoms in the discontinuation arm. Where these are not investigated as withdrawal symptoms or classified as withdrawal symptoms by the paper, they have not been extracted for the current review.

A number of efficacy studies were identified where one or more groups had active medication and one group had a placebo. After the treatment phase, the papers describe the taper for the active drug (either taper to no tablets or taper as a substitution to placebo), but the placebo group is continued during the withdrawal phase. Withdrawal outcomes are reported in some of these studies, but even if this is assessed in both groups, the placebo group have not been withdrawn from study medication. These studies were excluded (as described in the excluded studies table) as the comparison does not match the review protocol.

One Cochrane review[706] was identified as potentially relevant but not subsequently included, as the focus of the review was the effect of withdrawal versus continuation of antidepressants on relapse outcomes rather than withdrawal symptoms. As discussed above, this does not match the current review protocol. The references of all studies included in the review were checked for relevance to the current protocol. They identified one study reporting withdrawal symptoms, which has been included in the current review.

See the excluded studies list in Appendix I.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review - Opioids

Study	Intervention and comparison	Population	Outcomes	Comments
Afilalo, 2010[10]	**Withdrawal from opioids (Tapentadol 100-250mg twice daily or Oxycodone 20-50mg)** Vs **Withdrawal from placebo** 12-week treatment and follow-up 14 days after last intake of study medication.	Osteoarthritis of the knee requiring analgesics for at least 3 months prior to screening N=1030* (n discontinuing =309) Age, years, mean (SD): tapentadol: 58.4 (10.09), oxycodone: 58.2 (10.29), placebo: 58.2 (9.15) Gender: Male %: tapentadol: 37.2%, oxycodone: 40.9%, placebo: 40.7% Multicentre: USA, Canada, New Zealand and Australia.	Mild opioid withdrawal as assessed on clinical opiate withdrawal scale - COWS (protocol outcome: intensity of withdrawal symptoms; at follow-up 2 - <5 days after last dose) Moderate opioid withdrawal as assessed on COWS (protocol outcome: intensity of withdrawal symptoms; at follow-up 2 - <5 days after last dose)	Taper details: not described but assumed from study to be abrupt. For the placebo arm, unclear if the placebo was withdrawn or not during the taper phase. The treatment phase included washout, 3 weeks titration, 12 weeks maintenance, and 14 days follow up. The 14 days follow up were not double-blind. *N is total randomised, however COWS only reported in those who discontinue prematurely or do not enter the open-label extension of the study. Subjective opiate withdrawal scale also reported by the study, but only reported as 'no statistically significant differences between groups.

Study	Intervention and comparison	Population	Outcomes	Comments
Langford, 2006[372]	**Withdrawal from opioids (Transdermal fentanyl 25-100ug fentanyl/hour)** Vs **Withdrawal from placebo** Intervention + follow up: 6-week treatment phase + gradual withdrawal (final assessment 3 days after last patch removed)	Hip or knee OA and requiring joint replacement surgery N=416 (n entering taper not reported) Age, years, mean (range): transdermal fentanyl: 66 (40-86); placebo: 66 (40-90). Gender (M:F): 134/265 Conducted in Canada, Czech Republic, Hungary, Poland, Slovakia	Moderate or severe aches and pains (on the short opiate withdrawal scale); protocol outcome: specific withdrawal symptom; at follow-up 3days after last patch removed) Mild or moderate problems sleeping (on short opiate withdrawal scale; protocol outcome: specific withdrawal symptom; at follow-up 3days after last patch removed) Severe insomnia (on short opiate withdrawal scale; protocol outcome: specific withdrawal symptom; at follow-up 3-days after last patch removed) Short opiate withdrawal scale score (protocol outcome: intensity of withdrawal symptoms; at follow-up 3 days after last patch removed).	Taper details: gradual withdrawal at the rate of 1 patch every 3 days. For the short opiate withdrawal scale, the number of participants included in the analysis was assumed to be ITT numbers. The statistics section of methods states ITT with LOCF, and although there were high dropouts during the treatment phase, it is possible the short opiate withdrawal scale was still assessed for a taper for dropouts. The treatment phase included a 1-week run-in on usual treatment, followed by fentanyl 25ug/hour replaced every 72 hours for 6 weeks. Dose could be increased if required up to a maximum of 4 patches. Concurrent medication/care: Participants continued to receive stable doses of anti-inflammatory agents (steroids or NSAIDs, including COX-2 inhibitors) that were prescribed before the study, but all weak opioids were stopped.
Yovell, 2016[775]	**Withdrawal from opioids (beginning with Buprenorphine 0.1 or 0.2 mg/day, maximal daily dose 0.8 mg.)** Vs	Clinically significant suicidal ideation. N= 88 Age, years, mean (SD): 37.3 (13.9).	Any withdrawal symptom (at 5 weeks = follow-up: 1 week-post last dose)	Taper details: abrupt discontinuation More than 70% were on antidepressants, and almost all took some psychotropic medication other than the study drug. Buprenorphine was provided as an adjunct to usual treatment to test the hypothesis that it could help alleviate suicidal ideation.

Study	Intervention and comparison	Population	Outcomes	Comments
	Withdrawal from placebo	Gender (M:F): 25/63 Israel		The treatment phase was 4 weeks duration. N 67 had at least 1 dose of the study drug.

Table 3: Summary of studies included in the evidence review - Benzodiazepines

Study	Intervention and comparison	Population	Outcomes	Comments
Connor, 1998[133]	**Discontinuation of clonazepam (1.0, 1.5, 2.0 or 2.5mg/day)** **Vs** **Continuation of clonazepam**	Fulfilled DSM-III-R criteria for a principal diagnosis of social phobia, between the ages of 18 and 55. N= 56 Age, years, mean (SD): continuation group: 40.6 (8.2), discontinuation group: 39.5 (7.0). Gender (M:F): continuation group: 11/6, discontinuation group: 12/7 Unknown country	Withdrawal intensity: Benzodiazepine Withdrawal Checklist (BWC total score) (protocol outcome: intensity of withdrawal symptoms (continuous)) Timepoint of outcome: after completion of taper	BWC is an unvalidated scale Taper details: A fixed-dose taper of 0.25mg every 2 weeks was established. 6 weeks of tapered dose was required for the group receiving 1.0mg/day to reach 0.0mg, 10 weeks for the 1.5mg group, 14 weeks for the 2.0mg group and 18 weeks for the 2.5mg group. Treatment phase was 6 months.
Curran, 2003[149]	**Withdrawal from benzodiazepines** Vs	Age ≥65 years, taking benzodiazepines on a repeated, daily basis for at least 6 months; wishing to discontinue N=138	Intensity of withdrawal (protocol outcome: intensity of withdrawal symptoms at 3-4 weeks after discontinuation)	Taper details: Participants had their dose of benzodiazepine gradually tapered over the first 8 or 9 weeks and then remained on placebo through to week 24. A dose titration regime was devised to minimise the risk of withdrawal symptoms, and this was done according to each patient's original

Study	Intervention and comparison	Population	Outcomes	Comments
	Continuation with benzodiazepine treatment Patients continued taking their normal benzodiazepine for the next 3 months. 24 weeks in total, 12-week outcome used.	Age, years, mean (range): 77 (65-93). Gender: 71%F, 29%M United Kingdom		dose and particular benzodiazepine. For example,10 mg of temazepam was reduced by 2.5 mg every 2 weeks according to the following schedule: week 1 (10 mg); weeks 2 and 3 (7.5 mg); weeks 4 and 5 (5 mg); weeks 6 and 7 (2.5 mg); week 8 onwards (0 mg i.e., placebo only). Mean (SD) years of benzodiazepine use 13.96 (7.99)
Feltner, 2003[200]	**Withdrawal from benzodiazepines (lorazepam 6mg/day)** Vs **Withdrawal from placebo** Intervention time: 4 weeks, plus 1 week taper	Generalised anxiety disorder N=271 total, 135 included in the lorazepam and placebo arms N entering taper = 116 Age, years, mean (SD): Lorazepam group: 39.2 (11.7). Placebo group: 37.8 (10.8). Gender: Lorazepam group: 28M/ 40F, Placebo group: 33M/34F Unknown multicentre	Physician's Withdrawal Checklist (PWC) score (protocol outcome: intensity of withdrawal symptoms; at post-intervention (immediately after 1 week taper))	Taper details: 1 week For the placebo arm, unclear if placebo was withdrawn or not during the taper phase. Treatment phase was 4 weeks.
Hayward, 1996[266]	**Withdrawal from benzodiazepines** (regular use over the past year) **Vs**	Diagnosis of agoraphobia meeting both DSM III-R and ICD 9 criteria N=40 Age, years, mean (SD): 43.6 (13.4).	Intensity of withdrawal (protocol outcome: intensity of withdrawal symptoms at 3-4 weeks after discontinuation)	Taper details: abrupt discontinuation with placebo Part of a longer 15-week study comparing diazepam and exposure treatment. Original study randomised benzodiazepine users and non-users to diazepam or

Study	Intervention and comparison	Population	Outcomes	Comments
	Continuation of benzodiazepines (5-15mg diazepam per day) **4 weeks**	Gender: 80%F Unknown country		placebo. Study results presented by users/non-users. Only benzodiazepine user groups are reported in this review. Randomised numbers available for study assessment 1, only overall number of benzodiazepine users available at baseline. Mean (SD) years of benzodiazepine use 10.5 (6.1) Withdrawal Symptom Questionnaire: unclear scale.
Kasper, 2014[320]	**Withdrawal from benzodiazepines (lorazepam 3-4mg/day)** Vs **Withdrawal from placebo** Study duration was 2 periods of 12 weeks treatments followed by 1 week taper and 1 week follow-up.	Generalised anxiety disorder N= 203 included for this comparison (615 total) N entering taper = 125 Age, years, mean (SD): lorazepam: 42.6 (11.2). Gender: Male, N (%): Lorazepam group: 81 (39.9) Conducted in Multiple countries (60 centres in 16 countries)	Any discontinuation emergent sign and symptom* (protocol outcome: any withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose)) Anxiety as a discontinuation emergent sign and symptom* (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose)) Headache as a discontinuation emergent sign and symptom* (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))	Taper details: (double-blind): 1 week. Generally consistent with product labelling and was intended to minimize 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 the when treatment was discontinued. The placebo group had already received 12 weeks of lorazepam before switching to placebo (whilst blinded to treatment).

Study	Intervention and comparison	Population	Outcomes	Comments
			Insomnia as a discontinuation emergent sign and symptom* (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))	Treatment phase was 24 weeks, in 2 12-week stages, so that discontinuation effects after both 12 week and 24-week exposure to lorazepam could be evaluated. *Defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks.
Noyes, 1991[472]	**Withdrawal from benzodiazepine (diazepam 5mg per day)** **Vs** **Withdrawal from placebo** **8 months, plus 5 weeks discontinuation**	Adults with panic disorder who had taken part in an 8-month treatment study and responded to treatment. N= 25 N completing discontinuation phase = 12 Age, years, mean (SD): 39.1 (9.8) including alprazolam group which is not included in current analysis. Gender: NR Unknown country	Rebound- increase in anxiety of ≥50% as measured with Hamilton anxiety scale compared with baseline (protocol outcome, specific withdrawal symptom during the discontinuation period) Rebound- increase in panic attacks of ≥100% compared with baseline (protocol outcome: specific withdrawal symptom during the discontinuation period) Rebound- Global Improvement Score ≤3 (indicating symptoms worse than at baseline) (protocol outcome: specific withdrawal symptom during the discontinuation period) Rebound- increase in anxiety of ≥10% as measured with	Taper: At the end of the treatment study participants were asked to reduce the dose of study medication by one capsule every 3 days until the dose reached 2 capsules/ day. At that point, the dose of study drug was reduced at the same rate (1 capsule every 3 days). The start of the taper was adjusted so that the last dose of study medication would coincide with a regularly scheduled visit. Treatment phase was 8 weeks, followed by a 6-month double-blind extension for responders who elected to continue. Discontinuation phase was after 8 months of treatment. Selection bias: randomised numbers for original treatment phase not reported. Baseline values are for discontinuation phase only. Attrition bias: high dropout rate overall, including during discontinuation period.

Study	Intervention and comparison	Population	Outcomes	Comments
			Hamilton anxiety scale compared with baseline (protocol outcome: specific withdrawal symptom during the discontinuation period) Development of new symptoms (protocol outcome: any withdrawal symptom during discontinuation period) Increase in withdrawal symptoms of ≥100% (protocol outcome: intensity of withdrawal symptoms during the discontinuation period)	Study had an extra arm of people taking alprazolam (not reported)
Pande, 2003[506]	**Withdrawal from benzodiazepines (lorazepam 6mg OD)** **Vs** **Withdrawal from placebo** Intervention time: 4 weeks, plus 1 week taper	Generalised anxiety disorder N= 137 included for this comparison (276 total) N entering taper = 98 Age, years, mean (SD): 35.8 (11.1). Gender: NR USA	Physician's Withdrawal Checklist (PWC) score (protocol outcome: intensity of withdrawal symptoms; at post-intervention (immediately after 1 week taper))	Taper details: 1 week For the placebo arm, unclear if placebo was withdrawn or not during the taper phase. Treatment phase included 1 week placebo lead-in and 4 weeks treatment.

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

Study	Intervention and comparison	Population	Outcomes	Comments
Kasper, 2014[320]	**Withdrawal from gabapentinoids (Withdrawal from low (150-300mg/day) and withdrawal from high (450-600mg/day) dose pregabalin)** Vs **Withdrawal from placebo** Flexible dose (week 1-6), Fixed dose (weeks 7-12), Double-blind, 12 weeks, 1 week taper, 1 week follow-up	Generalised anxiety disorder N= 412 included for this comparison (615 total) n entering taper phase = 285 Age, years, mean (SD): high dose pregabalin: 42.4 (11.5), low dose pregabalin: 40.5 (12.3) Gender: Male, N (%): pregabalin group 1: 87 (42.2), placebo group 2: 73 (35.4) Conducted in Multiple countries	Any discontinuation emergent sign and symptom* (protocol outcome: any withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose)) Anxiety as a discontinuation emergent sign and symptom* (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose)) Headache as a discontinuation emergent sign and symptom* (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose)) Insomnia as a discontinuation emergent sign and symptom* (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))	Taper details: (double-blind): 1 week. Generally consistent with product labelling and was intended to minimize 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 the when treatment was discontinued. The placebo group had already received 12 weeks of pregabalin before switching to placebo (whilst blinded to treatment). Treatment phase was 24 weeks, in 2 12-week stages, so that discontinuation effects after both 12 week and 24-week exposure to pregabalin could be evaluated (12-week data not reported for outcomes relevant to this review protocol). *Defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks.

Study	Intervention and comparison	Population	Outcomes	Comments
				Withdrawal from low (150-300mg/day) and withdrawal from high (450-600mg/day) dose pregabalin arms combined for analysis as per protocol (no stratification by dose). Study also had 2 separate withdrawal from placebo arms, these were also combined for analysis.
Feltner, 2003[200]	**Withdrawal from gabapentinoids (low dose of 150mg/day and high dose of 600mg/day)** Vs **Withdrawal from placebo** Intervention time: 4 weeks, plus 1 week taper	Generalised anxiety disorder N= 203 included for this comparison (271 total) n entering taper phase = 147 Age, years, mean (SD): Pregabalin 50mg group: 37.9 (10.9); Pregabalin 200mg group: 36.3 (10.9), Placebo group: 37.8 (10.8) Gender (M:F): Pregabalin 50mg group: 34M/36F; Pregabalin 200mg group: 33M/33F, Placebo group: 33M/34F Unknown multicentre	Physician's Withdrawal Checklist (PWC) score (protocol outcome: intensity of withdrawal symptoms; at post-intervention (immediately after 1 week taper))	Taper details: 1 week For the placebo arm, unclear if placebo was withdrawn or not during the taper phase. Treatment phase was 4 weeks. 2 comparisons (high dose vs placebo and low dose vs placebo). Results from high and low dose not combined, as study reported mean differences which could not be combined. Therefore, the study appears as 2 comparisons.
Pande 2003[506]	**Withdrawal from gabapentinoids (pregabalin: low dose of 150mg/day and high dose of 600mg/day)**	Generalised anxiety disorder N=208 included for this comparison (276 total) N entering taper = 166	Physician's Withdrawal Checklist (PWC) score (protocol outcome: intensity of withdrawal symptoms; at post-intervention (immediately after 1 week taper))	Taper details: 1 week For the placebo arm, unclear if placebo was withdrawn or not during the taper phase. Treatment phase included 1 week placebo lead-in and 4 weeks treatment.

Study	Intervention and comparison	Population	Outcomes	Comments
	Vs **Withdrawal from placebo** Intervention time: 4 weeks, plus 1 week taper	Age, years, mean (SD): 35.8 (11.1). Gender: NR USA		2 comparisons (high dose vs placebo and low dose vs placebo). Results from high and low dose not combined, as study reported mean differences which could not be combined. Therefore, the study appears as 2 comparisons.

Table 5: Summary of studies included in the evidence review - Z-drugs

Study	Intervention and comparison	Population	Outcomes	Comments
Hajak, 1998[254]	**Withdrawal from Z-drugs zopiclone (7.5 mg)** **Vs** **Withdrawal from placebo** **6 weeks plus 3 days**	Insomnia of at least 4-week duration N= 910 (1507 including the flunitrazepam and triazolam arms which are not included) Age, years, mean (SD): 51 (11). Gender: Zopiclone group: 223M/ 388F; Placebo group 112M/ 185F Unknown multicentre	Rebound insomnia* (protocol outcome: specific withdrawal symptom at 14 days following abrupt taper)	Taper details: abrupt withdrawal from Z-drug and placebo on day 29 Treatment period, 28 days. Numbers calculated from percentages reported *A person was counted as having rebound according to the following: deterioration in at least one of the three sleep quality parameters (a) sleep latency, (b) total sleep time, or (c) number of nocturnal awakenings; or deterioration in at least one parameter of daytime well-being defined as (d) a feeling of being refreshed on awakening in the morning, or as an impairment in daytime well-being as a result of (e) tiredness or (f)anxiety

Table 6: Summary of studies included in the evidence review - Antidepressants

Study	Intervention and comparison	Population	Outcomes	Comments
Fava, 1997[197]	**Withdrawal from ADs (75-225 mg/day of extended-release venlafaxine)** **Vs** **Withdrawal from placebo** **10 weeks (1 week placebo wash-out, 8-week treatment period)**	Met the DSM-IV criteria for major depressive disorder as determined by the Structured Clinical Interview for DSM-III-R—Patient Version. N=20 started study, N entering taper = 18 Age, years, mean (SD): 36.5 (10.7). Gender: 11M/9F USA	Withdrawal symptoms: any protocol outcome: any withdrawal symptom (dichotomous)) Timepoint of outcome: during the 3 days after discontinuation of treatment. Withdrawal intensity: number of mild/ moderate adverse events Timepoint of outcome: during the post taper period (mean 5 days after discontinuation of treatment).	Taper details: All of the study completers taking two or three capsules per day were required to taper their study medication by reducing the dose by one capsule per week, while those taking one capsule of study medication per day (75 mg of extended-release venlafaxine) were allowed to stop taking the medication without further tapering. Other outcomes: Number of adverse events during post taper period Treatment phase consisted of 8-week double-blind period No details of whether people were already using antidepressants at enrolment, but there was a 1-week washout period before starting the study.
Jain, 2013[296]	**Withdrawal from vortioxetine 5mg OD** **Vs.** **Withdrawal from placebo**	Adults aged 18-75 with major depressive disorder N=600 (number entering taper not reported), N=480 completed study, including taper period. Gender: 114M/186F (vortioxetine group), 136M/164F (placebo group)	Adverse events emerging during the 2-week taper phase (protocol outcome: any withdrawal symptom (dichotomous))	Taper details: 2 weeks 'medication free discontinuation period'. No further details – assumed as abrupt taper. For the placebo arm, unclear if placebo was withdrawn or not during the taper phase. Treatment phase consisted of 6-week treatment period + 2-week discontinuation phase

Study	Intervention and comparison	Population	Outcomes	Comments
	6-week treatment period + 2-week taper phase	Age: 42.5 (13.0) vortioxetine group 42.4 (12.7 (placebo group) USA		People were excluded if they had failed on 2 antidepressants previously, medication history collected but not reported, therefore not clear if any were on antidepressants at enrolment.
Khan, 2014[334]	**Withdrawal from desvenlafaxine 50mg/d** **Vs** **Continuation of desvenlafaxine 50mg/d**	Adult outpatients (≥ 18 years of age) with a primary diagnosis of single or recurrent MDD without psychotic features. Patients were required to have depressive symptoms for ≥ 30 days prior to the screening visit and a 17-item Hamilton Depression Rating Scale total score ≥ 14 at baseline. N=361 Age - Mean (SD): Taper: 47.9 (11.2); abrupt discontinuation (placebo): 47.8 (13.7); no discontinuation: 46.7 (11.3). Gender (M:F): 85/103.	DESS total score (protocol outcome: intensity of withdrawal symptoms, continuous) Timepoint: during first 2 weeks of the double-blind phase DESS symptoms (Protocol outcome: withdrawal symptoms: specific, dichotomous) Timepoint: during double-blind weeks 1-4	Taper details: abrupt discontinuation, or 1-week reduced dose taper. Also reports: • Discontinuation Symptoms Severity Index (DSSI) - the mean +SD of DESS positive items, related to discontinuation, and • Discontinuation syndrome as a dichotomised version of the total DESS score. Neither extracted as overlap with DESS results and would be double counting data. People were not on antidepressants at baseline, but were entered into a 24-week open-label treatment with desvenlafaxine prior to the discontinuation trial. People who completed this 24-week treatment were randomly assigned to either continuation, abrupt withdrawal or 1 week taper. The discontinuation period lasted 4 weeks.
Montgomery, 2004[442]	**Withdrawal from agomelatine 25mg per day/ paroxetine 20 mg per day**	Outpatients with Major Depressive Disorder N= 192	DESS (protocol outcome: withdrawal intensity, continuous) Rebound (protocol outcome: specific withdrawal symptom (dichotomous)	Taper details: abrupt DESS was clinician rated but unclear if this was a blinded clinician or a blinded/non blinded assessor

Study	Intervention and comparison	Population	Outcomes	Comments
	Vs **Continuation of agomelatine 25mg per day/ paroxetine 20mg per day** **Intervention + follow up: 14 weeks**	Age - Mean (SD): Agomelatine group: 42.6 (14.1), Paroxetine group: 42.5 (12.7). Gender (M:F): Agomelatine group: 30%M/70%F, Paroxetine group: 35%M/65%F	Timepoint: 2 weeks post withdrawal	Treatment phase consisted of 12-week treatment period + 2-week taper phase 3–5-day washout period, but unclear if any were receiving antidepressants prior to enrolment.
Montgomery, 2005[443]	**Withdrawal from escitalopram (abrupt switch to placebo)** **Vs** **Continuation on escitalopram (no withdrawal)**	Female and male outpatients between 18 and 80 years with a primary diagnosis of generalised social anxiety disorder (SAD) according to DSM-IV criteria N=372 (number entering the randomised continuation vs discontinuation (switch to placebo) phase; prior open-label treatment phase included n=517) Gender: 194 M/177 F Age: Escitalopram: 36 (18-78); placebo 38 (19-68) 76 centres in 11 countries in Europe, Canada and South Africa	DESS total score (protocol outcome: intensity of withdrawal symptoms (continuous)) Timepoint: • 1-week post-randomisation to abruptly withdraw/continue • 2 weeks post-randomisation to abruptly withdraw/continue	Taper: discontinuation arm was abrupt switch to placebo at the start of the 24-week continuation/discontinuation phase (DESS outcomes assessed for first 2 weeks of this 24-week phase) Study also reports 'treatment-emergent adverse events' during the continuation vs placebo (discontinuation) phase. Some of these adverse events may be considered withdrawal symptoms, but not extracted as not specifically defined as withdrawal symptoms, and could also reflect side effects in the continuation arm. DESS score of ≥4 also reported but not extracted as it's a dichotomised version of the DESS total score (protocol outcome: intensity of withdrawal symptoms) Treatment phase consisted of 12 week open-label treatment phase (10mg/day, which could be increased to 20mg if

Study	Intervention and comparison	Population	Outcomes	Comments
				clinically indicated) + 24-week continuation/discontinuation phase
Perahia, 2009[527]	**Withdrawal from duloxetine (60-120mg/day)** **Vs** **Withdrawal from placebo** **Taper phase results reported here (withdrawal from duloxetine vs withdrawal from placebo)** No relevant result reported for the double-blind phase (i.e., under the comparison of withdrawal vs continuation)	Aged 18 years and over who met the criteria for recurrent major depressive disorder N=288 number entering randomised double blind phase and subsequent taper (analysed here); prior open-label treatment phase included n=514 Gender: 82 M/206 F Age: Duloxetine 47.1 (12.8); placebo: 48.0 (12.3) UK	1 or more discontinuation-emergent adverse event (DEAE; protocol outcome: any withdrawal symptom (dichotomous)) Timepoint: during the 3-week taper phase	Taper: gradual over 2-3 weeks Taper phase was optional – not all completers of double blind phase entered the taper phase. 50/146 and 69/142 discontinued treatment in the double blind phase early. However, methods state that could still be eligible to enter the optional taper phase. Those withdrawing from placebo had previously received 34 weeks treatment with duloxetine during the open-label phase. They had been tapered off duloxetine over 4 weeks at the start of the double-blind phase and then been taking placebo for the remainder of the double blind phase. However, those discontinuing double blind phase early were eligible to enter the taper phase (some may have been taking placebo for less time). Treatment phase consisted of 34 week open-label phase (all on duloxetine) + 52-week double-blind phase (duloxetine or placebo) + optional 3-week taper phase Participants required to be off antidepressants for at least 2 months prior to presenting episode.

Study	Intervention and comparison	Population	Outcomes	Comments
Raskin, 2005[561]	**Withdrawal from duloxetine 60mg QD** **Vs** **Withdrawal from duloxetine 60mg BID** **Vs** **Withdrawal from placebo** Combined for analysis: withdrawal from 60mg QD and withdrawal from 60mg BID	Adults (18 years or older) with pain due to bilateral peripheral neuropathy caused by type 1 or type 2 diabetes, daily pain for at least 6 months N=348, N entering taper phase: 274 Gender: 162 M/186 F Age: 58.8 (10.1) USA (worldwide recruitment)	Adverse events emerging during the 1-week taper phase (protocol outcome: any withdrawal symptom (dichotomous)) Timepoint: 12-13 weeks (during 1 week taper)	Taper: 1 week. Duloxetine dose halved at start of taper week. Downgraded for intervention indirectness: for the 2 duloxetine arms, the duloxetine dose was halved at the start of the 1-week taper phase, but unclear if taper phase was complete withdraw of duloxetine. For the placebo arm, unclear if placebo was withdrawn or not during the taper phase, just says 1 week study drug taper period. 12-week treatment period + 1-week taper phase Chronic use of antidepressants was an exclusion criterion. No other details of prior antidepressant use.
Raskin 2008[562]	**Withdrawal from ADs (Duloxetine 60 mg/daily)** **Vs** **Withdrawal from placebo**	Elderly people with major depressive disorder n=311 (number entering taper not reported) Gender, female, n (%): Withdrawal from duloxetine group: 125 (60.4), Withdrawal from placebo group: 60 (57.7) Mean age, years (SD): Withdrawal from duloxetine group: 72.6 (5.7),	Incidence of at least one discontinuation-emergent adverse event (protocol outcome: any withdrawal symptom, dichotomous) Timepoint of outcome: during discontinuation phase	17 in duloxetine and 1 in placebo group started the study at full dose and had a subsequent dose reduction For the placebo arm, unclear if placebo was withdrawn or not during the taper phase. Unclear if duloxetine was completely stopped at the end of the taper phase 8 weeks treatment, 1 week discontinuation

Study	Intervention and comparison	Population	Outcomes	Comments
		Withdrawal from placebo group: 73.3 (5.7) USA		
Rickels, 2010[584]	**Withdrawal from desvenlafaxine (200mg/day or 400mg/day)** **Vs** **Withdrawal from placebo** Taper phase results reported here (withdrawal from desvenlafaxine vs withdrawal from placebo) Unable to use any results from the double-blind phase (i.e., under the comparison of withdrawal vs continuation) as the results were reported by subgroups of those previously on 200mg or 400mg, and no N numbers	Male and female outpatients, 18-75 years old; primary diagnosis of MDD N=375 number entering randomised double blind phase and subsequent taper (analysed here); prior open-label treatment phase included n=594 N= 216 entering taper, however a taper was carried out for those discontinuing early also. Gender: 122 M/253 F Age: Desvenlafaxine: 42.7 (12.3); Placebo: 42.8 (11.8). Europe, US, Taiwan	Any taper/post-therapy-emergent adverse events (TEAEs) (protocol outcome: any withdrawal symptom (dichotomous)) Headache as a TEAE reported by at least 5% in placebo arm (protocol outcome: specific withdrawal symptom (dichotomous)) Insomnia as a TEAE reported by at least 5% in placebo arm (protocol outcome: specific withdrawal symptom (dichotomous)) Nausea as a TEAE reported by at least 5% in placebo arm (protocol outcome: specific withdrawal symptom (dichotomous)) Timepoint: ‘During the taper phase’	Taper: during the taper phase: 1-2 weeks (which could be extended, shortened or omitted at the discretion of the investigator). DESS score was also reported during the taper phase. However, results were not usable as the outcome was only reported for the subgroup previously on 400mg/day, and N numbers for this subgroup not reported. Those withdrawing from placebo had previously received 12 weeks treatment with desvenlafaxine during the open-label phase. They had been tapered off desvenlafaxine over 2 weeks at the start of the double-blind phase and then been taking placebo for the remainder of the 24-week double blind phase (for approximately 22 weeks). 58/190 and 101/185 discontinued treatment in the double blind phase early. However, methods state that 1–2-week taper of double blind study medication was carried out even for people who discontinued early. Unclear whether TEAEs were assessed during taper for those discontinuing early.

Study	Intervention and comparison	Population	Outcomes	Comments
	provided for subgroup data.			Outcome reporting: results for both arms only reported for the specific TEAEs which occurred in >5% of the placebo arm (headache, insomnia and nausea). Study also reported TEAEs of dizziness (22%), irritability (10%), diarrhoea (7%), anxiety (6%), fatigue (5%), abnormal dreams (5%) and hyperhidrosis (5%) in the desvenlafaxine arm, which occurred in >5% of the desvenlafaxine arm, however these outcomes could not be used as the numbers of events were not reported in the placebo arm. 12 week open-label phase (all on desvenlafaxine) + 24-week double-blind phase (desvenlafaxine or placebo) + 1–2-week taper phase.
Rynn 2008[612]	**Withdrawal from duloxetine 60-120mg/day** **Vs** **Withdrawal from placebo**	Adults with a primary diagnosis of DSM-IV-defined GAD N=327 began the study, N=205 completed taper Gender: 125 M/202 F Age: Duloxetine 42.2 (13.9); placebo 41.0 (14.2) USA	Discontinuation-emergent adverse event (protocol outcome: any withdrawal symptom (dichotomous)) Dizziness: discontinuation-emergent adverse event (protocol outcome: specific withdrawal symptom (dichotomous)) Timepoint: during the 2-week discontinuation phase	Taper: occurred over a 2-week period Downgraded for intervention indirectness: for the placebo arm, unclear if placebo was withdrawn or not during the taper phase, only reports that tapering occurred over a 2-week period (presumed to mean both duloxetine and placebo arm). 10-week treatment period + 2-week taper phase

See Appendix E for full evidence tables.

1.1.6 Summary of the effectiveness evidence

1.1.6.1 Opioids

1.1.6.1.1 Withdrawal from opioids vs continuation on opioids

No evidence identified for withdrawal from opioids vs continuation on opioids

1.1.6.1.2 Withdrawal from opioids vs withdrawal from placebo

Table 7: Clinical evidence summary: withdrawal from opioids vs withdrawal from placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with withdrawal from placebo	Risk difference with Withdrawal from opioids
Any withdrawal symptom (at week 5 = follow-up: 1 week-post last dose) assessed with: assessed at appointment with psychiatrist to screen for possible withdrawal symptoms	88 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	not estimable	0 per 1,000	0 fewer per 1,000 (50 fewer to 50 more)[c]
Moderate or severe aches and pains on the short opiate withdrawal scale (protocol outcome: specific withdrawal symptom; at follow-up 3-days after last patch removed) assessed with: short opiate withdrawal scale consisted of 10 items rated on a 4-point Likert scale (0-3, none to severe).	399 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	RR 1.00 (0.86 to 1.17)	619 per 1,000	0 fewer per 1,000 (87 fewer to 105 more)
Mild or moderate problems sleeping on the short opiate withdrawal scale (protocol outcome: specific withdrawal symptom; at follow-up 3-days after last patch removed) assessed with: short opiate withdrawal scale consisted of 10 items rated on a 4-point Likert scale (0-3, none to severe).	399 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 0.98 (0.75 to 1.26)	371 per 1,000	7 fewer per 1,000 (93 fewer to 96 more)
Severe insomnia on the short opiate withdrawal scale (protocol outcome: specific withdrawal symptom; at follow-up 3-days after last patch removed) assessed with: short opiate withdrawal scale consisted of 10 items rated on a 4-point Likert scale (0-3, none to severe).	399 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	RR 2.68 (1.57 to 4.59)	81 per 1,000	136 more per 1,000 (46 more to 292 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with withdrawal from placebo	Risk difference with Withdrawal from opioids
Short opiate withdrawal scale score (protocol outcome: intensity of withdrawal symptoms; at follow-up 3 days after last patch removed) assessed with: short opiate withdrawal scale consisted of 10 items rated on a 4-point Likert scale (0-3, none to severe). Total score range of possible scores 0-3 (top=poor outcome)	399 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	-	The short opiate withdrawal scale score final value was 0.39	MD 0.27 higher (0.18 higher to 0.36 higher)
Mild opioid withdrawal as assessed on COWS (protocol outcome: intensity of withdrawal symptoms; at follow-up 2 - <5 days after last dose) assessed with: COWS based on 11 items of opioid withdrawal symptoms, each rated 0-5, higher values being worse. 5-12 is mild, 13-24 is moderate, 25-36 is moderately severe, > or equal to 36 is severe [d]	95 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,f]	Peto OR 4.38 (1.02 to 18.84)	0 per 1,000	150 more per 1,000 (50 more to 250 more)[c]
Moderate opioid withdrawal as assessed on COWS (protocol outcome: intensity of withdrawal symptoms; at follow-up 2 - <5 days after last dose) assessed with: COWS based on 11 items of opioid withdrawal symptoms, each rated 0-5, higher values being worse. 5-12 is mild, 13-24 is moderate, 25-36 is moderately severe, > or equal to 36 is severe [d,e]	95 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,f]	not estimable	0 per 1,000	0 fewer per 1,000 (60 fewer to 60 more)[c]
Mild opioid withdrawal as assessed on COWS (protocol outcome: intensity of withdrawal symptoms; at follow-up ≥5 days after last dose) assessed with: COWS based on 11 items of opioid withdrawal symptoms, each rated 0-5, higher values being worse. 5-12 is mild, 13-24 is moderate, 25-36 is moderately severe, > or equal to 36 is severe [d]	213 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,f]	RR 0.84 (0.31 to 2.32)	85 per 1,000	14 fewer per 1,000 (58 fewer to 112 more)
Moderate opioid withdrawal as assessed on COWS (protocol outcome: intensity of withdrawal symptoms; at follow-up ≥5 days after last dose) assessed with: COWS based on 11 items of opioid withdrawal symptoms, each rated 0-5, higher values being worse. 5-12 is mild, 13-24 is moderate, 25-36 is moderately severe, > or equal to 36 is severe [d]	213 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,f]	Peto OR 4.01 (0.18 to 89.47)	0 per 1,000	10 more per 1,000 (20 fewer to 40 more)[c]

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

*b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control groups for continuous outcomes). For studies with zero events in both arms: no imprecision (sample size >350); serious imprecision (sample size >70<350); very serious imprecision (sample size <70). Continuous outcome MIDS were as follows: for short opiate withdrawal scale score: 0.14 (0.5*SD for the final value for the control group used (as baseline values not available)*
c. Absolute effect calculated from the risk difference due to zero events in one or both arms.
d. Study also reported the number of people with 'no withdrawal' as assessed on COWS. This was not analysed as it is the 'opposite' outcome and would be double counting. The COWS score was dichotomised: 5-12 is mild, 13-24 is moderate, 25-36 is moderately severe, > or equal to 36 is severe. Presumably no-one had moderately severe or severe withdrawal, as the numbers in the other 3 categories add up to the total number of people in the study.
e. Reviewer determined that no one had 'moderate withdrawal' at this timepoint due to number of people with 'no withdrawal' or 'mild withdrawal' adding up to the total number of participants
f. It was unclear whether the placebo group were withdrawn from study medication during the taper phase.

1.1.6.2 Benzodiazepines

1.1.6.2.1 Withdrawal from benzodiazepines vs continuation on benzodiazepines

Table 8: Clinical evidence summary: withdrawal from benzodiazepines vs continuation on benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuation with BZDs	Risk difference with withdrawal from BZDs
BWSQ (protocol outcome: intensity of withdrawal symptoms at 3 weeks after discontinuation)	91 (1 RCT)	⊕⊕◯◯ LOW [a,b]	-	The mean BWSQ was 32.7	MD 2.1 higher (5.49 lower to 9.69 higher)
Withdrawal Symptoms scale (protocol outcome: intensity of withdrawal symptoms at 4 weeks after discontinuation)	30 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	-	The mean Withdrawal Symptoms scale score was 158.6	MD 49 higher (82.51 lower to 180.51 higher)
Total BWC score (protocol outcome: intensity of withdrawal symptoms at the end of the taper period)	36 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	-	The mean total BWC score was 6.4	MD 1.8 higher (4.11 lower to 7.71 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 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. For continuous outcomes the MID was calculated as 3.0 for BWC, 8.1 for BSWQ and 68.3 for Withdrawal Symptom scale (0.5 median baseline SDs of intervention and control groups).*

1.1.6.2.2 Withdrawal from benzodiazepines vs withdrawal from placebo

Table 9: Clinical evidence summary: withdrawal from benzodiazepines vs withdrawal from placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with withdrawal from placebo	Risk difference with withdrawal from BZDs
Patients with anxiety as a discontinuation emergent sign and symptom (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))	130 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	Peto OR 3.95 (0.73 to 21.45)	0 per 1,000	80 more per 1,000 (10 more to 150 more)[d]
Patients with headache as a discontinuation emergent sign and symptom (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))	130 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	Peto OR 3.71 (0.14 to 100.72)	0 per 1,000	20 more per 1,000 (from 30 fewer to 70 more)[d]
Patients with insomnia as a discontinuation emergent sign and symptom (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))	130 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 0.90 (0.19 to 4.23)	67 per 1,000	7 fewer per 1,000 (54 fewer to 215 more)
Rebound- increase in anxiety of ≥50% as measured with Hamilton anxiety scale compared with baseline (protocol outcome: specific withdrawal symptom during the discontinuation period)	25 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	Peto OR 4.20 (0.26 to 66.87)	0 per 1,000	160 more per 1,000 (from 100 fewer to 410 more)[d]
Rebound- increase in panic attacks of ≥100% compared with baseline (protocol outcome: specific withdrawal symptom during the discontinuation period)	25 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.26 (0.17 to 9.24)	167 per 1,000	43 more per 1,000 (138 fewer to 1,373 more)
Rebound- Global Improvement Score ≤3 (indicating symptoms worse than at baseline) (protocol outcome: specific withdrawal symptom during the discontinuation period)	25 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	Peto OR 4.50 (0.39 to 52.29)	0 per 1,000	210 more per 1,000 (from 50 fewer to 470 more)[d]

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with withdrawal from placebo	Risk difference with withdrawal from BZDs
Rebound- increase in anxiety of ≥10% as measured with Hamilton anxiety scale compared with baseline (protocol outcome: specific withdrawal symptom during the discontinuation period)	25 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 2.21 (0.34 to 14.54)	167 per 1,000	202 more per 1,000 (110 fewer to 2,257 more)
Patients with any discontinuation emergent sign and symptom defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks(protocol outcome: any withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))	130 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 2.10 (0.80 to 5.51)	133 per 1,000	147 more per 1,000 (27 fewer to 601 more)
Development of new symptoms (protocol outcome: any withdrawal symptom during discontinuation period)	25 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.89 (0.58 to 6.18)	333 per 1,000	297 more per 1,000 (140 fewer to 1,727 more)
PWC score (protocol outcome: intensity of withdrawal symptoms; at post-intervention (immediately after 1 week taper))	180 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,e]	-	The mean PWC change score was 0.51	MD 3.8 higher (1.92 higher to 5.69 higher)
Increase in withdrawal symptoms of ≥100% (protocol outcome: intensity of withdrawal symptoms during the discontinuation period)	25 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,]	RR 0.32 (0.02 to 4.32)	167 per 1,000	113 fewer per 1,000 (163 fewer to 553 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. For continuous outcomes the MID was 0.5 * median of baseline SD of the intervention and control groups. Continuous outcome MIDS were as follows: for PWC score: 2.97 (0.5*SD for the change score for the control group used (as baseline or final values not available; change score control group SD only available for Feltner)*
c. Participants in the placebo groups had previously been taking active medication; some participants leaving the study early also underwent the taper
d. Absolute effect calculated from the risk difference due to zero events in control arm.
e. For the placebo group, it was unclear whether medication was stopped during the taper phase in both studies

1.1.6.3 Gabapentinoids

1.1.6.3.1 Withdrawal from gabapentinoids vs continuation on gabapentinoids

No evidence identified for withdrawal from gabapentinoids vs continuation on gabapentinoids

1.1.6.3.2 Withdrawal from gabapentinoids vs withdrawal from placebo

Table 10: Clinical evidence summary: withdrawal from gabapentinoids vs withdrawal from placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with withdrawal from placebo	Risk difference with Withdrawal from Pregabalin
Patients with any discontinuation emergent sign and symptom defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks (protocol outcome: any withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))	262 (1 RCT)[a]	⨁◯◯◯ VERY LOW [b,c,d]	RR 1.23 (0.72 to 2.09)	220 per 1,000	51 more per 1,000 (62 fewer to 240 more)
Patients with anxiety as a discontinuation emergent sign and symptom defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose)) [e]	262 (1 RCT)[a]	⨁◯◯◯ VERY LOW [b,c,d]	RR 2.03 (0.26 to 16.21)	17 per 1,000	17 more per 1,000 (13 fewer to 258 more)
Patients with headache as a discontinuation emergent sign and symptom defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose)) [e]	262 (1 RCT) [a]	⨁◯◯◯ VERY LOW [b,c,d]	RR 1.16 (0.25 to 5.33)	34 per 1,000	5 more per 1,000 (25 fewer to 147 more)
Patients with insomnia as a discontinuation emergent sign and symptom defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose)) [e]	262 (1 RCT) [a]	⨁◯◯◯ VERY LOW [b,c,d]	RR 2.03 (0.63 to 6.58)	51 per 1,000	52 more per 1,000 (19 fewer to 284 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with withdrawal from placebo	Risk difference with Withdrawal from Pregabalin
PWC score (protocol outcome: intensity of withdrawal symptoms; at post-intervention (immediately after 1 week taper))	305 (4 RCTs) [f]	⊕◯◯◯ VERY LOW [b,d,g]	-	The median PWC change score was 0.04	MD 2.58 higher (1.04 higher to 4.13 higher)

a. Withdrawal from low (150-300mg/day) and withdrawal from high (450-600mg/day) dose pregabalin arms combined for analysis as per protocol (no stratification by dose). Study also had 2 separate withdrawal from placebo arms, these were also combined for analysis. For dichotomous outcomes the number of events and number of people for the 2 arms were added together. For continuous outcomes, the mean and SD for the 2 arms combined was calculated.
b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
c. Participants in the placebo groups had previously been taking active medication; some participants leaving the study early also underwent the taper
*d. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control groups for continuous outcomes). Continuous outcome MIDS were as follows: for PWC score: 2.97 (0.5*SD for the change score for the control group used (as baseline or final values not available; change score control group SD only available for Feltner)*
e. Specific discontinuation emergent signs and symptoms only reported in paper for those events which occurred in at least 5% of people
f. 2 studies, each with 2 comparisons (high dose vs placebo and low dose vs placebo). Results from high and low dose not combined, as studies reported mean differences. Therefore, each study appears as 2 comparisons: problem with the placebo arm being repeated twice addressed by halving the n in each of the repeated placebo arms to counteract the gain in statistical power from effectively double counting the placebo arm (this calculates a greater SE for the MD, conferring an appropriate reduction in precision to compensate for the placebo arm being used twice)
g. it was unclear whether placebo was withdrawn during the taper period for both studies

1.1.6.4 Z-drugs

1.1.6.4.1 Withdrawal from Z-drugs vs continuation on Z-drugs

No evidence identified for withdrawal from Z-drugs vs continuation on Z-drugs

1.1.6.4.2 Withdrawal from Z-drugs vs withdrawal from placebo

Table 11: Clinical evidence summary: withdrawal from Z-drugs vs withdrawal from placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with withdrawal from placebo	Risk difference with withdrawal from Z-drugs
Rebound insomnia (protocol outcome: specific withdrawal symptom at 14 days following abrupt taper). Assessed with: a deterioration below individual mean pre-treatment values of the scores given on the visual analogue scales during the discontinuation period. A patient was counted as having rebound according to the following: deterioration in at least one of the three sleep quality parameters (a) sleep latency, (b) total sleep time, or (c) number of nocturnal awakenings; or deterioration in at least one parameter of daytime well-being defined as (d) a feeling of being refreshed on awakening in the morning, or as an impairment in daytime well-being as a result of (e) tiredness or (f)anxiety	910 (1 RCT)	⨁⨁⨁⨁ HIGH	RR 0.95 (0.82 to 1.09)	487 per 1,000	24 fewer per 1,000 (88 fewer to 44 more)

1.1.6.5 Antidepressants

1.1.6.5.1 Withdrawal from antidepressants vs continuation on antidepressants

Table 12: Clinical evidence summary: Other antidepressant class: withdrawal from other antidepressants vs continuation on other antidepressants

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuation of ADs	Risk difference with discontinuation of ADs
Total no. of emergent DESS symptoms (protocol outcome: intensity of withdrawal symptoms) during first 2 weeks of discontinuation	445 (2 RCTs)	⨁⨁◯◯ LOW [a]	-	The mean total no. of emergent DESS	MD 0.14 lower (1.2 lower to 0.91 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuation of ADs	Risk difference with discontinuation of ADs
				symptoms was 4 and 3	
Rebound: return to a MADRS score equal to or higher than the original score at the entry of the acute treatment study (protocol outcome: specific withdrawal symptom during week 1 of discontinuation)	88 (1 RCT)	⊕⊕◯◯ LOW [b]	Peto OR 0.24 (0.00 to 16.57)	0 per 1,000	20 fewer per 1,000 (from 80 fewer to 50 more)[c]
Rebound: return to a MADRS score equal to or higher than the original score at the entry of the acute treatment study (protocol outcome: specific withdrawal symptom during week 2 of discontinuation)	88 (1 RCT)	⊕⊕◯◯ LOW [b]	Peto OR 0.24 (0.00 to 16.57)	0 per 1,000	20 fewer per 1,000 (from 80 fewer to 50 more)[c]
Nervousness/ anxiety (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.24 (0.81 to 1.88)	264 per 1,000	63 more per 1,000 (50 fewer to 232 more)
Elevated mood, feeling high (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.14 (0.25 to 5.15)	28 per 1,000	4 more per 1,000 (21 fewer to 115 more)
Irritability (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕⊕◯◯ LOW [a]	RR 1.99 (1.29 to 3.07)	236 per 1,000	234 more per 1,000 (68 more to 489 more)
Sudden worsening of mood (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.45 (0.83 to 2.53)	167 per 1,000	75 more per 1,000 (28 fewer to 255 more)
Sudden outbursts of anger (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.24 (0.66 to 2.32)	139 per 1,000	33 more per 1,000 (47 fewer to 183 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuation of ADs	Risk difference with discontinuation of ADs
Sudden panic or anxiety attacks (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.88 (0.37 to 2.11)	83 per 1,000	10 fewer per 1,000 (53 fewer to 92 more)
Bouts of crying or tearfulness (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.87 (1.09 to 3.23)	167 per 1,000	145 more per 1,000 (15 more to 372 more)
Agitation (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.14 (0.72 to 1.81)	236 per 1,000	33 more per 1,000 (66 fewer to 191 more)
Feeling unreal or detached (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.92 (0.44 to 1.92)	111 per 1,000	9 fewer per 1,000 (62 fewer to 102 more)
Confusion or trouble concentrating (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.36 (0.84 to 2.22)	208 per 1,000	75 more per 1,000 (33 fewer to 254 more)
Forgetfulness or problems with memory (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 2.20 (1.05 to 4.61)	97 per 1,000	117 more per 1,000 (5 more to 351 more)
Mood swings (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.35 (0.69 to 2.62)	125 per 1,000	44 more per 1,000 (39 fewer to 203 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuation of ADs	Risk difference with discontinuation of ADs
Trouble sleeping, insomnia (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.94 (0.68 to 1.29)	403 per 1,000	24 fewer per 1,000 (129 fewer to 117 more)
Increased dreaming, nightmares (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.21 (0.74 to 1.98)	208 per 1,000	44 more per 1,000 (54 fewer to 204 more)
Sweating more than usual (protocol outcome : specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.83 (0.43 to 1.61)	139 per 1,000	24 fewer per 1,000 (79 fewer to 85 more)
Shaking, trembling (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.76 (0.31 to 1.84)	83 per 1,000	20 fewer per 1,000 (57 fewer to 70 more)
Muscle tension or stiffness (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 2.15 (0.96 to 4.81)	83 per 1,000	96 more per 1,000 (3 fewer to 317 more)
Muscle aches or pains (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 2.17 (1.03 to 4.53)	97 per 1,000	114 more per 1,000 (3 more to 343 more)
Restless feeling in legs (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.22 (0.53 to 2.83)	83 per 1,000	18 more per 1,000 (39 fewer to 153 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuation of ADs	Risk difference with discontinuation of ADs
Muscle cramps, spasms, twitching (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.17 (0.57 to 2.40)	111 per 1,000	19 more per 1,000 (48 fewer to 156 more)
Fatigue, tiredness (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.15 (0.80 to 1.64)	333 per 1,000	50 more per 1,000 (67 fewer to 213 more)
Unsteady gait or incoordination (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 3.66 (0.89 to 14.99)	28 per 1,000	74 more per 1,000 (3 fewer to 389 more)
Blurred vision (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.80 (0.33 to 1.93)	83 per 1,000	17 fewer per 1,000 (56 fewer to 77 more)
Sore eyes (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.60 (0.49 to 5.26)	42 per 1,000	25 more per 1,000 (21 fewer to 178 more)
Uncontrolled mouth/ tongue movements (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [b]	RR 0.25 (0.04 to 1.76)	28 per 1,000	21 fewer per 1,000 (27 fewer to 21 more)
Problems with speech or speaking clearly (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.09 (0.32 to 3.74)	42 per 1,000	4 more per 1,000 (28 fewer to 114 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuation of ADs	Risk difference with discontinuation of ADs
Headache (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⨁⨁◯◯ LOW [a]	not estimable	0 per 1,000	0 fewer per 1,000 (from 20 fewer to 20 more)[c]
Increased saliva in mouth (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	Peto OR 3.58 (0.56 to 23.01)	0 per 1,000	20 more per 1,000 (from 0 fewer to 50 more)[c]
Dizziness, light-headedness or sensation of spinning (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⨁⨁◯◯ LOW [a]	RR 3.24 (1.47 to 7.14)	83 per 1,000	187 more per 1,000 (39 more to 512 more)
Nose running (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.09 (0.57 to 2.06)	139 per 1,000	13 more per 1,000 (60 fewer to 147 more)
Shortness of breath (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.35 (0.40 to 4.50)	42 per 1,000	15 more per 1,000 (25 fewer to 146 more)
Chills (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 0.63 (0.25 to 1.57)	83 per 1,000	31 fewer per 1,000 (63 fewer to 48 more)
Fever (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 0.34 (0.12 to 0.94)	83 per 1,000	55 fewer per 1,000 (73 fewer to 5 fewer)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuation of ADs	Risk difference with discontinuation of ADs
Vomiting (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.59 (0.16 to 2.22)	42 per 1,000	17 fewer per 1,000 (35 fewer to 51 more)
Nausea (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.84 (0.47 to 1.52)	167 per 1,000	27 fewer per 1,000 (88 fewer to 87 more)
Diarrhoea (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.57 (0.63 to 3.89)	69 per 1,000	40 more per 1,000 (26 fewer to 201 more)
Stomach cramps (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.31 (0.52 to 3.30)	69 per 1,000	22 more per 1,000 (33 fewer to 160 more)
Stomach bloating (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.52 (0.61 to 3.77)	69 per 1,000	36 more per 1,000 (27 fewer to 192 more)
Unusual visual sensations (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.61 (0.22 to 1.67)	69 per 1,000	27 fewer per 1,000 (54 fewer to 47 more)
Burning, numbness (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 2.40 (0.57 to 10.07)	28 per 1,000	39 more per 1,000 (12 fewer to 252 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuation of ADs	Risk difference with discontinuation of ADs
Unusual sensitivity to sound (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.40 (0.16 to 0.99)	97 per 1,000	58 fewer per 1,000 (82 fewer to 1 fewer)
Ringing or noises in the ears (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.91 (0.35 to 2.37)	69 per 1,000	6 fewer per 1,000 (45 fewer to 95 more)
Unusual tastes or smells (protocol outcome: specific withdrawal symptoms) during study weeks 1-4	357 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 2.27 (0.29 to 17.66)	14 per 1,000	18 more per 1,000 (10 fewer to 231 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. For the total number of emergent DESS symptoms, 43.8% of the evidence was at very high risk of bias, and 56.2% of the evidence was at low 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. Absolute effect calculated from the risk difference due to zero events in one or both arms

Table 13: Clinical evidence summary: SSRI antidepressants: withdrawal from SSRI antidepressants vs continuation on SSRI antidepressants

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no withdrawal of SSRIs	Risk difference with discontinuation of SSRIs
Total no. of emergent DESS symptoms (protocol outcome: intensity of withdrawal symptoms at 2 weeks post-abrupt-discontinuation)	104 (2 RCTs)	⊕⊕◯◯ LOW [b]	-	The mean total no. of emergent DESS symptoms was 0	MD 0.69 higher (0.16 higher to 1.22 higher)
Rebound: return to a MADRS score equal to or higher than the original score at the entry of the acute treatment	104 (1 RCT)	⊕⊕◯◯ LOW [b]	RR 0.71 (0.07 to 7.58)	33 per 1,000	10 fewer per 1,000

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no withdrawal of SSRIs	Risk difference with discontinuation of SSRIs
study (protocol outcome: specific withdrawal symptom 2 weeks post-abrupt-discontinuation)					(30 fewer to 216 more)
Discontinuation Emergent Signs and Symptoms (DESS) score of ≥4 (protocol outcome: intensity of withdrawal symptoms at 2 weeks post-abrupt-discontinuation)	371 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 2.03 (1.13 to 3.66)	79 per 1,000	81 more per 1,000 (10 more to 210 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. For continuous outcomes (DESS score) the MID was calculated as 1.75 (0.5*SD for the final value score for the control group used (as baseline values not available; final value control group SD only available for Montgomery 2004)*

1.1.6.5.2 Withdrawal from antidepressants vs withdrawal from placebo

Table 14: Clinical evidence summary: other antidepressant class: withdrawal from other antidepressants vs withdrawal from placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with withdrawal from placebo	Risk difference with withdrawal from ADs
Withdrawal symptoms during discontinuation (protocol outcome: any withdrawal symptom during the discontinuation period))	1828 (6 RCTs)	⨁◯◯◯ VERY LOW [a,c]	RR 1.53 (1.26 to 1.87)	145 per 1,000	77 more per 1,000 (38 more to 126 more)
Withdrawal symptoms (protocol outcome: any withdrawal symptom at 3 days after discontinuation of treatment)	18 (1 RCT)	⨁⨁◯◯ LOW [a,b]	RR 3.50 (0.98 to 12.48)	222 per 1,000	556 more per 1,000 (4 fewer to 2,551 more)
Headache as a DEAE (protocol outcome: specific withdrawal symptom during the discontinuation period)	375 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,d]	RR 1.72 (0.90 to 3.30)	70 per 1,000	51 more per 1,000 (7 fewer to 162 more)
Insomnia as a DEAE (protocol outcome: specific withdrawal symptom during the discontinuation period)	375 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,d]	RR 1.15 (0.53 to 2.50)	59 per 1,000	9 more per 1,000 (28 fewer to 89 more)
Nausea as a DEAE (protocol outcome: specific withdrawal symptom during the discontinuation period)	375 (1 RCT)	⨁⨁◯◯ LOW [a,d]	RR 2.92 (1.41 to 6.04)	49 per 1,000	93 more per 1,000 (20 more to 245 more)
Dizziness as a DEAE (protocol outcome: specific withdrawal symptom during the discontinuation period)	205 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,e]	RR 2.32 (0.60 to 9.01)	27 per 1,000	36 more per 1,000 (11 fewer to 218 more)
Mild adverse events (protocol outcome: intensity of withdrawal symptoms at mean 5 days after discontinuation of treatment)	18 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The mean number of mild adverse events was 0.2	MD 1.5 higher (0.49 higher to 2.51 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with withdrawal from placebo	Risk difference with withdrawal from ADs
Moderate adverse events (protocol outcome: intensity of withdrawal symptoms at mean 5 days after discontinuation of treatment)	18 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The mean number of moderate adverse events was 0.2	MD 0.9 higher (0.55 lower to 2.35 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. For the withdrawal symptoms during discontinuation outcome, the majority of 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 0.2 for number of mild adverse events and 0.35 number of mild adverse events (0.5 control group SD final value).*
c. in 3/6 studies, participants in the placebo groups had previously been taking active medication; in 4/6 studies it was unclear if placebo was withdrawn or not during the taper phase
d. participants in the placebo groups had previously been taking active medication
e. unclear if placebo was withdrawn or not during the taper phase

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 C section C.3.

1.1.8 Summary of included economic evidence

None.

1.1.9 Economic model

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

1.1.10 Evidence statements

1.1.10.1 Economic

- No relevant economic evaluations were identified.

1.2 Qualitative

1.2.1 Qualitative evidence

1.2.1.1 Included studies

Nineteen qualitative studies were included in this review; 6 for opioids, 4 for benzodiazepines and 9 for antidepressants;[31, 46, 67, 69, 117, 188, 216, 235, 272, 386, 471, 508, 514, 532, 633, 704, 705, 716, 722] these are summarised in Table 15 below. Key findings from these studies are summarised in the clinical evidence summaries below (Table 16 to Table 19). See also Appendix F section F.2 (Table 30 to Table 59

Table 59: Summary of evidence: Antidepressants: Review finding 14) for full qualitative evidence tables. See also the study selection flow chart in section C.2 of Appendix C, study evidence tables in Appendix E section E.2 and excluded studies lists in Appendix I section I.2.

The majority of studies across drug classes used semi-structured interviews and included a mixed population of chronic prescribed medicine users who were either currently receiving the medicines, currently tapering off the medicines or who had completed tapering.

There were 6 studies conducted in the UK and 4 in the USA. Studies were also conducted in Australia, Canada, Ireland, the Netherlands, New Zealand, South Africa and Sweden.

No relevant studies relating to the use of Z-drugs or gabapentinoids were identified.

1.2.1.2 Excluded studies

More details on excluded studies can be found in Appendix I.

1.2.2 Summary of studies included in the qualitative evidence

Table 15: Summary of studies included in the evidence review

Study	Design	Population	Research aim	Comments
Opioids				
Frank 2016[216]	Semi-structured interviews and thematic analysis	Adult primary care patients who were currently or had previously been, on chronic opioid therapy n=24 Mean age 52 years (range 31-73 years) Colorado, USA	To explore patients' perspectives on opioid tapering.	Status of opioid therapy: 6 participants (25%) were on chronic opioid therapy and not tapering, 12 (50%) were currently tapering opioid therapy, and 6 (25%) had discontinued opioid therapy.
Goesling 2019[235]	Semi-structured focus-groups and thematic analysis.	Adults, with a history of taking opioids every day for 3 months or longer and no current opioid use N=24 (formed 4 focus groups) Mean age (SD) for participants forming the focus groups is not provided; mean age (SD) of n=49 participants included in the wider mixed-method study was 49.3 (10.2) years. Michigan, USA	To identify themes pertaining to former opioid user's experiences before, during, and after opioid cessation	The qualitative focus groups were part of a mixed-method study (n=49) also using quantitative survey data to explore the study aim.

Study	Design	Population	Research aim	Comments
Henry 2019[272]	Focus groups (n=21 participants) and follow-up interviews (with n=7 of participants from the focus groups) with grounded theory analysis.	Adults with chronic back or neck pain in different stages of opioid tapering n=21 Mean age: 58 years. USA	To gain insight into patient experiences with opioid tapering by conducting focus groups and individual interviews with patients suffering from chronic neck and/or back pain.	Status of opioid therapy: 14 had recently completed an opioid taper (with 4 no longer taking opioids); 4 were in the process of tapering and 3 had discussed tapering but had not made changes Of the 7 patients who completed interviews, 4 had completed tapering, 2 were currently tapering, and 1 had been recommended to taper.
Scott 2020[633]	Mixed methods study involving semi-structured interviews and thematic analysis	Long-term opioid users receiving ≥3 opioid prescriptions in a 3-month period, who had taken opioids ≥3 months n=34 Mean age (SD): 51 (10) years Interviews were conducted with 18 service users. UK	To evaluate a one-to-one pain review service (based in two GP practices) and its potential impact on opioid use, health and wellbeing outcomes and quality of life (QoL), and to help inform future service provision.	Status of opioid therapy: out of the total sample, 3 were no longer taking opioids at the end of the study and 4 had reduced their opioid dose; unclear if and how many of those were interviewed. 17/34 (50%) receiving codeine; 10/34 (29.4%) tramadol. Back pain was the most common reported reason for prescription (9/32, 28.1%) Many service users were also taking other medication at baseline including benzodiazepines 12/34 (35.3%), amitriptyline 12/34 (35.3%), SSRIs 8/34 (23.5%), gabapentin 7/34 (20.6%) but paper is only relevant to opioid withdrawal

Study	Design	Population	Research aim	Comments
Van Hout 2017[705]	In-depth interviews and Empirical Phenomenological Psychological five-step method analysis.	Adult codeine misusers and dependents n=25 Mean age (range) 43 (21 to 74) with 67% (n=15) aged between 30-49 years n=20 admitted misusing codeine within the last 12 months and n=13 (52%) scored 10 or above on the severity of dependence screener (a five-item questionnaire with score over 5 indicating dependence use in the past 12 months) South Africa	To gain an understanding of unique individual and collective experiences of trajectories of codeine misuse and dependence in South Africa.	Excluded individuals reporting codeine use within accepted medical guidelines, but paper reports that initially for many participants codeine use was appropriate and for legitimate reasons, prescribed or over the counter to manage discrete episodes of pain. 'Many' were reported to be taking codeine-based medications to manage physical pain as a result of a chronic condition such as arthritis and severe headaches or to relieve pain (acute or chronic) following surgical interventions. Moderate concerns over applicability: 'A number' of participants had a history of illicit drug use such as heroin, cannabis, cocaine and ecstasy. Some used codeine in combination with alcohol with a small number of female participants combining with diet pills.
Van Hout 2018[704]	In-depth interviews and Empirical Phenomenological Psychological five-step method analysis.	Adult codeine misusers and dependents both actively using, in treatment and recovery n=21	To gain an understanding of individual and collective experiences of codeine use, pathways to misuse and dependence and experiences of treatment services in Ireland following the introduction of such guidelines for the safe supply	N=18 (86%) participants reported codeine-based medications (e.g., Solpadol, Nurofen Plus or Solpadeine) with n=1 reporting heroin and n=1 reporting distalgesic; n=13 (62%) reported Nurofen plus was their primary drug of use.

Study	Design	Population	Research aim	Comments
		Mean age (range): 39 (26 to 62) n=15 admitted using codeine within the last 12 months with majority scoring 10 or above (80%, n=12) in the SDS (score over 5 indicating dependence use in the past 12 months) Ireland	of over-the-counter codeine-based products.	Moderate concerns over applicability due to some participants combining codeine with illicit drug use and currently being on methadone maintenance (n=14) or suboxone (n=3) Study included as all participants were current or past codeine users regardless of any additional drugs use.
Benzodiazepines				
Barter 1996[67]	Semi-structured interviews and qualitative analysis (grounded theory)	Elderly patients who had received a benzodiazepine prescription for hypnotic use continuously for a minimum of one year n=11 Mean age: not stated UK	To gain an understanding of why patients continue to use benzodiazepines using a semi-structured interview technique and by comparing to non-benzodiazepine users.	Status of benzodiazepine therapy: currently prescribed temazepam: (n=5), nitrazepam (n=3), diazepam (n=2), lormetazepam (n=1)
North 1995[471]	Semi-structured interviews and qualitative analysis (not specified)	Two groups of long-term benzodiazepine users (n=22): community-based benzodiazepine uses (n=15) and members of a self-help group (n=7) from TRANX (a tranquilizers self-help group for those wanting to withdraw from benzodiazepines)	To gain an understanding of the reasons benzodiazepines continue to be used, and the relationships users have formed with their medication using in-depth interviews.	Status of benzodiazepine therapy: n=8 had experienced or were experiencing withdrawal under supervision (7 of these were members of TRANX).

Study	Design	Population	Research aim	Comments
		Mean age (range): 61 (34-82) All were anxiolytic and/or hypnotic users New Zealand		
Parr 2006[514]	Semi-structured interviews and qualitative analysis (Consensual Qualitative Research approach)	GPs (n=28); users of benzodiazepine s n=23 Mean age (range): 50 (25-79) years Users had at some time been prescribed daily benzodiazepine s for 3 months or more. For the purpose of this review, in line with the protocol, only findings reported by benzodiazepine users are extracted, not the GPs. Australia	To gain more detailed understanding of perceptions relating to starting, continuing and stopping benzodiazepine use and examine the degree of similarities between these perceptions.	Status of benzodiazepine therapy: 52% reported they had stayed on the dose originally prescribed by their doctor; 6 (26%) were currently prescribed benzodiazepine s for panic attacks, nerves, sleeping problems, anxiety, obsessive-compulsive behaviour or because they were addicted to them.
Voyer 2004[722]	'Directive' interviews & inspection of medication containers; qualitative analysis method not reported.	Long-term (minimum 6-months) elderly users of benzodiazepines n=45	To elicit descriptions of dependence from elderly long-term users of benzodiazepines that might reveal potential indicators of dependence other than long-	Status of benzodiazepine therapy: 75% were prescribed benzodiazepines on an 'as needed' basis.

Study	Design	Population	Research aim	Comments
		Mean age (SD): 79 (7.1) years Canada	term use (defined as six months or longer).	Psychotropic polypharmacy was notable, with 28.8% of the sample prescribed two or more drugs (more than one benzodiazepine or antidepressant); N=9 (20%) received concomitant prescriptions of antidepressants Moderate concerns over applicability: benzodiazepines included: clonazepam, lorazepam (n=18), oxazepam, temazepam which met the protocol but also alprazolam, bromazepam, flurazepam which were not part of the agreed guideline medicine list, but percentage of people prescribed each drug is not given. In line with the protocol the study is included and downgraded for concerns over applicability.
Antidepressants				
Anderson 2013[31]	Supplementary (i.e., in-depth) secondary analysis of narrative interviews.	People with different types of depression and treatment experiences n=80 42 adults and 38 young people (age range 16-75). UK	To examine patient and health professional understanding of what it is like to use antidepressants from initiation of therapy and to determine factors which influence decisions about adherence to antidepressants in terms of perceived outcomes and determining factors that influenced their views.	Strata: mixed/unclear antidepressants Interviews were part of the Healthtalkonline database and were conducted in the University of Oxford as part of a primary study. The Healthtalkonline project uses narrative interviews to explore health and social care issues.

Study	Design	Population	Research aim	Comments
Avery 2011[46]	Mixed methods (HTA) A purposive sample was taken from a range of different categories of Yellow Card reports. Extracts were quoted verbatim. A range of extracts from Yellow Card Reports were used to illustrate the findings, representing different patients, reactions and drugs. A number of major categories arose from the content analysis, and these informed the in-depth qualitative analysis.	Patient reports of suspected adverse drug reactions reported to the yellow card scheme. n=270 Mean age (SD) 44.2 (1.61) years UK	To evaluate patient reporting of suspected ADRs to the YCS (Yellow card scheme) in the UK by assessing the pharmacovigilance contribution of patient reports.	Study included reports on the following antidepressants (Paroxetine, citalopram, sertraline, venlafaxine). Only findings for relevant drugs from the HTA are reported in this review, and only responses relevant to withdrawal symptoms.
Bayliss 2015[69]	Semi structured interview about experiences. (thematic analysis)	Adults who had received treatment with antidepressant medication and CBT for depression. n=12 Mean age (calculated): 43.83 (range:22-56) years UK	To develop a preliminary model of the experiences of people undergoing combined treatment with antidepressant medication and cognitive-behavioural therapy (CBT) for depression.	Patient experiences with antidepressants only have been reported in this review.
Cartwright 2018[117]	Telephone interviews (unclear if structured or semi-structured) and thematic analysis	Women who had been prescribed and used antidepressants in the previous five years n=50	To understand how the experiences of using antidepressants and engaging in other activities and practices promote or diminish women's sense of agency in regard to their recovery.	Strata: mixed/unclear antidepressants Status of antidepressant therapy: n=35 were still using antidepressants at the time of the interview and n=15 were not.

Study	Design	Population	Research aim	Comments
		Mean age (range): 44.5 (27 to 62 years) New Zealand		Women had originally taken part in a large anonymous online survey about antidepressant and the current study included a range of women from the three groups: reporting positive (n=23), negative (n=4) and mixed experiences (n=22) of antidepressants, including participants who had been on antidepressants in the short, medium and long term.
Eveleigh 2019[188]	Semi-structured interviews and thematic analysis	People on long-term antidepressant treatment without a current indication (no psychiatric diagnosis) n= 16 Mean age (range) 57 (women: 31-76; men: 51-79) years Netherlands	To explore the attitudes of patients, who are using antidepressants long term without a proper current indication, towards the discontinuation of these drugs, and to explore their attitudes towards the discontinuation advice they received when participating in an RCT.	Strata: mixed (SSRI, tricyclics and other) antidepressants Participants were recruited from the intervention group of a cluster-RCT. As part of the intervention, they had been provided advice to stop antidepressants. n=7 participants intended to comply with the discontinuation advice during the RCT and n=5 of these actually discontinued during or after the RCT.
Leydon 2007[386]	Face-to-face semi-structured qualitative interviews with thematic analysis	People taking SSRIs n=17 UK	To explore patient experiences of and beliefs about their long-standing SSRI use and understand the barriers and facilitators to discontinuation.	Strata: SSRIs Seven participants described this as their first and only episode of depression. Of the rest, six talked in terms of previous distinct episodes, while four described their depression as ‘ongoing’ or ‘long term’.

Study	Design	Population	Research aim	Comments
Papp 2018[508]	Qualitative analysis of unsolicited posts on mental health website: Mental Health Daily The paper also includes quantitatively analysed data from the qualitative responses, but only qualitative findings have been extracted.	N=595 posts on a website, generated between December 2014 and December 2016, made anonymously and with no discernible demographic information. USA	To gather information as reported spontaneously by internet users about the specific symptoms experiences while having brain zaps.	Mixed strata: SSRIs & other antidepressants (60% SSRI's; 37.1% other antidepressants; 2.7% bupropion not meeting guideline medicine list) Mental Health Daily is a popular website devoted to a myriad of mental health issues, that contains a forum dedicated to posting about brain zaps. The most frequently reported action preceding brain zaps was abrupt stopping (39.9%), followed by tapering (25.7%) and skipping doses (12.5%). Moderate concerns about applicability due to a lack of sufficient information on the characteristics of peopled from which the information emerged and the data being unverified due to the nature of the source (anonymous posts on mental health website).
Pestello 2008[532]	Analysis of postings on a health-related website. Themes for analysis were derived inductively through a grounded theory approach.	People posting details of side effects, and withdrawal symptoms on a website. n=277 Mean age not reported.	To examine the experience of taking antidepressant medications and the impact on the sense of self.	Population details/characteristic not reported.

Study	Design	Population	Research aim	Comments
		Country not specified.		
Vilhelmsson 2012[716]	Content analysis of free text comments from consumer reports	People reporting adverse drug reactions to antidepressant medications n=181 consumer reports) Mean age not reported Sweden	To qualitatively analyse the free text comments appended to consumer reports on antidepressant medication.	Mixed strata: SSRIs (66.4%) & other antidepressants The antidepressants most reported for a diagnosis of depression were Sertraline (23.8%), Citalopram (23.8%), Venlafaxine (23.2%), Mirtazapine (10.5%), Paroxetine (7.7%), Escitalopram (6.1%) and Fluoxetine (5.0%). Minor concerns about applicability due to participants being limited to people experiencing adverse drug reactions. The majority of findings have been synthesised within the SSRI stratum as quotes used to illustrate them in the paper were from people on SSRIs.

See **section E.2.** of Appendix E for full evidence tables.

1.2.3 Summary of the qualitative evidence

Table 16: Review findings: Opioids

Main findings	Statement of finding
Worsening of symptoms for which the medication was prescribed[235, 272]	Ones' original symptoms such as back pain can get worse with tapering
Fluctuations/ variability in withdrawal symptoms[272]	Symptoms experienced during tapering such as pain and the need for opioids fluctuated from day to day, getting better or worse.
Fear of pain exacerbation and loss of function[216, 272, 704]	The experience of fear of worse pain and loss of function associated with past opioid withdrawal was central in the experience of tapering and warranted management as it could lead to an exacerbation of pain or prevent future tapering attempts.
Increased pain levels and headaches[272, 633, 704, 705]	Increased physical pain including headaches, cramps, pain in the legs and arms was experienced by people as a result of opioid (including codeine) reduction, the intensity of which could often vary from physical discomfort to 'screaming pain' depending on adherence to the tapering plan.
Gastrointestinal problems[216, 272, 704]	People tapering off opioids and codeine misusers and dependents reported withdrawal symptoms including stomach sickness or pain, emesis, vomiting, diarrhoea and loss of appetite which were described as very unpleasant, and in some cases supported continued use.
Sweating, 'cold shakes', fever[216, 235, 633, 704, 705]	People tapering off opioids including codeine experienced sweating, 'cold shakes', cold and hot sweats, and fever.
Sleep problems[704, 705]	Experiencing insomnia and disturbed sleep patterns were barriers to stopping codeine misuse.
Mood problems[235, 704, 705]	Long-term opioid users and codeine misusers and dependents reported psychological pain, fear, crying, self-pity, irritability, anxiety attacks, aggression and feeling very agitated, which appeared to contribute to sustained misuse or needed separate management with medication.
Cravings[704, 705]	Codeine misusers and dependents experienced strong cravings, with some resorting to illicit drugs (cannabis) to manage them, which often led to relapses whereas using drugs that acted on cravings to treat dependence (suboxone) were reported to lead to instant stopping.
Duration of withdrawal symptoms[272]	Withdrawal symptoms could last from weeks to months or could persist a year after stopping opioids.
Little or no withdrawal symptoms[216, 705]	Some people described little or no opioid withdrawal symptoms during tapering.

Table 17: Review findings: Benzodiazepines

Main findings	Statement of finding
Return of the original symptoms for which the medication was prescribed[67, 471, 514, 722]	Participants reported a return of their original symptoms of insomnia or anxiety following attempts to reduce or stop their benzodiazepine use, that persisted

Main findings	Statement of finding
	a month after stopping or were relieved only by restoring the initial dose or made stopping undesirable, an inability to function or cope with their ongoing mental health problems.
Worry as part of withdrawal[67, 514, 722]	Benzodiazepine withdrawal evoked feelings of worry and burden with people wishing to keep some benzodiazepines for psychological reasons, to have just in case.
Intensity of withdrawal symptoms[67, 471, 514]	Several, particularly those on rapid withdrawal experienced adverse withdrawal symptoms including chest pain and hang-over effects, with the intensity of the symptoms during past attempts to reduce use, leading to an inability to cease benzodiazepines or to taking other medication to cope.
Disturbed dreams[67]	A number of elderly participants experienced what they called 'disturbed dreams' after stopping benzodiazepines which appeared to impact their daily life.
Lack of withdrawal symptoms[67, 471]	Several people prescribed hypnotic and/or anxiolytic benzodiazepines, including people who had stopped receiving prescriptions for several months or periods at a time over the years, did not experience problems when stopping or slowly reducing their medicines.

Table 18: Review findings: Antidepressants (mixed/unclear)

Main findings	Statement of finding
Severity of withdrawal symptoms[46, 117, 508]	People experienced severe withdrawal symptoms, also in the period between prescriptions, which were sometimes experienced as debilitating, resulted in feeling out of control, regretting stopping and recontinuing antidepressants.
Fear of discontinuation[69, 117, 188]	People became overwhelmed by fears and worries as a result of antidepressant discontinuation, that were fuelled by past negative experiences of discontinuation attempts and contributed to attributions about their lifelong need for medication despite wanting to discontinue.
Dizziness, nausea and loss of appetite[46, 532]	People on venlafaxine experienced nausea and dizziness during discontinuations and after stopping, accompanied by loss of appetite and abdominal pain (in one person).
Increase in negative emotions[69, 117, 188]	People reported an inability to regulate emotions without the medicine, feeling depressed, anxious, tearful, increased feelings of loneliness and abandonment during discontinuation, which sometimes led to restarting the medicines, contributing to further negative feelings about themselves.
Strange sensation in the head[31, 46, 117, 508, 532]	People reported experiencing strange withdrawal symptoms that included 'electric shock-like sensations' in the brain, a head buzz or brain zap that often persisted after stopping the medicine and were sometimes accompanied by vertigo or associated with making a rapid mascle movement.

Table 19: Review findings: Antidepressants (SSRIs)

Main findings	Statement of finding
Severity of withdrawal symptoms[46, 386, 532]	People experienced severe withdrawal symptoms, the unpleasantness of which was comparable to the initial depressive symptoms, often led to feelings of regret about trying to stop, relapse and prevented future discontinuation attempts contributing to sustained use.
Fear of discontinuation and relapse[386, 716]	People experienced fear about the process of discontinuation, about discontinuation symptoms and the consequences of stopping which was thought to potentially lead to relapse of depression and was often driven by past attempts to stop; this fear sometimes ultimately prevented discontinuation.
Suicidal thoughts[46]	Both paroxetine and citalopram users experienced persistent suicidal thoughts during withdrawal from antidepressants with some having made multiple suicide attempts; these were also experienced during dose reductions.
Nausea and dizziness[46, 532]	People coming off paroxetine experience nausea and dizziness
Insomnia[46]	Insomnia was one of the withdrawal symptoms experienced since starting to reduce antidepressants.
Psychiatric adverse reactions[46, 532, 716]	People experienced unmanageable stress, excessive anxiety that were much higher to pre-antidepressant levels, irrational fears (e.g., fear of dying), panic attacks, became violent towards the self or others since beginning discontinuation or particularly after a significant dose reduction (e.g., to 10mg) which were interpreted as withdrawal symptoms by patients but often as relapse/recurrence of depression indicating the need for continued treatment by doctors.
Changes in mood[46]	Sudden changes in mood and crying were experienced since beginning to reduce the medicine but also after a significant reduction in dose.
Other bodily symptoms[46, 386]	Since beginning to reduce their medicine people experienced symptoms including agitation, sweating and palpitations but also flu-like symptoms including debilitating tiredness, headaches, aching joints and muscles particularly (5 weeks) after dropping the antidepressant dose.
Onset of withdrawal symptoms[386, 716]	The onset of withdrawal symptoms was not until 3-5 days after the discontinuation attempt (involving reducing and stopping antidepressants).

See Appendix F section F2 for full qualitative evidence tables.

1.2.3.1 Narrative summary of review findings: Opioids

Review finding 1: Worsening of symptoms for which the medication was prescribed

People experienced worsening pain symptoms when they tapered their opioid use. One participant stated, “My pain was much worse because they really did work for me pain wise”. More time was spent on trying different procedures, surgeries or medications when an effective treatment could not be found. Worsening of pain without an alternative treatment impacted mood for some people. A patient tapering off opioids after having trouble finding a primary care clinician willing to prescribe them after his original clinicians’ retirement, reported his back pain was getting worse and wished to have another prescription of opioids.

Explanation of quality assessment: minor concerns over methodological limitations due to the potential influence of the researcher on the findings not being discussed in 2 studies and minor possibility of selection bias in patients interviewed in the one study; no concerns about coherence; no concerns over relevance; serious concerns about adequacy with the finding emerging from limited information from 2 studies. Overall assessment of confidence was low due to the concerns over methodological limitations and adequacy.

Review finding 2: Fluctuations/ variability in withdrawal symptoms

People who had recently completed tapering or were currently tapering off opioids experienced tapering as dynamic because their pain and perceived need for opioids varied from day to day and because their pain was frequently affected (either positively or negatively) by changes in their social relationships and emotional state. Patients repeatedly emphasised that tapering requires planning and sustained effort, that 'it's a process' and involves going through a lot of different changes', that requires patients to adjust and recalibrate in response to these changes. When asked how she would advise others about tapering, one patient said, 'it's just that pain changes, it doesn't stay the same, there's constant change. It may take a while for it to change, it may get worse, it may get better'.

Explanation of quality assessment: minor concerns over methodological limitations due to the potential influence of the researcher on the findings not being discussed and the minor possibility of selection bias in patients interviewed in the contributing study; no concerns about coherence; no concerns over relevance; minor concerns about adequacy with sufficient information to support the theme but coming from one study. Overall assessment of confidence was moderate due to the concerns over methodological limitations and adequacy.

Review finding 3: Fear of pain exacerbation, withdrawal, and loss of function

Fear emerged as a uniquely powerful emotion affecting both patients' willingness to taper and the overall tapering experience of people who had completed or were tapering off opioids and those who had discussed tapering. Most patient fears involved the possibility of worse pain and withdrawal owing to decreased opioids. For most patients, the prospect of tapering evoked fears involving a mix of pain, withdrawal, and loss of function, with one participant reporting 'I don't want to be in that situation again'. One patient described inchoate fear after a clinician refused to refill her oxycodone. Fears of addiction and overdose were less prominent than fears of pain and withdrawal. Managing emotions during tapering mostly entailed managing the fears of pain and loss of function. One patient noted that having fewer pills heightened the fears of uncontrollable pain, which required her to expend more energy controlling these fears. 'I have the side effect of obsessing about how many (pills) I have'. Failure to control one's fear often made the pain worse with one patient particularly reporting: 'I would start to feel the pain coming on and it would be like my mind would say, 'Oh my god, you're going to… it's like this fear of the worst pain you ever had and it literally almost makes it manifest'

Past experiences of opioid withdrawal produced fear and anxiety about future opioid tapering or discontinuation, with some reporting getting 'so sick not having' the drugs and feeling very insecure.

Despite becoming aware of habit-forming use and harm, people actively misusing codeine described they were unable to stop with fears around existing pain conditions underpinning difficulties in ceasing use.

Explanation of quality assessment: minor concerns over methodological limitations with nothing to lower our confidence in one study, minor concerns in one study due to the potential influence of the researcher not being discussed and minor possibility of selection bias in patients interviewed, due to the influence of the researcher not being discussed in

one study; no concerns about coherence; moderate concerns over relevance with moderate concerns in one study due to some participants combining codeine with illicit drug use and currently being on methadone maintenance potentially for withdrawal of other medicines which could influence their experience of codeine withdrawal or whose experience may differ from that of people not on methadone maintenance but no concerns in two studies and fear over withdrawal potentially not being an actual withdrawal symptom despite having been explicitly reported as such (in one study[272]); no concerns about adequacy with sufficient information to support the theme. Overall assessment of confidence was low due to minor methodological limitations and moderate concerns over relevance.

Review finding 4: Increased pain levels and headaches

People who had recently completed opioid tapering or were currently tapering reported withdrawal side effects, including increased pain levels and headaches as a result of reducing opioids. Some reported they had to continuously exert self-control to balance their immediate desire for pain relief against their fear of worse pain or withdrawal if they ran out of opioids in the future. Physical discomfort relating to pain was reported as a result of sticking to the tapering plan, whereas 'screaming pain' and headaches were reported where people were taking too much medication one day or for a few weeks and not having enough for the next day or final week of the month.

Codeine misusers and dependents also reported experiencing unpleasant withdrawal symptoms that included pain in the legs, arms and stomach and 'blinding' headaches, which supported continued use of codeine.

Explanation of quality assessment: minor concerns over methodological limitations with moderate concerns in one study due to role of the researcher not being discussed and limited relevance of the study aim to the review topic with very limited information to contribute to the review, but minor concerns in the other 3 contributing studies due to the potential influence of the researcher on the findings not being discussed in 3 studies and also minor possibility of selection bias in patients interviewed in one study; no concerns about coherence; moderate concerns over relevance due to moderate concerns across the majority of contributing studies due to some participants combining codeine with illicit drug use in 2 studies and with participants in one study being pain service users receiving an individually tailored one-to-one tapering program whose experience of withdrawal may differ to that of people with no access to similar support; no concerns about adequacy with sufficient information from four studies to support the theme. Overall assessment of confidence was low due to the methodological limitations and concerns over relevance identified.

Review finding 5: Gastrointestinal problems

Patients reported that tapering off opioids often required them to expend more effort adjusting their habits and opioid consumption to maintain functionality. They noted that managing opioids became more difficult as tapering progressed with one particularly reporting getting stomach sickness by delaying the opioid dose by an hour.

Another patient reported vomiting and stomach cramps among other withdrawal symptoms, which were referred to as being 'pretty bad'.

Codeine misusers and dependents also described unpleasant withdrawal symptoms centred on emesis, diarrhoea, stomach pain, loss of appetite, which were unpleasant and supported continued use.

Explanation of quality assessment: minor concerns over methodological limitations due to the potential influence of the researcher on the findings not being discussed in two studies and also minor possibility of selection bias in patients interviewed in one study and nothing to lower our confidence in one study; no concerns about coherence; no concerns over

relevance with moderate concerns in one study due to some participants combining codeine with illicit drug use but no concerns in the other 2 contributing studies; minor concerns about adequacy with the theme supported by 3 studies but with relatively limited information from each study. Overall assessment of confidence was moderate due to the methodological limitations and concerns over adequacy identified.

Review finding 6: Sweating, 'cold shakes', fever

A small number of people tapering off opioids via a pain service clinic reported withdrawal side effects including sweating, as a result of reducing opioids. People on previous opioid therapy emphasising the difficulty of withdrawal also reported 'cold shakes and fever or experiencing cold and hot sweats' for 3 days.

Codeine misusers and dependents reported sweating and perspiration as unpleasant withdrawal symptoms, with one participant mentioning experiencing 'the turkey skin and shivering' and shock down my body'.

Explanation of quality assessment: minor concerns over methodological limitations with moderate concerns in one study due to role of the researcher not being discussed and limited relevance of the study aim to the review topic with very limited information to contribute to the review but nothing to lower our confidence in one study, very minor concerns in one study due to the role of the researcher not being discussed and no further concerns, and minor concerns in 2 studies due to the potential influence of the researcher on the findings not being discussed; minor concerns about coherence with participants across contributing studies reporting those similar-nature symptoms but with not all symptoms reported across the 4 studies; moderate concerns over relevance due to moderate concerns across the majority of contributing studies due to some participants combining codeine with illicit drug use in 2 studies and with participants in one study being pain service users receiving an individually tailored one-to-one tapering program whose experience of withdrawal may differ to that of people with no access to similar support; moderate concerns about adequacy with the theme supported by 5 studies but with limited information from each study. Overall assessment of confidence was very low due to the concerns identified across elements of quality assessment.

Review finding 7: Sleep problems

Codeine misusers and dependents reported insomnia, restlessness and not being able to sleep or having disturbed sleep patterns, among other withdrawal symptoms they experienced, which supported their continued use.

Explanation of quality assessment: minor concerns over methodological limitations due to the potential influence of the researcher not being discussed in both contributing studies and no further concerns to lower our confidence; no concerns about coherence; moderate concerns over applicability due to some participants in both contributing studies combining codeine with illicit drug use and participants of one study also currently being on methadone maintenance potentially for withdrawal of other medicines which could influence their experience of codeine withdrawal or whose experience may differ from that of people not on methadone maintenance; serious concerns about adequacy with very limited information to support the theme. Overall assessment of confidence was very low due to concerns over methodological limitations, relevance, and adequacy.

Review finding 8: Mood problems

Among the unpleasant withdrawal symptoms that people using codeine described, they reported psychological pain, fear, crying, self-pity, irritability, anxiety, aggression and feeling very agitated, which appeared to contribute to sustained misuse. Long-term opioid users also

reported agitation and anxiety attacks and needing to take separate medication to manage them.

Explanation of quality assessment: minor concerns over methodological limitations due to the potential influence of the researcher not being discussed across contributing studies and no further concerns to lower our confidence; no concerns about coherence; moderate concerns over applicability due to some participants in 2 contributing studies combining codeine with illicit drug use and participants of one study also currently being on methadone maintenance potentially for withdrawal of other medicines which could influence their experience of codeine withdrawal or whose experience may differ from that of people not on methadone maintenance; serious concerns about adequacy with very limited information to support the theme. Overall assessment of confidence was very low due to concerns over methodological limitations, relevance, and adequacy.

Review finding 9: Cravings

Several codeine misusers or dependents described strong cravings, with some resorting to other illicit drugs such as cannabis (smoking weed) or engaging a hobby as a means for managing the cravings for codeine.

Relapse with codeine phosphate tapering appeared to be universal due to lack of effect on cravings and instances of ‘topping up’ with Nurofen Plus. On the other hand, Suboxone (a drug used to treat opioid dependence) in particular was viewed very positively in the removal of cravings and withdrawal effects, with one participant in particular reporting instantly stopping codeine and experiencing no withdrawal symptoms.

Explanation of quality assessment: minor concerns over methodological limitations due to the potential influence of the researcher not being discussed in both contributing studies and no further concerns to lower our confidence; no concerns about coherence; moderate concerns over applicability due to some participants in both contributing studies combining codeine with illicit drug use and participants of one study also currently being on methadone maintenance potentially for withdrawal of other medicines which could influence their experience of codeine withdrawal or whose experience may differ from that of people not on methadone maintenance; serious concerns about adequacy with very limited information to support the theme. Overall assessment of confidence was very low due to concerns over methodological limitations, relevance, and adequacy.

Review finding 10: Duration of withdrawal symptoms

Patients who tapered off opioids noted that withdrawal symptoms lasted weeks to months, with one patient still experiencing withdrawal symptoms 1 year after stopping oxycodone.

Explanation of quality assessment: minor concerns over methodological limitations due to the potential influence of the researcher not being discussed and minor possibility of selection bias in patients interviewed in the contributing study; no concerns about coherence; no concerns over relevance; serious concerns about adequacy with very limited information from one study to support the finding. Overall assessment of confidence was very low due to the concerns over methodological limitations, relevance, and adequacy.

Review finding 11: Little or no withdrawal symptoms

In contrast to those experiencing withdrawal symptoms, there were several disconfirming cases in patients who described little or no opioid withdrawal symptoms during tapering. One patient particularly reported ‘I didn’t stop under doctor’s orders or discussion or anything, I just got up one day and I’m done. Instead of taking four, I took three and I did that for a couple of weeks and then I took two and I took one. I never felt any discomfort or anxiety or anything so… it worked for me’.

Similarly, while most codeine misusers or dependents described strong craving and withdrawal effects, one young male participant reported how he successfully managed to reduce his misuse of codeine. He reported tapering down gradually on his own using 'fewer and fewer' and that 'there were still a little bit of withdrawal symptoms, but it wasn't as bad as what it could have been if I stopped immediately'.

Explanation of quality assessment: very minor concerns over methodological limitations with nothing to lower our confidence in one study and minor limitations in the other contributing study due to the potential influence of the researcher on the findings not being discussed; minor concerns about coherence with information being in contrast with the experience of most participants in both studied but emerging from 2 separate studies; minor concerns over relevance with moderate concerns in one study due to some participants combining codeine with illicit drug use but no concerns in the other contributing study; moderate concerns about adequacy with relatively limited information from 2 studies to support the finding. Overall assessment of confidence was low due to concerns over coherence, relevance, and adequacy.

1.2.3.2 Narrative summary of review findings: Benzodiazepines

Review finding 1: Return of the original symptoms for which the medication was prescribed

Elderly people receiving benzodiazepines for hypnotic use reported they had tried to stop but resumed even the same night due to experiencing insomnia, with some being unable to sleep until early in the morning. Insomnia appeared to persist a month after stopping, with one participant particularly reporting being unable to sleep, 'getting up at night and wandering around'.

Several participants who had been taking hypnotic and/or anxiolytic benzodiazepines also reported they had attempted to withdraw or reduce their medication at some stage and soon found their original symptoms of anxiety or insomnia had returned and were only suppressed by restoring the initial dosage. The experience of anxiety and sleep problems made stopping undesirable in some cases.

People were prescribed benzodiazepines for a variety of reasons, including one or more mental health conditions (including: panic disorder, depression, anxiety and post-traumatic stress disorder, panic attacks, sleeping problems, anxiety, and obsessive compulsive behaviour), found they could not sleep, function or cope with ongoing mental health problems as benzodiazepines helped them keep emotions and thoughts under control, and helped them cope with distressing symptoms associated with their medical conditions.

Explanation of quality assessment: minor concerns about methodological limitations in three contributing studies due to limited information and quotes to support the study findings and the Interviewer qualification being unclear in one study, lack of details on the analysis in one other study, the role of the researcher not being discussed and findings supported by single quotes in one study and serious concerns in only one study due to the role of the researcher not being explored, the recruitment strategy with participants selected for a different project, the data analysis being unclear; no concerns about coherence; minor concerns over relevance with no concerns in 3 studies but moderate concerns in one study with at least some participants taking benzodiazepines that did not meet the protocol; minor concerns about adequacy, with 4 studies supporting the theme but information within each study being limited. Overall assessment of confidence was moderate due to the concerns over methodological limitations, relevance, and adequacy identified being minor.

Review finding 2: Worry as part of withdrawal

Some participants found the idea of stopping to be difficult. People reported benzodiazepines helped them keep emotions and thoughts under control, to feel less burdened and worried and cope with adverse life circumstances and distressing symptoms associated with their medical conditions. Some indicated a desire to stop but that at the same time they did not want to distance themselves from the drugs completely, reporting a desire to 'keep the pills that are leftover in case' as it would be 'a relief' to know that they had some in case something happened, or they experienced severe withdrawal symptoms.

Explanation of quality assessment: moderate concerns about methodological with minor concerns in 2 studies due to limited information and quotes to support the study findings and the Interviewer qualification being unclear in one study, the role of the researcher not being discussed and themes supported by single quotes in one study but serious limitations in one study contributing the majority of the information for this theme, due to the role of the researcher not being explored, the recruitment strategy with participants selected for a different project, the data analysis being unclear; no concerns about coherence; moderate concerns over relevance with no concerns in two studies but moderate concerns in one study with at least some participants taking benzodiazepines that did not meet the protocol and due to the feeling of worry potentially developed before and not necessarily as a result of withdrawal; moderate concerns about adequacy with three studies supporting the theme but with information in each study being very limited. Overall assessment of confidence was very low due to concerns over methodological limitations, relevance and adequacy.

Review finding 3: Intensity of withdrawal symptoms

For people prescribed benzodiazepines for a variety of reasons, including one or more mental health conditions, the intensity of withdrawal symptoms associated with previous attempts to cut down was identified as contributing to an inability to cease benzodiazepine use. Others found within a short period of time of commencing that they felt addicted because of the adverse symptoms experienced when they tried to stop them. They endured 'hangover' effects in the morning; or took other medication to cope with withdrawal symptoms.

A participant who had stopped using sleeping tablets for 5 days particularly reported 'it was awful, my chest, I was in pain' with another saying that 'When the drug was taken away it nearly killed me.'

In contrast to those slowly reducing their medication, those on rapid withdrawal described the experience as 'a journey to hell', or 'the most horrific time of my life'.

Explanation of quality assessment: Minor concerns about methodological limitations across three contributing studies due to limited information and quotes to support the study findings and the Interviewer qualification being unclear in one study, lack of details on the analysis in one study, the role of the researcher not being discussed and findings illustrated by single quotes in the other study; no concerns about coherence; no over relevance; minor concerns over adequacy with information from three studies being relatively limited. Overall assessment of confidence was moderate due to the minor concerns over methodological limitations and adequacy.

Review finding 4: Disturbed dreams

A number of elderly participants who had been prescribed hypnotic benzodiazepines experiencing withdrawal symptoms reported having 'disturbed dreams.' One participant who had stopped for 1 month particularly reported, 'if I don't take a tablet then, well it is just nasty dreams, very disturbed'. These could interfere with daily life to the extent that a participant

who had stopped for 1 month expressed being left ‘a bit upset and shattered the next morning’.

Explanation of quality assessment: minor concerns over methodological limitations due to limited information and quotes to support the study findings and the Interviewer qualification being unclear; no concerns about coherence; minor concerns about relevance with the population contributing to the theme being limited to elderly people; serious concerns over adequacy with the theme supported by very limited information coming from one study. Overall assessment of confidence was very low due to the concerns over adequacy, methodological limitations, and relevance.

Review finding 5: Lack of withdrawal symptoms

Several participants who had been prescribed hypnotic and/or anxiolytic benzodiazepines reported had withdrawn from their medication with ease, experiencing no problems as they slowly reduced the medication over months. Similarly, some elderly participants prescribed benzodiazepines for hypnotic use reported no issues with stopping their medication. Three participants had stopped using sleeping tablets and receiving prescriptions for several months or periods at a time over the years. No reports of disturbed sleep or illness were mentioned upon discontinuation.

Explanation of quality assessment: minor concerns about methodological limitations due to limited information and quotes to support the study findings and the Interviewer qualification being unclear in one study, and lack of details on the analysis in the other study; no concerns about coherence; no concerns over relevance; no concerns about adequacy with sufficient information to support the finding overall. Overall assessment of confidence was moderate due to minor concerns over methodological limitations.

1.2.3.3 Narrative summary of review findings: Antidepressants (mixed/ unclear)

Review finding 1: Severity of withdrawal symptoms

Participants described previous experiences of severe withdrawal symptoms that led them to feel out of control. One participant talked about a 2–3-week period between prescriptions (Mirtazapine or Venlafaxine) that was ‘just horrible’ when she was ‘feeling really like, almost aggro and really anxious and tearful’. Severe withdrawal symptoms often led women to recontinue antidepressants, with one woman on Fluoxetine reporting stopping was a ‘big mistake’. A small number of people experiencing ‘brain zaps’ reported these resulted in significant disability, and one person taking venlafaxine also reported experiencing ‘debilitating withdrawal’

Explanation of quality assessment: minor concerns about methodological limitations with no notable limitations identified for one study, serious limitations in one study making a minor contribution to the theme, due to potential selection bias as the method used to select website posts was not specified and lack of sufficient detail on the data analysis, but minor methodological limitations due to the potential influence of the researcher on the findings not being discussed in the study contributing the majority of the information to this theme; no concerns about coherence; minor concerns over relevance with moderate concerns over one study with the information emerging being specifically about ‘brain zaps’ and due to a lack of sufficient information on the characteristics of peopled from which the information emerged and the data being unverified due to the nature of the source (anonymous posts on mental health website), but the study contributing limited information to the theme, no concerns in one study and minor concerns in the study contributing the most information to the theme due to the all-female sample included; minor concerns about adequacy with information emerging from 3 studies but being very limited in 2 out of 3 contributing studies. Overall assessment of confidence was moderate due to the concerns identified over methodological limitations, relevance and adequacy being minor.

Review finding 2: Fear of discontinuation

People expressed fear of attempting to discontinue fuelled by experiences during prior discontinuation attempts, often resulting in losing their stability. Some expressed a fear that discontinuation could cause a crisis. One participant, in particular, described this as a 'really horrible, very frightening thought' and that despite being a very capable person who would like to think she could manage without antidepressants, she reported to 'lose sight of reality' and starting to 'get overwhelmed by fears and worries.'

Because of this difficulty tapering and discontinuation symptoms, attributions concerning lifelong need and anticipation fear were reconfirmed, with one participant characteristically reporting 'you have to put a bit of faith in the tablets', despite not wanting to rely on them and wishing to stop the medication. The confidence a participant had beforehand in the success of a discontinuation attempt was important. If the participant could be convinced the attempt would be successful, the fear to discontinue would diminish. The GP played an important role in this, both as a 'safety net' and as a 'partner or counsellor' during the discontinuation attempt.

Explanation of quality assessment: Moderate methodological limitations due to the potential influence of the researcher on the findings not being discussed in 2 studies and issues with data richness in two studies with themes mostly supported by limited information in one study and with a very small sample included in one study; no concerns about coherence; moderate concerns over applicability due to fear not necessarily experienced during withdrawal by all participants raising it and due to the all-female sample of one study; no concerns about adequacy as despite concerns over data richness in individual studies, collectively there was sufficient information across three studies to support the finding. Overall assessment of confidence was low due to concerns over methodological limitations and relevance.

Review finding 3: Dizziness, nausea, loss of appetite

Nausea and dizziness were among the physical side effects people experienced when discontinuing antidepressants. One person trying to reduce Venlafaxine reported having 'horrible dizzy spells and nausea' whenever trying to lower the dose of the drug, while another experienced nausea, ongoing irritable bowel syndrome and dizziness, after tapering down as per doctor's instructions and then stopping. Apart from nausea, one person reported no appetite, even for liquids, and pains in the abdomen.

Explanation of quality assessment: moderate concerns over methodological limitations with no notable limitations in one study but serious limitation in the other study due to the research design/methods, data collection method and analysis (postings on health website); minor concerns about coherence with loss of appetite reported in only one person in one study; minor concerns over relevance with moderate concerns in one study due to a lack of sufficient information on the characteristics of people from which the information emerged and the data being unverified due to the nature of the source (anonymous posts on health website) but no concerns in the other study; moderate concerns about adequacy with information only emerging from a small number of people in 2 studies. Overall assessment of confidence was very low due to the concerns identified across elements of quality assessment.

Review finding 4: Increase in negative emotions

People experienced difficulty coming off antidepressants, reporting feeling uncomfortable and getting 'really depressed'. One participant talked about a 2-3-week period between prescriptions (Mirtazapine or Venlafaxine) that was 'just horrible' when she was 'feeling really like, really anxious and tearful'. Severe withdrawal symptoms often led women to recontinue antidepressants with one woman on Fluoxetine reporting stopping was a 'big mistake' as 'you get depressed again and then you start taking it again and you get all the side

effects…so the trick is not to just stop taking it'. Unsuccessful attempts to withdraw diminished women's sense of agency in relation to managing their own well-being and increased feelings of dependency on the medication. This contributed to negative feelings about themselves and an inability to regulate emotions without them. One patient who had made a prior attempt to taper but did not discontinue reported that, during that time, he had more feelings of loneliness and abandonment, didn't feel well at all and didn't know what to do. He reported that he kept coming back and he started to question why he should stop the medication and eventually restarted the medication.

Explanation of quality assessment: minor concerns over methodological limitations with moderate concerns in one study due to the potential impact of the researcher on the findings not being explored and issues with data richness with themes mostly supported by limited information and single quotes but minor limitations in two studies again due to the potential influence of the researcher on the findings not being discussed in one study and due to concerns over data richness with a very small sample (n=12) included in one study; moderate concerns about coherence with negative feelings varying across participants; moderate concerns over applicability with minor concerns in one study due to the all-female sample but also due to concerns over some negative feelings described being related to recurrence of depression rather than being withdrawal symptoms; minor concerns about adequacy with relatively limited information from three studies supporting the theme. Overall assessment of confidence was very low due to concerns identified across elements of quality assessment.

Review finding 5: Strange sensation in the head

Some people, including people who had been taking SSRIs experienced strange withdrawal symptoms, with one reporting: 'when you make a gross movement, a gross muscle movement, you get this incredible…It's not a tingling, you get this incredible buzz in your head'. Others reported still feeling 'electric shocks' in the brain or 'electric shock-like sensations, also called brain shivers', and an inability to 'deal with rapid movements' that persisted after tapering down and stopping the medicine. Relying on antidepressants increased feelings of abnormality, with one patient reporting being on medication and when coming off them always feeling that there is 'something not quite right in my brain- that I just need to keep taking them'.

Some people experienced what they called a 'brain zap' that was most often linked to an electric shock felt inside the skull, lasting a few seconds, with several reporting experiences that seem like momentary dissociations. The zap experience was often accompanied by vertigo as well as hearing a sound, including people reporting 'hearing their eyes move'

Explanation of quality assessment: moderate concerns over methodological limitations with no notable limitation in one study, minor limitations in two studies due to the potential influence of the researchers on the findings not being discussed and very minor concerns over potential bias in recruitment with participants having already been selected for a different project but serious limitations in two studies in one study due to the research design/methods, data collection method and analysis (postings on health website), and due to potential selection bias as the method used to select posts was not specified, lack of sufficient detail on the data analysis in the other study; no concerns about coherence; moderate concerns over relevance with moderate concerns in two studies due to a lack of sufficient information on the characteristics of people from which the information emerged and the data being unverified due to the nature of the source (anonymous posts on health websites), minor concerns in one study due to the all-female sample included and no concerns in two studies; no concerns about adequacy with the theme supported by five studies. Overall assessment of confidence was low due to moderate concerns over methodological limitations and relevance.

1.2.3.4 Narrative summary of review findings: Antidepressants (SSRIs)

Review finding 6: Severity of withdrawal symptoms

People who had been taking SSRIs had experienced quite severe problems associated with discontinuation. Several of those who had tried stopping reported bad experiences, with one reporting a relapse experience so bad that he regretted ever trying. Experiences of withdrawal led one participant to restart their medication after 1 week. Another participant described how it was difficult to say which was worse, the experience of withdrawal effects or the initial depressive symptoms. Problems of withdrawal on previous occasions could become a conscious key driver for continuing to take medication and could forestall attempts to discontinue. One participant reported 'the major factor' driving sustained antidepressant use was the side effects of coming off them, saying: 'I don't think I take them to sustain my mood but purely to stop the side effects'. One participant who had been reducing paroxetine medication prescribed for mild sleeplessness reported experiencing prolonged and severely debilitating symptoms, particularly since reaching an amount of 5 mg after having to use the liquid version with a syringe, making reductions of 1 mg per month; this was described as the worst stage so far. Withdrawal symptoms were also described as horrendous, with one person describing having to quit his job because of feeling sick 'all the time'.

Explanation of quality assessment: moderate concerns over methodological limitations with no concerns in one study, minor concerns one contributing study where participants were only recruited from one group practice within one primary care trust and serious concerns in one study due to the research design/methods, data collection method and analysis (postings on health website); no concerns about coherence; minor concerns over relevance with moderate concerns in one study due to a lack of sufficient information on the characteristics of people from which the information emerged and the data being unverified due to the nature of the source (anonymous posts on health website) but no similar concerns in the other contributing studies; no concerns about adequacy. Overall assessment of confidence was low due to concerns over methodological limitations and relevance.

Review finding 7: Fear of discontinuation and relapse

People described uncertainty about the potential for bad consequences when stopping, as well as uncertainty about the process itself, which could invoke fear. In addition to anticipated problems, actual problems encountered during past attempts to stop. The suspected adverse reactions were not just perceived as unpleasant but also created a fear of stopping taking the antidepressant drug, instilling trepidation about future attempts to stop. A number of people expressed concerns that stopping the medication could precipitate a relapse of depression and fear that stopping may leave them back in the initial distressing phase of depression. Fear of discontinuation symptoms made some patients afraid of ending their treatment. These patients often continued to take antidepressants, despite the fact that they did not want to be dependent on them.

Explanation of quality assessment: moderate concerns about methodological limitations with minor concerns in one study where participants were only recruited from one group practice within one primary care trust, but serious concerns in the other contributing study due to the study design and data collection (retrospective analysis of independently submitted free text feedback from consumers), study design dictated by the data/consumer feedback process, results (themes) were reported interspersed with references and insights from other studies, making it unclear what conclusions were based on this study alone; no concerns about coherence; moderate concerns about relevance with fear potentially not emerging as a result of discontinuation but preceding it in some participants in both studies and due to participants in one study being limited to people experiencing adverse drug reactions; no concerns about adequacy. Overall assessment of confidence was low due to concerns over methodological limitations and relevance.

Review finding 8: Suicidal thoughts

One paroxetine user who had been reducing their medication reported experiencing 18 months of severely debilitating symptoms, the principal of which was persistent suicidal thoughts, while another paroxetine user reported having tried suicide on several attempts and even having attacked their father ‘for no reason”. Similarly, one citalopram user who was no longer on medication, reported that withdrawing from the drug caused them to feel suicidal and having made two suicide attempts during withdrawal. Recurrent suicidal thoughts were also experienced following a reduction in dose as reported by one citalopram user who had first increased his dose from 40 mg to 60mg and then reduced to 50mg.

Explanation of quality assessment: no concerns over methodological limitations with no notable limitations in the contributing study; no concerns about coherence; no concerns about relevance; serious concerns about adequacy with information from a very small number of participants in one study supporting the theme. Overall assessment of confidence was low due to serious concerns over the adequacy of information supporting the theme.

Review finding 9: Nausea and dizziness

Withdrawal symptoms experienced since beginning to reduce paroxetine included stomach upsets, nausea, dizziness. One person reported not being able to move their neck or eyes without feeling dizzy ‘like the room is spinning’ when coming off paroxetine.

Explanation of quality assessment: moderate concerns over methodological limitations with no notable limitations in one study but serious limitations in the other study due to the research design/methods, data collection method and analysis (postings on health website); no concerns about coherence; minor concerns over relevance with moderate concerns in one study due to a lack of sufficient information on the characteristics of people from which the information emerged and the data being unverified due to the nature of the source (anonymous posts on health website) but no concerns in the other study; serious concerns about adequacy with limited information emerging from a very small number of people in two studies. Overall assessment of confidence was very low due to the concerns identified across elements of quality assessment.

Review finding 10: Insomnia

Insomnia was also one of the withdrawal symptoms experienced, with one person reporting: ‘terrible withdrawal symptoms, which have included insomnia’ since beginning to reduce paroxetine.

Explanation of quality assessment: no concerns over methodological limitations; no concerns about coherence; no concerns about relevance; serious concerns about adequacy with very limited information from one participant in one study reporting insomnia. Overall assessment of confidence was very low due to serious concerns over the adequacy of information to support the theme.

Review finding 11: Psychiatric adverse reactions

People experienced adverse psychiatric reactions during the discontinuation of antidepressant drugs. One female patient (aged 35 years; SSRI: Sertraline) following doctor’s orders to discontinue antidepressants in four days, going ‘from normal dosage of 50mg to 25 mg in four days and then nothing’ reported experiencing ‘a fear of dying and extreme anxiety’ after 3 days and having ‘several panic attacks; ‘I woke up and found myself standing with a knife towards my stomach on one occasion and on another with the bathrobe belt in my hand. I no longer tolerate any stress at all, which makes me panic and experience dizziness. Since the psychiatric events reported may often also occur as a symptom of the illness for which the antidepressant had been prescribed, they sometimes caused conflict

between patients and doctors during discontinuation, with the former almost always interpreting negative experiences as belonging to the drug while the doctor interpreted them as evidence of the initial depression recurring and the patient having a relapse that needs continued treatment. As reported by one participant, the doctor 'ignores discontinuation symptoms from the drug and wants me to start medicating again after I have been through ten days of hell. She (the doctor) believes that my depression had returned…It is totally wrong'. Excessive and unbearable anxiety, and agitation were experienced since beginning to reduce the medicine (paroxetine and citalopram) that were reported to be 'five times' higher compared to before starting the antidepressant while panic attacks, inability to cope with stress, becoming increasingly confused, violent and abusive towards others were also reported after a dose drop of citalopram to 10mg.

Explanation of quality assessment: Serious concerns about methodological limitations with no concerns in one study but serious concerns in two studies, in one study due to the study design and data collection (retrospective analysis of independently submitted free text feedback from consumers), study design dictated by the data/consumer feedback process, results (themes) were reported interspersed with references and insights from other studies, making it unclear what conclusions were based on the study alone and in the other study also due to the research design/methods, data collection method and analysis (postings on health website); no concerns about coherence; moderate concerns about relevance with no concerns in one study but minor concerns in another contributing study due to participants in one study being limited to people experiencing adverse drug reactions and moderate concerns in the third contributing study due to a lack of sufficient information on the characteristics of people from which the information emerged and the data being unverified due to the nature of the source (anonymous posts on health website); no concerns about adequacy with sufficient information from three studies illustrating the theme. Overall assessment of confidence was low due to the concerns identified over methodological limitations and relevance but with a wealth of information to support the theme, slightly minimising those concerns.

Review finding 12: Changes in mood

Sudden changes in emotion, mood and crying were experienced since beginning to reduce the medicine but also after a significant reduction in dose, as reported by one participant: 'After the dose drop to 10 mg, I had mood swings'.

Explanation of quality assessment: no concerns over methodological limitations; no concerns about coherence; no concerns about relevance; serious concerns about adequacy with very limited information from two participants in one study. Overall assessment of confidence was very low due to serious concerns over the adequacy of information to support the theme.

Review finding 13: Other bodily symptoms

Since beginning to reduce their medicine, people described withdrawal symptoms including agitation, sweating and palpitations but also what was described as flu-like symptoms, including debilitating tiredness, headaches, aching joints and muscles, particularly 5 weeks after dropping the antidepressant dose. One participant reported only stopping their medicine for a week 'not because of the moods… this wasn't a moods situation. It was my body…was reacting, not how I expected it to react. It had the shakes…um…bit like a junkie'.

Explanation of quality assessment: minor concerns over methodological limitations with no notable limitation in one study and minor limitations in the other contributing study due to participants only recruited from one group practice within one primary care trust; no concerns about coherence; no concerns about relevance; serious concerns about adequacy with very limited information from two studies supporting the theme. Overall assessment of confidence was very low due to minor methodological limitations and serious concerns over the adequacy of information to support the theme.

Review finding 14: Onset of withdrawal symptoms

A male patient who had tried stopping and had relapsed reported: 'I didn't turn into a blubbering mess straight away, it was about 4-5 days afterwards'. Similarly, a female patient following doctor's orders to discontinue antidepressants in four days, going 'from normal dosage of 50mg to 25 mg in four days and then nothing' reported experiencing 'a fear of dying and extreme anxiety' after 3 days and having 'several panic attacks. She reported having been without antidepressant medication for nine days and experiencing 'hell on earth'.

Explanation of quality assessment: moderate concerns over methodological limitations with minor limitation in one study with participants only recruited from one group practice within one primary care trust but serious limitations in the other study due to the research aim, design and data collection (retrospective analysis of independently submitted free text feedback from consumers), the study design being dictated by the data/consumer feedback process and results being reported interspersed with references and insights from other studies, making it unclear what conclusions were based on this study alone; minor concerns about coherence with slightly different days of onset reported and it was not always clear if these were relevant to the start of reduction or complete discontinuation; minor concerns over relevance due to the sample of one study being limited to people who experienced adverse drug reactions from antidepressants; moderate concerns over adequacy with limited information from two studies supporting the theme. Overall assessment of confidence was very low due to the concerns identified across elements of quality assessment. [272]

1.2.4 Economic evidence

The committee agreed that health economic studies would not be relevant to the qualitative section of this review, and so were not sought.

1.3 The committee's discussion and interpretation of the evidence

The committee's discussion of the quantitative and the qualitative evidence of the mixed methods review on withdrawal symptoms associated with prescribed medicines is included here. The committee discussed the evidence and how it informed recommendations after reviewing the findings from both the intervention and the qualitative review.

1.3.1 The outcomes that matter most

Quantitative evidence

This review aimed to identify the symptoms associated with withdrawal of prescribed opioids, benzodiazepines, Z-drugs, gabapentinoids or antidepressants.

The primary (critical) outcomes for this review were: specific withdrawal symptoms, including rebound symptoms as specified in the studies and the number of people with specific withdrawal symptoms, any withdrawal symptoms (i.e., all symptoms grouped together), the intensity of withdrawal symptoms and the duration of the withdrawal syndrome.

The committee acknowledged when developing the protocol that it may be difficult to determine whether symptoms reported in the studies are withdrawal symptoms (including rebound symptoms), or whether they are an increase in symptoms for which the medication was originally prescribed (i.e., a re-emergence of symptoms). They agreed to rely on how the studies define the symptoms and only report those determined to be withdrawal symptoms by the study authors so as not to introduce reviewer bias. There were no further core outcome measures considered relevant for this protocol.

Evidence was identified for specific withdrawal symptoms, any withdrawal symptoms and the intensity of withdrawal symptoms. Outcomes relevant to specific withdrawal symptoms included: moderate or severe aches and pains, mild or moderate problems sleeping, severe insomnia, anxiety, headache, insomnia, rebound symptoms such as insomnia (defined as a deterioration below individual mean pre-treatment scores), irritability, sudden worsening of mood, sudden outbursts of anger or panic or anxiety attacks, agitation, forgetfulness or problems with memory, muscle tension or stiffness, fatigue, dizziness, light-headedness or sensation of spinning, fever. Outcomes relevant to the intensity of withdrawal symptoms included mild or moderate opioid withdrawal on the clinical opiate withdrawal scale (COWS), short opiate withdrawal scale, increase in withdrawal symptoms of ≥100% during discontinuation, the total number of discontinuation emergent signs and symptoms (DESS), mild or moderate adverse events after discontinuation, rebound: return to a Montgomery-Asberg Depression Rating Scale (MADRS) score equal to or higher than the original score.

No evidence was identified for the duration of the withdrawal syndrome.

Qualitative evidence

This review aimed to identify people's perceptions of the withdrawal symptoms experienced with prescribed opioids, benzodiazepines, Z-drugs, gabapentinoids or antidepressants. Information emerging from qualitative data regarding the experience of different withdrawal symptoms was summarised into different themes. Themes were derived from the evidence identified and were not pre-specified by the committee.

Only findings that were relevant to the review question were extracted; patient experiences with the prescribed medicine or side effects while taking the medicine rather than experiences of withdrawal symptoms were not extracted.

1.3.2 The quality of the evidence

Quantitative evidence

Evidence from 21 RCTs was identified for the following drug classes; opioids (n=3), benzodiazepines (n=7; 3 of which also reported data for opioids), Z-drugs (n=1), gabapentinoids (n=3) and antidepressants (n=10).

The majority of the evidence was of low and very low quality. The main reasons for downgrading were risk of bias (most commonly due to selection bias and occasionally incomplete outcome data) and imprecision in the effects estimate, reflected in the confidence intervals. There was some moderate quality evidence for opioids, downgraded for risk of bias, for 2 specific withdrawal symptoms outcomes and the intensity of withdrawal symptoms. There was also very limited high-quality evidence for the outcome of rebound insomnia relevant to Z-drugs.

The committee noted treatment durations and follow-up across the majority of studies were very short, with participants followed up for a few days up to 4 weeks after discontinuation but mostly only up to one week after tapering. They agreed this is likely to be very different of what takes place in everyday practice.

Qualitative evidence

Evidence from 19 qualitative studies was available for opioids (n=6), benzodiazepines (n=4) and antidepressants (n=9). No relevant qualitative evidence was identified for Z-drugs or gabapentinoids.

Populations varied across studies in that they included a mixed sample of people at different stages of prescribing, who were currently tapering, who had completed tapering or who had made past discontinuation attempts but were currently using medicines.

A variety of qualitative methodologies were used to inform the research across different studies, including mostly semi-structured interviews but also focus groups, the qualitative analysis of anonymous posts from health-related websites and qualitative analysis of extracts from yellow card reports. Across drug classes, confidence in the review findings was mainly rated as low to very low, with only a small number of findings relevant to opioids and benzodiazepines rated as moderate. The main reasons for downgrading were concerns regarding methodological limitations in the individual studies contributing to each review finding (such as potential selections bias, the potential influence of the researcher on the review findings not being discussed, issues with data richness due to limited information to support the study conclusions), relevance and adequacy. Concerns over relevance of review findings to the phenomenon of interest were often due to concerns over characteristics of the population included in the studies potentially limiting the applicability of the findings to the population of interest for example where studies included codeine users that were also on methadone maintenance and whose experiences may differ from codeine users not on methadone maintenance, or where the population experiencing a particular withdrawal symptoms was limited to elderly participants. The original aim of most studies differed to that of the current review. This often resulted in information emerging for the different withdrawal symptoms being very limited in each study, which resulted in concerns over the adequacy of information supporting the review findings and in turn, compromised the overall confidence rating given to the review findings.

The committee carefully considered the level of confidence in each review finding and were able to utilise their clinical experience to determine the weight placed in each review finding when making recommendations.

1.3.3 Benefits and harms

Quantitative evidence

Opioids

There was a clinically important benefit of withdrawing from placebo compared to withdrawing from opioids in terms of occurrence of insomnia (reported as a withdrawal symptom), suggesting that this may be one of the symptoms people experience when withdrawing from opioids. However, there was no clinically important difference in terms of other withdrawal symptoms reported in the evidence or when reported as ‘any withdrawal symptom’. Evidence on the intensity of withdrawal symptoms showed a clinically important benefit of withdrawal from placebo in terms of mild opioid withdrawal 2-<5 days after the last dose but no difference in any of the further four intensity of withdrawal symptoms outcomes. The committee considered this evidence to be very limited, and in isolation, was not particularly useful to inform decision making.

Benzodiazepines

There was no clinically important difference observed between withdrawing from benzodiazepines compared to continuing benzodiazepine use in terms of outcomes indicating the intensity of withdrawal symptoms. There was no evidence for any further outcomes compared to continued medicine use.

Evidence comparing withdrawal from benzodiazepines to withdrawal from placebo was mixed in terms of specific withdrawal symptoms experienced, showing a clinically important benefit of withdrawal from placebo in terms of anxiety (as a DESS) and in 3 outcomes indicating rebound during 5 weeks of discontinuation, but no clinically important difference in terms of insomnia (as a DESS) or rebound of the original symptoms during discontinuation. The committee noted that there was evidence of a clinically important benefit of withdrawal from placebo compared to withdrawal from benzodiazepines in terms ‘any withdrawal symptoms’, but this was limited to 2 outcomes. Evidence on the intensity of withdrawal

symptoms was also contradictory, showing a clinically important benefit of withdrawal from placebo in terms of the physician withdrawal checklist score but a clinically important benefit of withdrawal from benzodiazepines as there was an increase in withdrawal symptoms of ≥100% during discontinuation. The committee agreed the conflicting evidence limited the extent to which they could draw conclusions about the withdrawal symptoms experienced when discontinuing benzodiazepines.

Z-drugs

The evidence demonstrated no clinically important difference between withdrawal from Z-drugs compared to withdrawal from placebo in terms of rebound insomnia assessed with a deterioration below individual mean pre-treatment values during the discontinuation period. The committee noted the evidence was of high quality but was limited to one outcome from a single study and therefore could not be considered representative of the withdrawal symptoms people discontinuing Z-drugs may experience.

Gabapentinoids

Evidence demonstrated a clinically important benefit of withdrawal from placebo compared to withdrawal from pregabalin in terms of any withdrawal symptom experienced and insomnia (as a DESS) but no clinically important difference in terms of anxiety or headache and no further evidence on specific withdrawal symptoms, providing limited evidence on the experience of withdrawal symptoms associated with discontinuation of pregabalin. Evidence for the intensity of withdrawal symptoms showed a clinically important benefit of withdrawing from placebo, but was also limited to one outcome (physician withdrawal checklist score). The committee agreed the evidence suggested an increased occurrence of symptoms when withdrawing from gabapentinoids, but noted again that the evidence base was very limited.

Antidepressants

Evidence demonstrated a clinically important benefit of continuing on ‘other’ antidepressants compared to withdrawing from antidepressants in terms of specific withdrawal symptoms of nervousness/anxiety, irritability, sudden worsening of mood, bouts of crying or tearfulness, confusion or trouble concentrating, forgetfulness/problems with memory, muscle tension/stiffness, muscle aches or pains, fatigue/tiredness, unsteady gait/incoordination, dizziness/light-headedness/sensation of spinning during study weeks 1-4. This indicated that withdrawing from antidepressants increased the likelihood of experiencing the aforementioned withdrawal symptoms. Contrarily, the evidence showed a clinically important benefit of withdrawing from other antidepressants on specific withdrawal symptoms of fever and unusual sensitivity to sound. The committee noted that those findings were counterintuitive when considered alongside the other increased symptoms. No clinically important difference was found in terms of the experience of specific withdrawal symptoms of rebound during weeks 1 and 2 of withdrawal, elevated mood, sudden outbursts of anger, sudden panic or anxiety attacks, agitation, feeling unreal/detached, mood swings, trouble sleeping/insomnia, increased dreaming/nightmares, sweating more than usual, shaking/ trembling, restless feeling in legs, muscle cramps/ spasms/twitching, blurred vision, sore eyes, uncontrolled mouth/ tongue movements, problems with speech or speaking clearly, headache, increased saliva in the mouth, nose running, shortness of breath, chills, vomiting, nausea, diarrhoea, stomach cramps, stomach bloating, unusual visual sensations, burning/ numbness, ringing or noises in the ears, unusual tastes/ smells between people withdrawing from antidepressants and those continuing on the medicine, suggesting these symptoms were less likely to be experienced as a result of withdrawing from antidepressants. The evidence also demonstrated no clinical difference in the intensity of withdrawal symptoms (total number of emergent DESS symptoms) experienced by people withdrawing from antidepressants during the first 2 weeks of discontinuation compared to people continuing the medicine.

The committee noted that the majority of the evidence for this comparison came from a single study, and although it provided some potentially useful information about withdrawal symptoms that may be experienced with antidepressants, conclusions should be drawn with caution. The committee discussed that evidence suggesting no difference for particular symptoms should not be interpreted as evidence that these symptoms don't occur when withdrawing from antidepressants. In their experience, withdrawal symptoms vary within and between people, and so data from a limited number of studies would not reliably inform which symptoms would and would not be experienced.

Evidence showed a clinically important benefit of withdrawal from placebo for specific withdrawal symptoms of headache and nausea (as a DEAE) during the discontinuation period, suggesting these are potential symptoms people withdrawing from antidepressants are likely to experience. On the other hand, there was no clinical difference in terms of specific withdrawal symptoms of insomnia and dizziness (as a DEAE). There was a clinically important benefit of withdrawal from placebo compared to withdrawal from other antidepressants in terms of 'any withdrawal symptoms' during the discontinuation period and 3 days after discontinuation and in the intensity of withdrawal symptoms at 7 days. The committee agreed this provided some evidence for the experience of withdrawal symptoms when discontinuing antidepressants but did not capture the variability of withdrawal symptoms seen in clinical practice.

Evidence from people discontinuing SSRIs was mixed. There was a clinically important benefit of continuing compared to withdrawing from SSRIs in terms of one intensity of withdrawal symptoms outcome (DESS score ≥4) but no clinical difference in terms of another intensity of withdrawal symptoms outcome (total number of emergent DESS symptoms) at 2 weeks post-abrupt discontinuation. Evidence also showed no clinical difference between people withdrawing from SSRIs compared to people continuing on SSRIs in terms of specific withdrawal symptoms reported (rebound: return to a MADRS score equal or higher than the original score). The committee noted the evidence for withdrawing from SSRIs was very limited and inconclusive.

Overall

The committee discussed that the quantitative evidence across drug classes did not reflect the range or intensity of withdrawal symptoms they were aware of from their personal experience or clinical practice. The committee noted that the quantitative evidence of withdrawal symptoms was mostly informed by studies primarily designed to assess the efficacy of the medicines considered. Therefore, only limited information was available from the withdrawal phases of these studies.

Furthermore, the committee noted that the majority of studies looked at withdrawal after a relatively short period of use of the medicine (from 4 to 24 weeks), and therefore was not reflective of the typical population withdrawing from these medicines who have usually been taking the medicines for a long time. The committee also noted that although the treatment phase was most often followed by abrupt discontinuation, taper details were not always available. They agreed this limited the conclusions about the experience of withdrawal symptoms that could be drawn from the evidence.

Some of the included studies had either abrupt or very rapid withdrawal (over 1-2 weeks), which was not considered to be what would happen in current practice. The short follow up of the trials was noted as a further limitation. Follow up frequently only lasted for the duration of the withdrawal phase. After reviewing the qualitative evidence, and taking their experience into account, the committee noted that some people experience tardive withdrawal, where symptoms emerge weeks after tapering off the medicines. Thus, considering the duration of the quantitative studies, the current evidence may not have been able to adequately capture people's experience of withdrawal symptoms.

The committee agreed that due to these limitations, recommendations could only be made following consideration of the qualitative evidence, as was the intention of this mixed methods review.

Qualitative evidence

Opioids

People who had been tapering off opioids reported experiencing withdrawal symptoms that could last from weeks to months or even persist a year after stopping the medicine. They reported a worsening of symptoms for which the medication was prescribed (such as back pain), fluctuations in the symptoms experienced during withdrawal, fear of pain exacerbation and withdrawal, increased pain intensity, gastrointestinal problems including stomach sickness or pain and diarrhoea, sweating, cold shakes or fever, sleep problems, mood problems including psychological pain, irritability and anxiety. Codeine users also experienced cravings. There was also a smaller number of people experiencing little or no withdrawal symptoms.

Although most of the evidence was of low and very low confidence, the committee agreed it reflected their experience of some of the withdrawal symptoms people withdrawing from opioids endure. The committee discussed concerns over applicability of the evidence for some themes due to the characteristics of the study populations (such as codeine users, some of whom were taking other medication: suboxone, instead of stopping completely), but agreed such populations do still represent a subset of the population of interest for this review. They noted that apart from specific physical symptoms, including cold shakes or fever, people can also experience psychological symptoms and agreed that physical and psychological experiences influence the overall withdrawal experience. The committee emphasised that it can be difficult to distinguish between physical pain, often in the form of a return of previously well-controlled symptoms and psychological pain, which can also be caused by fear surrounding withdrawal. They considered that the experience of the latter may influence the subjective experience of the former with fear or pain exacerbation or psychological pain contributing to the experience of physical pain and vice versa.

Benzodiazepines

Evidence demonstrated that several people withdrawing from benzodiazepines, particularly those withdrawing rapidly, experienced severe withdrawal symptoms. Similar to opioid withdrawal, people experienced a return of original symptoms for which medication was prescribed; when withdrawing from benzodiazepines they experienced feelings of worry, about withdrawal and being without the medicine. The committee noted this resembled the feelings of fear reported by people tapering off opioids.

Evidence showed that some people reported experiencing disturbed dreams when withdrawing from benzodiazepines, while there was also a number of people who did not experience any problems when withdrawing from benzodiazepines. The committee agreed that as seen in opioids, there are people who experience little or no withdrawal symptoms when withdrawing from benzodiazepines and that this variability between individuals was in line with what they see in clinical practice and is true across drug classes.

Antidepressants

Findings emerging from the qualitative evidence on antidepressants was limited to the experience of people taking SSRIs or mixed antidepressants where a breakdown was not provided. However, the committee agreed that evidence from both was similar.

Patient experiences of severe withdrawal symptoms emerged from both people on SSRIs and people on other antidepressants. The experience of fear of discontinuation and dizziness and nausea were also common between different antidepressant strata. People on other antidepressants also reported an increase in negative emotions and a strange electroshock-

like sensation in the head described as a ‘head buzz’ or ‘brain zap’. Since beginning to reduce their medicine, people on SSRIs reported experiencing insomnia, adverse psychiatric reactions including excessive anxiety, unmanageable stress, panic attacks, violent tendencies towards the self or others, sudden changes in mood, other bodily symptoms including sweating, palpitations and flu-like symptoms such as debilitating tiredness, headaches, aching joints or muscles. Suicidal thoughts and suicide attempts were also reported during withdrawal from SSRIs. Some people reducing or stopping SSRIs reported that the onset of withdrawal symptoms did not occur until 3-5 days after the discontinuation attempt. The committee agreed this was consistent with their experience that some people experience tardive withdrawal that may even occur weeks after withdrawal.

Similar to other drug classes, the committee noted that it is difficult to distinguish between withdrawal symptoms and symptoms indicating a re-emergence of the underlying condition for which medicines were originally prescribed. They raised that some antidepressants have a very long half-life which may delay the onset of withdrawal symptoms and lead to certain symptoms being overlooked or falsely interpreted as recurrence of the original symptoms. The committee also noted that “brain zaps” and aching muscles or joints differ from symptoms of depression, and it can thus be concluded with greater certainty that these are withdrawal symptoms.

Summary

The committee noted that although the evidence across drug classes did highlight that people experience a spectrum of symptoms, it did not adequately capture the range of withdrawal symptoms people can experience, which, based on the committee’s experience, are not limited to the symptoms reported in the current evidence. It was acknowledged that symptoms do vary from person to person, and the individual variability was clearly evident from the data reviewed, but the committee would have expected there to have been more qualitative information on the impact that withdrawal can have on the person’s life.

The committee noted that themes emerging from the qualitative evidence included people reporting that symptoms fluctuate from day to day, people reporting problematic symptoms, but there were also reports of people who had been on opioids and benzodiazepines who had experienced little or no problems withdrawing from the medicines. Based on their experience, the committee highlighted that withdrawal symptoms could range from severe and life-changing to less severe; they can stop and restart persist for a very long time after tapering and discontinuation or be delayed in onset not occurring until after discontinuation of the medicine. The committee agreed it was important to highlight the variability in the withdrawal experience in the guideline recommendations, both so that people may be prepared that this could occur, but also to highlight that some people have no or minimal problems. The variability was considered relevant to the occurrence of different symptoms such as physical and psychological symptoms, as well as their possible severity and duration.

It was noted that it isn’t possible to predict who is likely to endure worse or more prolonged withdrawal symptoms, nor who will be likely to experience no symptoms. However, the committee did discuss that previous trauma from adverse childhood experiences or past withdrawal attempts, was an important factor to consider in terms of who was more likely to take these medicines and become dependent and could also impact withdrawal management. The committee considered that the individual variability was so great that further research would be unlikely to help inform who was likely to experience withdrawal symptoms, in the same way it is not possible to determine who is most likely to experience side effects of a medicine and therefore a research recommendation was not included on this topic. The committee also raised that the reason for withdrawal is also likely to influence the withdrawal experience but that this could not be determined from the current evidence.

The committee noted that there were some important themes emerging from the evidence reviewed that should be highlighted within the recommendations. This included fear of pain exacerbation when withdrawing from opioids, which affected both people's willingness to taper, and their experience of withdrawal. The committee agreed that the experience of fear, worry or anxiety surrounding discontinuation, often resulting from past unsuccessful discontinuation attempts, was true across drug classes, and patient accounts of how feelings of fear can ultimately prevent discontinuation highlighted the importance of supporting people to manage such feelings. They agreed it was important that recommendations reflect that people may be reluctant or anxious about talking about withdrawal, and agreed that this can in part be addressed by explaining that dependence is an expected effect of the medicine but that some people can experience problems associated with dependence. The committee also agreed it was important to acknowledge that withdrawal symptoms can be difficult, but reassure them that support would be available during the process of withdrawal and to explain to people the options available for managing withdrawal symptoms if they occur. The committee emphasised the importance of avoiding the use of language that may be perceived as ascribing blame to the person experiencing problems associated with dependence and acknowledging and discussing differences of opinion about withdrawal as well as queries about the reasons for past prescribing.

The committee discussed that one factor that did not emerge from the review but was consistent with their experience, was that the trajectory of the taper or withdrawal process was not always smooth. They highlighted that although people may feel well for a while, this can suddenly change. In these cases, the committee noted that it may even be necessary to pause the withdrawal for a period of time. Lay members on the committee agreed this was an important point to highlight and noted that this was a phenomenon recognised by patient groups as 'windows and waves' in antidepressant withdrawal. The committee agreed to include a consensus recommendation to highlight that symptoms can vary over time, and that the process can be difficult and may take several months or more. The committee considered that recommendations informed from the Withdrawal interventions evidence review, to base the taper schedule on what was most suitable for the person, and agreeing regular reviews, would also be relevant here as they agreed the withdrawal schedule should be reviewed as necessary during this process.

The qualitative data highlighted that people reported both a recurrence of the original symptoms and a worsening of the original symptoms. It was agreed that the difficulty in separating withdrawal symptoms from those caused by the original condition being treated should be highlighted within the recommendations, noting that healthcare professionals should listen to the patients' experience of the original condition and withdrawal to help determine what the cause of the symptom might be, and not to dismiss symptoms as recurrence of the original condition without first exploring this. The committee raised that there are many variables to consider when determining if a symptom indicates relapse of the original condition or is due to the withdrawal of medicines. Although they agreed it is difficult to determine with certainty whether the early onset of symptoms experienced at the beginning of tapering or after a dose reduction indicates withdrawal symptoms rather than symptoms of the underlying condition and whether the late onset of symptoms indicates relapse, it was agreed that the onset of symptoms could be a useful variable to consider. Furthermore, the committee highlighted that experiencing new symptoms or symptoms that are qualitatively different from the original symptoms for which the medicine was prescribed or symptoms that are more intense than previously are likely to indicate the experience of withdrawal symptoms rather than a re-emergence of the original underlying condition. To highlight the complexity of the issue, the committee noted that sometimes neither timing of onset, nor symptom severity, nor the nature of symptoms during dose reductions or cessation can reliably distinguish between symptoms of withdrawal or relapse, as the extent to which symptoms experienced will reflect relapse or withdrawal will vary from person to person as well as across different drugs, but that these are important factors to consider alongside one another. In the committee's view, the inherent difficulty in distinguishing

between symptoms of withdrawal and recurrence highlighted the importance of discussion with patients as well as the importance of continuity of care that can ensure that information relevant to patient history can help distinguish withdrawal symptoms from relapse are adequately considered.

Compared to the quantitative evidence, the committee agreed that although there were limitations in the available qualitative data, it was more reflective of what they would expect based on their clinical experience. However, considering the nature of qualitative evidence that highlights people's subjective experiences and the aim of the research studies, which was most often not to identify withdrawal symptoms and their prevalence, the committee agreed that it was not possible to objectively determine the frequency, severity or the duration of withdrawal symptoms. The committee discussed the evidence within the review on the specific withdrawal symptoms experienced and considered whether this was sufficient to inform a recommendation highlighting the most common withdrawal symptoms. It was agreed that the evidence identified in this review was too limited to reliably inform this. More evidence was available for antidepressants, and some symptoms emerged from both the qualitative and quantitative evidence. However, there were significant limitations in this evidence, discussed above, which limited its generalisability. Thus, they agreed that although informative, the current evidence did not support conclusions about a specific list of the most common withdrawal symptoms that people experience when withdrawing from medicines. It was discussed that although this was in part due to the limitations of the evidence, the individual variability that is seen in the experience of withdrawal also meant that a list of symptoms could have a negative effect. The difficulty in distinguishing between withdrawal symptoms with a return of the original symptoms for which the medicines were prescribed further confounded this. The committee considered that including a suggested list of common symptoms in the guideline could imply that symptoms that were not on the list were not withdrawal symptoms and would risk them being dismissed or overlooked. The committee agreed that there was reason to believe withdrawal symptoms can be overlooked or dismissed as re-emergence of the underlying condition already, and including a list may further confound this. The committee also discussed that it is also possible that a symptom experienced during withdrawal is due to a new condition, and further examinations should not be precluded where relevant. Again, if such a symptom was included within a list of likely withdrawal symptoms, this could lead to the missed diagnosis of a new condition. The committee agreed that in cases where people develop new symptoms, health professionals should use their clinical judgment to determine whether the symptoms experienced require further investigation to rule out the emergence of a new pathology that requires separate management.

1.3.4 Cost effectiveness and resource use

No economic evidence was found for this question.

The committee made recommendations to help clinicians distinguish between withdrawal symptoms and the re-emergence of underlying conditions. These recommendations should raise awareness on withdrawal symptoms, help clinicians make an informed decision, and offer adequate support and assistance to those experiencing severe symptoms. It is possible that a better understanding of withdrawal symptoms will lead to more people being referred to withdrawal management services, thus potentially increasing the cost for the NHS. Nevertheless, any additional cost should be balanced by benefits due to a reduction of adverse events and better management of withdrawal symptoms, thus ultimately increasing the efficiency of the NHS.

1.4 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.3, 1.5.9, 1.5.13, 1.5.14., 1.5.17, 1.5.18, 1.5.19, and 1.5.20. No research recommendations were made from this evidence review.

Other evidence supporting these recommendations can be found in the evidence reviews on C Safe Withdrawal.

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Appendices

Appendix A Review protocols

A.1 Review protocol for Withdrawal Symptoms

Field	Content
PROSPERO registration number	CRD42020214163
Review title	Withdrawal symptoms associated with prescribed medicines
Review question	What are the withdrawal symptoms associated with prescribed medicines?
Objective	To identify the symptoms associated with withdrawal of these prescribed medicines (opioids, benzodiazepines, Z-drugs, gabapentinoids, or antidepressants). **Intervention:** To identify any comparative studies looking at withdrawal of one of the prescribed medicines listed vs no withdrawal, OR withdrawal from one of the prescribed medicines vs withdrawal from placebo, and reporting the withdrawal effects. **Qualitative:** To identify perceptions of patients of the withdrawal symptoms associated with these prescribed medicines.
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 • CINAHL, Cumulative Index to Nursing and Allied Health Literature • PsycINFO • ASSIA 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	Withdrawal symptoms associated with prescribed opioids, benzodiazepines, Z-drugs, gabapentinoids, or antidepressants
Population	Inclusion: adults (≥18 years) taking prescribed medicines* that are associated with dependence or withdrawal symptoms (opioids, benzodiazepines, Z-drugs, gabapentinoids, or antidepressants). NB. for this question, include prescription medicines which can also be bought over the counter (e.g., codeine, co-codamol) *Note: for a study to be included, the medicine should be listed on the guideline medicine list (see Appendix K). See also decision rule below.

	Stratification Drug class Opioids Benzodiazepines, Gabapentinoids (further stratified by gabapentin and pregabalin) Z-drugs Antidepressants (further stratified by SSRIs, MAOIs, tricyclics, others). Rationale: withdrawal symptoms expected to differ between drug classes, and within class for antidepressants. No other population strata **Exclusions:** Children and young people (<18 years) People taking opioids prescribed 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 (with the exception of prescription medicines which can also be bought over the counter (these will be included in this question) **Decision rules for inclusion of primary studies** If the study includes people <18 years old, the study will only be included if at least 80% of people were ≥18 years old. If the study includes mixed populations, some taking prescribed drugs and some taking illicit drugs, the study will only be included if at least 80% of people were taking prescribed drugs. If the study includes people on medicines NOT listed on the guideline medicine list, the study will be included if at least 80% of the population are on medicines listed on the guideline medicine list. If there is no breakdown reported, but some people were on medicines not listed on the guideline medicine list, the study will be included but the population will be downgraded for indirectness.
Intervention/Phenomena of interest	<u>Intervention data:</u> Withdrawal from/stopping use of one of the prescribed medicines <u>Qualitative data:</u>

	Perceptions and experiences of patients of the withdrawal symptoms experienced from stopping one of these prescribed medicines
Comparator	Intervention data: - withdrawal from one of the prescribed medicines listed vs no withdrawal, OR - withdrawal from one of the prescribed medicines vs withdrawal from placebo Qualitative data: n/a
Types of study to be included	Intervention studies: Randomised controlled trials Systematic review of randomised controlled trials. (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). Published NMAs and IPDs will be considered for inclusion. Qualitative studies: Qualitative studies (e.g., transcript data collected from focus groups/semi structured interviews) **Exclusions:** For intervention studies: Non-randomised comparative studies Before and after studies Non-comparative studies For qualitative studies: Quantitative studies (i.e., closed questionnaire surveys; surveys will only be included if they contain open ended free text answers)

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 Antipsychotic and stimulant medicines. Use of gabapentinoids when prescribed for epilepsy Medicines to treat drug misuse disorders (e.g., methadone and buprenorphine when prescribed for withdrawal from illicit drugs). Withdrawal from illicit drugs (e.g., heroin). Non-English language studies. Conference abstracts will be excluded as they will not provide enough information to inform analysis.
Context	The review will help inform on the different symptoms associated with withdrawal from each of the relevant drug classes. There has been a suggestion that withdrawal symptoms can be overlooked or considered to be re-emergence of the existing condition in some cases. The review therefore can be used to improve awareness of the symptoms associated, and recognise withdrawal symptoms when they are experienced.
Primary outcomes (critical outcomes)	<u>Intervention data</u>: Specific withdrawal symptoms including rebound symptoms (specify what the symptoms are reported in the study, and number of people having the symptom where available, dichotomous outcome) Any withdrawal symptom (i.e., all symptoms lumped together (dichotomous outcome) Intensity of withdrawal symptoms (validated scales only, continuous outcome) Duration of withdrawal syndrome (continuous outcome) *Timepoint: post-intervention and longest follow-up.* <u>Qualitative data:</u> Themes emerging from qualitative data (themes will be derived from the evidence identified for this review and not pre-specified)

Secondary outcomes (important outcomes)	Not applicable
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. 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. Qualitative: Once saturation is considered to have been reached (all the themes are already covered in the data extraction) data from other included papers will not be extracted or critically appraised, but the paper will still be read to check for any additional themes and will be noted in the included studies. The point at which data extraction is reached will be noted within the review.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Intervention:

	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) <u>Qualitative:</u> For this review the Critical Appraisal Skills Programme (CASP) qualitative checklist will be used to assess risk of bias of individual studies. 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 with the exception of antidepressants. <u>Intervention:</u> 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. <u>Qualitative:</u> The synthesis of qualitative data will follow a thematic analysis approach. Information will be synthesised into main review findings. Results will be presented in a detailed narrative and in table format with summary statements of main review findings. GRADE CERQual will be used to synthesise the qualitative data and assess the certainty of evidence for each review finding.	
Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: Higher potency/shorter half-life and lower potency/longer half-life benzodiazepines will be pooled unless heterogeneity is observed.	
Type and method of review	☐	Intervention
	☐	Diagnostic
	☐	Prognostic

	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☒	Other: Mixed methods
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=CRD42020214163
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 health economic evidence

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 D 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).[457] **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:

- Withdrawal symptoms associated with prescribed medicines

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[457] For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

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.

Table 20: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 - 15 June 2021	Randomised controlled trials Systematic review studies Qualitative studies Exclusions (animal studies, letters, comments)
Embase (OVID)	1974 - 15 June 2021	Randomised controlled trials Systematic review studies Qualitative 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 - 15th June 2021	None
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	Inception - 15 June 2021	Qualitative studies
PsycINFO (ProQuest)	Inception - 15 June 2021	Qualitative studies
ASSIA, Applied Social Sciences Index and Abstracts (ProQuest)	Inception - 15 June 2021	Qualitative studies

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.	Qualitative research/ or Narration/ or exp Interviews as Topic/ or exp Questionnaires/ or Health care surveys/
81.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
82.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
83.	or/80-82
84.	68 and (68 or 79 or 83)

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/61-69
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/71-80
82.	health survey/ or exp questionnaire/ or exp interview/ or qualitative research/ or narrative/
83.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
84.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
85.	or/82-84
86.	60 and (70 or 81 or 85)

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*))]

CINAHL (EBSCO) search terms

S1.	(MH "Substance Use Disorders") OR (MH "Substance Withdrawal Syndrome") OR (MH "Inappropriate Prescribing") OR (MH "Drugs, Prescription")

S2.	TI ((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*) n2 (drug* or medicine* or medicat* or medical* or pharm*))
S3.	AB ((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*) n2 (drug* or medicine* or medicat* or medical* or pharm*))
S4.	TI ((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 innapropriate) n3 (prescription* or prescrib*))
S5.	AB ((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 innapropriate) n3 (prescription* or prescrib*))
S6.	TI (addict* n3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*))
S7.	AB (addict* n3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*))
S8.	TI (deprescription* or de-prescription* or deprescrib* or de-prescrib*)
S9.	AB (deprescription* or de-prescription* or deprescrib* or de-prescrib*)
S10.	TI ((therap* or treat*) n2 (manag* or substit*))
S11.	AB ((therap* or treat*) n2 (manag* or substit*))
S12.	TI ((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) n2 symptom*)
S13.	AB ((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) n2 symptom*)
S14.	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S15.	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website
S16.	S14 NOT S15
S17.	(MH "Narcotics+") OR (MH "Antianxiety Agents, Benzodiazepine+") OR (MH "Antidepressive Agents+") OR (MH "Antidepressive Agents, Second Generation+") OR (MH "Antidepressive Agents, Tricyclic+") OR (MH "Zolpidem") OR (MH "Eszopiclone") OR (MH "Analgesics, Opioid+")
S18.	TI ((analgesic* n3 narcotic n3 agent*) or (opioid* or opiate*))
S19.	AB ((analgesic* n3 narcotic n3 agent*) or (opioid* or opiate*))
S20.	TI (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*)
S21.	AB (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*)
S22.	TI (z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon)
S23.	AB (z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon)
S24.	TI (generation n3 hypnotic*)
S25.	AB (generation n3 hypnotic*)
S26.	TI (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)
S27.	AB (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)
S28.	TI (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*)
S29.	AB (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*)
S30.	TI (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)
S31.	AB (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)
S32.	TI (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)
S33.	AB (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)
S34.	TI (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)
S35.	AB (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)
S36.	(MH "Gabapentin") OR (MH "Pregabalin")
S37.	TI (gabapentin* or pregabalin*)
S38.	AB (gabapentin* or pregabalin*)

S39.	S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38
S40.	S16 AND S39
S41.	TI ((withdraw* or prescription* or prescrib*) n2 opi*) OR AB ((withdraw* or prescription* or prescrib*) n2 opi*)
S42.	S40 OR S41
S43.	(MH "Qualitative Studies+")
S44.	(MH "Qualitative Validity+")
S45.	(MH "Interviews+") OR (MH "Focus Groups") OR (MH "Surveys") OR (MH "Questionnaires+")
S46.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*)
S47.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*)
S48.	S42 OR S43 OR S44 OR S45 OR S46
S49.	S42 and S48

PsycINFO (ProQuest) search terms

1.	"Substance Use Disorder"/ or "Substance Related and Addictive Disorders"/ or Prescription Drug Misuse/ or Drug Withdrawal/
2.	((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.
3.	((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 innapropriate) adj3 (prescription* or prescrib*)).ti,ab.
4.	(addict* adj3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)).ti,ab.
5.	(deprescription* or de-prescription* or deprescrib* or de-prescrib*).ti,ab.
6.	((therap* or treat*) adj2 (manag* or substit*)).ti,ab.
7.	((drug* or medic*) adj2 (prescription* or prescrib*)).ti,ab.
8.	((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) adj2 symptom*).ti,ab.
9.	or/1-8
10.	((withdraw* or prescription* or prescrib*) adj2 opi*).ti,ab.
11.	"opioid use disorder"/
12.	10 or 11
13.	exp narcotic drugs/
14.	((analgesic* adj3 narcotic) or (opioid* or opiate*)).ti,ab.
15.	(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.

16.	(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.
17.	(generation adj3 hypnotic*).ti,ab.
18.	exp Benzodiazepines/
19.	(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.
20.	exp antidepressant drugs/
21.	(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.
22.	(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.
23.	(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.
24.	(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.
25.	Gabapentin/ or pregabalin/
26.	(gabapentin* or pregabalin*).ti,ab.
27.	or/13-26
28.	9 and 27
29.	12 or 28
30.	exp Qualitative Methods/ or Narratives/ or exp Questionnaires/ or exp Interviews/ or exp Health Care Services/
31.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
32.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical-sampl* or purposive-sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
33.	or/30-32
34.	29 and 33
35.	limit 34 to English language

ASSIA (ProQuest) search terms

1.	((TI,AB:withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* N/2 symptom*) AND (MAINSUBJECT.EXACT("Gabapentin") OR MAINSUBJECT.EXACT.EXPLODE("Narcotics") OR MAINSUBJECT.EXACT.EXPLODE("Benzodiazepines") OR MAINSUBJECT.EXACT.EXPLODE("Antidepressant drugs") OR MAINSUBJECT.EXACT("Zolpidem") OR ti,ab(opioid* OR opiate*) OR ti,ab(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 ti,ab(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 ti,ab(generation NEAR/3 hypnotic*) OR ti,ab(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)) AND (MAINSUBJECT.EXACT.EXPLODE("Interviews") OR MAINSUBJECT.EXACT.EXPLODE("Qualitative research") OR MAINSUBJECT.EXACT.EXPLODE("Questionnaires") OR MAINSUBJECT.EXACT.EXPLODE("Narratives") OR ti,ab(qualitative or interview* or focus group* or theme* or questionnaire* or survey*) or ti,ab(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* near/3 analys*) or theoretical-sampl* or purposive-sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*))) NOT ((((MAINSUBJECT.EXACT("Substance dependency") OR MAINSUBJECT.EXACT("Substance abuse disorders") OR MAINSUBJECT.EXACT("Overprescribing") OR MAINSUBJECT.EXACT("Withdrawal symptoms") OR MAINSUBJECT.EXACT("Withdrawal")) OR ti,ab(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 addict* or depend*) OR ti,ab(prescription* OR prescrib*) OR ti,ab(deprescription* OR de-prescription* OR deprescrib* OR de-prescrib*)) AND (MAINSUBJECT.EXACT("Gabapentin") OR MAINSUBJECT.EXACT.EXPLODE("Narcotics") OR MAINSUBJECT.EXACT.EXPLODE("Benzodiazepines") OR MAINSUBJECT.EXACT.EXPLODE("Antidepressant drugs") OR MAINSUBJECT.EXACT("Zolpidem") OR ti,ab(opioid* OR opiate*) OR ti,ab(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 ti,ab(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 ti,ab(generation NEAR/3 hypnotic*) OR ti,ab(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))) AND (MAINSUBJECT.EXACT.EXPLODE("Interviews") OR MAINSUBJECT.EXACT.EXPLODE("Qualitative research") OR MAINSUBJECT.EXACT.EXPLODE("Questionnaires") OR MAINSUBJECT.EXACT.EXPLODE("Narratives") OR ti,ab(qualitative or interview* or focus group* or theme* or questionnaire* or survey*) or ti,ab(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* near/3 analys*) or theoretical-sampl* or purposive-sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*)))

B.2 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.

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Table 21: 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

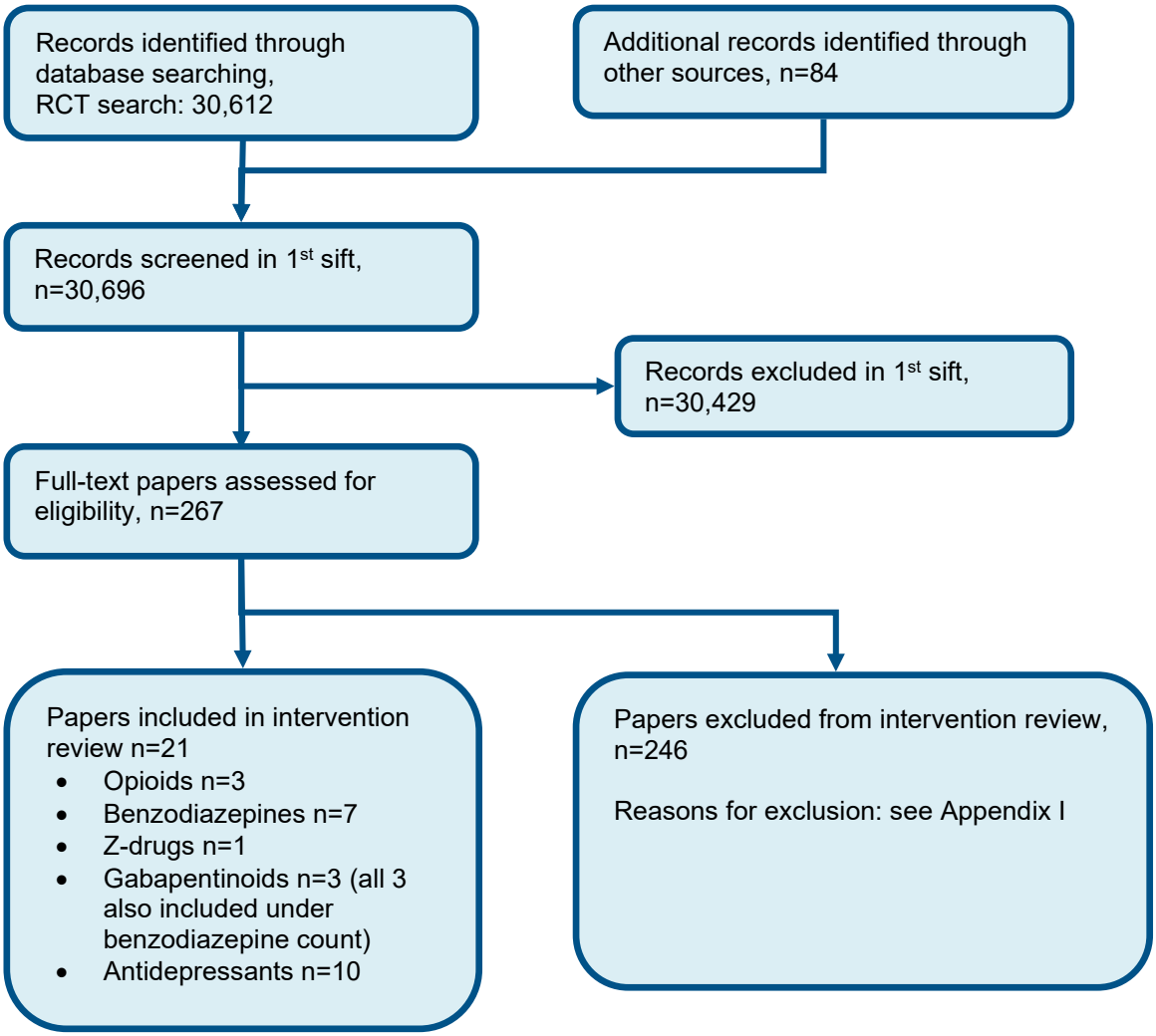
#1.	(MeSH DESCRIPTOR Substance-Related Disorders)
#2.	(MeSH DESCRIPTOR Substance Withdrawal Syndrome)
#3.	(MeSH DESCRIPTOR Inappropriate Prescribing EXPLODE ALL TREES)

#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)

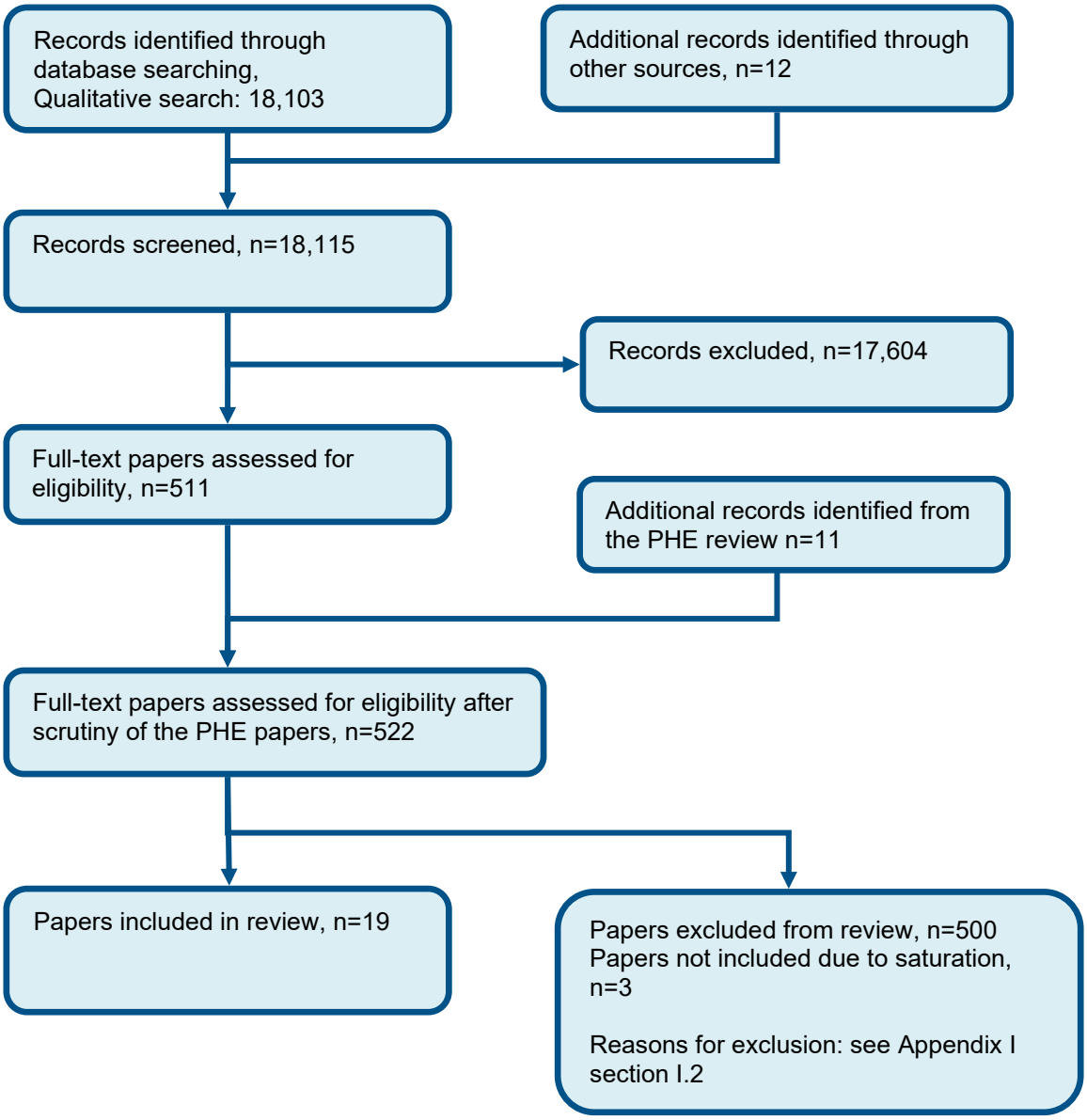
#34.	((Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline 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 Study selection

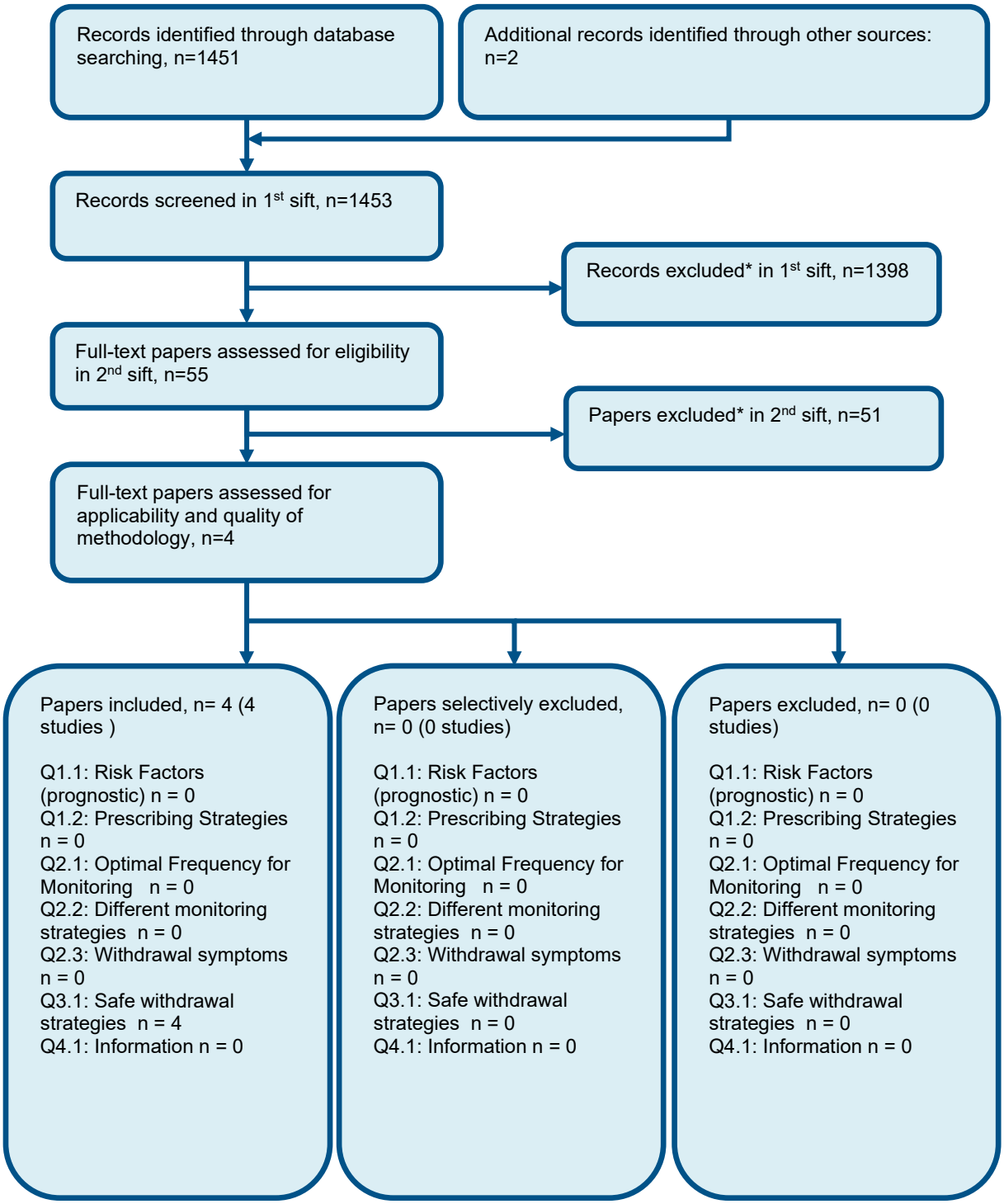
C.1 Quantitative evidence: Flow chart of quantitative evidence study selection for the review of withdrawal symptoms



C.2 Flow chart of qualitative evidence study selection for the review of withdrawal symptoms



C.3 Economic evidence study selection



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

Appendix D Quantitative evidence: Forest plots

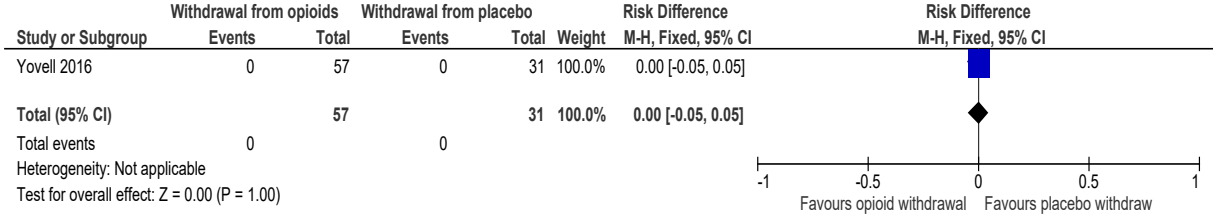
D.1 Opioids

D.1.1 Withdrawal from opioids vs continuation on opioids

No evidence identified for comparison

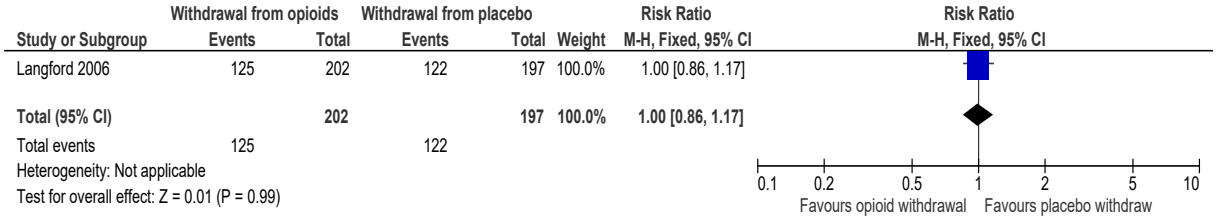
D.1.2 Withdrawal from opioids vs withdrawal from placebo

Figure 1: Any withdrawal symptom (at 5 weeks = follow-up: 1 week-post last dose)



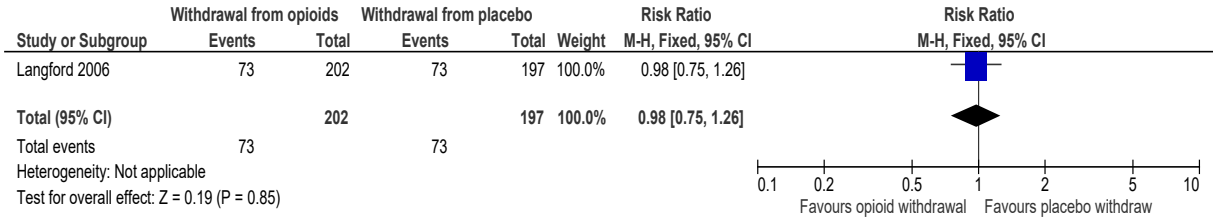
Note: assessed at appointment with psychiatrist to screen for possible withdrawal symptoms

Figure 2: Moderate or severe aches and pains (on short opiate withdrawal scale; protocol outcome: specific withdrawal symptom; at follow-up 3-days after last patch removed)



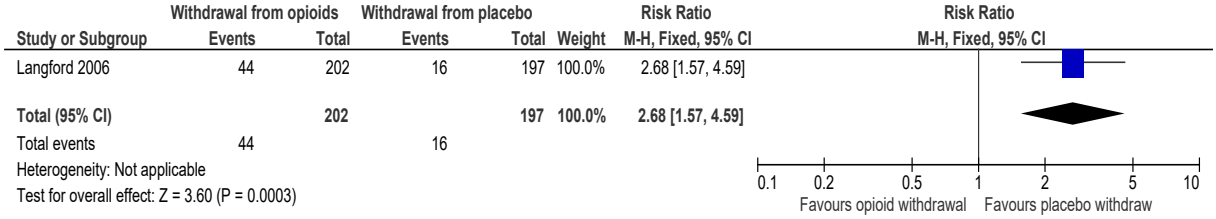
Note: short opiate withdrawal scale consisted of 10 items rated on a 4-point Likert scale (0-3, none to severe).

Figure 3: Mild or moderate problems sleeping (on short opiate withdrawal scale; protocol outcome: specific withdrawal symptom; at follow-up 3-days after last patch removed)



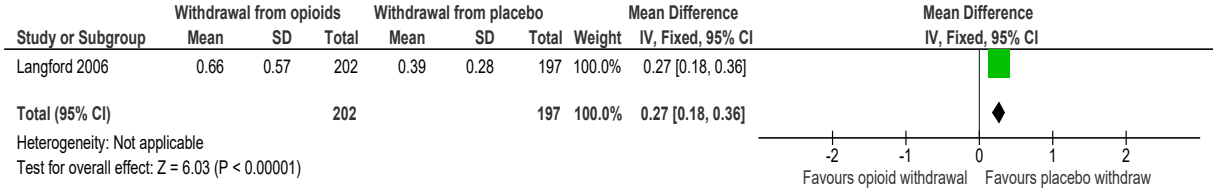
Note: short opiate withdrawal scale consisted of 10 items rated on a 4-point Likert scale (0-3, none to severe).

Figure 4: Severe insomnia (on short opiate withdrawal scale; protocol outcome: specific withdrawal symptom; at follow-up 3-days after last patch removed)



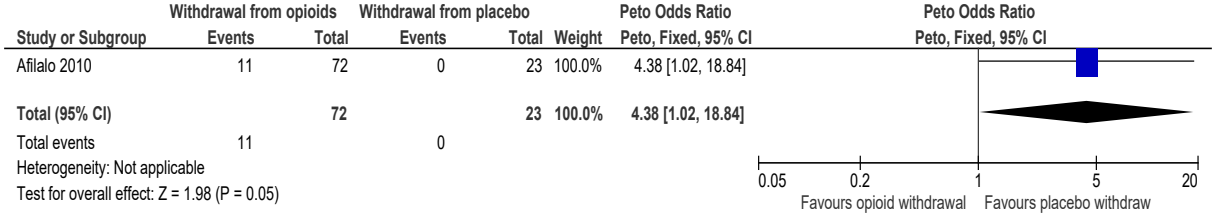
Note: short opiate withdrawal scale consisted of 10 items rated on a 4-point Likert scale (0-3, none to severe).

Figure 5: Short opiate withdrawal scale score (protocol outcome: intensity of withdrawal symptoms; at follow-up 3 days after last patch removed)



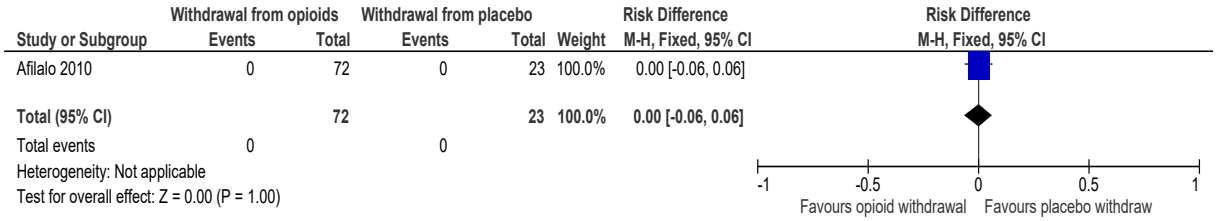
Note: short opiate withdrawal scale consisted of 10 items rated on a 4-point Likert scale (0-3, none to severe). Total score range of possible scores 0-3 (top=poor outcome)

Figure 6: Mild opioid withdrawal as assessed on COWS (protocol outcome: intensity of withdrawal symptoms; at follow-up 2 - <5 days after last dose)



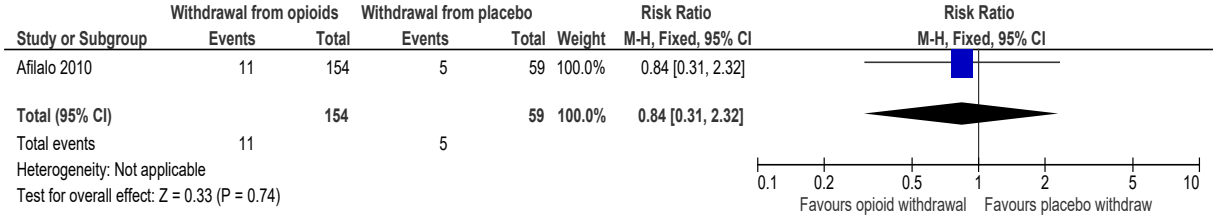
Note: COWS based on 11 items of opioid withdrawal symptoms, each rated 0-5, higher values being worse. 5-12 is mild, 13-24 is moderate, 25-36 is moderately severe, > or equal to 36 is severe. Study also reported the number of people with 'no withdrawal' (61/72 and 23/23) as assessed on COWS. This was not analysed as it is the 'opposite' outcome and would be double counting. Presumably no-one had moderately severe or severe withdrawal, as the numbers in the other 3 categories add up to the total number of people in the study.

Figure 7: Moderate opioid withdrawal as assessed on COWS (REVIEWER DETERMINED FROM NO.S OF 'NO' AND 'MILD' WITHDRAWAL protocol outcome: intensity of withdrawal symptoms; at follow-up 2 - <5 days after last dose)



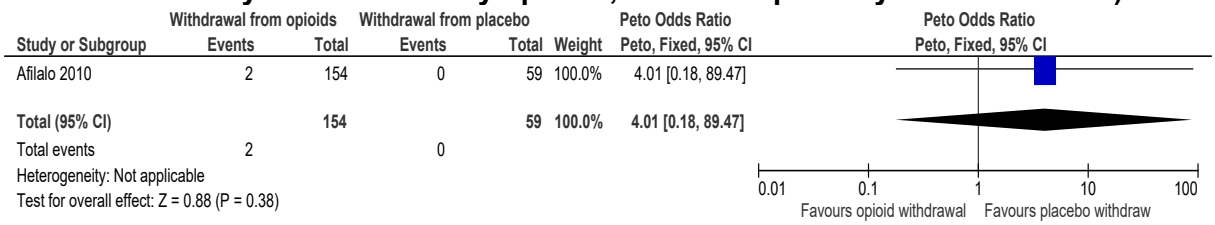
Note: *COWS based on 11 items of opioid withdrawal symptoms, each rated 0-5, higher values being worse. 5-12 is mild, 13-24 is moderate, 25-36 is moderately severe, > or equal to 36 is severe. Study also reported the number of people with 'no withdrawal' (61/72 and 23/23) as assessed on COWS. This was not analysed as it is the 'opposite' outcome and would be double counting. Presumably no-one had moderately severe or severe withdrawal, as the numbers in the other 3 categories add up to the total number of people in the study.* ***Reviewer determined that no one had 'moderate withdrawal' at this timepoint due to number of people with 'no withdrawal' or 'mild withdrawal' adding up to the total number of participants***

Figure 8: Mild opioid withdrawal as assessed on COWS (protocol outcome: intensity of withdrawal symptoms; at follow-up ≥5 days after last dose)



Note: *COWS based on 11 items of opioid withdrawal symptoms, each rated 0-5, higher values being worse. 5-12 is mild, 13-24 is moderate, 25-36 is moderately severe, > or equal to 36 is severe. Study also reported the number of people with 'no withdrawal' (141/154 and 54/59) as assessed on COWS. This was not analysed as it is the 'opposite' outcome and would be double counting. Presumably no-one had moderately severe or severe withdrawal, as the numbers in the other 3 categories add up to the total number of people in the study.*

Figure 9: Moderate opioid withdrawal as assessed on COWS (protocol outcome: intensity of withdrawal symptoms; at follow-up ≥5 days after last dose)

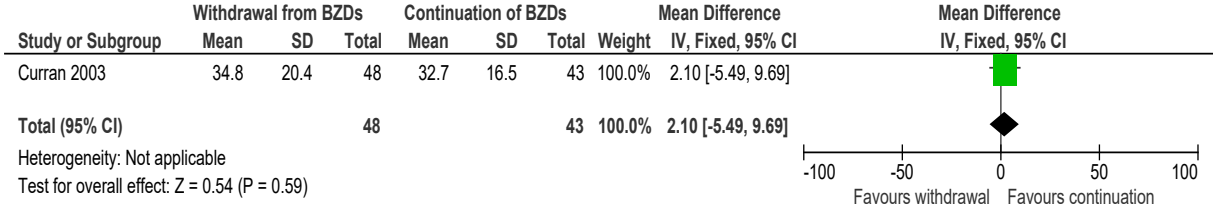


Note: COWS based on 11 items of opioid withdrawal symptoms, each rated 0-5, higher values being worse. 5-12 is mild, 13-24 is moderate, 25-36 is moderately severe, > or equal to 36 is severe. Study also reported the number of people with 'no withdrawal' (141/154 and 54/59) as assessed on COWS. This was not analysed as it is the 'opposite' outcome and would be double counting. Presumably no-one had moderately severe or severe withdrawal, as the numbers in the other 3 categories add up to the total number of people in the study.

D.2 Benzodiazepines

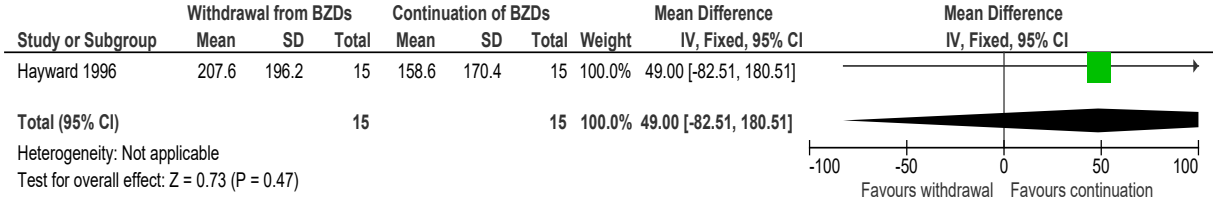
D.2.1 Withdrawal from benzodiazepines vs continuation on benzodiazepines

Figure 10: BWSQ (protocol outcome: intensity of withdrawal symptoms at 3 weeks after discontinuation)



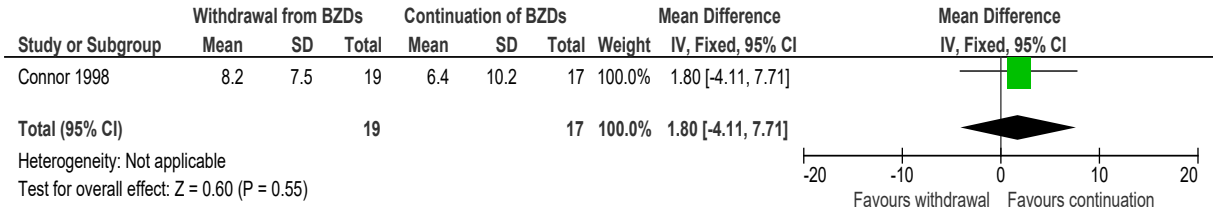
Benzodiazepine Withdrawal Symptom Questionnaire is a self-report questionnaire measuring 20 symptoms with a maximum score of 40, higher values are worse.

Figure 11: Withdrawal Symptom Scale (protocol outcome: intensity of withdrawal symptoms at 4 weeks after discontinuation)



The Withdrawal Symptom scale (Hayward) total was unclear.

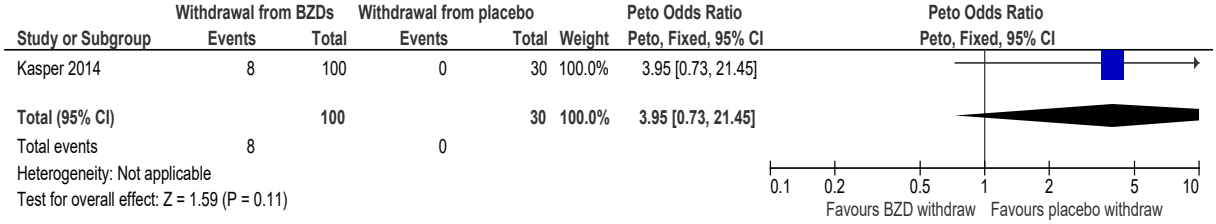
Figure 12: Total BWC score (protocol outcome: intensity of withdrawal symptoms at the end of the taper period)



Based on 33 symptom scale (Benzodiazepine Withdrawal Checklist), with each item rated on a scale of 0-4, with higher value being worse. Scale 0-132.

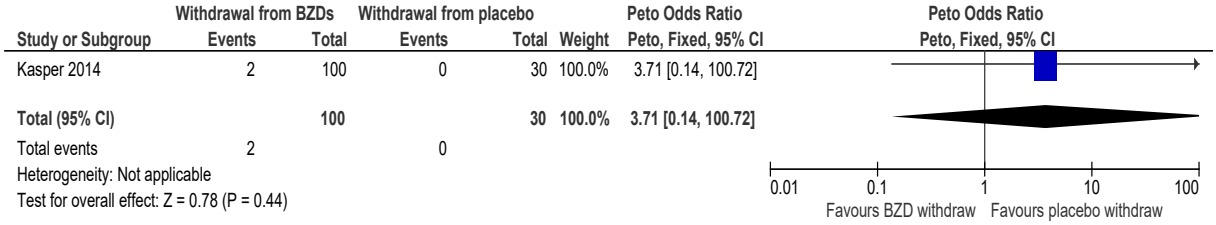
D.2.2 Withdrawal from benzodiazepines vs withdrawal from placebo

Figure 13: Anxiety as a discontinuation emergent sign and symptom* (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))



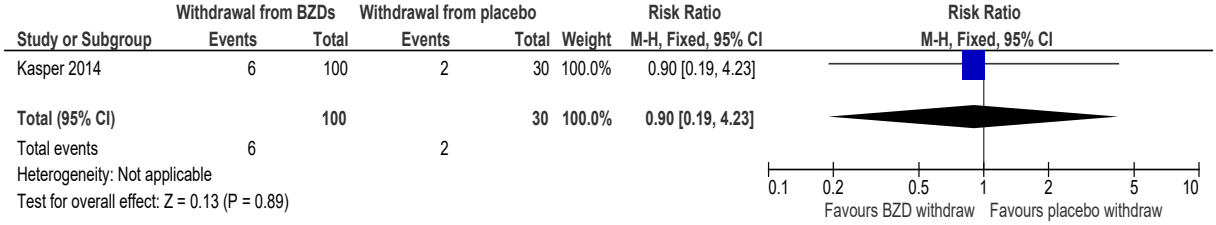
**defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks.*

Figure 14: Headache as a discontinuation emergent sign and symptom* (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))



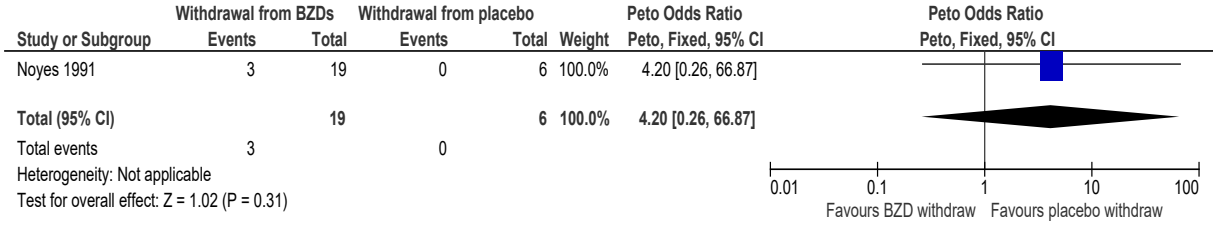
**defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks.*

Figure 15: Insomnia as a discontinuation emergent sign and symptom* (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))



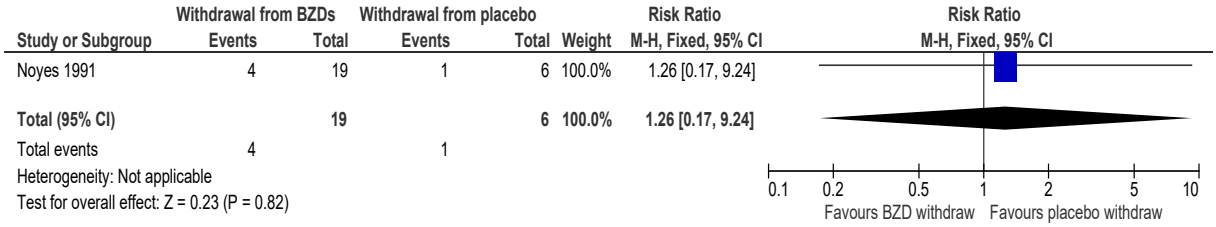
** defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks.*

Figure 16: Rebound- increase in anxiety of ≥50% as measured with Hamilton anxiety scale compared with baseline (protocol outcome; specific withdrawal symptom during the discontinuation period)



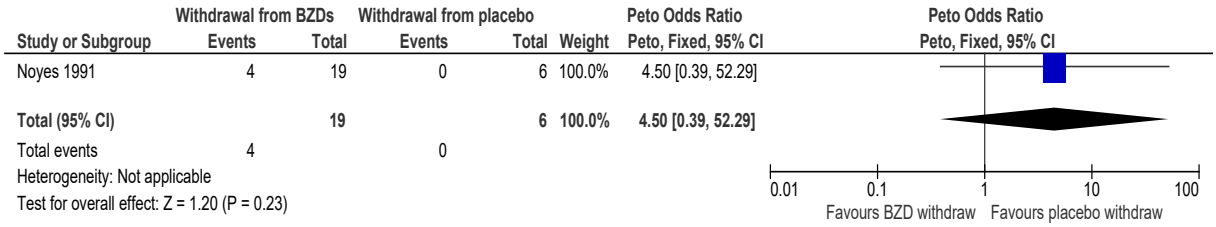
Rebound was judged to have occurred if the criteria were met at any visit

Figure 17: Rebound- increase in panic attacks of ≥100% compared with baseline (protocol outcome; specific withdrawal symptom during the discontinuation period)



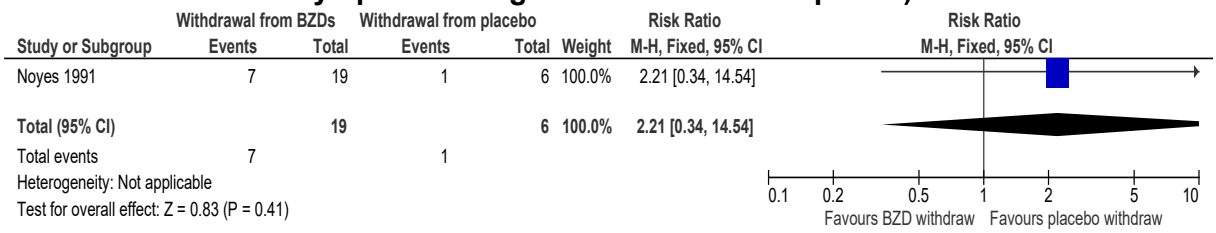
Rebound was judged to have occurred if the criteria were met at any visit

Figure 18: Rebound- Global Improvement Score ≤3 (indicating symptoms worse than at baseline) (protocol outcome; specific withdrawal symptom during the discontinuation period)



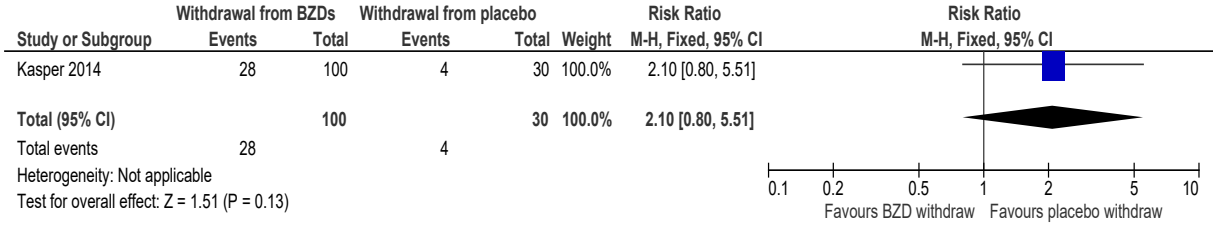
Range 0-10. Rebound was judged to have occurred if the criteria were met at any visit

Figure 19: Rebound- increase in anxiety of ≥10% as measured with Hamilton anxiety scale compared with baseline (protocol outcome; specific withdrawal symptom during the discontinuation period)



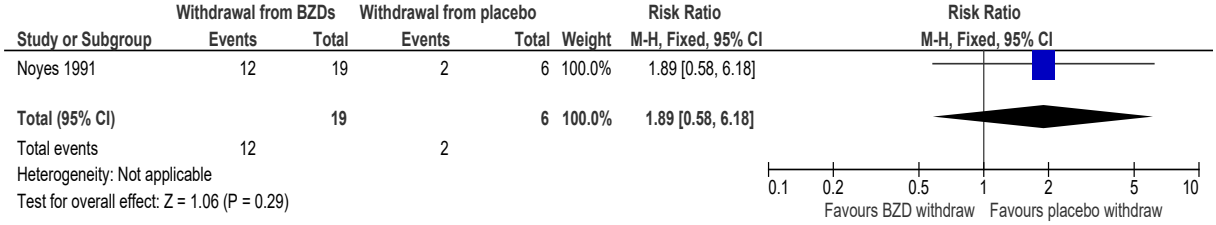
Rebound was judged to have occurred if the criteria were met at any visit

Figure 20: Patients with any discontinuation emergent sign and symptom* defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks (protocol outcome: any withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))



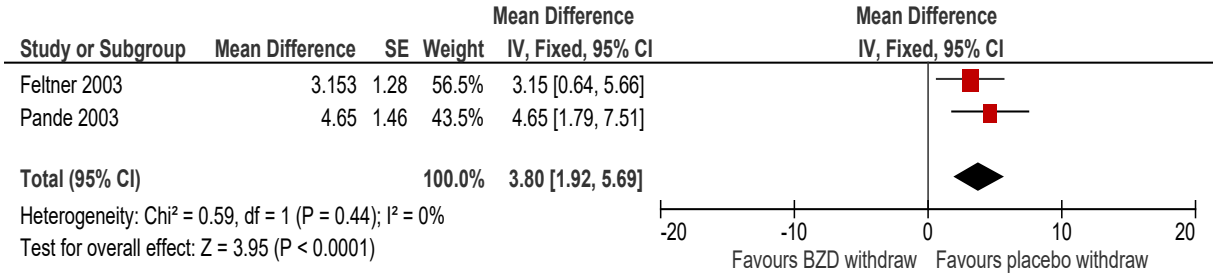
** defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks.*

Figure 21: Development of new symptoms (protocol outcome: any withdrawal symptom during discontinuation period)



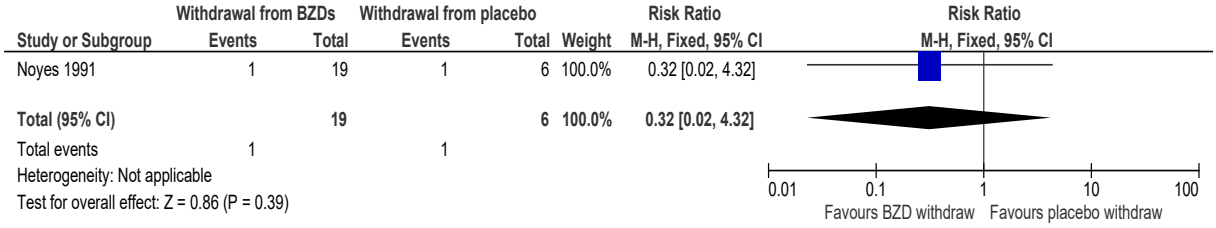
Source: <Insert Source text here>

Figure 22: PWC score (protocol outcome: intensity of withdrawal symptoms; at post-intervention (immediately after 1 week taper))



Physician Withdrawal Checklist is a clinician-rated instrument that measures 20 common symptoms of withdrawal (score range 0-60).

Figure 23: Increase in withdrawal symptoms of ≥100% (protocol outcome: intensity of withdrawal symptoms during the discontinuation period))



Using the 53 item Withdrawal Symptoms Checklist, symptoms that became worse during taper compared with baseline were identified. To do this, for each patient, the baseline value for each item was subtracted, rated on a 4-point scale from the highest value recorded during dose reduction or after discontinuation. The group's mean change from baseline was calculated and in this way 18 symptoms were identified that became worse than they had been at baseline. The sum of the ratings for these 18 symptoms yielded a total withdrawal symptom score for each patient at each observation period.

D.3 Gabapentinoids

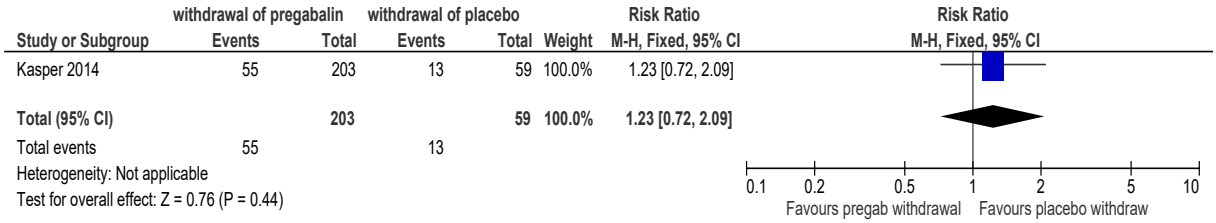
D.3.1 Withdrawal from gabapentinoids vs continuation on gabapentinoids

No evidence identified for comparison

D.3.2 Withdrawal from gabapentinoids vs withdrawal from placebo

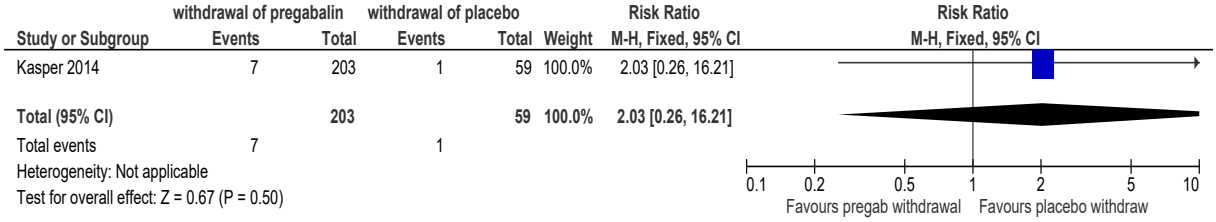
Evidence identified for pregabalin for comparison. No evidence identified for gabapentin.

Figure 24: Any discontinuation emergent sign and symptom* (protocol outcome: any withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))



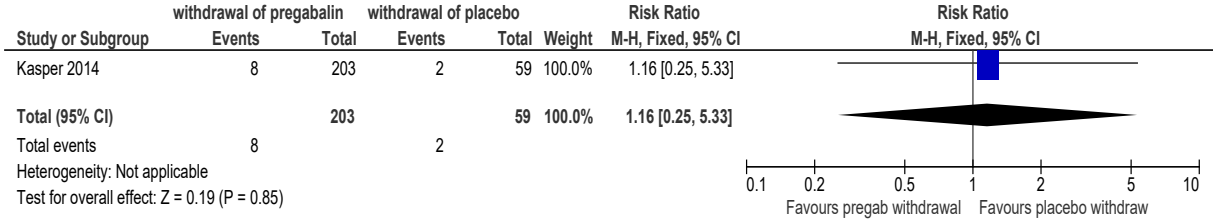
** defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks.*
Withdrawal from low (150-300mg/day) and withdrawal from high (450-600mg/day) dose pregabalin arms combined for analysis as per protocol (no stratification by dose). Study also had 2 separate withdrawal from placebo arms, these were also combined for analysis.

Figure 25: Anxiety as a discontinuation emergent sign and symptom* (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))



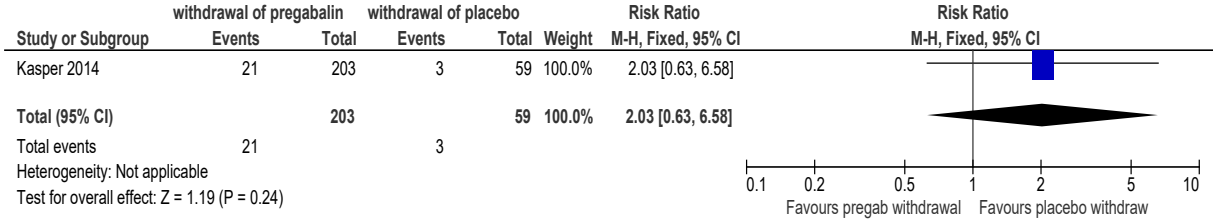
** defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks.*
Withdrawal from low (150-300mg/day) and withdrawal from high (450-600mg/day) dose pregabalin arms combined for analysis as per protocol (no stratification by dose). Study also had 2 separate withdrawal from placebo arms, these were also combined for analysis.

Figure 26: Headache as a discontinuation emergent sign and symptom* (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))



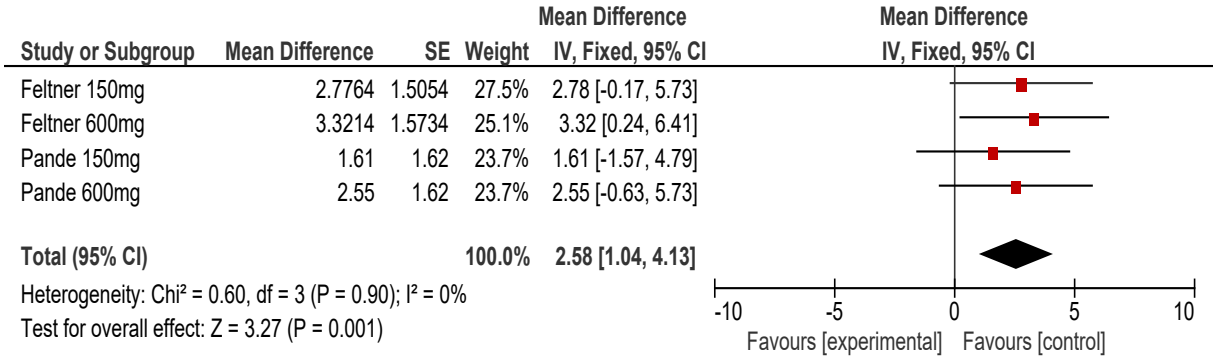
** defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks.*
Withdrawal from low (150-300mg/day) and withdrawal from high (450-600mg/day) dose pregabalin arms combined for analysis as per protocol (no stratification by dose). Study also had 2 separate withdrawal from placebo arms, these were also combined for analysis.

Figure 27: Insomnia as a discontinuation emergent sign and symptom* (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))



** defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks.*
Withdrawal from low (150-300mg/day) and withdrawal from high (450-600mg/day) dose pregabalin arms combined for analysis as per protocol (no stratification by dose). Study also had 2 separate withdrawal from placebo arms, these were also combined for analysis.

Figure 28: PWC score (protocol outcome: intensity of withdrawal symptoms; at post-intervention (immediately after 1 week taper))



2 studies, each with 2 comparisons (high dose vs placebo and low dose vs placebo). Results from high and low dose not combined, as studies reported mean differences. Therefore, each study appears as 2 comparisons: problem with the placebo arm being repeated twice addressed by halving the n in each of the repeated placebo arms to counteract the gain in statistical power from effectively double counting the placebo arm (this calculates

a greater SE for the MD, conferring an appropriate reduction in precision to compensate for the placebo arm being used twice)

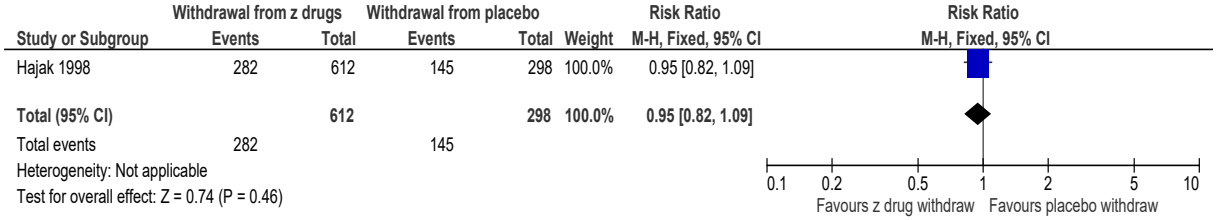
D.4 Z-drugs

D.4.1 Withdrawal from Z-drugs vs continuation on Z-drugs

No evidence identified for comparison

D.4.2 Withdrawal from Z-drugs vs withdrawal from placebo

Figure 29: Rebound insomnia (protocol outcome: specific withdrawal symptom at 14 days following abrupt taper)



Overall rebound-was a deterioration below individual mean pre-treatment values of the scores given on the visual analogue scales during the discontinuation period. A patient was counted as having rebound according to the following: deterioration in at least one of the three sleep quality parameters (a) sleep latency, (b) total sleep time, or (c) number of nocturnal awakenings; or deterioration in at least one parameter of daytime well-being defined as (d) a feeling of being refreshed on awakening in the morning, or as an impairment in daytime well-being as a result of (e) tiredness or (f)anxiety

D.5 Antidepressants

D.5.1 Withdrawal from antidepressants vs continuation on antidepressants

D.5.1.1 Other antidepressants

Figure 30: Total no. of emergent DESS symptoms (protocol outcome: intensity of withdrawal symptoms) during first 2 weeks of discontinuation

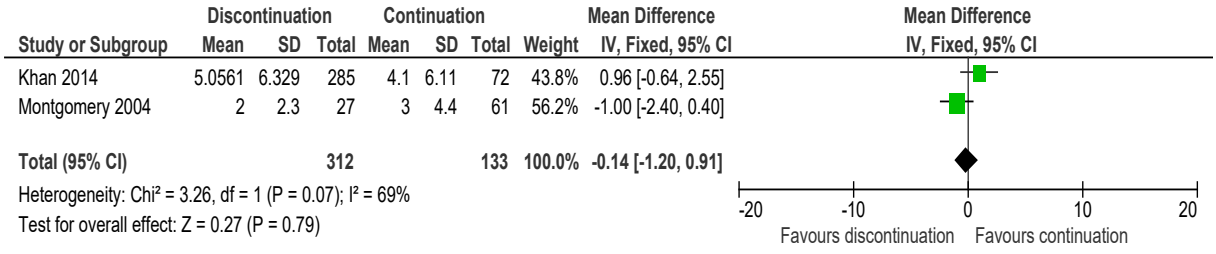


Figure 31: Rebound: return to a MADRS score equal to or higher than the original score at the entry of the acute treatment study (protocol outcome: specific withdrawal symptom during week 1 of discontinuation)

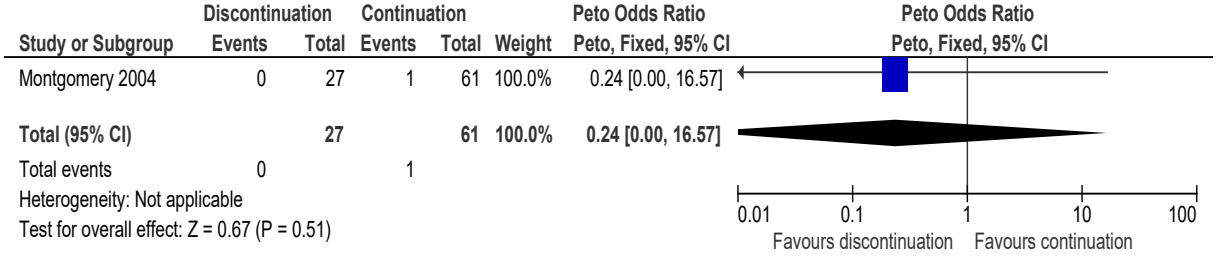


Figure 32: Rebound: return to a MADRS score equal to or higher than the original score at the entry of the acute treatment study (protocol outcome: specific withdrawal symptom during week 2 of discontinuation)

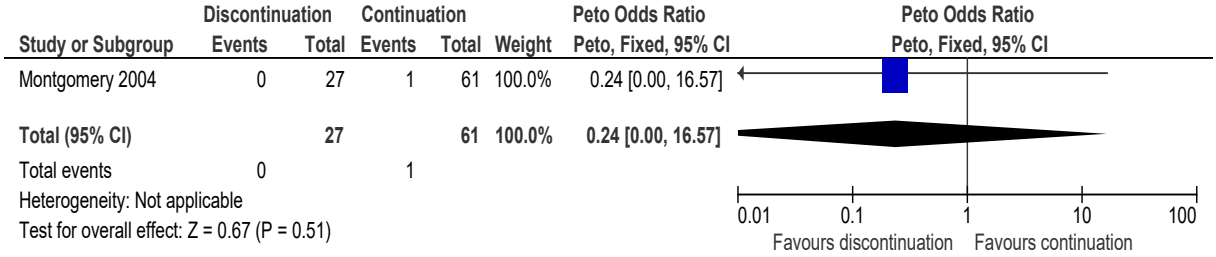


Figure 33: Nervousness/ anxiety (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

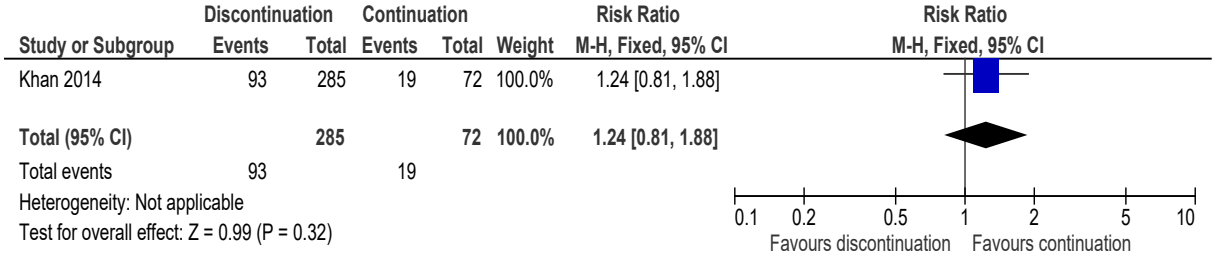


Figure 34: Elevated mood, feeling high (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

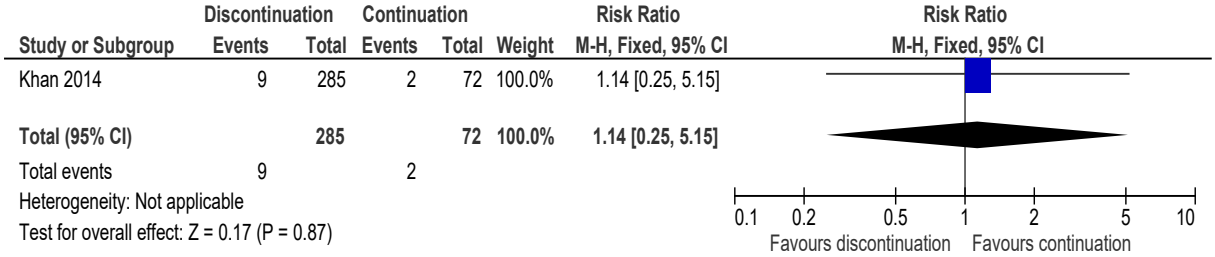


Figure 35: Irritability (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

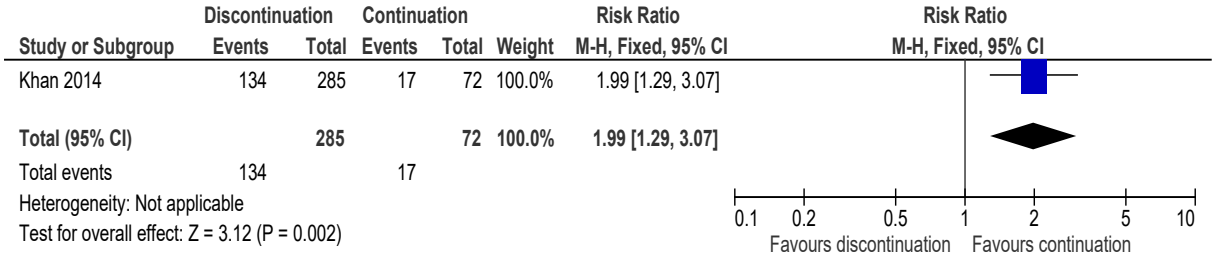


Figure 36: Sudden worsening of mood (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

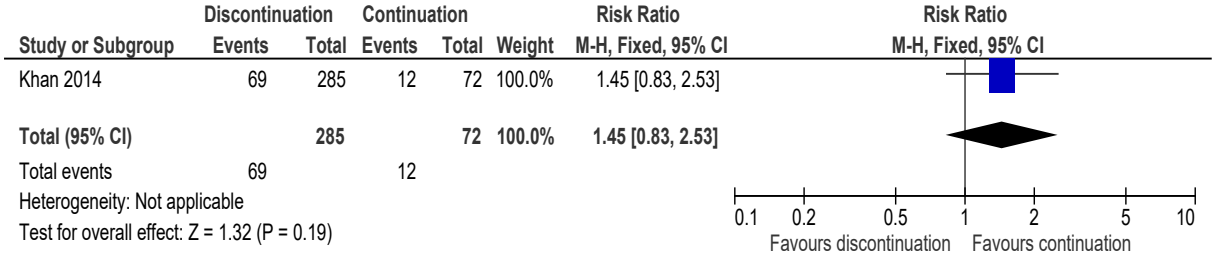


Figure 37: Sudden outbursts of anger (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

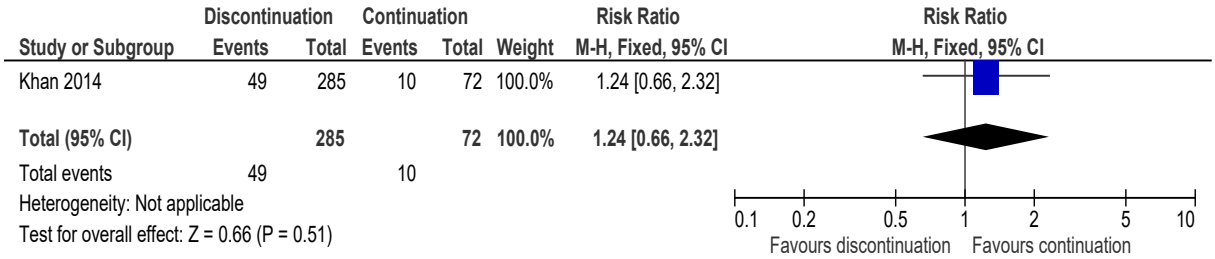


Figure 38: Sudden panic or anxiety attacks (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

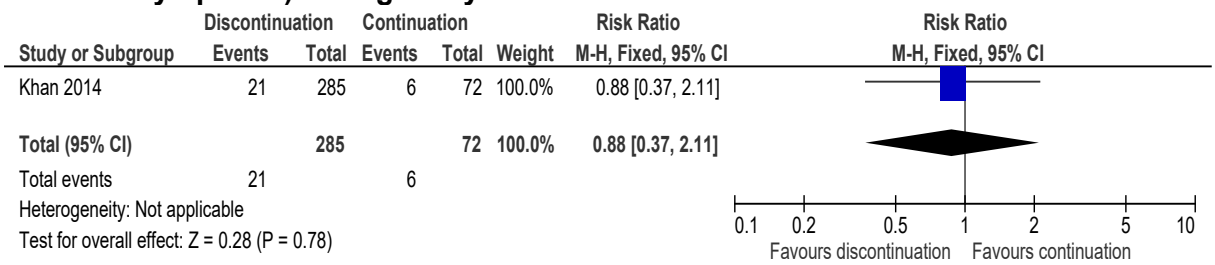


Figure 39: Bouts of crying or tearfulness (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

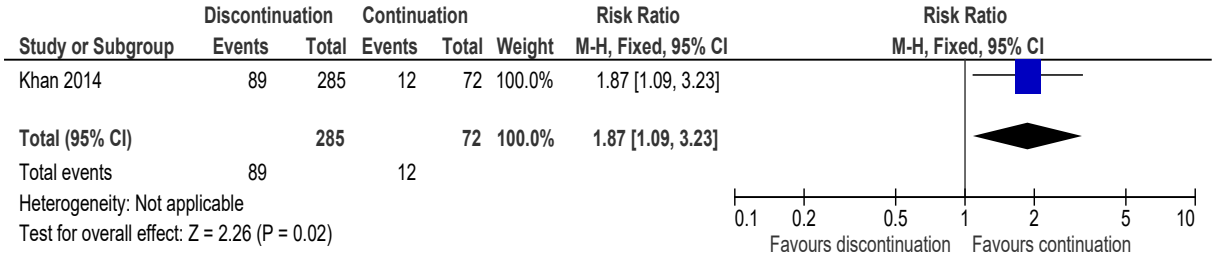


Figure 40: Agitation (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

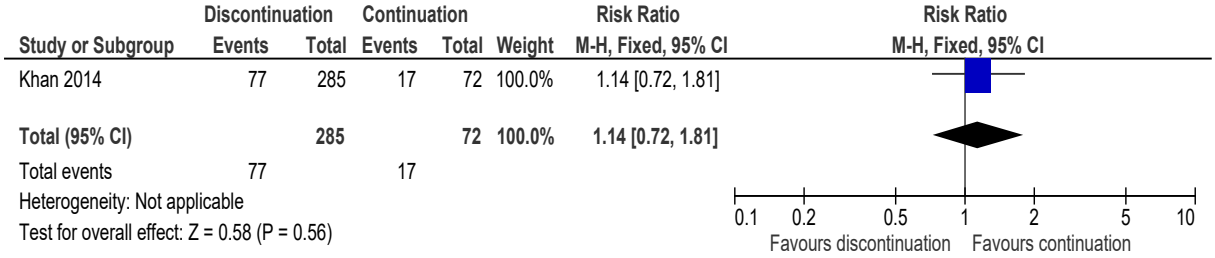


Figure 41: Feeling unreal or detached (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

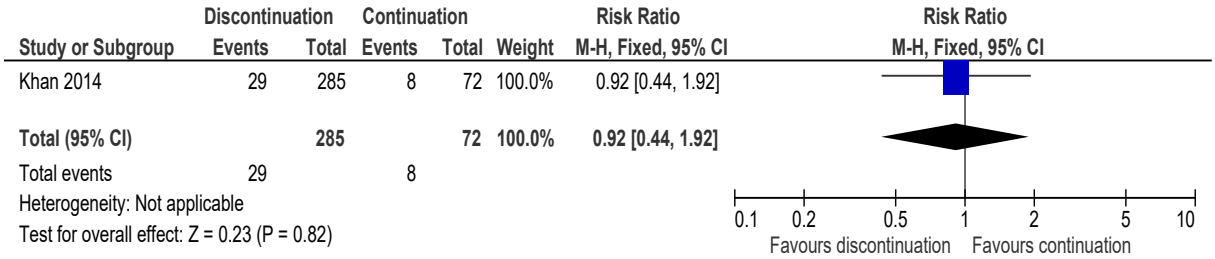


Figure 42: Confusion or trouble concentrating (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

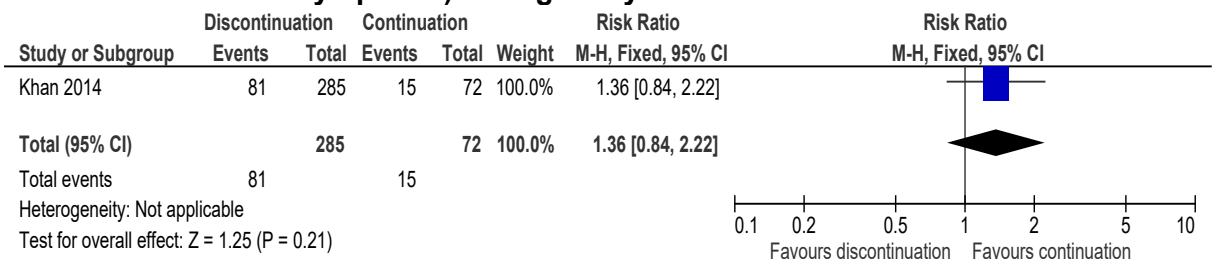


Figure 43: Forgetfulness or problems with memory (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

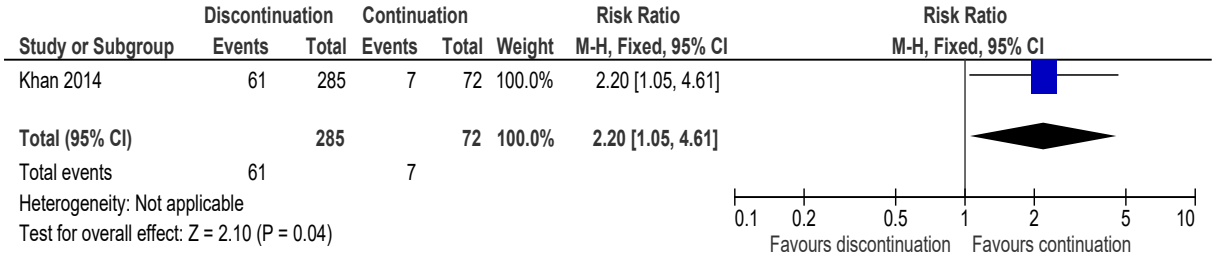


Figure 44: Mood swings (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

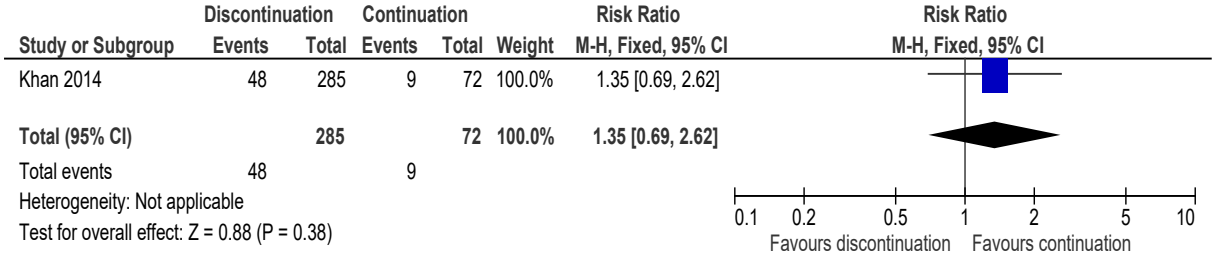


Figure 45: Trouble sleeping, insomnia (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

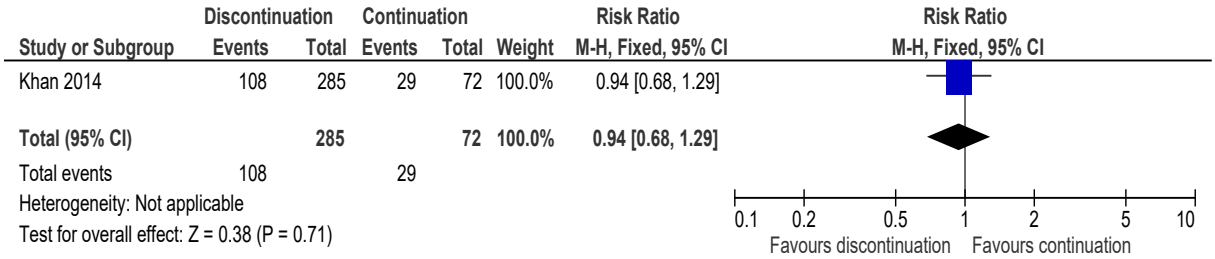


Figure 46: Increased dreaming, nightmares (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

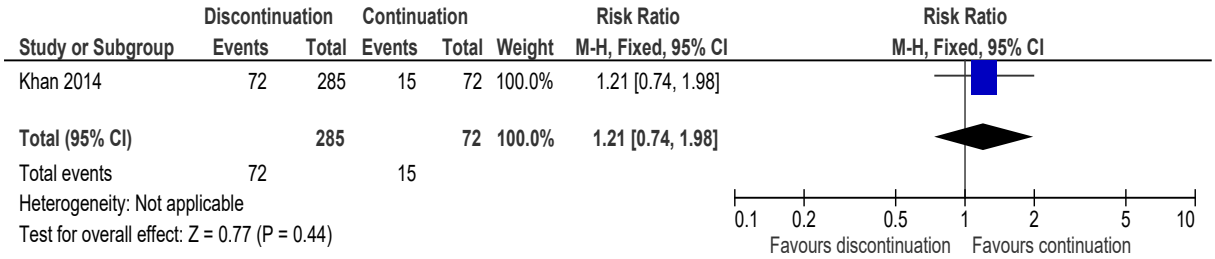


Figure 47: Sweating more than usual (protocol outcome : specific withdrawal symptoms) during study weeks 1-4

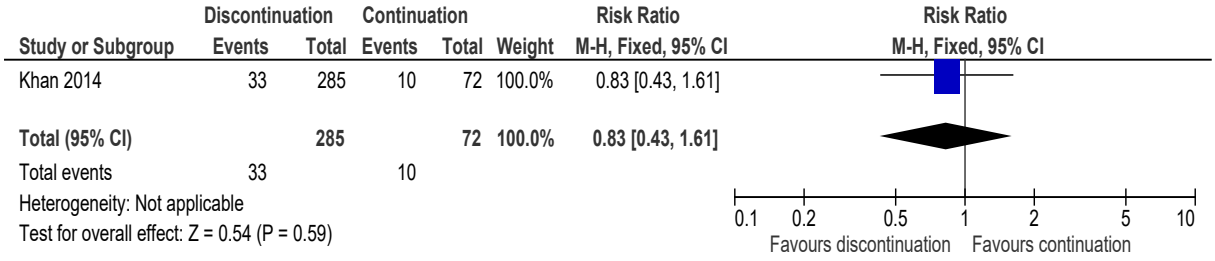


Figure 48: Shaking, trembling (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

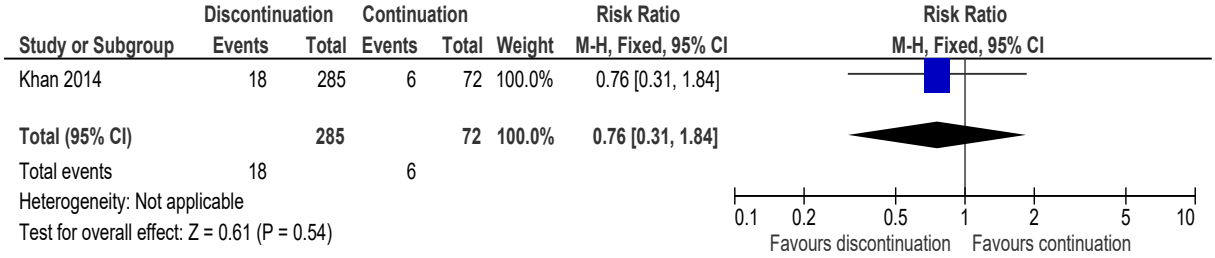


Figure 49: Muscle tension or stiffness (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

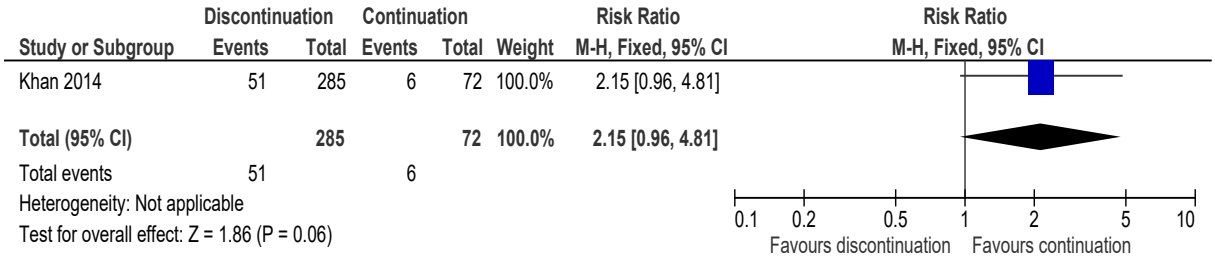


Figure 50: Muscle aches or pains (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

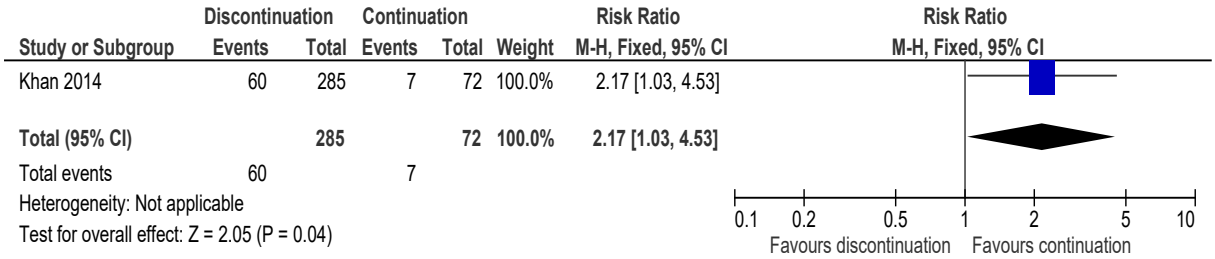


Figure 51: Restless feeling in legs (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

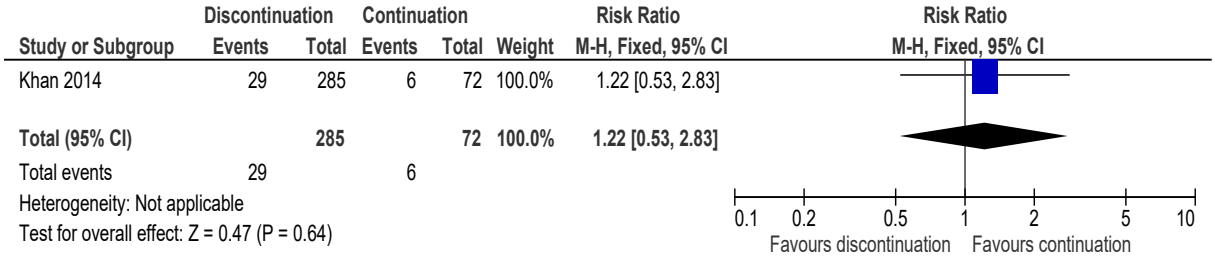


Figure 52: Muscle cramps, spasms, twitching (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

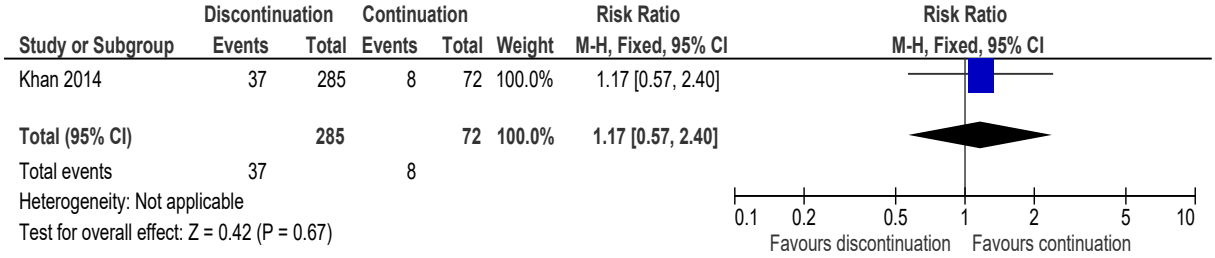


Figure 53: Fatigue, tiredness (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

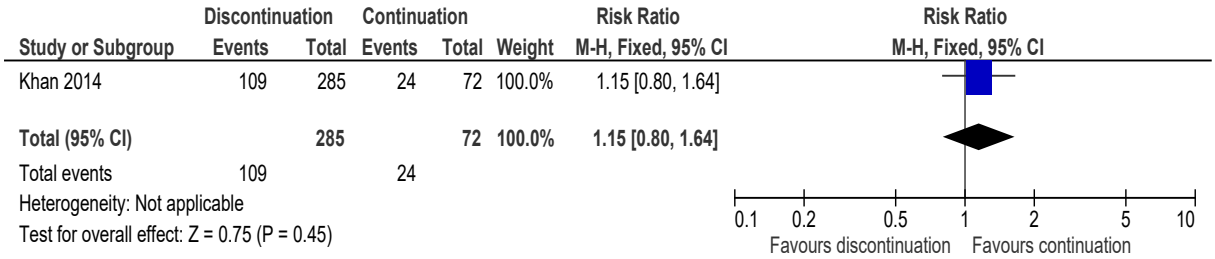


Figure 54: Unsteady gait or incoordination (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

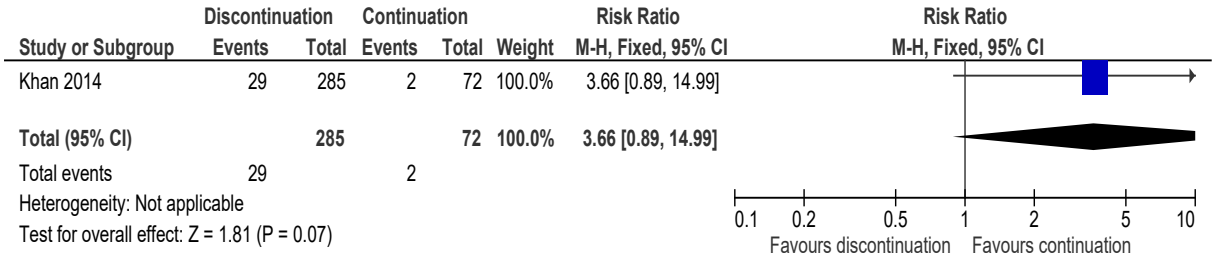


Figure 55: Blurred vision (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

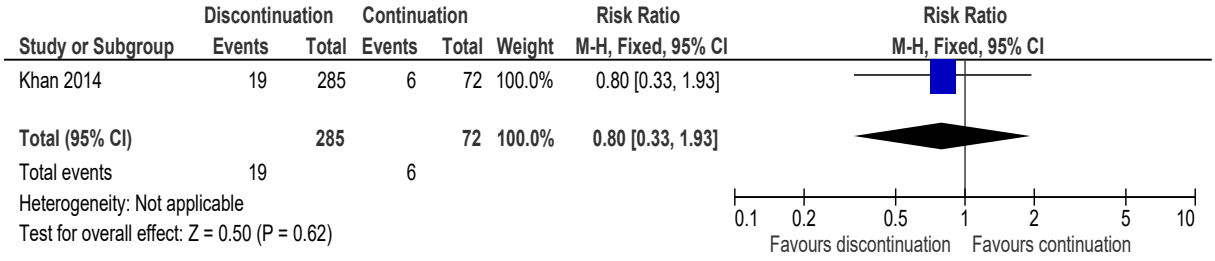


Figure 56: Sore eyes (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

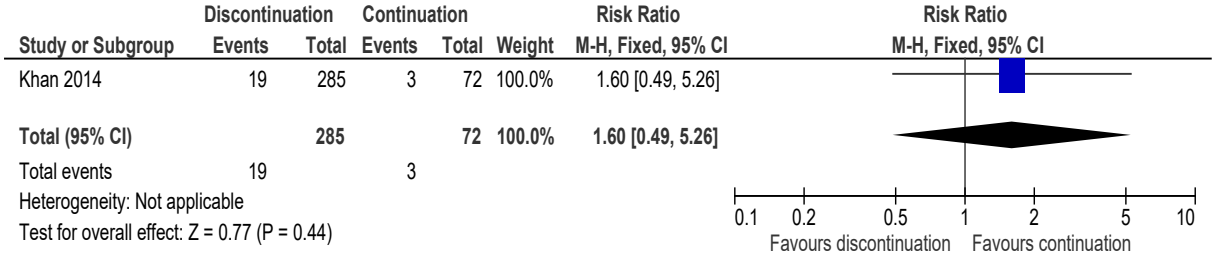


Figure 57: Uncontrolled mouth/ tongue movements (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

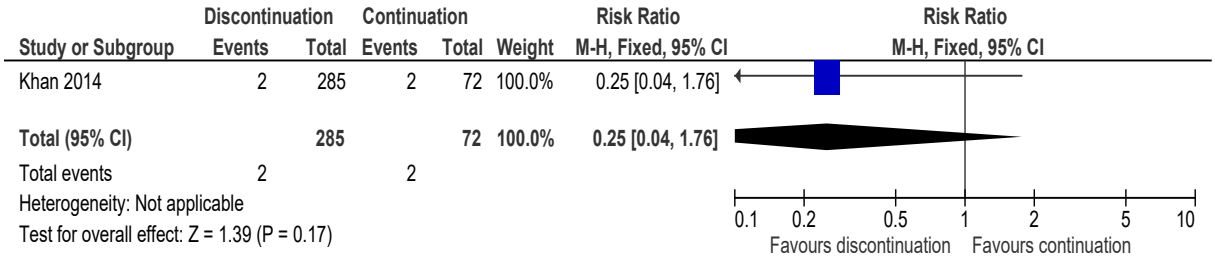


Figure 58: Problems with speech or speaking clearly (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

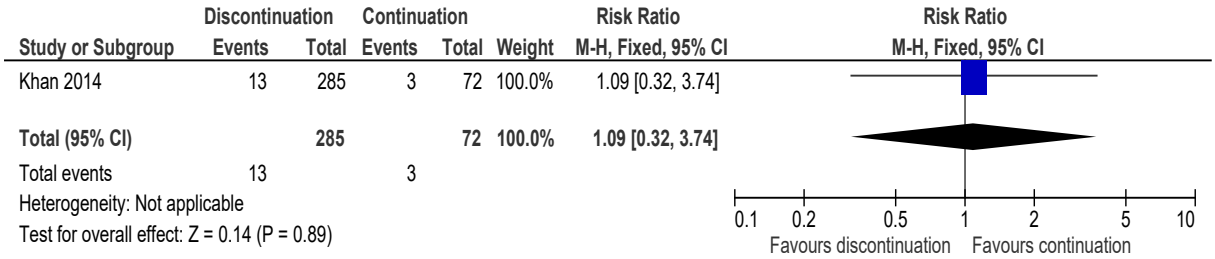


Figure 59: Headache (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

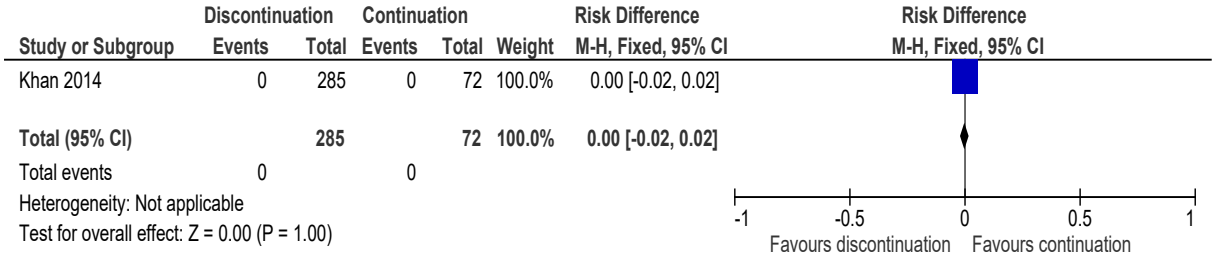


Figure 60: Increased saliva in mouth (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

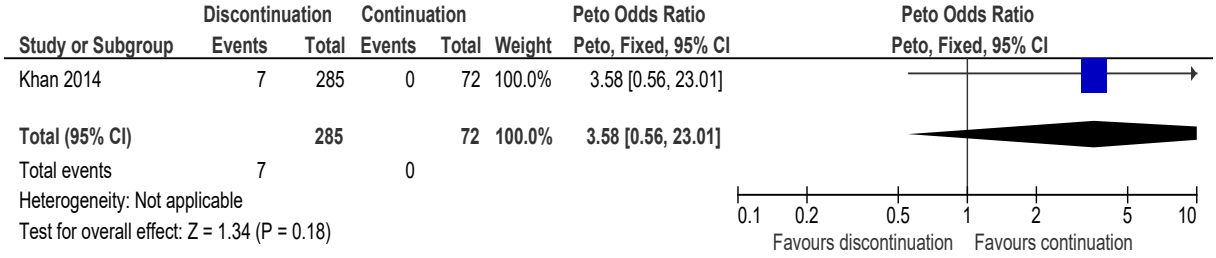


Figure 61: Dizziness, light-headedness or sensation of spinning (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

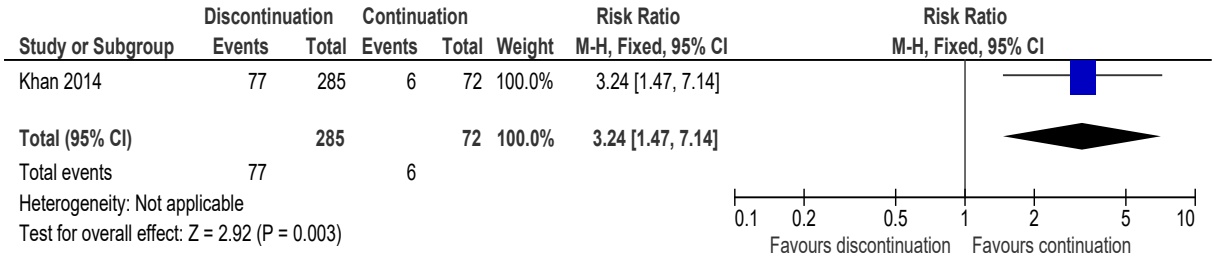


Figure 62: Nose running (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

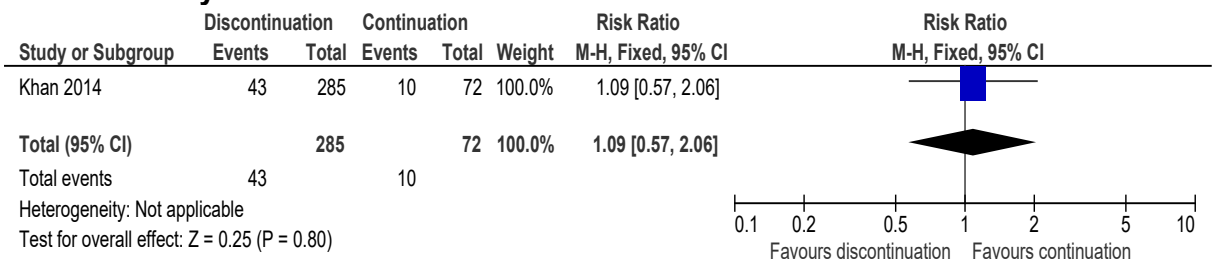


Figure 63: Shortness of breath (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

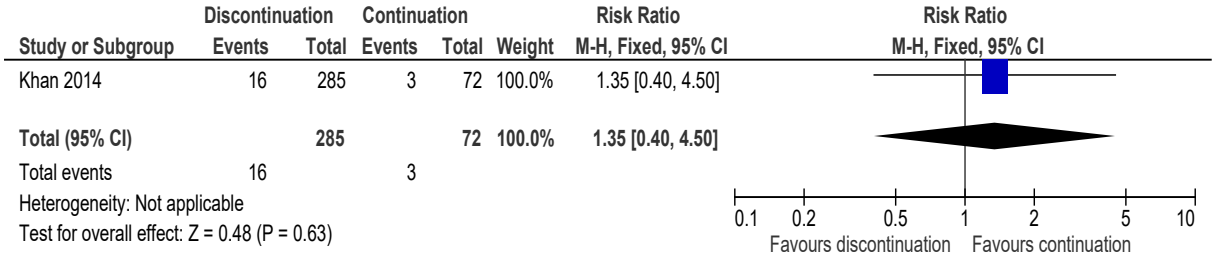


Figure 64: Chills (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

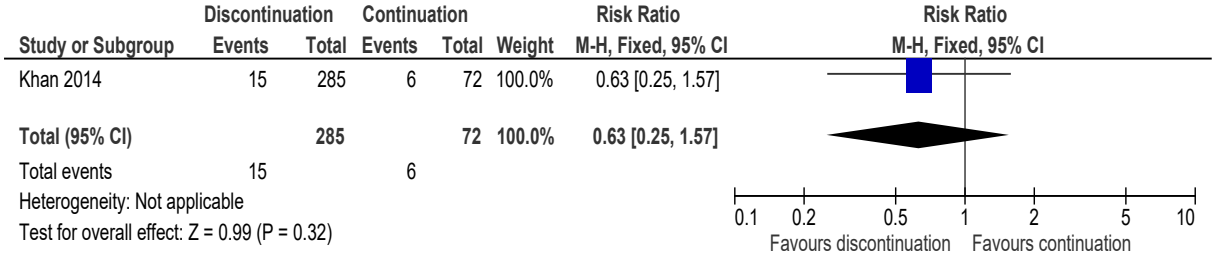


Figure 65: Fever (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

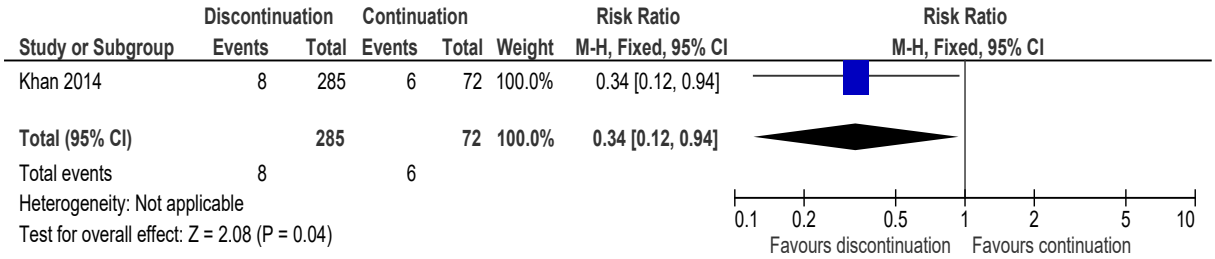


Figure 66: Vomiting (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

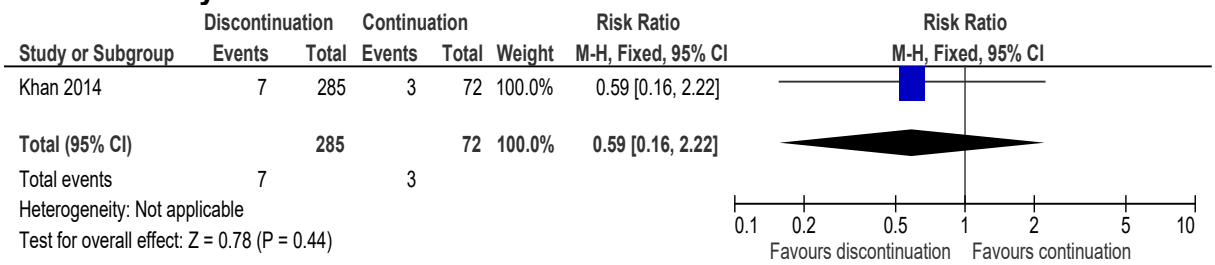


Figure 67: Nausea (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

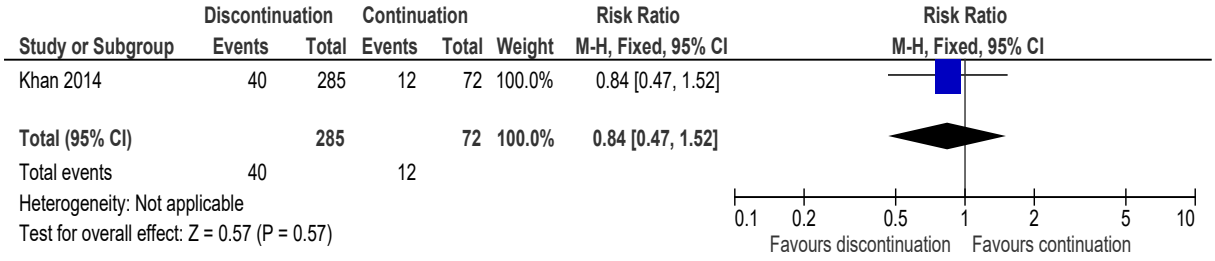


Figure 68: Diarrhoea (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

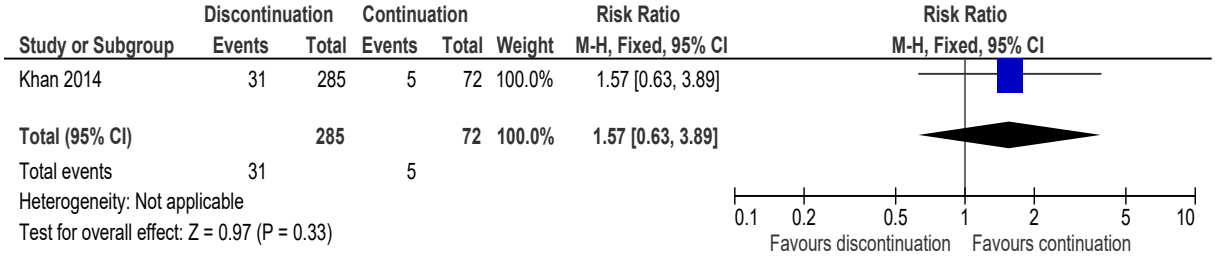


Figure 69: Stomach cramps (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

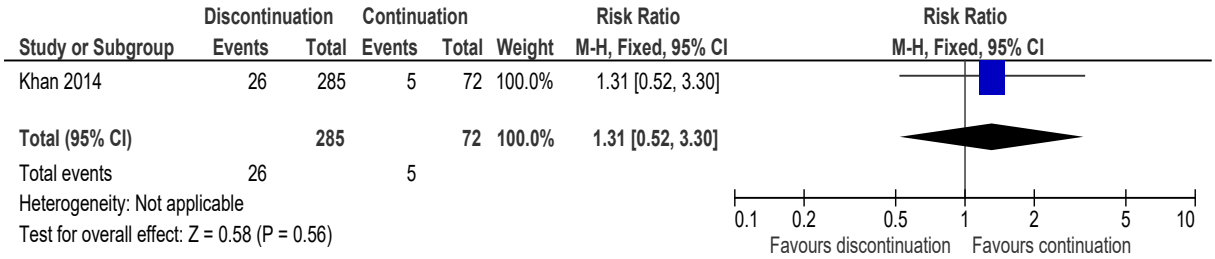


Figure 70: Stomach bloating (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

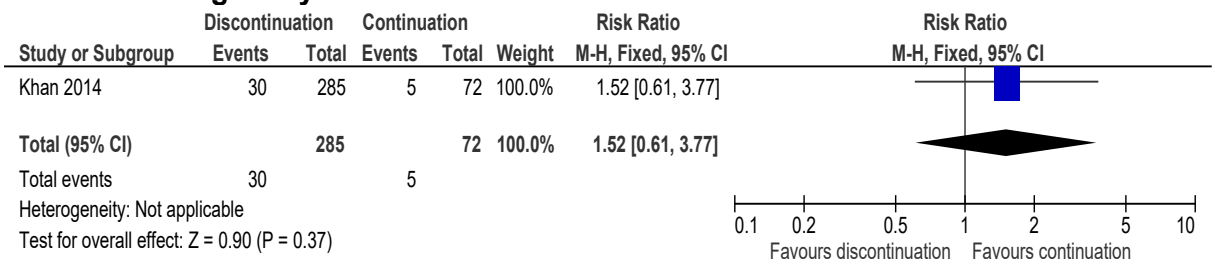


Figure 71: Unusual visual sensations (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

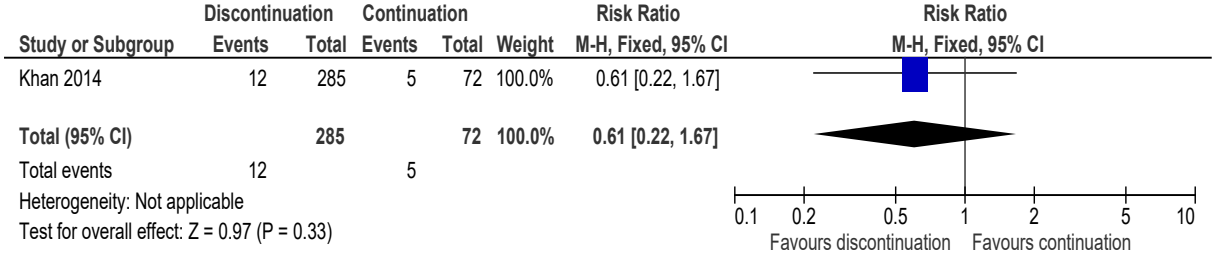


Figure 72: Burning, numbness (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

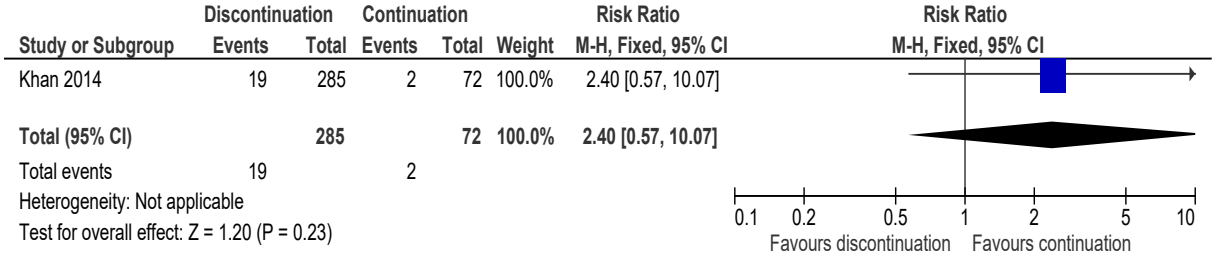


Figure 73: Unusual sensitivity to sound (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

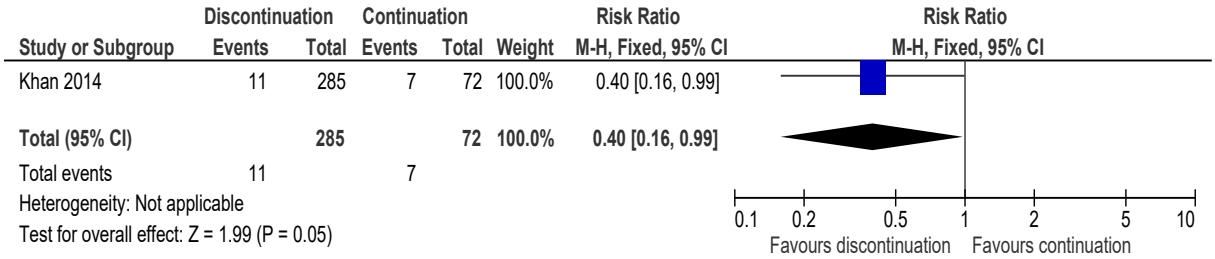


Figure 74: Ringing or noises in the ears (protocol outcome: specific withdrawal symptoms) during study weeks 1-4

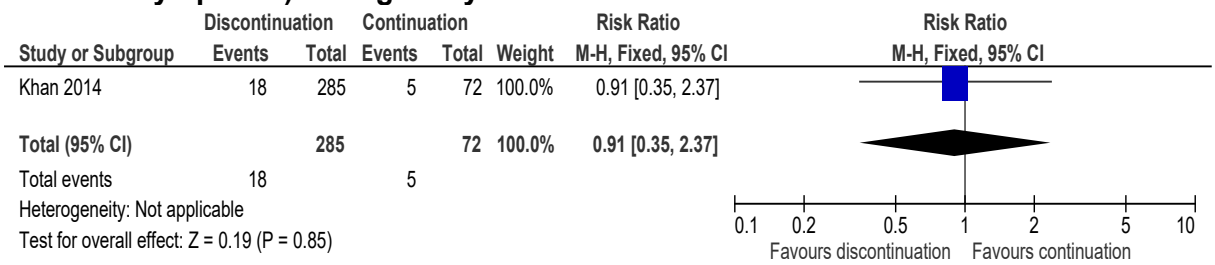
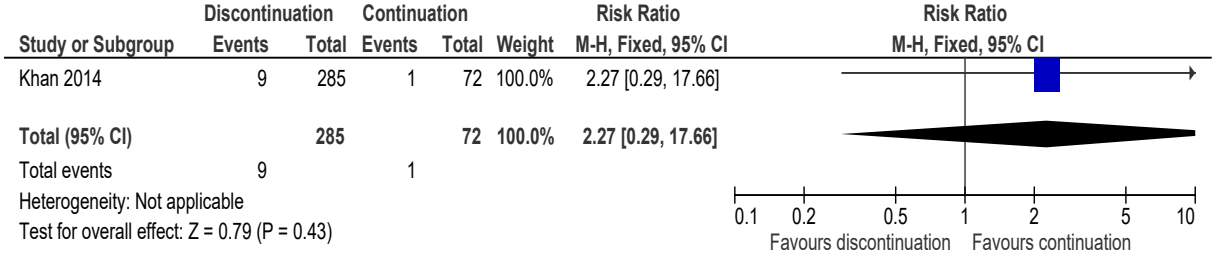


Figure 75: Unusual tastes or smells (protocol outcome: specific withdrawal symptoms) during study weeks 1-4



D.5.1.2 SSRIs

Figure 76: Rebound: return to a MADRS score equal to or higher than the original score at the entry of the acute treatment study (protocol outcome: specific withdrawal symptom 2 weeks post-abrupt discontinuation)

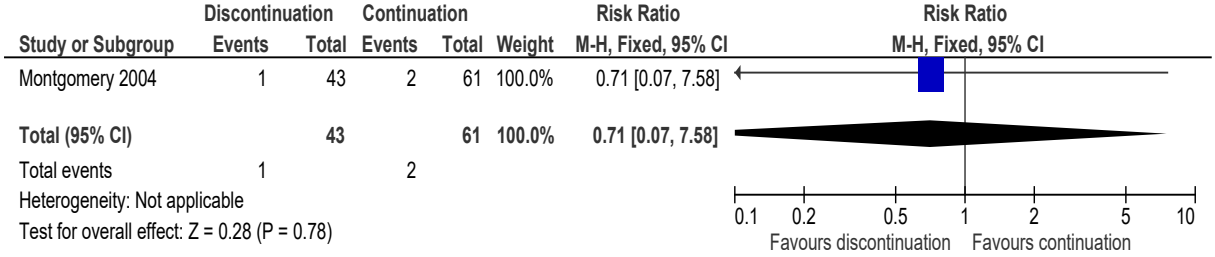


Figure 77: Total no. of emergent DESS symptoms (protocol outcome: intensity of withdrawal symptoms at 2 weeks post-abrupt discontinuation)

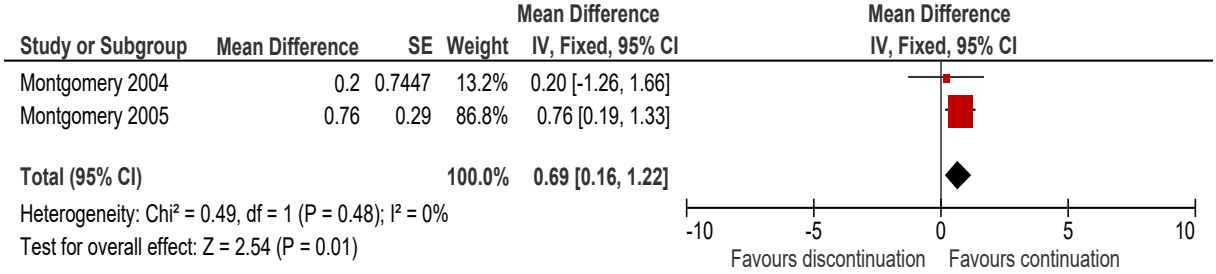
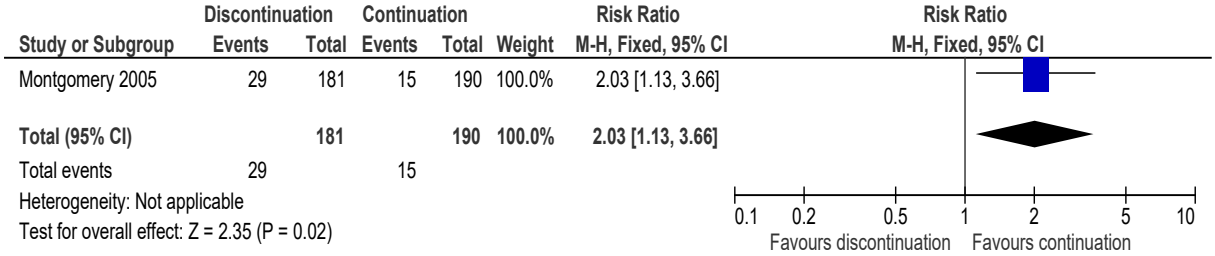


Figure 78: Discontinuation Emergent Signs and Symptoms (DESS) score of ≥4 (protocol outcome: intensity of withdrawal symptoms at 2 weeks post-abrupt discontinuation)



D.5.2 Withdrawal from antidepressants vs withdrawal from placebo

D.5.2.1 Other antidepressants

Figure 79: Withdrawal symptoms during discontinuation (protocol outcome: any withdrawal symptom during the discontinuation period))

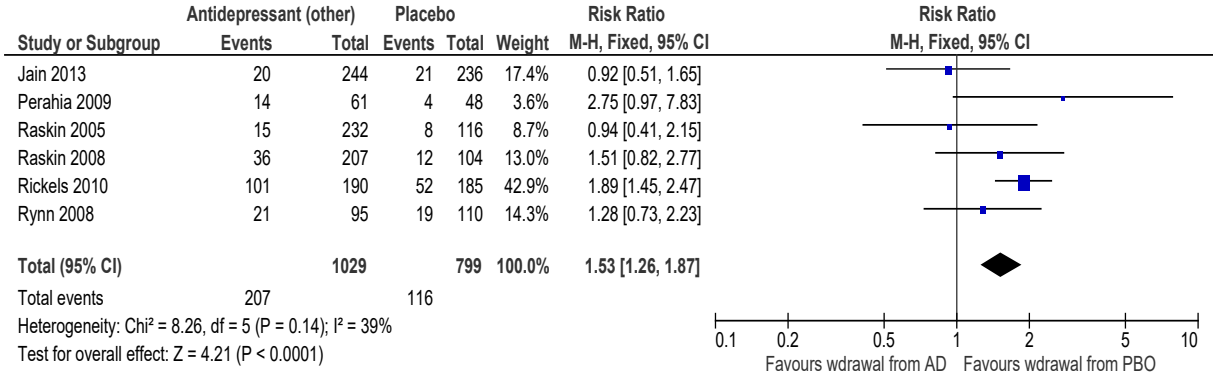


Figure 80: Withdrawal symptoms (protocol outcome: any withdrawal symptom at 3 days after discontinuation of treatment)

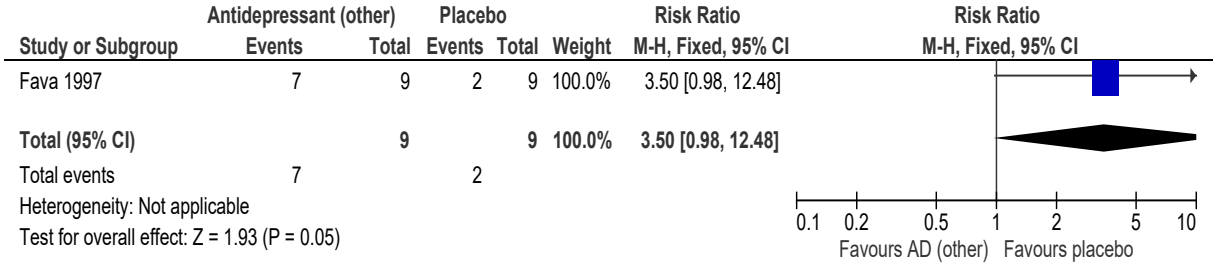


Figure 81: Headache as a DEAE (protocol outcome: specific withdrawal symptom during the discontinuation period)

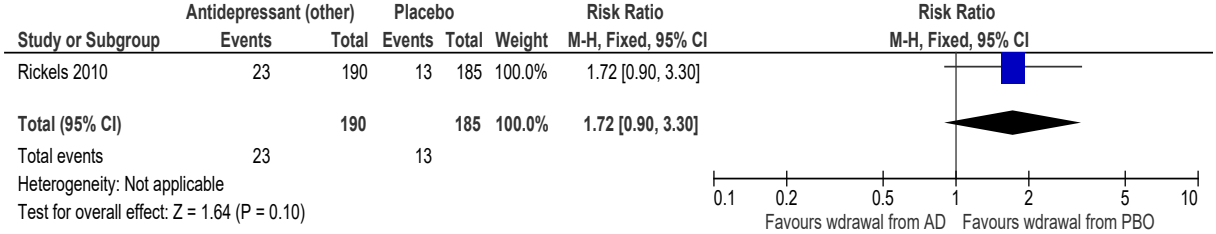


Figure 82: Insomnia as a DEAE (protocol outcome: specific withdrawal symptom during the discontinuation period)

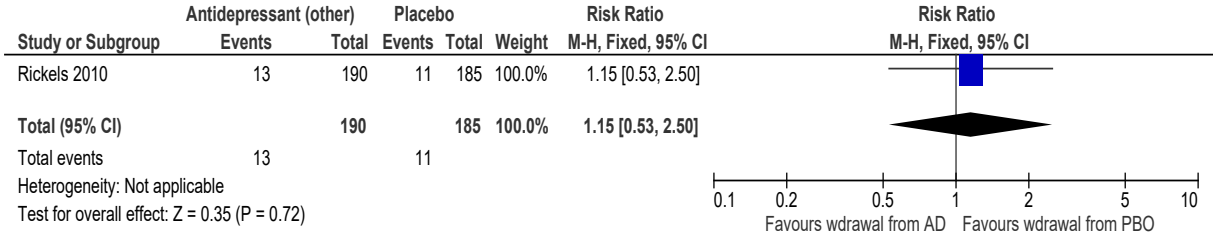


Figure 83: Nausea as a DEAE (protocol outcome: specific withdrawal symptom during the discontinuation period)

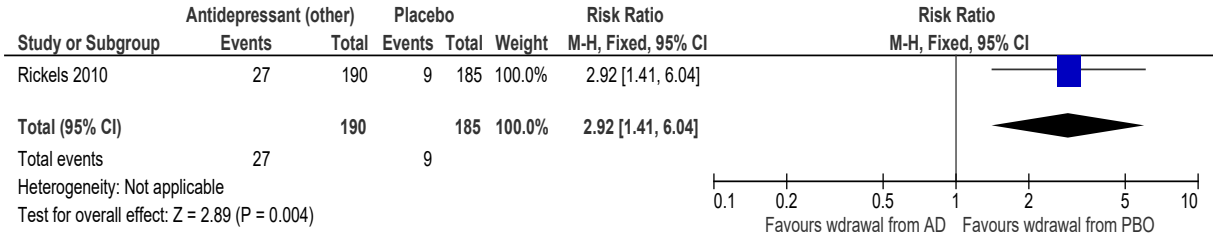


Figure 84: Dizziness as a DEAE (protocol outcome: specific withdrawal symptom during the discontinuation period)

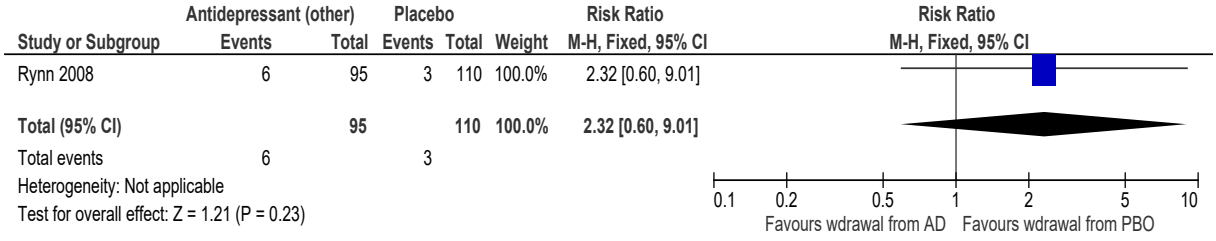


Figure 85: Mild adverse events (protocol outcome: intensity of withdrawal symptoms at mean 5 days after discontinuation of treatment)

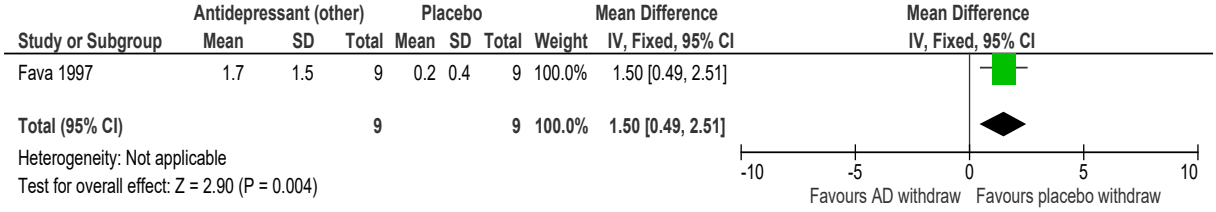
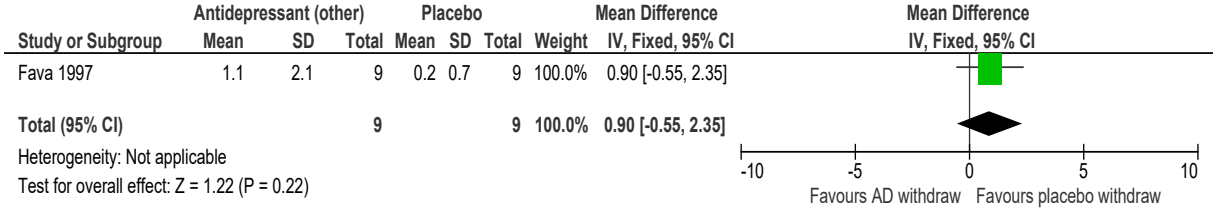


Figure 86: Moderate adverse events (protocol outcome: intensity of withdrawal symptoms at mean 5 days after discontinuation of treatment)



Appendix E Effectiveness evidence

E.1 Quantitative evidence

Study	**Afilalo 2010[10]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1030 randomised).
Countries and setting	87 sites in the US and 15 sites in Canada, 6 sites in New Zealand and 4 sites in Australia.
Duration of study	Titration 3 weeks, maintenance 12 weeks and follow-up 2 weeks after last intake of medication. Conducted from 7 February 2007 to 4 June 2008.
Inclusion criteria	Men and women ≥ 40years of age with a diagnosis of osteoarthritis for the knee, functional capacity class I –III, and apian at the reference joint requiring the use of analgesics (non-opioids or opioids at doses equivalent to ≤ 160 mg oral morphine/day) for ≥ 3 months prior to screening. A patient rated 11-point numerical rating scale (0=no pain, 10=pain as bad as you can imagine) was used to assess pain intensity twice daily. Patients were dissatisfied with their current analgesic therapy and had average pain intensity numerical rating scale score of ≥ 5 during the 3 days preceding randomization.
Exclusion criteria	Presence of clinically significant or unstable medical or psychiatric disease, requirement for painful procedures during the study that could influence efficacy or safety assessments, and history of substance abuse, epilepsy/seizure disorder, stroke; transient ischemic attach, malignancy, HIV, chronic hepatitis B or C, uncontrolled hypertension, severe renal impairment, moderate or severe hepatic impairment, ALT or AST concentrations over 3 times the upper limit of normal, and hypersensitivity to study medications or their excipients. Patients with conditions potentially influencing g the assessment of osteoarthritis pain were excluded. The use of concomitant analgesics was prohibited. Neuroleptics, tricyclic antidepressants, anticonvulsants, antiparkinsonian drugs and serotonin norepinephrine reuptake inhibitors were prohibited within 14 days prior to screening ad during the study because their use could confound efficacy or safety assessment. Medications other than those listed above such as SSRI were allowed for patients with diagnosed controlled psychiatric or neurological conditions if taken at a stable dose

Study	Afilalo 2010[10]
	for 3 or more months prior to randomization. Monoamine oxidase inhibitors were prohibited within 14 days prior to screening and during the std. Corticosteroids were prohibited during the trial and within 4 weeks to 6 months prior to screening, depending on route of administration.
Recruitment/selection of patients	Recruited patients with moderate to severe chronic pain due to osteoarthritis related to the knee.
Age, gender and ethnicity	Age, y, Mean (SD): Group 1: 58.4 (10.09), Group 2: 58.2 (10.29), Group 3: 58.2 (9.15) Male %: Group 1: 37.2%, Group 2: 40.9%, Group 3: 40.7% Race White: Group 1: 75.6%, Group 2: 71.6%, Group 3: 79.2% Black: Group 1: 14.2%, Group 2: 13.2%, Group 3: 11.3% Hispanic: Group 1: 6.1%, Group 2: 10.8%, Group 3: 5.9% Other: Group 1: 4.1%, Group 2: 4.4%, Group 3: 3.6% Authors reported that demographic and baseline characteristics were balanced across groups.
Extra comments	Efficacy, quality of life and treatment emergent adverse events were reported.
Indirectness of population	No indirectness.
Interventions & comparators	Period 1: Screening (≤ 14 days) Period 2: Washout (3-7 days, during which patients were to discontinue all analgesic medication) Period 3: Titration (3 weeks) Period 4: Maintenance (12 weeks) Period 5: Follow-up (14 days after last intake of study medication).

Study	Afilalo 2010[10]
	(n=346) Group 1: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from tapentadol, twice daily controlled, adjustable, oral doses of tapentadol ER 100-250 mg. Started with twice daily dose of tapentadol ER 50 mg. After the first 3 days, doses were increased to 100 mg twice daily; these were the minimum doses for the remainder of the study. At 3-day intervals, paints could increase their doses in consultation with a study investigator in twice –daily increments of tapentadol ER 50 mg (maximum twice daily doses of tapentadol ER 250 mg); downward titration was possible in twice daily decrements of tapentadol R 50 mg without a time restriction. All doses taken in the morning and evening. Paracetamol could be taken up to 3 days before the conclusion of the titration period. During the maintenance period patients were encouraged to remain on a steady dose of study medication but could request additional dose adjustment to maintain their optimal balance. After 12 weeks, the study medication was abruptly withdrawn. (n=345) Group 2: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from oxycodone HCI CR 20-50 mg Started with twice daily dose of oxycodone HCI CR 10mg. After the first 3 days, doses were increased to 20 mg twice daily; these were the minimum doses for the remainder of the study. At 3-day intervals, paints could increase their doses in consultation with a study investigator in twice –daily increments of oxycodone HCI CR 10 mg (maximum twice daily doses of oxycodone HCI CR 50 mg); downward titration was possible in twice daily decrements of oxycodone HCI CR 10mg without a time restriction. All doses taken in the morning and evening. Paracetamol could be taken up to 3 days before the conclusion of the titration period. During the maintenance period patients were encouraged to remain on a steady dose of study medication but could request additional dose adjustment to maintain their optimal balance. After 12 weeks, the study medication was abruptly withdrawn. (n=339) Group 3: Withdrawal from placebo After 12 weeks, the study medication was abruptly withdrawn.

Study	**Afilalo 2010[10]**
Funding	Johnson & Johnson Pharmaceutical Research and Development, L.L.C. Afilalo received funding for study support from Johnson and Johnson Pharmaceutical Research and Development, L.L.C. Most other authors are employees of Grunenthal GmbH.

RESULTS (NUMBER ANALYSED) AND RISK OF BIAS FOR COMPARISON: tapentadol versus oxycodone versus placebo

Protocol outcome 1: Intensity of withdrawal symptoms at post-intervention and longest follow-up Actual outcome: COWS scores for all treatment group for all time periods (in patients who did not use opioids following discontinuation of study medication)

COWS assessments completed ≥ 2 days to <5 days after last intake of medication:

No opioid withdrawal: Group 1: 29/35, Group 2: 32/37, Group 3: 23/23.

Mild opioid withdrawal: Group 1: 6/35, Group 2: 5/37, Group 3: 0/23.

COWS assessments completed ≥ 5 days after last intake of study medication:

No opioid withdrawal: Group 1: 69/70, Group 2: 72/84, Group 3: 54/59

Mild opioid withdrawal: Group 1: 1/70, Group 2: 10/84, Group 3: 5/59

Moderate opioid withdrawal: Group 1: 0/70, Group 2: 2/84, Group 0/59

Risk of bias:

All domain – High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement – Low, Crossover - Low; Indirectness of outcome: No indirectness; At end of study - Group 1 Number missing: 163; Group 2 Number missing: 224, Group 3 Number missing: 134, Reason*: patient choice (141), lost to follow-up (8), adverse event (223), lack of efficacy (57), study drug noncompliance (17), other (74), no drug received (7).

NB. No. missing includes dropouts during treatment phase of study.

The subjective opiate withdrawal scale was also used to assess subjectively reported symptoms consistent with opioid withdrawal throughout the 4 days after treatment discontinuation. Reported at 24, 48 and 72 hours after last dose of study medication. This was not extracted as only reported as no statistically significant differences between tapentadol and placebo groups.

Study	**Connor 1998[133]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=56 began open-label treatment; 36 analysed)
Countries and setting	Conducted in Unknown; Setting: NR
Line of therapy	Unclear
Duration of study	Intervention + follow up: 11 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fulfilled DSM-III-R criteria for a principal diagnosis of social phobia
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	Fulfilled DSM-III-R criteria for a principal diagnosis of social phobia, granted informed consent, between the ages of 18 and 55.
Exclusion criteria	History of schizophrenia, bipolar disorder, organic brain syndrome, antisocial personality disorder, mental retardation, major depression in the past 12 months, panic disorder, alcohol or substance abuse, the concomitant need for other psychotropic drugs or any ongoing psychotherapy.
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Mean (SD): continuation group: 40.6 (8.2), discontinuation group: 39.5 (7.0). Gender (M:F): continuation group: 11/6, discontinuation group: 12/7, discontinuation group: 12/7. Ethnicity: continuation group: white: 16 African American: 1; discontinuation group: white: 17 African American: 2

Study	**Connor 1998[133]**
Further population details	1. Half-life of benzodiazepine the population are taking: Long half-life benzodiazepine
Extra comments	No differences existed between the groups with respect to pre-randomisation clonazepam dose (1.64±0.57mg for continuation group and 1.94±0.59mg for discontinuation group).
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from clonazepam. Following 6 months of open-label clonazepam, individually determined doses were administered as required and gradually raised until the CGI scale was established at 1.0, 1.5, 2.0 or 2.5mg/day. At week 24 participants were randomised to discontinue medication. A fixed dose taper of 0.25mg every 2 weeks was established. 6 weeks of tapered dose was required for the group receiving 1.0mg/day to reach 0.0mg, 10 weeks for the 1.5mg group, 14 weeks for the 2.0mg group and 18 weeks for the 2.5mg group. discontinuation participants received the same number of pills per visit with diminishing doses supplemented with matching placebo. Dose tapering began at week 26 and participants continued to receive double-blind placebo after completion of their clonazepam taper until week 44, at which time they underwent a rapid 3-week taper (details not described, but no matching placebo substitution occurred at this point in the study). Duration 11 months. Concurrent medication/care: NR. Indirectness: Serious indirectness. (n=17) Intervention 2: No withdrawal/continuation on medicine - No withdrawal. Continuation of treatment. Following 6 months of open-label clonazepam, individually determined doses were administered as required and gradually raised until the CGI scale was established at 1.0, 1.5, 2.0 or 2.5mg/day. At week 24 participants were randomised to continue medication for a further 5 months. Between weeks 44 and 47 the groups taking 2.0 and 2.5mg had their dosages reduced each week to 1.5, 1.0, 0.5 and 0.0mg. The 1.5mg group dose was reduced each week to 1.0, 0.5, 0.25 and 0.0mg. The 1.0mg group dose was reduced each week to 0.75, 0.5, 0.25 and 0.0mg. . Duration 11 months. Concurrent medication/care: NR. Indirectness: Serious indirectness.
Funding	Other author(s) funded by industry (work was supported by a grant from Hoffmann-La Roche to Dr Jonathan Davidson)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM CLONAZEPAM versus CONTINUATION OF CLONAZEPAM Protocol outcome 1: Intensity of withdrawal symptoms at post-intervention and longest follow-up	

Study	**Connor 1998[133]**
- Actual outcome for Benzodiazepines: Total BWC score at the end of taper; Group 1: mean 8.2 (SD 7.5); n=19, Group 2: mean 6.4 (SD 10.2); n=17; Benzodiazepine Withdrawal Checklist 0-132 Top=High is poor outcome; Comments: BWC consists of a checklist of 33 withdrawal symptoms rated 0-4 where 0= not at all, 1= mild, 2= moderate, 3= severe and 4= very severe. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Unclear, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Unclear how many dropped out from either group during the discontinuation phase.	
Protocol outcomes not reported by the study	Any withdrawal symptom at post-intervention and longest follow-up; Specific withdrawal symptom at post-intervention and longest follow-up; Duration of withdrawal syndrome at n/a; Quality of life at n/a

Study	**Curran 2003[149]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=138 (including non-randomised group which is not included))
Countries and setting	Conducted in United Kingdom; Setting: General practices in inner city and suburban London and in rural areas from the teaching and research network of the Royal Free and UCL Medical School.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 52 weeks
Method of assessment of guideline condition	Method of assessment/diagnosis not stated: Included people taking BZDs on a repeated, daily basis.
Stratum	Benzodiazepines

Study	Curran 2003[149]
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥65 years, taking BZDs on a repeated, daily basis for at least 6 months; wishing to discontinue their sleeping tablets.
Exclusion criteria	Patients with dementia, or other organic states associated with cognitive dysfunction; severe deafness or severe visual impairment; current major psychiatric disorders; histories of seizures; those receiving terminal care. GPs could also exclude any patient for whom they felt discontinuation of BZD hypnotics was clinically inappropriate.
Recruitment/selection of patients	Identified through an audit of practice computer records.
Age, gender and ethnicity	Age - Other: Mean 77 (6.9), range 65-93. Gender (M:F): 71%F, 29%M. Ethnicity: NR
Further population details	1. Half-life of benzodiazepine the population are taking: Short half-life benzodiazepine (Temazepam (majority), nitrazepam (one third), loprazolam (remainder)).
Indirectness of population	No indirectness
Interventions	(n=55) Intervention 1: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from benzodiazepines. Following baseline assessment, patients had their dose of BZD gradually tapered over the first 8 or 9 weeks and then remained on placebo through to week 24. All drugs were formulated in identical opaque capsules and packed with lactose placebo to appear the same throughout the trial. A dose titration regime was devised to minimise the risk of withdrawal symptoms, and this was done according to each patient's original dose and particular BZD. For example, 10 mg of temazepam was reduced by 2.5 mg every 2 weeks according to the following schedule: week 1 (10 mg); weeks 2 and 3 (7.5 mg); weeks 4 and 5 (5 mg); weeks 6 and 7 (2.5 mg); week 8 onwards (0 mg i.e., placebo only). Tablet bottles were numbered consecutively from 1 to 24 and were given in monthly supplies to the patient or left at the GP surgery for the patient to collect. Tablet bottles were returned after use and pill counts made as an adherence check. As an additional check to confirm BZD withdrawal, urine samples were collected from patients at 52 weeks (as well as at baseline) for analysis of BZDs. Duration 24 weeks. Concurrent medication/care: Researchers trained in giving psychological support saw each patient at initial recruitment and at the four assessment times. Researchers were blind to group allocation. A pamphlet on sleep

Study	Curran 2003[149]
	and sleep hygiene was given to each patient and telephone support was also available to patients when needed. These measures aimed to both maximize the success rates of BZD withdrawal and to minimize any demands on GPs' time. Indirectness: No indirectness. (n=49) Intervention 2: No withdrawal/continuation on medicine - No withdrawal from benzodiazepines. Following baseline assessment, patients continued taking their normal BZD for the next 3 months and then received the same intervention as the abrupt taper group. All drugs were formulated in identical opaque capsules and packed with lactose placebo to appear the same throughout the trial. A dose titration regime was devised to minimise the risk of withdrawal symptoms, and this was done according to each patient's original dose and particular BZD. For patients in this group, the schedule was parallel with dose reduction beginning at week 13. The schedule for 5 mg nitrazepam was: week 1 (5 mg), weeks 2 to 5 (2.5 mg), weeks 6 to 12 (0 mg). The schedule was adjusted for larger doses. For example, the schedule for 20 mg temazepam was: week 1 (20 mg); week 2 and 3 (15 mg); week 4 and 5 (10 mg); week 6 and 7 (5 mg); week 8 and 9 (2.5 mg); week 10 onwards (0 mg). Tablet bottles were numbered consecutively from 1 to 24 and were given in monthly supplies to the patient or left at the GP surgery for the patient to collect. Tablet bottles were returned after use and pill counts made as an adherence check. As an additional check to confirm BZD withdrawal, urine samples were collected from patients at 52 weeks (as well as at baseline) for analysis of BZDs. Duration 24 weeks. Concurrent medication/care: Researchers trained in giving psychological support saw each patient at initial recruitment and at the four assessment times. Researchers were blind to group allocation. A pamphlet on sleep and sleep hygiene was given to each patient and telephone support was also available to patients when needed. These measures aimed to both maximize the success rates of BZD withdrawal and to minimize any demands on GPs' time. Indirectness: No indirectness.
Funding	Academic or government funding (NHS Executive, London (NHSE-LRO), Research and Development, Responsive Funding Programme).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DISCONTINUATION OF BZD versus CONTINUATION OF BZD

Protocol outcome 1: Intensity of withdrawal symptoms at post-intervention and longest follow-up

- Actual outcome for Benzodiazepines: BWSQ at 12 weeks; Group 1: mean 34.8 (SD 20.4); n=48, Group 2: mean 32.7 (SD 16.5); n=43; Benzodiazepine Withdrawal Symptom Questionnaire 0-40 Top=High is poor outcome; Comments: Baseline BWSQ:
Group A: 34.4 (18.7)
Group B: 34.5 (13.7)

Study	**Curran 2003**[149]
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 ; Group 1 Number missing: 7, Reason: Major illness (1), spouse died (1), problems taking medication (2), no reason given (3); Group 2 Number missing: 6, Reason: Major illness (1), died (1), unhappy with assessments (2), no reason given (2)	
Protocol outcomes not reported by the study	Any withdrawal symptom at post-intervention and longest follow-up; Specific withdrawal symptom at post-intervention and longest follow-up; Duration of withdrawal syndrome at n/a; Quality of life at n/a

Study	**Fava 1997**[197]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=20)
Countries and setting	Conducted in USA; Setting: Outpatients at the Depression Clinical and Research Program of the Massachusetts General Hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Antidepressants (others)
Subgroup analysis within study	Not applicable

Study	**Fava 1997[197]**
Inclusion criteria	The study participants had met the DSM-IV criteria for major depressive disorder as determined by the Structured Clinical Interview for DSM-III-R—Patient Version and had been required to have a score of 20 or higher on the 21-item Hamilton Depression Rating Scale at screening and to have had no greater than a 20% decrease in Hamilton depression score at the baseline visit.
Exclusion criteria	The exclusion criteria included pregnancy or breast feeding; serious suicidal risk; serious or unstable medical illness; history of seizure disorder; psychotic disorders not elsewhere classified; bipolar disorder; history of drug or alcohol dependence within the previous year; previous treatment with venlafaxine; myocardial infarction within 6 months; major abnormalities in laboratory test results; use of investigational drugs, antipsychotic drugs, or ECT within 30 days; use of fluoxetine within 21 days; use of monoamine oxidase inhibitors within 14 days; and use of other psychotropic drugs within 7 days of the start of the double-blind treatment.
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Mean (SD): 36.5 (10.7). Gender (M:F): 11M/9F. Ethnicity: NR
Further population details	1. Half-life of benzodiazepine the population are taking: Not stated/Unclear
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from extended-release venlafaxine. During the first 2 weeks of double-blind treatment, the patients received 75 mg/day of extended-release venlafaxine. After 2 weeks of treatment, if clinically indicated to improve response, the dose of extended-release venlafaxine was increased to 150 mg/day. After 4 weeks of treatment, a further increase in dose to 225 mg/day was allowed, if clinically indicated. All of the study completers taking two or three capsules per day were required to taper their study medication by reducing the dose by one capsule per week, while those taking one capsule of study medication per day (75 mg of extended-release venlafaxine) were allowed to stop taking the medication without further tapering. Duration 10 weeks. Concurrent medication/care: NR. Indirectness: No indirectness

Study	Fava 1997[197]
	(n=10) Intervention 2: Withdrawal from placebo. During the first 2 weeks of double-blind treatment, the patients received 75 mg/day of placebo. After 2 weeks of treatment, if clinically indicated to improve response, the dose of extended-release venlafaxine was increased to 150 mg/day. After 4 weeks of treatment, a further increase in dose to 225 mg/day was allowed, if clinically indicated. All of the study completers taking two or three capsules per day were required to taper their study medication by reducing the dose by one capsule per week, while those taking one capsule of study medication per day (75 mg of placebo) were allowed to stop taking the medication without further tapering. Duration 10 weeks. Concurrent medication/care: NR. Indirectness: No indirectness
Funding	Study funded by industry (Supported in part by a grant from Wyeth-Ayerst Laboratories.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM VENLAFAXINE versus WITHDRAWAL FROM PLACEBO

Protocol outcome 1: Any withdrawal symptom at post-intervention and longest follow-up

- Actual outcome for Antidepressants (others): Emergence of adverse events at During the 3 days after discontinuation ; Group 1: 7/9, Group 2: 2/9

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 ; Group 1 Number missing: 1, Reason: not stated; Group 2 Number missing: 1, Reason: not stated

- Actual outcome for Antidepressants (others): Number of adverse events at During the post taper period (mean 5 days after discontinuation of treatment.); Group 1: mean 2.8 (SD 2.3); n=9, Group 2: mean 0.2 (SD 1); n=9

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 ; Group 1 Number missing: 1, Reason: not stated; Group 2 Number missing: 1, Reason: not stated.

Protocol outcome 2: Intensity of withdrawal symptoms at post-intervention and longest follow-up.

- Actual outcome for Antidepressants (others): Moderate adverse events at During the post taper period (mean 5 days after discontinuation of treatment.); Group 1: mean 1.1 (SD 2.1); n=9, Group 2: mean 0.2 (SD 0.7); n=9.

Study	**Fava 1997[197]**
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 ; Group 1 Number missing: 1, Reason: not stated; Group 2 Number missing: 1, Reason: not stated. - Actual outcome for Antidepressants (others): Mild adverse events at During the post taper period (mean 5 days after discontinuation of treatment.); Group 1: mean 1.7 (SD 1.5); n=9, Group 2: mean 0.2 (SD 0.4); n=9 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 ; Group 1 Number missing: 1, Reason: not stated; Group 2 Number missing: 1, Reason: not stated.	
Protocol outcomes not reported by the study	Specific withdrawal symptom at post-intervention and longest follow-up; Duration of withdrawal syndrome at n/a; Quality of life at n/a

Study	**Feltner 2003[200]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	n= 271
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/ Benzodiazepines

Study	Feltner 2003[200]
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 (on the basis of 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), Lorazepam group: 39.2 (11.7). Placebo group: 37.8 (10.8). Gender (M:F): Pregabalin 50mg group: 34M/36F; Pregabalin 200mg group: 33M/33F, Lorazepam group: 28M/ 40F, Placebo group: 33M/34F. 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% Lorazepam group: White 73.5%, Black 17.6%, Hispanic 5.9%, Other 2.9% Placebo group: White 71.6%, Black 16.4%, Hispanic 10.4%, Other 1.5%
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, with the exception of zolpidem (5mg, <2 nights per week and not the night before a clinic visit).
Indirectness of population	No indirectness
Interventions	(n=70) Intervention 1: Withdrawal from 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.

Study	Feltner 2003[200]
	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, with the exception of zolpidem (5mg, <2 nights per week and not the night before a clinic visit). Indirectness: No indirectness. (n=66) Intervention 2: Withdrawal from 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, with the exception of zolpidem (5mg, <2 nights per week and not the night before a clinic visit). Indirectness: No indirectness. (n=68) Intervention 3: Withdrawal from lorazepam 2mg tid (6mg/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, with the exception of zolpidem (5mg, <2 nights per week and not the night before a clinic visit). Indirectness: No indirectness. (n=67) Intervention 4: Withdrawal from placebo 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, with the exception of zolpidem (5mg, <2 nights per week and not the night before a clinic visit). Indirectness: No indirectness

Study	**Feltner 2003[200]**
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 50mg vs Pregabalin 200mg vs Lorazepam 2mg vs placebo Protocol outcome 1: Intensity of withdrawal symptoms at 5 weeks - Actual outcome for Gabapentinoids/ Benzodiazepines: Physician's Withdrawal Checklist at Week 5; Group 1: difference from placebo: 2.776, 95% CI 0.42, 5.14 ; n=53, Group 2: difference from placebo: 3.322, 95% CI 0.78, 5.86 ; n=42, Group 3: difference from placebo: 3.153, 95% CI 0.63, 5.67 ; n=41. PWC 0-60 Top=High is poor outcome; Comments: The difference in adjusted means was based on ANCOVA model with treatment and centre in the model and PWC baseline score as a covariate. 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: Numbers reported are those completing double-blind phase. Unclear how many dropped out during 1-week taper phase. 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; Group 3 Number missing: 32, Reason: adverse event: 24, lack of efficacy: 1, lack of compliance: 3 other/administrative reason: 4; Group 4:Number missing: 19, Reason: adverse event: 4, lack of efficacy: 3, lack of compliance: 4, other/administrative reason: NB – this is from start of treatment.	
Protocol outcomes not reported by the study	Specific withdrawal symptoms, Any withdrawal symptom, duration of withdrawal syndrome

Study	**Hajak 1998[254]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=1507 (including the flunitrazepam and triazolam arms which are not included))
Countries and setting	Conducted in Unknown multicentre; Setting: Outpatients in private practice who were treated by 158 general practitioners, internists, psychiatrists, and neurologists.

Study	**Hajak 1998[254]**
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Z-drugs
Subgroup analysis within study	Not applicable
Inclusion criteria	Insomnia of at least 4-week duration and the presence of at least two of the following as a mean of 3 days before starting treatment (no- pill baseline): (a) sleep latency ≥ 45 min, (b) total sleep time ≤ 6 h, and (c) nocturnal awakening ≥ 3 times.
Exclusion criteria	Any patients who had taken a single daily dose of a benzodiazepine or any other hypnotic more than three times per week during the 14 days prior to admission, or any patients with psychiatric disorders (e.g., depression, schizophrenia, severe neuroses), or any patients who had contraindications for zopiclone, flunitrazepam, or triazolam were excluded.
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Mean (SD): 51 (11). Gender (M:F): Zopiclone group: 223M/388F; Placebo group 112M/185F. Ethnicity: 99.3% Caucasian, 0.9% other
Further population details	1. Half-life of benzodiazepine the population are taking: Not applicable
Extra comments	216 (14.3%) of the included patients suffered from difficulties falling and staying asleep but did not meet the criteria of severity given in the study design. The only concurrent therapies permitted consisted mainly of cardiovascular agents, drugs for metabolic disorders, and analgesics. Previous treatment with benzodiazepines had been undertaken in 30.9% of the subjects, whereas 12.5% had been treated with other centrally active drugs.

Study	**Hajak 1998[254]**
Indirectness of population	No indirectness
Interventions	(n=612) Intervention 1: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from zopiclone. Following a 3-day washout phase, patients took their capsules containing the original preparations of zopiclone (7.5 mg) every evening before going to bed for a period of 28 days. On day 29 the active drug was abruptly withdrawn, and the patients were observed for a further period of 14 days without medication. Duration 6 weeks plus 3 days. Concurrent medication/care: The only concurrent therapies permitted consisted mainly of cardiovascular agents, drugs for metabolic disorders, and analgesics. Indirectness: No indirectness. (n=298) Intervention 2: Withdrawal from placebo. Following a 3-day washout phase, patients took their capsules containing the original preparations of placebo (1 capsule) every evening before going to bed for a period of 28 days. On day 29 the placebo was abruptly withdrawn, and the patients were observed for a further period of 14 days without medication. Duration 6 weeks plus 3 days. Concurrent medication/care: The only concurrent therapies permitted consisted mainly of cardiovascular agents, drugs for metabolic disorders, and analgesics. Indirectness: No indirectness.
Funding	Study funded by industry (The study was supported by a grant from Rhone Poulenc Rorer GmbH, Cologne, Germany.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM ZOLPIDEM versus WITHDRAWAL FROM PLACEBO Protocol outcome 1: Specific withdrawal symptom at post-intervention and longest follow-up - Actual outcome for Z-drugs: Overall rebound rate at during 2-week discontinuation period; Group 1: 282/612, Group 2: 145/298; Comments: Overall rebound-was a deterioration below individual mean pre-treatment values of the scores given on the visual analogue scales during the discontinuation period. A patient was counted as having rebound according to the following: deterioration in at least one of the three sleep quality parameters (a) sleep latency, (b) total sleep time, or (c) number of nocturnal awakenings; or deterioration in at least one parameter of daytime well-being defined as (d) a feeling of being refreshed on awakening in the morning, or as an impairment in daytime well-being as a result of (e) tiredness or (f)anxiety. Numbers calculated by NGC from % given. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Unclear, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Study states that the patients' characteristics were comparable in all treatment groups regarding gender, age, height, weight, probable origin and duration of insomnia, and drug pre-treatment.; Blinding details: Outcome assessor was the patient.; Group 1 Number missing: ; Group 2 Number missing: Unclear how many dropped out from withdrawal phase.	

Study	Hajak 1998[254]
Protocol outcomes not reported by the study	Any withdrawal symptom at post-intervention and longest follow-up; Duration of withdrawal syndrome at n/a; Quality of life at n/a; Intensity of withdrawal symptoms at post-intervention and longest follow-up

Study	Hayward 1996[266]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=97 (n=40 without non-BZD users' group which are not analysed))
Countries and setting	Conducted in Unknown; Setting: NR
Line of therapy	Unclear
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: agoraphobia meeting DSM-III-R and ICD 9 criteria.
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of agoraphobia meeting both DSM III-R and ICD 9 criteria who were participating in a treatment trial comparing diazepam and exposure treatment.
Exclusion criteria	NR

Study	Hayward 1996[266]
Recruitment/selection of patients	Referred by psychiatrists and recruited through advertisements and contacts with self-help groups.
Age, gender and ethnicity	Age - Mean (SD): 43.6 (13.4). Gender (M:F): 80%F. Ethnicity: NR
Further population details	1. Half-life of benzodiazepine the population are taking: Long half-life benzodiazepine (Diazepam).
Extra comments	Participants were characterised as diazepam users if they had used BZDs regularly over the past year, and non-users if they had not used a BZD in the past year. Randomisation was carried out independently for users and non-users. Only the users' group has been included.
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal benzodiazepines. At the initial assessment (assessment 1) participants completed a battery of questionnaires including the 8-item withdrawal symptom form. Placebo. All participants were started on the so-called 'study medication'; numbered sets of 15 blister packs containing 21 placebo tablets in 3 lines of 7, so that each participant could take from one to three tablets daily. Participants were then reassessed following a 3-week drug transition period. Duration 4 weeks. Concurrent medication/care: NR. Indirectness: No indirectness Comments: randomised numbers not reported. Number reported is number from first assessment obtained from Wardle 1994 (original paper). This is the placebo arm from the BZD users' group. (n=21) Intervention 2: No withdrawal/continuation on medicine - No withdrawal. 5mg diazepam (Roche Pharmaceuticals) At the initial assessment (assessment 1) patients completed a battery of questionnaires All participants were started on the so-called 'study medication'; numbered sets of 15 blister packs containing 21 tablets in 3 lines of 7, so that each participant could take from one to three tablets daily. Each participant on active drug might be taking between 5 and 15mg per day. Duration 4 weeks. Concurrent medication/care: NR. Indirectness: No indirectness Comments: randomised numbers not reported. Number reported is number from first assessment obtained from Wardle 1994 (original paper).

Study	**Hayward 1996[266]**
Funding	Study funded by industry (Received support from Hoffmann LaRoche)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM DIAZEPAM versus NO WITHDRAWAL FROM DIAZEPAM Protocol outcome 1: Intensity of withdrawal symptoms at post-intervention and longest follow-up - Actual outcome for Benzodiazepines: Total score on Withdrawal Symptom Questionnaire (sum of 8 bipolar VAS score parts) at 4 weeks; Group 1: mean 207.6 (SD 196.2); n=15, Group 2: mean 158.6 (SD 170.4); n=15; Comments: Baseline values: discontinuation group: 163.5 (106.5), continuation group: 185.6 (166.7) Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Comments - Drop out numbers were calculated using the number of participants completing assessment 1 as baseline as the number randomised was not reported. The total drop out number will therefore be higher than that reported, but the exact numbers are unclear.; Indirectness of outcome: No indirectness ; Baseline details: Baseline values: discontinuation group: 163.5 (106.5), continuation group: 185.6 (166.7); Group 1 Number missing: 4, Reason: Objected to new medication, other reasons; Group 2 Number missing: 6, Reason: Objected to new medication, other reasons.	
Protocol outcomes not reported by the study	Any withdrawal symptom at post-intervention and longest follow-up; Specific withdrawal symptom at post-intervention and longest follow-up; Duration of withdrawal syndrome at n/a; Quality of life at n/a

Study	**Jain 2013[296]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=600)
Countries and setting	Conducted in USA; Setting: 47 sites in USA
Line of therapy	Unclear
Duration of study	Intervention + follow up: 8 weeks (6-week intervention plus 2-week follow-up)

Study	**Jain 2013[296]**
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of MDD of at least 3 months' duration, based on DSM 4th edition.
Stratum	Antidepressants (others)
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults aged 18-75 years with a diagnosis of major depressive disorder of at least 3 months' duration, based on the DSM 4th Edition, Text Revised were eligible to the study. All participants were required to have a baseline MADRS total score ≥30 with no co-morbid psychiatric disorder, as assessed by the MINI.
Exclusion criteria	Participants were excluded if they had failed two previous antidepressant treatments (of at least 6 weeks in duration) or if they were considered by the investigator to pose a significant risk of suicide, had a score ≥on item 10 (suicidal thoughts) of the MADRS or had made a suicide attempt in the previous 6 months. Participants were also excluded if they had a history of a neurological or substance abuse disorder, current clinically significant medical illness or clinically significant abnormalities in vital signs or laboratory values.
Recruitment/selection of patients	Recruited by psychiatrists or primary care physicians working in private practice, at research centres or at academic sites.
Age, gender and ethnicity	Age - Mean (SD): Vortioxetine group: 42.5 (13), Placebo group: 42.4 (12.7). Gender (M:F): Vortioxetine group: 38%male, 62% female. Placebo group: 45.3% male, 54.7% female. Ethnicity: Vortioxetine group: White: 69.7%, Black: 27%, Asian: 2.7% American Indian/ Alaskan: 0.3%, Pacific Islander: 0.3% Vortioxetine group: White: 72%, Black: 26%, Asian: 1.3% American Indian/ Alaskan: 0.7%, Pacific Islander: 0.0%
Further population details	1. Half-life of benzodiazepine the population are taking: Not applicable
Indirectness of population	No indirectness

Study	**Jain 2013[296]**
Interventions	(n=300) Intervention 1: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from vortioxetine. 5mg vortioxetine once daily on an outpatient basis. Duration 6 weeks. Concurrent medication/care: Concomitant use of any neuroactive medication was prohibited 2-5 weeks (depending on drug half-life) prior to the start of the study and throughout the treatment period. Indirectness: No indirectness (n=300) Intervention 2: Withdrawal from placebo. Placebo (identical in appearance to study drug) once daily. Duration 6 weeks. Concurrent medication/care: Concomitant use of any neuroactive medication was prohibited 2-5 weeks (depending on drug half-life) prior to the start of the study and throughout the treatment period. Indirectness: No indirectness
Funding	Study funded by industry (Sponsored by the Takeda Pharmaceutical Company Ltd as part of a joint clinical development programme with H. Lundbeck A/S.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM VORTIOXETINE versus WITHDRAWAL FROM PLACEBO Protocol outcome 1: Any withdrawal symptom at post-intervention and longest follow-up - Actual outcome for Antidepressants (others): Adverse events at During the 2 week discontinuation period; Group 1: 20/244, Group 2: 21/236 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 56, Reason: adverse events (9), lack of efficacy (11), non-compliance (3), protocol deviations (5), voluntary withdrawal (8), lost to follow-up (17), other (3); Group 2 Number missing: 64, Reason: adverse events (11), lack of efficacy (6), non-compliance (2), protocol deviations (11), voluntary withdrawal (12), lost to follow-up (22), other (0)	
Protocol outcomes not reported by the study	Specific withdrawal symptom at post-intervention and longest follow-up; Duration of withdrawal syndrome at n/a; Quality of life at n/a; Intensity of withdrawal symptoms at post-intervention and longest follow-up

Study	**Kasper 2014[320]**
Study type	RCT (Patient randomised; Parallel)

Study	**Kasper 2014[320]**
Number of studies (number of participants)	(n=615)
Countries and setting	Conducted in Multiple countries
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/ Benzodiazepines
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 (with the exception of current or past diagnosis of depression not otherwise specified, specific phobia, somatization disorder, nicotine or caffeine abuse/dependence or past 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 weeks 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.

Study	Kasper 2014[320]
Recruitment/selection of patients	Recruited from the clinic population, clinic referrals or from advertisements.
Age, gender and ethnicity	Baseline from treatment period 1: Male, N (%): Group 1 (high dose pregabalin): 87 (42.2), Group 2 (low dose pregabalin): 73 (35.4), Group 3 (lorazepam): 81 (39.9) Age, years – Mean (SD): Group 1: 42.4 (11.5), Group 2: 40.5 (12.3), Group 3: 42.6 (11.2). Duration of illness, years – Mean (SD): Group 1: 2.2 (4.4), Group 2: 2.1 (4.3), Group 3: 2.4 (4.3). Treatment duration, days – Median (SD): Group 1: 139.4 (55.1), Group 2: 133.2 (58.3), Group 3: 136.7 (59.4). Authors reported that the six treatment groups in treatment period 2 did not differ significantly on available baseline characteristics or median treatment duration.
Further population details	1. Gabapentinoids:
Indirectness of population	No indirectness
Interventions	**All Patients Study Schedule:** **Screen**: 1 week **Period 1:** Flexible dose (week 1-6), Fixed dose (weeks 7-12), Double-blind, 12 weeks. Patients who showed a clinical response with a Clinical Global Impressions-Improvement (CGI-I) score of 1 or 2 at week 6 continued treatment; those who had a CGI-I 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. **Period 2:** Fixed dose, double-blind, 12 weeks. Patients who showed a clinical response (CGI-I score of 1 or 2) at week 6 of period 1 continued treatment. 25% of patients from each medication group were randomised to discontinue active medication and received placebo during treatment period 2. 75% continued on the active treatment.

Study	Kasper 2014[320]
	Taper (double-blind): 1 week. Generally consistent with product labelling and was intended to minimize 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 the when treatment was discontinued. **Follow-up**: 1 week. (n=154) Intervention 1: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from high dose pregabalin. 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. At the end of week 12, patients continued on to treatment period 2 on the same fixed dose for 12 weeks. 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: Serious indirectness; Indirectness comment: Some participants leaving the study early also underwent the taper 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 2: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from low dose pregabalin. Treatment was initiated with a 150mg/d starting dose of pregabalin. Upward dose escalation occurred during the first 3 weeks.

Study	Kasper 2014[320]
	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. 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: Serious indirectness; Indirectness comment: Some participants leaving the study early also underwent the taper 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=153) Intervention 3: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from lorazepam. Treatment was initiated with a 2mg/d starting dose of lorazepam. Upward dose escalation occurred during the first 3 weeks. Following dose escalation, patients received lorazepam 3- 4 mg/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. The patients who continued with active medication during treatment period 2 underwent a 1-week double-blind taper at the beginning of week 25.

Study	Kasper 2014[320]
	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: Serious indirectness; Indirectness comment: Some participants leaving the study early also underwent the taper. (n=52) Intervention 4: Withdrawal from placebo (after high dose pregabalin). 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. At the end of week 12, patients were tapered to placebo so that discontinuation symptoms could be evaluated. Following the double-blind taper, these patients received double-blind placebo in treatment period 2 (12 weeks). This was followed by a 1-week double-blind taper beginning at 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: Serious indirectness; Indirectness comment: Participants in the placebo groups had previously been taking active medication; some participants leaving the study early also underwent the taper (n=52) Intervention 5: Withdrawal from placebo (after low dose pregabalin). 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 were tapered to placebo so that discontinuation symptoms could be evaluated. Following the

Study	Kasper 2014[320]
	double-blind taper, these patients received double-blind placebo in treatment period 2 (12 weeks). This was followed by a 1-week double-blind taper beginning at 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: Serious indirectness; Indirectness comment: Participants in the placebo groups had previously been taking active medication; some participants leaving the study early also underwent the taper (n=50) Intervention 6: Withdrawal from placebo (after lorazepam). Treatment was initiated with a 2mg/d starting dose of lorazepam. Upward dose escalation occurred during the first 3 weeks. Following dose escalation, patients received lorazepam 3- 4 mg/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 were tapered to placebo so that discontinuation symptoms could be evaluated. Following the double-blind taper, these patients received double-blind placebo in treatment period 2 (12 weeks). This was followed by a 1-week double-blind taper beginning at 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: Serious indirectness; Indirectness comment: Participants in the placebo groups had previously been taking active medication; some participants leaving the study early also underwent the taper.
Funding	Equipment/drugs provided by industry (Pfizer Inc.)
RESULTS (NUMBER ANALYSED) AND RISK OF BIAS FOR COMPARISON: Pregabalin high dose versus Pregabalin low dose versus Lorazepam	
Protocol outcome 1: any withdrawal symptom- post intervention and longest follow-up.	

Study	Kasper 2014[320]
- Actual outcome: any discontinuation emergent sign and symptom (DESS) defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks (i.e., from the first day of the first taper dose, through the last available visit in either the taper week or the week following taper). Note: paper uses DESS acronym, but this does not seem to refer to the DESS checklist. Comments: 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. DESS during the 2 weeks following taper initiation after treatment period 2 (at weeks 25-26): Patients with any DESS, n (%): Group 1 (active treatment in period 2): 34/109 (31.2), Group 1 (placebo treatment in period 2): 4/30 (13.3), Group 2 (active): 21/94 (22.3), Group 2 (placebo): 9/29 (31.0), Group 3 (active): 28/100 (28.0), Group 3 (placebo): 4/30 (13.3) 55 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 efficacy study - Group 1 Number missing: 77; Group 2 Number missing: 91, Group 3 Number missing: 81, Reason: discontinued (249), adverse events (70), lack of efficacy (50), miscellaneous (129). In taper phase 200 receiving pregabalin entered taper, 9 dropped out, 95 receiving lorazepam entered taper, 2 dropped out, 85 receiving placebo entered taper, 3 dropped out. Protocol outcome 2: specific withdrawal symptom- post intervention and longest follow-up - Actual outcome: specific discontinuation emergent sign and symptom (DESS: paper reports those specific events which occurred in >5% of people) defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks (i.e., from the first day of the first taper dose, through the last available visit in either the taper week or the week following taper). Note: paper uses DESS acronym, but this does not seem to refer to the DESS checklist. Comments: 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. Anxiety, n (%): Group 1 (active treatment in period 2): 7/109 (6.4), Group 1 (placebo treatment in period 2): 1/30 (3.3), Group 2 (active): 4/94 (4.3), Group 2 (placebo): 0/29 (0), Group 3 (active): 8/100 (8.0), Group 3 (placebo): 0/30 (0) Headache, n (%): Group 1 (active treatment in period 2): 5/109 (4.6), Group 1 (placebo treatment in period 2): 0/30 (0), Group 2 (active): 3/94 (3.2), Group 2 (placebo): 2/29 (6.9), Group 3 (active): 2/100 (2.0), Group 3 (placebo): 0/30 (0) Insomnia, n (%): Group 1 (active treatment in period 2): 13/109 (11.9), Group 1 (placebo treatment in period 2): 1/30 (3.3), Group 2 (active): 8/94 (8.5), Group 2 (placebo): 2/29 (6.9), Group 3 (active): 6/100 (6.0), Group 3 (placebo): 2/30 (6.7) Risk of bias: All domain – High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - high, Measurement – Low, Crossover - Low; Indirectness of outcome: No indirectness; At end of study - Group 1 Number missing: 77; Group 2 Number missing: 91, Group 3 Number missing: 81,	

Study	Kasper 2014[320]
Reason: discontinued (249), adverse events (70), lack of efficacy (50), miscellaneous (129). In taper phase 200 receiving pregabalin entered taper, 9 dropped out, 95 receiving lorazepam entered taper, 2 dropped out, 85 receiving placebo entered taper, 3 dropped out.	
Protocol outcomes not reported by the study	Specific withdrawal symptom at post-intervention and longest follow-up; Duration of withdrawal syndrome at n/a; Quality of life at n/a; Intensity of withdrawal symptoms at post-intervention and longest follow-up

Study	Khan 2014[334]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=361 completed treatment phase and assigned to discontinuation)
Countries and setting	Conducted in USA; Setting: Outpatients: 38 clinical research centres
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 weeks (4-week intervention and 2-week follow-up)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People with a primary diagnosis of single or recurrent major depressive disorder (see inclusion criteria for assessment) put onto 24-week treatment with desvenlafaxine.
Stratum	Antidepressants: others: All on Desvenlafaxine
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult outpatients (≥ 18 years of age) with a primary diagnosis of single or recurrent MDD without psychotic features consistent with criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, using the modified Mini International Neuropsychiatric Interview. Patients were required to have depressive symptoms for ≥ 30 days prior to the screening visit and a 17-item Hamilton Depression Rating Scale total score ≥ 14 at baseline.

Study	Khan 2014[334]
	Note: People were not on antidepressants at baseline, but were entered into a 24-week open-label treatment with desvenlafaxine prior to the discontinuation trial. People who completed this 24-week treatment were randomly assigned.
Exclusion criteria	A current primary diagnosis of anxiety disorder, significant risk of suicide based on the Columbia Suicide Severity Rating Scale at screening or baseline, current psychoactive substance abuse or dependence, clinically important medical illness (unstable hepatic, renal, pulmonary or cardiovascular (including uncontrolled hypertension, unstable angina, recent myocardial infarction) ophthalmologic or neurologic disorder; uncontrolled diabetes), clinically important abnormalities on physical or laboratory evaluation, or history of seizure disorder, gastrointestinal disease, neoplastic disorder, or narrow-angle glaucoma.
Recruitment/selection of patients	Adult outpatients meeting the criteria
Age, gender and ethnicity	Age - Mean (SD): Taper: 47.9 (11.2); abrupt discontinuation (placebo): 47.8 (13.7); no discontinuation: 46.7 (11.3). Gender (M:F): 85/103. Ethnicity: Around 80% white; 17%; 1% American Indian/Alaskan Native; 2% other.
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable 3. Setting: Outpatient
Extra comments	Baseline doses: all on desvenlafaxine 50mg/day at randomisation
Indirectness of population	No indirectness
Interventions	(n=148) Intervention 1: Withdrawal from one of the prescribed medicines (other antidepressants): abrupt discontinuation: switch straight to placebo for 4 weeks (this was following the 24-week open-label treatment phase with 50mg/d desvenlafaxine). Duration 4 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness. (n=140) Intervention 2: Withdrawal from one of the prescribed medicines (other antidepressants): tapered discontinuation: 1 week taper: received 25mg/d desvenlafaxine for 1 week, then placebo for 3 weeks (this was following the 24-week open-label treatment phase with 50mg/d desvenlafaxine). Duration 4 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service.

Study	Khan 2014[334]
	(n=72) Intervention 3: No withdrawal/ continuation of antidepressant for 4 weeks (this was following the 24-week open-label treatment phase with 50mg/d desvenlafaxine). Duration 4 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service
Funding	Study funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DISCONTINUATION (abrupt or tapered) versus CONTINUATION	
Protocol outcome 1: Specific withdrawal symptoms	
- Actual outcome for Antidepressants: others: DESS items measured at weeks 1-4 (during discontinuation); Nervousness/anxiety: Group 1: 50/146, Group 2: 43/139 , Group 3: 19/72	
Elevated mood/feeling high: Group 1: 5/146, Group 2: 4/139, Group 3: 2/72	
Irritability: Group 1: 72/146, Group 2: 62/139, Group 3: 17/72	
Sudden worsening of mood: Group 1: 39/146, Group 2: 30/139 , Group 3: 12/72	
Sudden outbursts of anger: Group 1: 28/146, Group 2: 21/139 , Group 3: 10/72	
Sudden panic or anxiety attacks: Group 1: 11/146, Group 2: 10/139 , Group 3: 6/72	
Bouts of crying or tearfulness: Group 1: 45/146, Group 2: 44/139 , Group 3: 12/72	
Agitation: Group 1: 39/146, Group 2: 38/139 , Group 3: 17/72	
Feeling unreal or detached: Group 1: 18/146, Group 2: 11/139, Group 3: 8/72	
Confusion or trouble concentrating: Group 1: 47/146, Group 2: 34/139, Group 3: 15/72	
Forgetfulness or problems with memory: Group 1: 33/146, Group 2: 28/139, Group 3: 7/72	
Mood swings: Group 1: 30/146, Group 2: 18/139, Group 3: 9/72	
Trouble sleeping, insomnia: Group 1: 59/146, Group 2: 49/139, Group 3: 29/72	

Study	Khan 2014[334]
Increased dreaming or nightmares: Group 1: 35/146, Group 2: 37/139, Group 3: 15/72	
Sweating more than usual: Group 1: 15/146, Group 2: 18/139, Group 3: 10/72	
Shaking, trembling: Group 1: 12/146, Group 2: 6/139, Group 3: 6/72	
Muscle tension or stiffness: Group 1: 31/146, Group 2: 20/139, Group 3: 6/72	
Muscle aches or pains: Group 1: 35/146, Group 2: 25/139, Group 3: 7/72	
Restless feeling in legs: Group 1: 18/146, Group 2: 11/139, Group 3: 6/72	
Muscle cramps, spasms, twitching: Group 1: 16/146, Group 2: 21/139, Group 3: 8/72	
Fatigue, tiredness: Group 1: 56/146, Group 2: 53/139, Group 3: 24/72	
Unsteady gait or incoordination: Group 1: 10/146, Group 2: 19/139, Group 3: 2/72	
Blurred vision: Group 1: 8/146, Group 2: 11/139, Group 3: 6/72	
Sore eyes: Group 1: 12/146, Group 2: 7/139, Group 3: 3/72	
Uncontrolled mouth/ tongue movements: Group 1: 2/146, Group 2: 0/139, Group 3: 2/72	
Problems with speech or speaking clearly: Group 1: 6/146, Group 2: 7/139, Group 3: 3/72	
Headache: Group 1: 0/146, Group 2: 0/139, Group 3: 0/72	
Sudden panic or anxiety attacks: Group 1: 11/146, Group 2: 10/139, Group 3: 6/72	
Increased saliva in mouth: Group 1: 1/146, Group 2: 6/139, Group 3: 0/72	
Dizziness light-headedness or sensation of spinning: Group 1: 41/146, Group 2: 36/139, Group 3: 6/72	
Nose running: Group 1: 23/146, Group 2: 20/139, Group 3: 10/72	
Shortness of breath, gasping for air: Group 1: 11/146, Group 2: 5/139, Group 3: 3/72	
Chills: Group 1: 8/146, Group 2: 7/139, Group 3: 6/72	

Study	Khan 2014[334]
Fever: Group 1: 5/146, Group 2: 3/139, Group 3: 6/72 Vomiting: Group 1: 6/146, Group 2: 1/139, Group 3: 3/72 Nausea: Group 1: 22/146, Group 2: 18/139, Group 3: 12/72 Diarrhoea: Group 1: 21/146, Group 2: 10/139, Group 3: 5/72 Stomach cramps: Group 1: 13/146, Group 2: 13/139, Group 3: 5/72 Stomach bloating: Group 1: 17/146, Group 2: 13/139, Group 3: 5/72 Unusual visual sensations: Group 1: 8/146, Group 2: 4/139, Group 3: 5/72 Burning, numbness: Group 1: 9/146, Group 2: 10/139, Group 3: 2/72 Unusual sensitivity to sound: Group 1: 6/146, Group 2: 5/139, Group 3: 7/72 Ringing or noises in the ears: Group 1: 11/146, Group 2: 7/139, Group 3: 5/72 Unusual tastes or smells: Group 1: 6/146, Group 2: 3/139, Group 3: 1/72 Comments: Mild/ moderate/ severe intensity combined. Risk of bias: All domain – Very High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: number without at least 1 post-randomisation record (reason not reported); Group 2 Number missing: 1, Reason: number without at least 1 post-randomisation record (reason not reported). Group 3 Number missing: 1, Reason: number without at least 1 post-randomisation record (reason not reported). Note: DESS reported at 2-week timepoint. This would have been 2 weeks of drug-free wash-out for the abrupt discontinuation arm, but only 1 week of drug-free wash-out for the taper arm. This was taken into account within the risk of bias assessment for the DESS outcomes. Protocol outcome 3: Intensity of withdrawal symptoms. - Actual outcome for Antidepressants: others**:** Discontinuation Emergent Signs and Symptoms (DESS) scale total score during the first 2 weeks of discontinuation. Adjusted mean (SE): abrupt 5.3 (0.52), taper 4.8 (0.54), no discontinuation 4.1 (0.72).	

Study	**Khan 2014[334]**
Adjusted means compared with no discontinuation: (abrupt) MD; 1.16 (95%CI -0.51 to 2.83); (taper) MD; 0.66 (95%CI -1.03 to 2.35). DESS total score (unclear if there is a range of values, suggests this is the number of DESS) Top=High is poor outcome, Comments: MD from ANCOVA. Control group adjusted final value (mean, SE) abrupt: 5.3 (0.52); taper: 4.8 (0.54); continuation: 4.1 (0.72). Note: investigator training on DESS was performed before the study to emphasise the definition of 'new' and 'old' symptoms. Discontinuation symptoms were defined as events that were reported by the patient on the DESS and judged to be related to discontinuation by the investigator completing the DSSI. Range of values for DESS not reported - checked original paper (Rosenbaum 1998) - it is a 43-item list based on signs and symptoms and the patient chooses from 1 of 4 responses (new symptom, old symptom but worse, old symptom but improved, old symptom but unchanged or symptom not present) - total score seems to be the mean number of DESS. Risk of bias: All domain – Very High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: number without at least 1 post-randomisation record (reason not reported); Group 2 Number missing: 1, Reason: number without at least 1 post-randomisation record (reason not reported). Group 3 Number missing: 1, Reason: number without at least 1 post-randomisation record (reason not reported). Study also reports DSSI (an exploratory scale relating DESS items severity and relationship to discontinuation)- continuous outcome measured after double blind period had ended, and Proportion of people with discontinuation syndrome (increase in DESS score of more than or equal to 4 between baseline and mean score for the first 2 weeks of discontinuation). Not extracted due to being a reanalysis of data already reported.	
Protocol outcomes not reported by the study	Any withdrawal symptom at post-intervention and longest follow-up; Duration of withdrawal syndrome

Study	**Langford 2006[372]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=416)
Countries and setting	Conducted in Canada, Czech Republic, Hungary, Poland, Slovakia; Setting: Not reported

Study	**Langford 2006[372]**
Line of therapy	1st line
Duration of study	Intervention + follow up: 6-week treatment phase + gradual withdrawal (final assessment 3 days after last patch removed)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Opioids: Transdermal fentanyl (TDF)
Subgroup analysis within study	Not applicable:
Inclusion criteria	At least 40 years old; meeting the American College of Rheumatology diagnostic criteria for hip or knee OA and requiring joint replacement surgery, with radiographic evidence of disease in the affected joint(s); awaiting surgery, refused surgery, or unable to undergo surgery for medical reasons; experienced joint pain for more than 3 months, and for at least 20 days each month
Exclusion criteria	Received any strong opioid in the 4 weeks before the study or had recently started a new therapy (e.g., physiotherapy or acupuncture); deemed unsuitable for treatment with a strong opioid (e.g., because of suspected alcohol or drug abuse, or because they were considered at risk for respiratory depression)
Recruitment/selection of patients	May 2002 to April 2004
Age, gender and ethnicity	Age - Mean (range): TDF: 66 (40-86); placebo: 66 (40-90). Gender (M:F): 134/265. Ethnicity: Not reported
Further population details	1. Half-life of benzodiazepine the population are taking: Not applicable
Extra comments	All participants had moderate or severe pain that was not adequately controlled with weak opioids, with or without paracetamol. To be eligible for the study, patients had to have mean daily VAS pain scores of ≥50 at the start and end of the 7-day pre-treatment run-in phase prior to initiation of treatment and a mean VAS pain score of ≥50 for the entire 7 days of the pre-treatment phase.

Study	Langford 2006[372]
Indirectness of population	No indirectness
Interventions	(n=202) Intervention 1: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from transdermal fentanyl (6-week treatment phase followed by gradual withdrawal at the rate of 1 patch every 3 days): 1-week run-in phase in which participants received their normal treatment, including weak opioids, paracetamol, and NSAIDs. Treatment phase (6 weeks): TDF (Durogesic; Janssen-Cilag, Beerse, Belgium), starting with a dosage of 25ug/hour. The patches were replaced every 72 hours. The treatment dosage could be increased, if required because of inadequate pain relief, at the rate of 1 extra patch every 3 days, up to a maximum of 4 patches (equivalent to 100ug fentanyl/hour) after consultation with the clinician. Duration 6-week treatment followed by gradual withdrawal at the rate of 1 patch every 3 days. Concurrent medication/care: Participants continued to receive stable doses of anti-inflammatory agents (steroids or NSAIDs, including COX-2 inhibitors) that were prescribed before the study, but all weak opioids were stopped. Participants could also take up to 4 grams of paracetamol per day (but not combination preparations of paracetamol and weak opioids). Participants were encouraged to take metoclopramide (supplied as 10-mg tablets) immediately if they experienced any nausea or vomiting. They were also encouraged to take a laxative if they had constipation. Indirectness: No indirectness. (n=197) Intervention 2: Withdrawal from placebo. Placebo patches (6-week treatment phase followed by gradual withdrawal at the rate of 1 patch every 3 days): 1-week run-in phase in which participants received their normal treatment, including weak opioids, paracetamol, and NSAIDs. Treatment phase (6 weeks): identical placebo patches. The patches were replaced every 72 hours. The treatment dosage could be increased, if required because of inadequate pain relief, at the rate of 1 extra patch every 3 days, up to a maximum of 4 patches after consultation with the clinician. Duration 6-week treatment followed by gradual withdrawal at the rate of 1 patch every 3 days. Concurrent medication/care: Participants continued to receive stable doses of anti-inflammatory agents (steroids or NSAIDs, including COX-2 inhibitors) that were prescribed before the study, but all weak opioids were stopped. Participants could also take up to 4 grams of paracetamol per day (but not combination preparations of paracetamol and weak opioids). Participants were encouraged to take metoclopramide (supplied as 10-mg tablets) immediately if they experienced any nausea or vomiting. They were also encouraged to take a laxative if they had constipation. Indirectness: No indirectness.

Study	**Langford 2006[372]**
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM TRANSDERMAL FENTANYL versus WITHDRAWAL FROM PLACEBO PATCHES

Protocol outcome 1: Specific withdrawal symptom at post-intervention and longest follow-up

- Actual outcome for Opioids: Reporting aches and pains symptom (as moderate or severe) on the short opiate withdrawal scale at 3-days after last patch removed (once test substance washed out sufficiently); Group 1: 125/202, Group 2: 122/197; Comments: Reported as % of people having the symptom (scoring as moderate or severe). Dichotomous numbers calculated from percentages. Total numbers of participants included in the analysis unclear, but assumed to be ITT numbers for this calculation. Statistics section of methods states ITT with LOCF, and although there were high dropouts during the treatment phase, it is possible the short opiate withdrawal scale was still assessed for taper for dropouts.

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: N/A; Group 1 Number missing: 96, Reason: 96 withdrew early from treatment phase: adverse event 54, insufficient efficacy 15, withdrew consent 17, other 10; Group 2 Number missing: 104, Reason: 104 withdrew early from treatment phase: adverse event 20, insufficient efficacy 64, withdrew consent 13, other 7

- Actual outcome for Opioids: Reporting mild or moderate problems with sleeping on the short opiate withdrawal scale at 3-days after last patch removed (once test substance washed out sufficiently); Group 1: 73/202, Group 2: 73/197; Comments: Reported as % of people having the symptom. Dichotomous numbers calculated from percentages. Total numbers of participants included in the analysis unclear, but assumed to be ITT numbers for this calculation. Statistics section of methods states ITT with LOCF, and although there were high dropouts during the treatment phase, it is possible the short opiate withdrawal scale was still assessed for taper for dropouts.

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: N/A; Group 1 Number missing: 96, Reason: 96 withdrew early from treatment phase: adverse event 54, insufficient efficacy 15, withdrew consent 17, other 10; Group 2 Number missing: 104, Reason: 104 withdrew early from treatment phase: adverse event 20, insufficient efficacy 64, withdrew consent 13, other 7.

- Actual outcome for Opioids: Reporting severe insomnia on the short opiate withdrawal scale at 3-days after last patch removed (once test substance washed out sufficiently); Group 1: 44/202, Group 2: 16/197; Comments: Reported as % of people having the symptom. Dichotomous numbers calculated from percentages. Total numbers of participants included in the analysis unclear, but assumed to be ITT numbers for this calculation. Statistics section of methods

Study	Langford 2006[372]
states ITT with LOCF, and although there were high dropouts during the treatment phase, it is possible the short opiate withdrawal scale was still assessed for taper for dropouts. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: N/A; Group 1 Number missing: 96, Reason: 96 withdrew early from treatment phase: adverse event 54, insufficient efficacy 15, withdrew consent 17, other 10; Group 2 Number missing: 104, Reason: 104 withdrew early from treatment phase: adverse event 20, insufficient efficacy 64, withdrew consent 13, other 7. Protocol outcome 2: Intensity of withdrawal symptoms at post-intervention and longest follow-up - Actual outcome for Opioids: Short opiate withdrawal scale at 3-days after last patch removed (once test substance washed out sufficiently); Group 1: mean 0.66 (SD 0.57); n=202, Group 2: mean 0.39 (SD 0.28); n=197; short opiate withdrawal scale 0-3 Top=High is poor outcome; Comments: short opiate withdrawal scale consisted of 10 items rated on a 4-point Likert scale (0-3, none to severe). SD calculated from SEM (0.04 and 0.02 for TDF and placebo, respectively) and number of participants in each group. Number of participants included in the analysis assumed to be ITT numbers. Statistics section of methods states ITT with LOCF, and although there were high dropouts during the treatment phase, it is possible the short opiate withdrawal scale was still assessed for taper for dropouts. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: N/A; Group 1 Number missing: 96, Reason: 96 withdrew early from treatment phase: adverse event 54, insufficient efficacy 15, withdrew consent 17, other 10; Group 2 Number missing: 104, Reason: 104 withdrew early from treatment phase: adverse event 20, insufficient efficacy 64, withdrew consent 13, other 7	
Protocol outcomes not reported by the study	Any withdrawal symptom at post-intervention and longest follow-up; Duration of withdrawal syndrome at n/a; Quality of life at n/a

Study	Montgomery 2004[442]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=192)

Study	Montgomery 2004[442]
Countries and setting	Conducted in Australia, Canada, France, United Kingdom; Setting: Outpatients
Line of therapy	Unclear
Duration of study	Intervention + follow up: 14 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Antidepressants (mixed)
Subgroup analysis within study	Not applicable
Inclusion criteria	Depressed outpatients, aged 18 years and above, who fulfilled the diagnostic criteria for Major Depressive Disorder of DSM-IV (American Psychiatric Association, 1994), single or recurrent episode, were recruited to the study. The diagnosis of Major Depressive Episode and any comorbid psychiatric disorders was documented using the Mini International Neuropsychiatric Interview No other Axis I or II disorders could be included. A minimum score of 18 and a maximum score of 27 on the MADRS was required at the entry of the study to ensure a homogeneous population. Patients who reached defined criteria for sustained remission in the 12-week treatment period were eligible for the discontinuation study.
Exclusion criteria	Patients having any concomitant severe and/or unstable medical illnesses likely to interfere with the conduct of the study were also excluded.
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Mean (SD): Agomelatine group: 42.6 (14.1), Paroxetine group: 42.5 (12.7). Gender (M:F): Agomelatine group: 30%M/70%F, Paroxetine group: 35%M/65%F. Ethnicity: NR

Study	Montgomery 2004[442]
Further population details	1. Half-life of benzodiazepine the population are taking: Not applicable
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from agomelatine. Following a 3–5-day drug-free, run-in period, patients were randomly assigned to 12 weeks of treatment with agomelatine 25 mg/day under double-blind conditions. Patients who achieved sustained remission, defined as a MADRS score r12 at weeks 8, 10 and 12, were re-randomized under double-blind conditions, with separate randomization for the two active treatments, to receive placebo for 2 weeks. Duration 2 weeks. Concurrent medication/care: No concomitant psychotropic medications, specifically including benzodiazepines for hypnotic or anxiolytic use, were permitted for the 8 weeks before and during the 2 weeks of discontinuation. Indirectness: No indirectness. (n=61) Intervention 2: No withdrawal/continuation on medicine - No withdrawal from agomelatine. Following a 3–5-day drug-free, run-in period, patients were randomly assigned to 12 weeks of treatment with agomelatine 25 mg/day under double-blind conditions. Patients who achieved sustained remission, defined as a MADRS score r12 at weeks 8, 10 and 12, were re-randomized under double-blind conditions, with separate randomization for the two active treatments, to continue their active treatment for 2 weeks. Duration 2 weeks. Concurrent medication/care: No concomitant psychotropic medications, specifically including benzodiazepines for hypnotic or anxiolytic use, were permitted for the 8 weeks before and during the 2 weeks of discontinuation. Indirectness: No indirectness. (n=43) Intervention 3: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from paroxetine. Following a 3–5-day drug-free, run-in period, patients were randomly assigned to 12 weeks of treatment with paroxetine 20 mg/day under double-blind conditions. Patients who achieved sustained remission, defined as a MADRS score r12 at weeks 8, 10 and 12, were re-randomized under double-blind conditions, with separate randomization for the two active treatments, to receive placebo for 2 weeks. Duration 2 weeks. Concurrent medication/care: No concomitant psychotropic medications, specifically including benzodiazepines for hypnotic or anxiolytic use, were permitted for the 8 weeks before and during the 2 weeks of discontinuation. Indirectness: No indirectness. (n=61) Intervention 4: No withdrawal/continuation on medicine - No withdrawal from paroxetine. Following a 3–5-day drug-free, run-in period, patients were randomly assigned to 12 weeks of treatment with paroxetine 20 mg/day under double-blind conditions. Patients who achieved sustained remission, defined as a MADRS score r12 at weeks 8, 10 and 12, were re-

Study	Montgomery 2004[442]
	randomized under double-blind conditions, with separate randomization for the two active treatments, to continue their active treatment for 2 weeks. Duration 2 weeks. Concurrent medication/care: No concomitant psychotropic medications, specifically including benzodiazepines for hypnotic or anxiolytic use, were permitted for the 8 weeks before and during the 2 weeks of discontinuation. Indirectness: No indirectness.
Funding	Study funded by industry (Institut Recherches Internationales Servier)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM AGOMELATINE versus NO WITHDRAWAL FROM AGOMELATINE

Protocol outcome 1: Specific withdrawal symptom at post-intervention and longest follow-up

- Actual outcome for Antidepressants (others): Rebound (return to a MADRS score equal to or higher than the original score at the entry of the acute treatment study.) at During week 1 of the discontinuation period ; Group 1: 0/27, Group 2: 1/61

Risk of bias: All domain - Low, Selection - Low, 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: States that there were no significant demographic differences between treatment groups and mean MADRS, HAM-A and CGI severity score at entry of the discontinuation period were also comparable.; Group 1 Number missing: 0; Group 2 Number missing: 1

- Actual outcome for Antidepressants (others): Rebound (return to a MADRS score equal to or higher than the original score at the entry of the acute treatment study.) at During week 2 of the discontinuation period ; Group 1: 0/27, Group 2: 1/61

Risk of bias: All domain - Low, Selection - Low, 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: States that there were no significant demographic differences between treatment groups and mean MADRS, HAM-A and CGI severity score at entry of the discontinuation period were also comparable.; Group 1 Number missing: 0; Group 2 Number missing: 1

Protocol outcome 2: Intensity of withdrawal symptoms at post-intervention and longest follow-up

- Actual outcome for Antidepressants (others): Total number of emergent DESS symptoms at During week 2 of the discontinuation period; Group 1: mean 2 (SD 2.3); n=27, Group 2: mean 3 (SD 4.4); n=61; Comments: This is a clinician rated instrument covering 43 signs and symptoms. Symptoms that occurred or worsened in the 7 days before interview were defined as treatment emergent. They were rated as ‘new’ if experienced for the first time during the discontinuation period and rated as ‘worsening’ if they occurred at a level which was worse than before the discontinuation period.

Study	Montgomery 2004[442]
Risk of bias: All domain - Low, Selection - Low, 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: States that there were no significant demographic differences between treatment groups and mean MADRS, HAM-A and CGI severity score at entry of the discontinuation period were also comparable.; Group 1 Number missing: 0; Group 2 Number missing: 1 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM PAROXETINE versus NO WITHDRAWAL FROM PAROXETINE Protocol outcome 1: Specific withdrawal symptom at post-intervention and longest follow-up - Actual outcome for Antidepressants (SSRIs): Rebound (return to a MADRS score equal to or higher than the original score at the entry of the acute treatment study.) at During week 1 of the discontinuation period ; Group 1: 1/43, Group 2: 1/61 Risk of bias: All domain - Low, Selection - Low, 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: States that there were no significant demographic differences between treatment groups and mean MADRS, HAM-A and CGI severity score at entry of the discontinuation period were also comparable.; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Antidepressants (SSRIs): Rebound (return to a MADRS score equal to or higher than the original score at the entry of the acute treatment study.) at During week 2 of the discontinuation period ; Group 1: 1/43, Group 2: 2/61 Risk of bias: All domain - Low, Selection - Low, 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: States that there were no significant demographic differences between treatment groups and mean MADRS, HAM-A and CGI severity score at entry of the discontinuation period were also comparable.; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Intensity of withdrawal symptoms at post-intervention and longest follow-up - Actual outcome for Antidepressants (SSRIs): Total number of emergent DESS symptoms at During week 1 of the discontinuation period; Group 1: mean 7.3 (SD 7.1); n=43, Group 2: mean 3.5 (SD 4.1); n=61; Comments: This is a clinician rated instrument covering 43 signs and symptoms. Symptoms that occurred or worsened in the 7 days before interview were defined as treatment emergent. They were rated as ‘new’ if experienced for the first time during the discontinuation period and rated as ‘worsening’ if they occurred at a level which was worse than before the discontinuation period. Risk of bias: All domain - Low, Selection - Low, 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: States that there were no significant demographic	

Study	Montgomery 2004[442]
differences between treatment groups and mean MADRS, HAM-A and CGI severity score at entry of the discontinuation period were also comparable.; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Antidepressants (SSRIs): Total number of emergent DESS symptoms at During week 2 of the discontinuation period; Group 1: mean 3 (SD 3.9); n=43, Group 2: mean 2.8 (SD 3.5); n=61; Comments: This is a clinician rated instrument covering 43 signs and symptoms. Symptoms that occurred or worsened in the 7 days before interview were defined as treatment emergent. They were rated as 'new' if experienced for the first time during the discontinuation period and rated as 'worsening' if they occurred at a level which was worse than before the discontinuation period. Risk of bias: All domain - Low, Selection - Low, 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: States that there were no significant demographic differences between treatment groups and mean MADRS, HAM-A and CGI severity score at entry of the discontinuation period were also comparable.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Any withdrawal symptom at post-intervention and longest follow-up; Duration of withdrawal syndrome at n/a; Quality of life at n/a

Study	Montgomery 2005[443]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=Open-label phase (517), randomised continuation/placebo phase reported here (n=372))
Countries and setting	Conducted in Multiple countries; Setting: 76 centres in 11 countries in Europe, Canada and South Africa
Line of therapy	1st line
Duration of study	Intervention time: 12-week open-label treatment phase, 24-week randomised phase (continuation or placebo (discontinuation) - discontinuation assessed during the first 2 weeks of the randomised phase

Study	Montgomery 2005[443]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Escitalopram: 36 (18-78); placebo 38 (19-68)
Stratum	Antidepressants (SSRIs): Escitalopram
Subgroup analysis within study	Not applicable:
Inclusion criteria	Female and male outpatients between 18 and 80 years with a primary diagnosis of generalised social anxiety disorder (SAD) according to DSM-IV criteria; total score of 70 or more on the Liebowitz Social Anxiety Scale (LSAS) with exhibited fear or avoidance traits in at least 4 social situations; score of 5 or more on 1 or more of the Sheehan Disability Scale (SDS) subscales.
Exclusion criteria	Another Axis I disorder that was considered the predominant diagnosis within the previous 6 months; severity of depressive symptoms likely to response to an antidepressant (MADRS score of 18 or more); 5 or more on MADRS item 10 (suicidal thoughts); DSM-IV diagnosis of alcohol or drug abuse, an eating disorder, MDD, PD, OCD, body dysmorphic disorder, schizophrenia/other psychotic disorder, mania or hypomania or history thereof, or presence of an Axis II diagnosis. Lack of therapeutic response to any SSRI. Treatment with a psychoactive drug within 2 weeks (5 weeks for fluoxetine). In the prior 2 weeks had received or planned to initiate formal psychotherapy.
Recruitment/selection of patients	Advertisements by psychiatrists in private or hospital outpatient clinics or by specialised clinical research centres.
Age, gender and ethnicity	Age - Mean (range): Gender (M:F): 194/177. Ethnicity: 95% white.
Further population details	1. Half-life of benzodiazepine the population are taking: Not applicable.
Extra comments	. For this analysis, only including results from the randomised continuation vs discontinuation (placebo) phase. Only responders to escitalopram entered this phase (based on the CGI-I score of 1 or 2).
Indirectness of population	No indirectness.

Study	Montgomery 2005[443]
Interventions	(n=191) Intervention 1: No withdrawal/continuation on medicine - No withdrawal. Continuation on escitalopram: randomised to continue escitalopram following the 12-week open-label treatment phase (open-label phase: 10mg/day, which could be increased to 20mg if clinically indicated, tablets, single daily dose). This continuation arm continued with the dose administered at the end of the open-label phase. No dose changes permitted during the 24-week randomised period. . Duration 12-week open-label + 24-week continuation/discontinuation period. Concurrent medication/care: Not reported. Indirectness: No indirectness. (n=181) Intervention 2: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from escitalopram (abrupt switch to placebo): randomised to switch to placebo following the 12-week open-label treatment phase (open-label phase: 10mg/day, which could be increased to 20mg if clinically indicated, tablets, single daily dose). Abrupt switch to placebo tablets (identical appearance, taste and smell). . Duration 12-week open-label + 24-week continuation/discontinuation period. Concurrent medication/care: Not reported. Indirectness: No indirectness.
Funding	Study funded by industry.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM ESCITALOPRAM (ABRUPT SWITCH TO PLACEBO) versus CONTINUATION ON ESCITALOPRAM (NO WITHDRAWAL)

Protocol outcome 1: Intensity of withdrawal symptoms at post-intervention and longest follow-up

- Actual outcome for Antidepressants (SSRIs): Discontinuation Emergent Signs and Symptoms (DESS) total score at 2 weeks after randomisation (2 weeks withdrawal); MD; 0.76 (SE 0.29), Comments: 43-item DESS checklist. Means provided for each arm but with no variance (1.78 and 1.02 for withdrawal and continuation respectively). SE for the MD calculated from the difference in means and the P value of P<0.01 (0.01 used for calculation). n=181 and n=190 respectively for withdrawal and continuation, respectively);

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Analysis was using the randomised population who had taken at least 1 dose. DESS score range not reported, downgraded for outcome reporting. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 not treated. Unclear if any other drop-outs during the first 2 weeks of the discontinuation period, as only reported for the whole 24-week period.; Group 2 Number missing: 0, Reason: Unclear if any drop-outs during the first 2 weeks of the discontinuation period, as only reported for the whole 24-week period.

Study	Montgomery 2005[443]
- Actual outcome for Antidepressants (SSRIs): Discontinuation Emergent Signs and Symptoms (DESS) score of ≥4 at 2 weeks after randomisation (2 weeks after withdrawal); Group 1: 29/181, Group 2: 15/190; Comments: Percentages provided in paper (16% and 8% in withdrawal and continuation arms, respectively). Numbers analysed reported as the randomised numbers who took at least one dose (n=181 and n=190 respectively). Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Analysis was using the randomised population who had taken at least 1 dose. DESS score range not reported, downgraded for outcome reporting. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 not treated. Unclear if any other drop-outs during the first 2 weeks of the discontinuation period, as only reported for the whole 24-week period.; Group 2 Number missing: 0, Reason: Unclear if any drop-outs during the first 2 weeks of the discontinuation period, as only reported for the whole 24-week period. - Actual outcome for Antidepressants (SSRIs): Discontinuation Emergent Signs and Symptoms (DESS) total score at 1 week after randomisation (1 week withdrawal); MD; 1.44 (SE 0.56), Comments: 43-item DESS checklist. Means provided for each arm but with no variance (2.61 and 1.17 for withdrawal and continuation respectively). SE for the MD calculated from the difference in means and the P value of P<0.01 (0.01 used for calculation). n=181 and n=190 respectively for withdrawal and continuation, respectively). Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Analysis was using the randomised population who had taken at least 1 dose. DESS score range not reported, downgraded for outcome reporting. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 not treated. Unclear if any other dropouts during the first 2 weeks of the discontinuation period, as only reported for the whole 24-week period.; Group 2 Number missing: 0, Reason: Unclear if any dropouts during the first 2 weeks of the discontinuation period, as only reported for the whole 24-week period. - Actual outcome for Antidepressants (SSRIs): Discontinuation Emergent Signs and Symptoms (DESS) score of ≥4 at 1 week after randomisation (1 week after withdrawal); Group 1: 49/181, Group 2: 17/190; Comments: Percentages provided in paper (27%% and 9% in withdrawal and continuation arms, respectively). Numbers analysed reported as the randomised numbers who took at least one dose (n=181 and n=190 respectively). Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Analysis was using the randomised population who had taken at least 1 dose. DESS score range not reported, downgraded for outcome reporting. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 not treated. Unclear if any other dropouts during the first 2 weeks of the discontinuation period, as only reported for the whole 24-week period.; Group 2 Number missing: 0, Reason: Unclear if any dropouts during the first 2 weeks of the discontinuation period, as only reported for the whole 24-week period.	

Study	Montgomery 2005[443]
Protocol outcomes not reported by the study	Any withdrawal symptom at post-intervention and longest follow-up; Specific withdrawal symptom at post-intervention and longest follow-up; Duration of withdrawal syndrome at n/a; Quality of life at n/a

Study	Noyes 1991[472]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=25)
Countries and setting	Conducted in Unknown; Setting: Outpatient
Line of therapy	Unclear
Duration of study	Intervention + follow up: 8 months treatment, 5 weeks discontinuation
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-III R criteria for extensive phobic avoidance, limited phobic avoidance, uncomplicated panic disorder, major depression (current or past)
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	Required to meet DSM-III-R criteria for panic disorder and to have at least one panic attack per week for 3 weeks.
Exclusion criteria	Participants were excluded if they had major physical or psychiatric illnesses including schizophrenia, bipolar disorder, melancholia, dementia or alcohol abuse within the past 6 months. Those with major depression were excluded if the onset preceded that of panic disorder or if depressive symptoms dominated the clinical picture.

Study	Noyes 1991[472]
Recruitment/selection of patients	Recruited through news media.
Age, gender and ethnicity	Age - Mean (SD): 39.1 (9.8) including alprazolam group which is not included. Gender (M:F): 24F/ 26M (including alprazolam group which is not included). Ethnicity: NR
Further population details	1. Half-life of benzodiazepine the population are taking: Long half-life benzodiazepine (Diazepam).
Extra comments	SCID was used to separate participants into panic disorder subtypes. Population details for those who entered the discontinuation phase reported.
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from diazepam. Original treatment study (8 weeks): after a one-week pre-treatment washout without any psychotropic drugs, participants were assigned to 10mg diazepam. The dose was adjusted to achieve maximum benefit within the limits of tolerance. During the initial phase, participants were seen weekly. At the end of this period, those who had responded to the study medication were invited to continue taking that medication for 6 months and were then eligible to take part in the discontinuation part of the study. At the end of the treatment study participants were asked to reduce the dose of medication by one capsule every 3 days until the dose reached 2 capsule/ day. At that point, half strength capsules of diazepam were substituted for the original capsules and the dose of drug or placebo was reduced at the same rate (1 capsule every 3 days). the start of the taper was adjusted so that the last dose of study medication would coincide with a regularly scheduled visit. During the discontinuation study participants were seen weekly and visits were continued until they had been without medication for at least 2 weeks. Duration 5 weeks. Concurrent medication/care: NR. Indirectness: No indirectness. (n=6) Intervention 2: Withdrawal from placebo. Original treatment study (8 weeks): after a one-week pre-treatment washout without any psychotropic drugs, participants were assigned to placebo. The dose was adjusted to achieve maximum benefit within the limits of tolerance. During the initial phase, participants were seen weekly. At the end of this period, those who had responded to the study medication were invited to continue taking that medication for 6 months and were then eligible to take part in the discontinuation part of the study.

Study	Noyes 1991[472]
	At the end of the treatment study participants were asked to reduce the dose of placebo by one capsule every 3 days until the dose reached 2 capsule/ day. At that point, the dose of placebo was reduced at the same rate (1 capsule every 3 days). The start of the taper was adjusted so that the last dose of study medication would coincide with a regularly scheduled visit. During the discontinuation study participants were seen weekly and visits were continued until they had been without medication for at least 2 weeks. Duration 5 weeks. Concurrent medication/care: NR. Indirectness: Serious indirectness; Indirectness comment: It is unclear if the placebo group discontinued during the discontinuation phase.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM DIAZEPAM 5MG versus WITHDRAWAL FROM PLACEBO

Protocol outcome 1: Any withdrawal symptom at post-intervention and longest follow-up

- Actual outcome for Benzodiazepines: Development of new symptoms at During the discontinuation period; Group 1: 12/19, Group 2: 2/6

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: States that there was no difference between the diazepam and alprazolam groups with respect to any baseline demographic or illness variable . Comparison with placebo group not reported.
Randomised numbers per group were not reported.; Group 1 Number missing: 11, Reason: NR; Group 2 Number missing: 2, Reason: NR NB this is from total number randomised.

Protocol outcome 2: Specific withdrawal symptom at post-intervention and longest follow-up

- Actual outcome for Benzodiazepines: Rebound- increase in anxiety of ≥50% as measured with Hamilton anxiety scale compared with baseline at During the discontinuation period; Group 1: 3/19, Group 2: 0/6; Comments: Rebound was judged to have occurred if the criteria were met at any visit.

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: States that there was no difference between the diazepam and alprazolam groups with respect to any baseline demographic or illness variable . Comparison with placebo group not reported.; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for Benzodiazepines: Rebound- increase in panic attacks of ≥100% compared with baseline at During the discontinuation period; Group 1: 4/19, Group 2: 1/6; Comments: Rebound was judged to have occurred if the criteria were met at any visit.

Study	Noyes 1991[472]
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: States that there was no difference between the diazepam and alprazolam groups with respect to any baseline demographic or illness variable . Comparison with placebo group not reported. Randomised numbers per group were not reported.; Group 1 Number missing: 11, Reason: NR; Group 2 Number missing: 2, Reason: NR NB this is from total number randomised. - Actual outcome for Benzodiazepines: Rebound- Global Improvement Score ≤3 (indicating symptoms worse than at baseline) range 0-10 at During the discontinuation period; Group 1: 4/19, Group 2: 0/6; Comments: Rebound was judged to have occurred if the criteria were met at any visit Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: States that there was no difference between the diazepam and alprazolam groups with respect to any baseline demographic or illness variable . Comparison with placebo group not reported. Randomised numbers per group were not reported.; Group 1 Number missing: 11, Reason: NR; Group 2 Number missing: 2, Reason: NR. - Actual outcome for Benzodiazepines: Rebound- increase in anxiety of ≥10% as measured with Hamilton anxiety scale compared with baseline at During the discontinuation period; Group 1: 7/19, Group 2: 1/6; Comments: Calculated from % reported. Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: States that there was no difference between the diazepam and alprazolam groups with respect to any baseline demographic or illness variable . Comparison with placebo group not reported. Randomised numbers per group were not reported.; Group 1 Number missing: 11, Reason: NR; Group 2 Number missing: 2, Reason: NR NB this is from total number randomised. Protocol outcome 3: Intensity of withdrawal symptoms at post-intervention and longest follow-up - Actual outcome for Benzodiazepines: Increase in withdrawal symptoms of ≥100% at During the discontinuation period; Group 1: 1/19, Group 2: 1/6; Comments: Using the 53 item Withdrawal Symptoms Checklist, symptoms that became worse during taper compared with baseline were identified. To do this, for each patient, the baseline value for each item was subtracted, rated on a 4-point scale from the highest value recorded during dose reduction or after discontinuation. The group's mean change from baseline was calculated and in this way 18 symptoms were identified that became worse than they had been at baseline. The sum of the ratings for these 18 symptoms yielded a total withdrawal symptom score for each patient at each observation period. Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: States that there was no difference between the diazepam and	

Study	**Noyes 1991[472]**
alprazolam groups with respect to any baseline demographic or illness variable . Comparison with placebo group not reported. Randomised numbers per group were not reported.; Group 1 Number missing: 11, Reason: NR; Group 2 Number missing: 2, Reason: NR NB this is from total number randomised.	
Protocol outcomes not reported by the study	Duration of withdrawal syndrome at n/a; Quality of life at n/a

Study	**Pande 2003[506]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=276)
Countries and setting	Conducted in USA; Setting: 5 outpatient clinical research sites based in Seattle, Portland, Ore., Lansing, Mich., Los Angeles and Durham, N.C.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 5 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: GAD according to DSM-IV criteria
Stratum	Pregabalin
Subgroup analysis within study	Not applicable
Inclusion criteria	Outpatients 18 years or older meeting a diagnosis of GAD according to DSM-IV criteria. At the screening and treatment assignment visits, patients were required to have a Covi Anxiety Scale total score ≥9 and Raskin Depression Scale total score ≥7

Study	Pande 2003[506]
	to ensure that anxiety was the predominant presentation among patients with depressive symptoms. Patients were required to have a Hamilton anxiety scale total score ≥20 at both the screening and treatment assignment visits.
Exclusion criteria	Patients were excluded if they suffered from any axis I disorder except dysthymia, simple phobia, social phobia, somatization disorder, or a history of major depressive disorder. Also, patients at suicide risk, as judged by the clinician on the basis of history or current severity of suicidal ideation.
Recruitment/selection of patients	Clinic referrals or advertisements
Age, gender and ethnicity	Age - Mean (SD): 35.8 (11.1). Gender (M:F): Define. Ethnicity: White: 83.7%, Black: 7.6%, Other: 8.7%
Further population details	1. Half-life of benzodiazepine the population are taking: Short half-life benzodiazepine (lorazepam).
Indirectness of population	No indirectness
Interventions	(n=69) Intervention 1: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from pregabalin 150mg/day (50mg tid) The study had 3 phases: a 1-week placebo lead in, a 4-week double-blind phase and a 1-week taper. The 1 week, single-blind placebo lead in phase was intended to establish the stability of GAD symptoms and eliminate the effects of prior treatment. If patients still met the study inclusion criteria at the end of this phase, as confirmed by a second clinical interview with the psychiatrist, they were randomly assigned to one of the four treatment conditions. Study medication was titrated during the first 6 days of double-blind treatment. On day 1, participants received one sixth of the randomly assigned dose, which was then increased daily until the targeted dose was reached. Following 4 weeks of treatment, the final efficacy assessments were made (termination visit). Study medication dose was tapered over 1 week, and the follow-up visit was conducted. Duration 5 weeks. Concurrent medication/care: Participants were required to be free of psychotropic medications for 2 weeks (5 weeks for fluoxetine) before enrolment. A urine drug screen was performed at screening and at termination, although a positive result at screening was not exclusionary. No psychotropic medications were allowed during the study with the exception of zolpidem (5mg) which was permitted on an as-needed basis for extreme sleeplessness. Zolpidem was not to be taken for more than 2 nights per week and not to be taken the night before a clinic visit.

Study	Pande 2003[506]
	(n=70) Intervention 2: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from pregabalin 600mg/day (200mg tid) The study had 3 phases: a 1-week placebo lead in, a 4-week double-blind phase and a 1-week taper. The 1 week, single-blind placebo lead in phase was intended to establish the stability of GAD symptoms and eliminate the effects of prior treatment. If patients still met the study inclusion criteria at the end of this phase, as confirmed by a second clinical interview with the psychiatrist, they were randomly assigned to one of the four treatment conditions. Study medication was titrated during the first 6 days of double-blind treatment. On day 1, participants received one sixth of the randomly assigned dose, which was then increased daily until the targeted dose was reached. Following 4 weeks of treatment, the final efficacy assessments were made (termination visit). Study medication dose was tapered over 1 week, and the follow-up visit was conducted. Duration 5 weeks. Concurrent medication/care: Participants were required to be free of psychotropic medications for 2 weeks (5 weeks for fluoxetine) before enrolment. A urine drug screen was performed at screening and at termination, although a positive result at screening was not exclusionary. No psychotropic medications were allowed during the study with the exception of zolpidem (5mg) which was permitted on an as-needed basis for extreme sleeplessness. Zolpidem was not to be taken for more than 2 nights per week and not to be taken the night before a clinic visit. (n=68) Intervention 3: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from lorazepam 6mg/day (2mg tid). The study had 3 phases: a 1-week placebo lead in, a 4-week double-blind phase and a 1-week taper. The 1 week, single-blind placebo lead in phase was intended to establish the stability of GAD symptoms and eliminate the effects of prior treatment. If patients still met the study inclusion criteria at the end of this phase, as confirmed by a second clinical interview with the psychiatrist, they were randomly assigned to one of the four treatment conditions. Study medication was titrated during the first 6 days of double-blind treatment. On day 1, participants received one sixth of the randomly assigned dose, which was then increased daily until the targeted dose was reached. Following 4 weeks of treatment, the final efficacy assessments were made (termination visit). Study medication dose was tapered over 1 week, and the follow-up visit was conducted. Duration 5 weeks. Concurrent medication/care: Participants were required to be free of psychotropic medications for 2 weeks (5 weeks for fluoxetine) before enrolment.

Study	Pande 2003[506]
	A urine drug screen was performed at screening and at termination, although a positive result at screening was not exclusionary. No psychotropic medications were allowed during the study with the exception of zolpidem (5mg) which was permitted on an as-needed basis for extreme sleeplessness. Zolpidem was not to be taken for more than 2 nights per week and not to be taken the night before a clinic visit. (n=69) Intervention 4: Withdrawal from placebo. The study had 3 phases: a 1-week placebo lead in, a 4-week double-blind phase and a 1-week taper. The 1 week, single-blind placebo lead in phase was intended to establish the stability of GAD symptoms and eliminate the effects of prior treatment. If patients still met the study inclusion criteria at the end of this phase, as confirmed by a second clinical interview with the psychiatrist, they were randomly assigned to one of the four treatment conditions. Study medication was titrated during the first 6 days of double-blind treatment. On day 1, participants received one sixth of the randomly assigned dose, which was then increased daily until the targeted dose was reached. Following 4 weeks of treatment, the final efficacy assessments were made (termination visit). Study medication dose was tapered over 1 week, and the follow-up visit was conducted. Duration 5 weeks. Concurrent medication/care: Participants were required to be free of psychotropic medications for 2 weeks (5 weeks for fluoxetine) before enrolment. A urine drug screen was performed at screening and at termination, although a positive result at screening was not exclusionary. No psychotropic medications were allowed during the study with the exception of zolpidem (5mg) which was permitted on an as-needed basis for extreme sleeplessness. Zolpidem was not to be taken for more than 2 nights per week and not to be taken the night before a clinic visit. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM PREGABALIN 150MG/DAY versus WITHDRAWAL FROM PLACEBO

Protocol outcome 1: Intensity of withdrawal symptoms at post-intervention and longest follow-up

- Actual outcome for Pregabalin: PWC at week 5 (immediately after completion of taper); MD; 1.61 (95%CI -0.96 to 4.18, Comments: Difference from placebo was 1.61. SE 1.31 calculated using p value method (p=0.22). CIs calculated using Revman.
PWC scores at endpoint (week 4) were subtracted from those at follow-up (week 5). Change scores were analysed using ANCOVA that included the effects of treatment and centre with baseline PWC scores entered as a covariate. Adjusted mean change scores in placebo and 50mg arms were 0.55 and 2.17, respectively (no variance reported for change scores).

Study	Pande 2003[506]
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; From start of treatment Group 1 Number missing: 7, Reason: Adverse event, lack of efficacy, lack of compliance, other/administrative; Group 2 Number missing: 19, Reason: Adverse event, lack of efficacy, lack of compliance, other/administrative. In taper phase for pregabalin 112 entered taper, 1 withdrew, for lorazepam 44 entered taper, 1 withdrew and for placebo 54 entered taper, 1 withdrew. RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM PREGABALIN 600MG/DAY versus WITHDRAWAL FROM PLACEBO Protocol outcome 1: Intensity of withdrawal symptoms at post-intervention and longest follow-up - Actual outcome for Pregabalin: PWC at week 5 (immediately after completion of taper); MD; 2.55 (95%CI -0.08 to 5.18, Comments: Difference from placebo was 2.55. SE 1.34 calculated using p value method (p=0.06). CIs calculated using Revman. PWC scores at endpoint (week 4) were subtracted from those at follow-up (week 5). Change scores were analysed using ANCOVA that included the effects of treatment and centre with baseline PWC scores entered as a covariate. Adjusted mean change scores in placebo and 200mg arms were 0.55 and 3.11, respectively (no variance reported for change scores). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were slightly more females in the placebo and lorazepam groups. Age at onset of GAD and duration of illness were similar across groups. A low level of comorbidity was observed. The frequency of comorbid social phobia was slightly greater in the placebo group than in the other 3 groups.; From start of treatment Group 1 Number missing: 15, Reason: Adverse event, lack of efficacy, lack of compliance, other/administrative; Group 2 Number missing: 19, Reason: Adverse event, lack of efficacy, lack of compliance, other/administrative In taper phase for pregabalin 112 entered taper, 1 withdrew and for placebo 54 entered taper, 1 withdrew. RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM LORAZEPAM versus WITHDRAWAL FROM PLACEBO Protocol outcome 1: Intensity of withdrawal symptoms at post-intervention and longest follow-up - Actual outcome for Benzodiazepines: PWC at week 5 (immediately after completion of taper); MD; 4.65 (95%CI 1.79 to 7.51, Comments: Difference from placebo was 4.65. SE 1.46 calculated using p value method. CIs calculated using Revman. PWC scores at endpoint (week 4) were subtracted from those at follow-up (week 5). Change scores were analysed using ANCOVA that included the effects of treatment and centre with baseline PWC scores entered as a covariate. Adjusted mean change scores in placebo and lorazepam arms were 0.55 and 5.20, respectively (no variance reported for change scores).	

Study	**Pande 2003[506]**
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were slightly more females in the placebo and lorazepam groups. Age at onset of GAD and duration of illness were similar across groups. A low level of comorbidity was observed. The frequency of comorbid social phobia was slightly greater in the placebo group than in the other 3 groups.; Group 1 Number missing: 22, Reason: Adverse event, lack of efficacy, lack of compliance, other/administrative; Group 2 Number missing: 19, Reason: Adverse event, lack of efficacy, lack of compliance, other/administrative NB – this is from start of treatment. In taper phase for pregabalin 112 entered taper, 1 withdrew and for placebo 54 entered taper, 1 withdrew.	
Protocol outcomes not reported by the study	Any withdrawal symptom at post-intervention and longest follow-up; Specific withdrawal symptom at post-intervention and longest follow-up; Duration of withdrawal syndrome at n/a; Quality of life at n/a

Study	**Perahia 2009[527]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=N=288 number entering randomised double blind phase and subsequent taper (analysed here); prior open-label treatment phase included n=514)
Countries and setting	Conducted in United Kingdom; Setting: Outpatients
Line of therapy	Unclear
Duration of study	Intervention time: 34 week open-label phase + 52-week discontinuation/continuation double blind phase + 3-week taper phase
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Antidepressants (others): Duloxetine
Subgroup analysis within study	Not applicable:

Study	Perahia 2009[527]
Inclusion criteria	Outpatients aged 18 years and over who met the criteria for recurrent MDD as defined by the DSM-IV and confirmed via the MINI. Patients had to have a Hamilton Depression Rating Scale score >18 and a CGI-S score >4, and at least 3 episodes of depression within the past 5 years.
Exclusion criteria	Current and primary axis disorder other than MDD, substance abuse or dependence within the past year, previous use of duloxetine.
Recruitment/selection of patients	Outpatients from 43 study centres across Europe were recruited.
Age, gender and ethnicity	Age - Mean (SD): Duloxetine 47.1 (12.8); placebo: 48.0 (12.3). Gender (M:F): 82/206. Ethnicity: White 97.9%; Black 1%; Hispanic 1%; East Asian 0.3%
Further population details	1. Half-life of benzodiazepine the population are taking: Not applicable
Extra comments	Double-blind phase (52 weeks) is withdrawal (to placebo) vs continuation on duloxetine. Treatment-emergent adverse events were reported for the withdrawal vs continuation phase; however, this outcome is not extracted in this review (as per protocol, not defined as withdrawal symptoms). Outcome reported in this review is withdrawal from duloxetine vs withdrawal from placebo from the 3-week taper phase of study (taper phase followed 52-week double-blind phase).
Indirectness of population	No indirectness
Interventions	(n=146) Intervention 1: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from duloxetine during taper phase (at end of 52-week double-blind phase). Optional 3-week taper follow-up phase: eligible to enter the taper phase following study completion or discontinuation (those who discontinued the double-blind phase due to recurrence were also eligible to enter taper phase). Down-titration over 2-3 weeks. Prior phases: 4–10-week acute phase where all participants received open-label 60-120mg/day duloxetine, followed by a 24-week continuation phase where dose was maintained (34 weeks total for the open-label phase). Responders were then randomised to be maintained duloxetine for 52 weeks.

Study	Perahia 2009[527]
	Duration 34 week open-label phase + 52-week discontinuation/continuation double blind phase + 2–3-week taper phase. Concurrent medication/care: Exclusion criteria was taking any excluded medications (mostly centrally acting medications such as antidepressants and antipsychotics). No other reported. Indirectness: No indirectness Comments: Follow-up phase was optional. Doses taken during double blind phase: 60mg/day 44%; 90mg/day 31%; 120mg/day 25%. (n=142) Intervention 2: Withdrawal from placebo during taper phase (at end of 52-week double-blind phase). Optional 3-week taper follow-up phase: eligible to enter the taper phase following study completion or discontinuation (those who discontinued the double-blind phase due to recurrence were also eligible to enter taper phase). Down-titration over 2-3 weeks. Prior phases: 4–10-week acute phase where all participants received open-label 60-120mg/day duloxetine, followed by a 24-week continuation phase where dose was maintained (34 weeks total for the open-label phase). Responders were then randomised to placebo for 52 weeks. Duration 34 week open-label phase + 52-week discontinuation/continuation double blind phase + 2–3-week taper phase. Concurrent medication/care: Exclusion criteria was taking any excluded medications (mostly centrally acting medications such as antidepressants and antipsychotics). No other reported. Indirectness: No indirectness. Comments: Follow-up phase was optional. Down-titration over 2-3 weeks presumed for placebo arm too- unclear from paper. Note: these people had previously received desvenlafaxine during the open-label phase of 34 weeks. Responders at the end of week 34 were randomised to placebo for the 52-week double-blind phase (this was a gradual taper to placebo over 4 weeks, then continued on placebo for the rest of the 52 weeks or until discontinuation).
Funding	Study funded by industry (Eli Lilly and Co. and Boehringer Ingelheim)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM DULOXETINE (AT END OF 52 WEEK double blind PHASE) versus WITHDRAWAL FROM PLACEBO (AT END OF 52 WEEK double blind PHASE)

Protocol outcome 1: Any withdrawal symptom at post-intervention and longest follow-up
- Actual outcome for Antidepressants (others): 1 or more discontinuation-emergent adverse event (DEAE; spontaneously reported adverse events recorded at each visit - visit frequency unclear during 3 week follow-up) at During 3 week taper phase; Group 1: 14/61, Group 2: 4/48.

Study	Perahia 2009[527]
Risk of bias: All domain - high, Selection - High, Blinding - Low, Incomplete outcome data - low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Those withdrawing from placebo had previously received 34 weeks treatment with duloxetine during the open-label phase. They had been tapered off over 4 weeks at the start of the double-blind phase and then been taking placebo for the remainder of the 52-week double blind phase (for approximately 48 weeks). However, methods also state that people could enter the optional taper phase even if discontinued the double blind phase early, so some people in the placebo arm may have been taking placebo for less time; Indirectness of outcome: No indirectness ; Group 1 Number missing: 85 overall, but no missing data for taper phase, Reason: 61 entered optional follow-up phase (not all double blind completers entered phase). 50 discontinued double blind treatment phase (although still eligible to enter follow-up phase, so unclear if any people who discontinued did); Group 2 Number missing: 94, Reason: 48 entered optional follow-up phase (not all double blind completers entered phase). 69 discontinued double blind treatment phase (although still eligible to enter follow-up phase, so unclear if any people who discontinued did).	
Protocol outcomes not reported by the study	Specific withdrawal symptom at post-intervention and longest follow-up; Duration of withdrawal syndrome at n/a; Quality of life at n/a; Intensity of withdrawal symptoms at post-intervention and longest follow-up

Study	Raskin 2005[561]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=348)
Countries and setting	Conducted in USA; Setting: 26 centres worldwide
Line of therapy	1st line
Duration of study	Intervention time: 12-week double-blind treatment period and 1-week taper period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Duloxetine for pain due to bilateral peripheral neuropathy (withdrawal from duloxetine vs withdrawal from placebo)
Stratum	Antidepressants (others): Duloxetine

Study	**Raskin 2005[561]**
Subgroup analysis within study	Not applicable:
Inclusion criteria	18 years or older; pain due to bilateral peripheral neuropathy caused by type 1 or type 2 diabetes (the pain had to begin in the feet and with relatively symmetrical onset). the daily pain must have been present for at least 6 months, and diagnosis was to be confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument (MNSI); patients had to have a mean score of 4 or more when assessed for a 24-hour average pain severity on the 11-point Likert scale and stable glycaemic control.
Exclusion criteria	Pregnant or breastfeeding; prior renal transplant or current renal dialysis; serious or unstable illness; symptomatic peripheral vascular disease; other medical condition or psychological conditions that might compromise participation in the study; current (1 year or less) DSM-IV Axis I diagnosis of MDD, dysthymia, GAD, alcohol, or eating disorders as determined by the Mini International Neuropsychiatric Interview (MINI), or if they had a DSM-IV diagnosis or a previous diagnosis of mania, bipolar disorder or psychosis. Historical exposure to drugs known to cause neuropathy; history of substance abuse or dependence within the previous year (excluding caffeine or nicotine), a positive urine drug screen for any substances of abuse or excluded medication, history of medical condition including pernicious anaemia and hypothyroidism that could have been responsible for neuropathy, and treatment with a MAOI or fluoxetine within 30 days of randomisation. Severe allergic reactions to multiple medications and prior participation in a study of duloxetine. Concomitant chronic use of antidepressants, antiemetics, analgesics with the exception of acetaminophen up to 4g/day and aspirin up to 325mg/day. Antimanics, antimigraine medications, antipsychotics, benzodiazepines, capsaicin, chloral hydrate, guanethidine, topical lidocaine, MAOIs, narcotics, psychostimulants, oral and injectable steroids and anticonvulsants.
Recruitment/selection of patients	November 2003 to March 2004
Age, gender and ethnicity	Age - Mean (SD): 58.8 (10.1). Gender (M:F): 162/186. Ethnicity: Caucasian 99.7%; East/Southeast Asian 0.3%
Further population details	1. Half-life of benzodiazepine the population are taking: Not applicable
Extra comments	.

Study	Raskin 2005[561]
Indirectness of population	No indirectness
Interventions	(n=116) Intervention 1: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from duloxetine 60mg QD: patients instructed to take two capsules by mouth every morning and evening (made up of 30mg capsules and placebo capsules depending on treatment arm). 12-week double-blind treatment phase followed by a 1-week study drug taper period (at the end of the treatment phase the patient's study drug was halved to 30mg QD). Duration 12-week treatment + 1 week taper. Concurrent medication/care: Concomitant medications allowed were antacids, antiasthma agents, aminophylline, birth control medications, cough/cold preparations, diuretics, inhaled and topical steroids, hypoglycaemics, insulin, laxatives, theophylline, anticoagulants, antibiotics, antidiarrheals, antihistamines. Medications including ACE inhibitors, angiotensin II receptor agonists, antiarrhythmics, anticoagulants, calcium channel blockers were allowed provided the patient had been on a stable dose for 3 months. Indirectness: Serious indirectness; Indirectness comment: Duloxetine dose halved at the start of the 1-week taper phase, but unclear if taper phase was complete withdraw of duloxetine. (n=116) Intervention 2: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from duloxetine 60mg BID: patients instructed to take two capsules by mouth every morning and evening (made up of 30mg capsules and placebo capsules depending on treatment arm). Treated initially with 60mg QD, after 3 days increased to 60mg BID. 12-week double-blind treatment phase followed by a 1-week study drug taper period (at the end of the treatment phase the patient's study drug was halved to 60mg QD). Duration 12 weeks treatment + 1 week taper. Concurrent medication/care: Concomitant medications allowed were antacids, antiasthma agents, aminophylline, birth control medications, cough/cold preparations, diuretics, inhaled and topical steroids, hypoglycaemics, insulin, laxatives, theophylline, anticoagulants, antibiotics, antidiarrheals and antihistamines. Medications including ACE inhibitors, angiotensin II receptor agonists, antiarrhythmics, anticoagulants, calcium channel blockers were allowed provided the patient had been on a stable dose for 3 months. Indirectness: Serious indirectness; Indirectness comment: Duloxetine dose halved at the start of the 1-week taper phase, but unclear if taper phase was complete withdraw of duloxetine. (n=116) Intervention 3: Withdrawal from placebo. Placebo: patients instructed to take two capsules by mouth every morning and evening (made up of 30mg capsules and placebo capsules depending on treatment arm). 12-week double-blind treatment phase followed by a 1-week study drug taper period. Duration 12-week treatment period + 1 week taper. Concurrent medication/care: Concomitant medications allowed were antacids, antiasthma agents, aminophylline, birth control medications, cough/cold preparations, diuretics, inhaled and topical steroids, hypoglycaemics, insulin, laxatives, theophylline, anticoagulants,

Study	Raskin 2005[561]
	antibiotics, antidiarrheals and antihistamines. Medications including ACE inhibitors, angiotensin II receptor agonists, antiarrhythmics, anticoagulants, calcium channel blockers were allowed provided the patient had been on a stable dose for 3 months. . Indirectness: Serious indirectness; Indirectness comment: Unclear if placebo was withdrawn or not during the taper phase, just says 1 week study drug taper period.
Funding	Principal author funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM DULOXETINE 60MG QD versus WITHDRAWAL FROM PLACEBO

Protocol outcome 1: Any withdrawal symptom at post-intervention and longest follow-up
- Actual outcome for Antidepressants (others): Adverse event emerging during the 1-week drug taper phase at 12-13 weeks (during 1-week taper phase); Group 1: 7/116, Group 2: 8/116.

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Blinded to treatment phase so assumed blinded to whether being withdrawn from drug or placebo; Group 1 Number missing: 20, Reason: Withdrew for all reasons during the treatment phase: 15; discontinued treatment phase due to adverse events: 5; Group 2 Number missing: 19, Reason: Withdrew for all reasons during the treatment phase: 16; discontinued treatment phase due to adverse events: 3

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM DULOXETINE 60MG BID versus WITHDRAWAL FROM PLACEBO

Protocol outcome 1: Any withdrawal symptom at post-intervention and longest follow-up.

- Actual outcome for Antidepressants (others): Adverse event emerging during the 1-week drug taper phase at 12-13 weeks (during 1-week taper phase); Group 1: 8/116, Group 2: 8/116

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - unclear, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Blinded to treatment phase so assumed blinded to whether being withdrawn from drug or placebo; Group 1 Number missing: 35, Reason: Withdrew for all reasons during the treatment phase: 21; discontinued treatment phase due to adverse events: 14; Group 2 Number missing: 19, Reason: Withdrew for all reasons during the treatment phase: 16; discontinued treatment phase due to adverse events: 3

Study	**Raskin 2005**[561]
Protocol outcomes not reported by the study	Specific withdrawal symptom at post-intervention and longest follow-up; Duration of withdrawal syndrome at n/a; Quality of life at n/a; Intensity of withdrawal symptoms at post-intervention and longest follow-up

Study	**Raskin 2008**[562]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=311 randomised)
Countries and setting	Multicenter, United States.
Duration of study	8 weeks treatment, 1 week discontinuation phase.
Inclusion criteria	All patients were 65 years and older. All patients met diagnostic criteria for MDD as defined in the Diagnostic and Statistical Manual of Mental disorders, Fourth Edition. The diagnosis was confirmed by the Mini International Neuropsychiatric Interview. Baseline diseased severity was defined by patient's scores on the $HAMD_{17}$. Patients were required to have $HAMD_{17}$ total score ≥ 18 at visits 1 and 2, mini-Mental State Examination score ≥ 20 with or without mild dementia; and at least one previous episode of MDD.
Exclusion criteria	Patients were excluded for the following reasons: current primary axis I diagnosis other than MDD or mild dementia; previous diagnosis of psychotic disorder; organic mental disorder, moderate to severe dementia or mental retardation diagnosis; and serious or unstable medical illness.
Recruitment/selection of patients	Elderly patients (≥ 65 years) with major depressive disorder.
Age, gender and ethnicity	Sex, female, n (%): Group 1: 125 (60.4), Group 2: 60 (57.7) Mean age, yr (SD): Group 1: 72.6 (5.7), Group 2: 73.3 (5.7)

Study	**Raskin 2008[562]**
	Age range: Group 1:65-90, Group 2: 65-89 Ethnicity: White: Group 1: 161 (77.8), Group 2:82 (78.8) Hispanic: Group 1: 31 (15.0), Group 2: 17 (16.3) African descent: Group 1: 13 (6.3), Group 2: 4 (3.8) Other: Group 1: 2 (1.0), Group 2: 1 (1.0)
Extra comments	Efficacy, clinical outcomes, and treatment emergent adverse events also reported.
Indirectness of population	No indirectness of population.
Interventions & comparators	Screening phase (1 week) Double-blind placebo phase (1 week) Treatment (8 weeks). If a patient could not tolerate the drug, the dose could be decreased from 60 to 30 mg/d but had to be at 60 mg/d by the end of the second week after randomization; otherwise, the patient was discontinued from the study. Double-blind discontinuation phase (1 week): dosage of the study drug was tapered. (n=207) Group 1 (Withdrawal from duloxetine): duloxetine 60 mg once daily (n=104) Group 2 (Withdrawal from placebo): Placebo
Funding	Eli Lilly and Company and Boehringer Ingelheim GmbH.
RESULTS (NUMBER ANALYSED) AND RISK OF BIAS FOR COMPARISON: Withdrawal from duloxetine vs Withdrawal from placebo Protocol outcome 1: Any withdrawal symptom at post-intervention and longest follow-up	

Study	**Raskin 2008[562]**
Actual outcome: Incidence of at least one discontinuation-emergent adverse event (defined as events that first occurred or worsened during the discontinuation phase of the study as compared with maximum severity at weeks 4 and 8). Group 1: 36/207 (17.3%), Group 2: 12/104 (11.3%) *NB – actual numbers assumed by NGC calculations, % only provided in study.* Risk of bias: All domain –High, Selection - High, Blinding - Low, Incomplete outcome data – unclear, Outcome reporting - Low, Measurement – Low, Crossover - Low; Indirectness of outcome: No indirectness; For the treatment phase, not including taper - Group 1 Number missing: 45; Group 2 Number missing: 24. Reason*: Adverse event (29), Lack of efficacy (16), not reported (24). Also reports: Incidence of most frequent discontinuation-emergent adverse events Headache: Group 1: 3.1%, group 2: 1.2% Dizziness: Group 1: 1.9%, Group 2: 1.2% Fatigue: Group 1: 2.5%, Group 2: 0% Nausea: Group 1: 2.5%, Group 2: 0% *Note: Study only provided percentage, but NGC could not work out crude figures as did not match therefore outcome not included in full analysis.* Risk of bias: All domain –Very high, Selection - High, Blinding - Low, Incomplete outcome data – Very high, Outcome reporting - Low, Measurement – Low, Crossover - Low; Indirectness of outcome: No indirectness; At end of study - Group 1 Number missing: 45; Group 2 Number missing: 24. Reason*: Adverse event (29), Lack of efficacy (16), not reported (24).	

Study	**Rickels 2010[584]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=594 for open-label phase. 375 responders randomised to double-blind phase and subsequent taper (analysis reported here))

Study	**Rickels 2010[584]**
Countries and setting	Conducted in Multiple countries; Setting: Outpatients; 49 sites (31 in Europe, 15 in the US, 3 in Taiwan)
Line of therapy	1st line
Duration of study	Intervention time: 12-week open-label phase + 24-week double-blind phase (withdrawal to placebo vs continuation) + 1–2-week taper phase (withdrawal from AD vs withdrawal from placebo)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Antidepressants (others): Desvenlafaxine
Subgroup analysis within study	Not applicable:
Inclusion criteria	Male and female outpatients, 18-75 years old; primary diagnosis of MDD using the DSM-IV criteria, single or recurrent episode, without psychotic features, and who had symptoms for at least 30 days before screening. The modified Mini-International Neuropsychiatric Interview was used to indicate the primary diagnosis of MDD and any comorbid psychiatric disorders, with confirmation by psychiatric interview. Minimum Hamilton Depression Rating Scale score of 20, score at least 2 on item 1 (depressed mood) of the Hamilton Depression Rating Scale, and a Clinical Global Impression Severity (CGI-S) of at least 4 on a scale of 7 (1, normal and 7, extremely ill). Patients with comorbid generalised anxiety, panic or social anxiety disorder were allowed to participate if MDD was the primary diagnosis.
Exclusion criteria	Current comorbid substance use disorders; treatment with desvenlafaxine at any time in the past; treatment with venlafaxine (IR or ER formulation) within 90 days; known hypersensitivity to venlafaxine (IR or ER); risk of suicide based on clinical judgement; pregnant, breast-feeding, or planning to become pregnant during the study; current (within 12 months) manic episodes, post-traumatic stress disorder, obsessive-compulsive disorder, or clinically important personality disorder; depression associated with organic mental disorder due to a general medical condition or neurological disorder; history of a seizure disorder; clinically important medical disease.

Study	Rickels 2010[584]
Recruitment/selection of patients	June 2003 to August 2005.
Age, gender and ethnicity	Age - Mean (SD): Desvenlafaxine: 42.7 (12.3); Placebo: 42.8 (11.8). Gender (M:F): 122/253. Ethnicity: Double-blind phase: White 88%; Black 5.1%; Hispanic 3.7%; Other 3.2%.
Further population details	1. Half-life of benzodiazepine the population are taking: Not applicable .
Extra comments	Double-blind phase is withdrawal (to placebo) vs continuation on desvenlafaxine. Taper phase (at the end of the 24-week double blind phase) provides results for withdrawal from desvenlafaxine vs withdrawal from placebo. DESS score was reported for the withdrawal vs continuation phase, however, this was reported for subgroups of those receiving 200mg and 400mg during the open-label phase separately, and N numbers are not provided for these subgroups in order to analyse the mean +SD (not usable). Study also reports DESS for week 3 of taper phase (withdrawal from desvenlafaxine vs withdrawal from placebo), but again this is reported for those who were on 400mg originally separately, with no N numbers in order to analyse the mean +SD (not usable).
Indirectness of population	No indirectness.
Interventions	(n=190) Intervention 1: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from desvenlafaxine during taper phase (at end of double-blind phase): those who continued on desvenlafaxine (200mg/day or 400mg/day) for the double-blind phase of 24 weeks were then tapered over a period of 1-2 weeks, which could be extended, shortened or omitted at the discretion of the investigator. 12 week open-label phase desvenlafaxine 200mg/day or 400mg/day, with the dosage determined by the investigator depending on efficacy and tolerability. Responders at the end of week 12 randomised to continue on desvenlafaxine at the same dosage they were on at the end of the open-label period (200mg/day or 400mg/day) for the 24-week double-blind phase. Doses of desvenlafaxine could not be changed during the double-blind phase other than a decrease from 400mg/day to 200mg/day due to tolerability reasons. Duration 12 week open-label phase + 24-week discontinuation/continuation double blind phase + 1–2-week taper phase. Concurrent medication/care: Not reported. Indirectness: No indirectness. (n=185) Intervention 2: Withdrawal from placebo during taper phase (at end of double-blind phase): those who were

Study	Rickels 2010[584]
	randomised to placebo for the double-blind phase of 24 weeks were then tapered over a period of 1-2 weeks, which could be extended, shortened or omitted at the discretion of the investigator. . Duration 12 week open-label phase + 24-week discontinuation/continuation double blind phase + 1–2-week taper phase. Concurrent medication/care: Not reported. Indirectness: No indirectness Comments: Note: these people had previously received desvenlafaxine during the open-label phase of 12 weeks (200mg/day or 400mg/day, with the dosage determined by the investigator depending on efficacy and tolerability). Responders at the end of week 12 were randomised to placebo for the 24-week double-blind phase (this was a taper to placebo of 200mg/day for week 1 and 100mg/day for week 2 of the double blind phase, then continued on placebo for the rest of the 24 weeks).
Funding	Study funded by industry.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM DESVENLAFAXINE (AT END OF 24 WEEK DOUBLE-BLIND PHASE) versus WITHDRAWAL FROM PLACEBO (AT END OF 24 WEEK DOUBLE-BLIND PHASE)

Protocol outcome 1: Any withdrawal symptom at post-intervention and longest follow-up

- Actual outcome for Antidepressants (others): Taper/post-therapy-emergent adverse events (those who were not present during the last 7 days of double blind treatment phase (with desvenlafaxine or placebo) or those that were present but became more severe) at During taper; Group 1: 101/190, Group 2: 52/185.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Those withdrawing from placebo had previously received 12 weeks treatment with desvenlafaxine during the open-label phase. They had been tapered off desvenlafaxine over 2 weeks at the start of the double-blind phase and then been taking placebo for the remainder of the 24-week double blind phase (for approximately 22 weeks). 58/190 and 101/185 discontinued treatment in the double blind phase early. However, methods state that 1–2-week taper of double blind study medication was carried out even for people who discontinued early. Unclear whether TEAEs were assessed during taper for those discontinuing early.; Indirectness of outcome: No indirectness. Group 1 Number missing: 190; Group 2 Number missing: 185. Drop-outs during taper were not reported.

Protocol outcome 2: Specific withdrawal symptom at post-intervention and longest follow-up.

- Actual outcome for Antidepressants (others): Headache (specific TEAEs reported by at least 5% in the placebo arm; TEAEs were defined as those who were not present during the last 7 days of double blind treatment phase (with desvenlafaxine or placebo) or those that were present but became more severe) at

Study	Rickels 2010[584]
During taper; Group 1: 23/190, Group 2: 13/185; Comments: Results reported as percentages and calculated from randomised numbers (12% and 7% in the desvenlafaxine and placebo groups, respectively). Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Those withdrawing from placebo had previously received 12 weeks treatment with desvenlafaxine during the open-label phase. They had been tapered off desvenlafaxine over 2 weeks at the start of the double-blind phase and then been taking placebo for the remainder of the 24-week double blind phase (for approximately 22 weeks). 58/190 and 101/185 discontinued treatment in the double blind phase early. However, methods state that 1–2-week taper of double blind study medication was carried out even for people who discontinued early. Unclear whether TEAEs were assessed during taper for those discontinuing early. Outcome reporting: results for both arms only reported for the specific TEAEs which occurred in >5% of the placebo arm (headache, insomnia and nausea). Study also reported TEAEs of dizziness (22%), irritability (10%), diarrhoea (7%), anxiety (6%), fatigue (5%), abnormal dreams (5%) and hyperhidrosis (5%) in the desvenlafaxine arm, which occurred in >5% of the desvenlafaxine arm, however these outcomes could not be used as the numbers of events were not reported in the placebo arm.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 190; Group 2 Number missing: 185. Drop-outs during taper were not reported. - Actual outcome for Antidepressants (others): Insomnia (specific TEAEs reported by at least 5% in the placebo arm; TEAEs were defined as those who were not present during the last 7 days of double blind treatment phase (with desvenlafaxine or placebo) or those that were present but became more severe) at During taper; Group 1: 13/190, Group 2: 11/185; Comments: Results reported as percentages and calculated from randomised numbers (7% and 6% in the desvenlafaxine and placebo groups, respectively). Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Those withdrawing from placebo had previously received 12 weeks treatment with desvenlafaxine during the open-label phase. They had been tapered off desvenlafaxine over 2 weeks at the start of the double-blind phase and then been taking placebo for the remainder of the 24-week double blind phase (for approximately 22 weeks). 58/190 and 101/185 discontinued treatment in the double blind phase early. However, methods state that 1–2-week taper of double blind study medication was carried out even for people who discontinued early. Unclear whether TEAEs were assessed during taper for those discontinuing early. Outcome reporting: results for both arms only reported for the specific TEAEs which occurred in >5% of the placebo arm (headache, insomnia and nausea). Study also reported TEAEs of dizziness (22%), irritability (10%), diarrhoea (7%), anxiety (6%), fatigue (5%), abnormal dreams (5%) and hyperhidrosis (5%) in the desvenlafaxine arm, which occurred in >5% of the desvenlafaxine arm, however these outcomes could not be used as the numbers of events were not reported in the placebo arm.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 190; Group 2 Number missing: 185. Drop-outs during taper were not reported.	

Study	**Rickels 2010[584]**
- Actual outcome for Antidepressants (others): Nausea (specific TEAEs reported by at least 5% in the placebo arm; TEAEs were defined as those who were not present during the last 7 days of double blind treatment phase (with desvenlafaxine or placebo) or those that were present but became more severe) at During taper; Group 1: 27/190, Group 2: 9/185; Comments: Results reported as percentages and calculated from randomised numbers (14% and 5% in the desvenlafaxine and placebo groups, respectively). Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Those withdrawing from placebo had previously received 12 weeks treatment with desvenlafaxine during the open-label phase. They had been tapered off desvenlafaxine over 2 weeks at the start of the double-blind phase and then been taking placebo for the remainder of the 24-week double blind phase (for approximately 22 weeks). 58/190 and 101/185 discontinued treatment in the double blind phase early. However, methods state that 1–2-week taper of double blind study medication was carried out even for people who discontinued early. Unclear whether TEAEs were assessed during taper for those discontinuing early. Outcome reporting: results for both arms only reported for the specific TEAEs which occurred in >5% of the placebo arm (headache, insomnia and nausea). Study also reported TEAEs of dizziness (22%), irritability (10%), diarrhoea (7%), anxiety (6%), fatigue (5%), abnormal dreams (5%) and hyperhidrosis (5%) in the desvenlafaxine arm, which occurred in >5% of the desvenlafaxine arm, however these outcomes could not be used as the numbers of events were not reported in the placebo arm.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 190; Group 2 Number missing: 185. Drop-outs during taper were not reported.	
Protocol outcomes not reported by the study	Duration of withdrawal syndrome at n/a; Quality of life at n/a; Intensity of withdrawal symptoms at post-intervention and longest follow-up

Study	**Rynn 2008[612]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=327)
Countries and setting	Conducted in USA; Setting: 27 outpatient treatment centres

Study	**Rynn 2008[612]**
Line of therapy	1st line
Duration of study	Intervention time: 10-week treatment phase + 2-week discontinuation phase
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Antidepressants (others): Duloxetine
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 18 years old; a primary diagnosis of DSM-IV-defined GAD, and severity ratings on the following measures: at least a 4 on the CGI-S, a Hospital Anxiety and Depression Scale (HADS) Anxiety subscale of 10 or more, a Covi Anxiety Scale (CAS) score of 9 or more, the CAS total score had to be greater than the Raskin Depression Scale total score. Medically healthy as determined by a physical exam, ECG and lab results (renal, liver and thyroid function tests). Adequate contraception for females of childbearing status.
Exclusion criteria	Recent (6 month) diagnosis of MDD or substance abuse/dependence; a past year history of panic disorder; post-traumatic stress disorder; or an eating disorder. A lifetime history of psychotic, bipolar, obsessive-compulsive disorder, or psychosis. Free of psychotropic medications for at least 2 weeks (4 weeks for fluoxetine)
Recruitment/selection of patients	not reported
Age, gender and ethnicity	Age - Mean (SD): Duloxetine 42.2 (13.9); placebo 41.0 (14.2). Gender (M:F): 125/202. Ethnicity: Caucasian 78.9%; African 12.6%; Hispanic 5.8%; Asian 2.8%
Further population details	1. Half-life of benzodiazepine the population are taking: Not applicable
Extra comments	. Patients also underwent urine screens for benzodiazepines and illicit drugs.

Study	**Rynn 2008[612]**
Indirectness of population	No indirectness
Interventions	(n=168) Intervention 1: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from duloxetine 6-120mg (10-week treatment phase + 2-week discontinuation phase): screening/washout phase (up to 30 days); 1-week single blind placebo lead-in phase; 10-week treatment phase; 2-week taper/discontinuation phase. Starting dose of 60mg, but a dose decrease to 30mg was possible during the first 2 weeks to acclimate to the medication. By week 2, patients were required to take a minimum dose of 60mg/day. Patients' doses were progressively titrated at each subsequent visit (in this case by 30mg duloxetine) if their CGI-I rating was 3 or more (minimal improvement, no change or worsening) and they were able to tolerate a dose increase. Patients could be increased to a maximum of 120mg/day. Tapering occurred over a 2-week period. Duration 10-week treatment period + 2-week discontinuation period. Concurrent medication/care: Antihypertensive medication was allowed if the patient had been on a stable dose for 3 months. Indirectness: No indirectness (n=159) Intervention 2: Withdrawal from placebo. (10-week treatment phase + 2-week discontinuation phase): screening/washout phase (up to 30 days); 1-week single blind placebo lead-in phase; 10-week treatment phase; 2-week taper/discontinuation phase. Patients' doses were progressively titrated at each subsequent visit (in this case placebo) if their CGI-I rating was 3 or more (minimal improvement, no change or worsening) and they were able to tolerate a dose increase. Tapering occurred over a 2-week period (unclear if this comment applies to placebo as well as drug arms). Duration 10-week treatment period + 2-week discontinuation period. Concurrent medication/care: Antihypertensive medication was allowed if the patient had been on a stable dose for 3 months. Indirectness: Serious indirectness; Indirectness comment: Not specifically stated that the placebo arm is withdrawn during the discontinuation phase, so unclear
Funding	Study funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM DULOXETINE 60-120MG versus WITHDRAWAL FROM PLACEBO Protocol outcome 1: Any withdrawal symptom at post-intervention and longest follow-up	

Study	**Rynn 2008[612]**
- Actual outcome for Antidepressants (others): Any discontinuation-emergent adverse event (DEAE) at During the discontinuation period; Group 1: 21/95, Group 2: 19/110; Comments: Total numbers analysed calculated from the percentages having the event provided (duloxetine 21 people had events (22.1%) and placebo 19 people had events (17.3%)). Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - Unclear, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 73 (during treatment phase), taper phase was unclear, Reason: Numbers analysed does not match number of people who discontinued during the treatment phase in the breakdown of reasons table, but main reasons for drop-out of the treatment phase were adverse events, patient decision or lost to follow-up; Group 2 Number missing: 49 (during treatment phase), taper phase was unclear, Reason: Numbers analysed does not match number of people who discontinued during the treatment phase in the breakdown of reasons table, but main reasons for drop-out of the treatment phase were adverse events, patient decision or lost to follow-up. Protocol outcome 2: Specific withdrawal symptom at post-intervention and longest follow-up. - Actual outcome for Antidepressants (others): Dizziness: discontinuation-emergent adverse event (DEAE) at During the discontinuation period; Group 1: 6/95, Group 2: 3/110; Comments: Only percentages of people having event for each arm reported (duloxetine 6.3%, placebo 2.7%), but assumed total numbers analysed was the same as for the DEAE outcome (for DEAE outcome, duloxetine n=95, placebo n=110), so dichotomous outcomes calculated. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Unclear, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Selective reporting of the dizziness DEAE outcome (the only DEAE to occur in >5% of duloxetine treated patients) and no other specific DEAE outcomes; Indirectness of outcome: No indirectness ; Group 1 Number missing: 73 (during treatment phase), taper phase was unclear, Reason: Numbers analysed does not match number of people who discontinued during the treatment phase in the breakdown of reasons table, but main reasons for drop-out of the treatment phase were adverse events, patient decision or lost to follow-up; Group 2 Number missing: 49 (during treatment phase), taper phase was unclear, Reason: Numbers analysed does not match number of people who discontinued during the treatment phase in the breakdown of reasons table, but main reasons for drop-out of the treatment phase were adverse events, patient decision or lost to follow-up.	
Protocol outcomes not reported by the study	Duration of withdrawal syndrome at n/a; Quality of life at n/a; Intensity of withdrawal symptoms at post-intervention and longest follow-up

Study	**Yovell 2016[775]**
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=88)
Countries and setting	Conducted in Israel; Setting: four medical and psychiatric centres in Israel
Line of therapy	Unclear
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Opioids: Buprenorphine
Subgroup analysis within study	Not applicable:
Inclusion criteria	Between 18 and 65 years of age and suffered from clinically significant suicidal ideation, as indicated by a score >11 on the self-report version of the Beck Scale for Suicide Ideation for at least 1 week.
Exclusion criteria	A lifetime history of opioid abuse, a lifetime diagnosis of schizophrenia, current psychosis, ECT within the past month, substance or alcohol abuse within the past 2 years, and benzodiazepine dependence within the past 2 years. Pregnant or lactating women; patients who suffered from any severe medical condition.
Recruitment/selection of patients	patients recruited from four medical and psychiatric centres in Israel, Jan 2010 to July 2013
Age, gender and ethnicity	Age - Mean (SD): 37.3 (13.9). Gender (M:F): 25/63. Ethnicity: not reported
Further population details	1. Half-life of benzodiazepine the population are taking: NA

Study	**Yovell 2016[775]**
Extra comments	. Aim of study was ultra-low-dose buprenorphine as a treatment for severe suicidal ideation
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: Withdrawal from placebo. 4-week treatment period + abrupt discontinuation ("at end of week 4, study medication discontinued without a taper"). Patients received placebo in place of study drug for treatment period. Identical sub-lingual placebo lozenges. Duration 4 weeks treatment + discontinuation without taper. Concurrent medication/care: Participants on antidepressants had to be taking them for at least 28 days, and no changes were allowed during the study period. More than 70% were on antidepressants, and almost all took some psychotropic medication other than the study drug. With the exception of antidepressants, the treating clinicians could modify the pharmacotherapy their patients were receiving, and could see them as frequently as deemed necessary. Indirectness: No indirectness (n=57) Intervention 2: Withdrawal from/stopping use of one of the prescribed medicines - Withdrawal from buprenorphine. 4-week treatment period + abrupt discontinuation ("at end of week 4, study medication discontinued without a taper"). Sublingual buprenorphine lozenges were administered on a flexible schedule, beginning with 0.1 or 0.2 mg/day. Once a week the daily dose could be raised in 0.1–0.2mg increments, to a maximal daily dose of 0.8 mg. A week's supply of medication (<5.6 mg, usually<2.8 mg) was not considered to present a high risk for suicide by overdose. The dose was not raised if participants were found to have reached full remission (i.e., had a score of zero on items 4 and 5 of the Beck Scale for Suicide Ideation) or if they experienced significant adverse events. Duration 4 weeks treatment + discontinuation without taper. Concurrent medication/care: Participants on antidepressants had to be taking them for at least 28 days, and no changes were allowed during the study period. More than 70% were on antidepressants, and almost all took some psychotropic medication other than the study drug. With the exception of antidepressants, the treating clinicians could modify the pharmacotherapy their patients were receiving, and could see them as frequently as deemed necessary. Indirectness: No indirectness
Funding	Academic or government funding (Dr. Yovell and Dr. Panksepp were supported by the Hope for Depression Research Foundation (New York). The study was also supported by the Neuropsychoanalysis Foundation and the Institute for the Study of Affective Neuroscience (University of Haifa).)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITHDRAWAL FROM BUPRENORPHINE versus WITHDRAWAL FROM PLACEBO	

Study	Yovell 2016[775]
	Protocol outcome 1: Any withdrawal symptom at post-intervention and longest follow-up. - Actual outcome for Opioids: Withdrawal symptoms (assessed at appointment with psychiatrist to screen for possible withdrawal symptoms) at 1 week post-abrupt-discontinuation ; Group 1: 0/57, Group 2: 0/31; Comments: Narrative comment that all participants denied withdrawal symptoms during their follow-up appointment. Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Incomplete outcome: analysis of safety population done on all randomly assigned participants who took at least one dose of study drug (all patients who were randomised received at least one dose, n=57 and n=31). n=24 and n=14 in drug and placebo arms, respectively, discontinued during the treatment phase, but unclear if people who discontinued early had a follow-up visit to assess withdrawal symptoms. Measurement: states that "all participants had an appointment with a study psychiatrist to screen for possible withdrawal symptoms", but unclear how withdrawal symptoms were assessed and whether this was consistent in all participants. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24, Reason: discontinued during treatment period: 13 due to adverse events, 5 lost to follow-up, 5 withdrew consent, 1 withdrawn due to protocol violation; Group 2 Number missing: 14, Reason: discontinued during treatment period: 5 due to adverse events, 4 lost to follow-up, 2 withdrew consent, 3 withdrawn due to protocol violation
Protocol outcomes not reported by the study	Specific withdrawal symptom at post-intervention and longest follow-up; Duration of withdrawal syndrome at n/a; Quality of life at n/a; Intensity of withdrawal symptoms at post-intervention and longest follow-up

E.2 Qualitative evidence

Study	Anderson 2013[31]
Aim	To examine patient and health professional understanding of what it is like to use antidepressants from initiation of therapy and to determine factors which influence decisions about adherence to antidepressants in terms of perceived outcomes and determining factors that influenced their views.

Study	**Anderson 2013[31]**
Population	A maximum variation sample of eighty people with different types of depression and treatment experiences, different age groups, ethnicities and social classes were recruited from a wide variety of locations across the UK. Adults n=42; male/female:16/26 age range: 20-75 Young people n=38; male/female:9/29; age range: 16-27 Strata: mixed/unclear antidepressants
Setting	University of Oxford
Study design	Secondary analysis of qualitative interview transcripts.
Methods and analysis	A supplementary secondary analysis of the Healthtalkonline database exploring patients' experiences of using medicines for depression was performed. Interviews of the primary study were held at the University of Oxford. The data had been previously coded into broad codes of experiences of medicines and side-effects, decisions about treatments etc. In the new analysis that was performed, a more in-depth focus was taken on emergent issues around the use of antidepressants which were not addressed or only partially addressed by the primary research. Thus, data about issues around antidepressant use was examined in more depth. In the initial study interviews ranged from 90-180 minutes and were audio or video recorded, transcribed and returned to the participants for review. Emerging themes were identified using a 'modified grounded theory' approach and multiple levels of analysis. The researchers coded the complete transcripts exploring the data for broad themes regarding the use of medicines across the data set as well as themes unique to antidepressants. Statements referring to similar topics were categorised together to form a basic coding framework which was extended as the content within each category increased. This process was iterative; whereby it was repeated until no new statements relating to antidepressants could be found. The concepts from the data were developed into new themes; two researchers and a public health doctor and academic pharmacist met to discuss emergent themes and develop a preliminary coding framework which was applied to another subset of transcripts and inter-rater reliability checks were made by the researchers. All transcripts were then coded by the main researcher and were then checked by the other researcher.
Findings	**Duration of withdrawal symptoms (1 week)**

Study	**Anderson 2013[31]**
	One participant reported: "I had a week of withdrawal. And when you experience those, they're the strangest things ever.
	Strange symptoms: head buzz
	Some participants were reported to describe withdrawal symptoms vividly. One participant reported: "I had a week of withdrawal. And when you experience those, they're the strangest things ever. When you make a gross movement, a gross muscle movement, you get this incredible, uh…It's not a tingling, you get this incredible buzz in your head'
Funding	The School of Pharmacy, University of Nottingham, United Kingdom.
Limitations and applicability of evidence	Overall CASP rating: Minor concerns (due to the potential influence of the researchers on the findings not being discussed and due to very minor concerns over potential bias in recruitment with participants having already been selected for a different project). No concerns over applicability

Study	**Avery, 2011[46]**
Aim	The HTA aimed to evaluate patient reporting of suspected ADRs (adverse drug reactions) to the YCS (Yellow card scheme) in the UK by assessing the pharmacovigilance contribution of patient reports, exploring the views of patient reporters and members of the public.
Population	N=270 patient reports. Mean age [standard deviation (SD)] in patient reports [44.2 (16.1) years The number of drugs that the patient was reported as taking [median 2 (IQR 1 to 3)
Country, Setting	UK
Study design	Mixed methods (HTA)

Study	**Avery, 2011[46]**
Methods and analysis	Yellow Card reports are submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) by post or telephone or via the internet. The MHRA electronically recorded and reviewed the information submitted, so that important safety issues could be detected. A purposive sample was taken from a range of different categories of Yellow Card reports. When describing patients reports, extracts were quoted verbatim and identified by reporter type (patient or professional group), gender of patient, age of patient (years), suspect drug name and reporting method. A range of extracts from Yellow Card Reports were used to illustrate the findings, representing different patients, reactions and drugs. A number of major categories arose from the content analysis, and these informed the in-depth qualitative analysis.
Findings	**Symptom description** <u>Paroxetine user,</u> ''Since beginning to reduce this medicine, I have had terrible withdrawal symptoms, these have included: sudden changes in emotion and mood, crying, insomnia, excessive anxiety and agitation, sweating and palpitations. There have also been bouts of stomach upsets, nausea, dizziness and headaches. Since reaching an amount of 5 mg I have had to use the liquid version with a syringe and make reductions of 1 mg per month, this has been the worst stage so far and I have been prescribed medication to alleviate the unbearable anxiety that this is causing! Still 2 mg to go before I am off this horrendous medicine! HEADACHE HEADACHE'' ''I was prescribed this medication for mild sleeplessness. I became addicted to it and after 18 months of severely debilitating symptoms, the principal symptom being persistent suicidal thoughts.''
	Dose relationship <u>Citalopram user</u> ''The following quotes show how patient reports linked suspected ADRs to a change in dose: I am presently taking 40 mg daily of this medication. On increasing the dose of citalopram, first to 60 mg and then reducing to 50 mg daily –I experienced severe agitation and a recurrent thought of ending my life. On 60 mg, I felt seriously suicidal, and had constant morbid thoughts and fixation. Increasing citalopram from 40mg daily to 60 mg daily made my depression and anxiety much worse, therefore having the reverse effect on my mood – inducing suicidal feelings''.
	Impact of the medication on their lives

Study	Avery, 2011[46]
	Forty-seven per cent of patient reports discussed the impact of the reaction on their lives. Three types of impact were discussed: impact on relationships and social life, occupational impact and emotional impact. Citalopram user, ''After the dose drop to 10 mg, I had mood swings, palpitations and a weird head lagging behind sensation which I believe were withdrawal symptoms. Five weeks after the dose drop, I got more symptoms – tiredness to the point of not being able to go to shops headaches, aching joints and muscles like having the flu, anxiety, sweating, finding it hard to speak, unable to cope with any stress, and feeling like I had been punched in the eyes. This belated effect is the bit I am worried about….'' ''I am a lab-based research student, and the above symptoms make it unsafe for me to Work… '' ''Became increasingly confused, violent and abusive towards his partner. Disorientated, and in his words thoroughly pissed off with life in total…'' Venlafaxine user ''I have suffered horrific adverse reactions to venlafaxine. I have been unable to work for over 18 months and started part time again, but have had another month of debilitating withdrawal.'' ''After tapering down as per doctor's instructions then stopping experienced nausea, ongoing irritable bowel syndrome, dizziness, fatigue, sweating, nightmares, electric shock-like sensations also called brain shivers, akathisia, abnormal vision, nervousness, panic attacks, depressed feelings, suicidal thoughts and confusion''. Paroxetine user ''I tried suicide on several attempts and even attacked my father for no reason''

Study	Avery, 2011[46]
	Impact of withdrawal Venlafaxine user ''Dizziness, nausea, alternate sweats and chills, unable to stand properly, balance affected. Dislike of bright lights, slurred speech, no appetite not even wanted liquids, pains in abdomen. Re-started medication, and symptoms increased in severity, vomited after 36 hours, once after taking first capsule and soup, saw out of hours doctor as blood pressure was raised, heart rate fast and blood in urine – on test strip. Away from home for few days, forgot medication. After 48 hours from previous dose symptoms began. Continued to worsen. Family members called NHS direct helpline. Doctor contacted advised withdrawal symptoms. Gave emergency prescription. GP said it was like 'heroin cold turkey'. I thought SSRIs were non-addictive, therefore I am very concerned about the severity of these symptoms and the duty doctor comparing it to a controlled drug withdrawal''. Citalopram user ''Withdrawing from this drug caused me to feel suicidal. I made two suicide attempts during withdrawal. I am now on no medication at all'' Paroxetine user ''As I started to come off the medicine, I started to feel anxious all over again despite feeling perfectly well prior to deciding to stop. Each time I have tried to come off the drug it has resulted in returning to the medication as the side effect s have too much impact on my daily routine. I have been taking the medicine again and plan to start to gradually withdraw using a liquid replacement of the tablet in the immediate future. Hopefully, this will allow me to reduce the quantity very gradually and have less effect.''
Funding	The National Institute for Health Research Health Technology Assessment programme.
Limitations and applicability of evidence	Overall CASP rating: No concerns. No concerns over applicability. Note: We have only reported findings for relevant drugs in this review.

Study	Barter 1996[67]
Aim	To gain an understanding of why patients continue to use benzodiazepines using a semi-structured interview technique and by comparing to non-benzodiazepine users.
Population	Elderly patients who had received a benzodiazepine prescription for hypnotic use continuously for a minimum of one year. Those with hearing difficulties, anyone suffering from a serious illness and those in crisis at the time of the study were excluded. N=11 (14 initially volunteered to participate, having been selected by their doctors according to the study criteria, 2 were unavailable and 1 patient was unobtainable); male/female: 1/10; mean age: stated to be elderly, no further details; benzodiazepine currently being taken: temazepam: 5, nitrazepam: 3, diazepam: 2, lormetazepam: 1. Duration of BZD use: 8.5 years (mean), 1-36 years (range)
Setting	Three group practices in or on the outskirts of two cities in the south and southwest of England
Study design	Qualitative study using in-person semi-structured interviews and a comparison group.
Methods and analysis	Patients' experiences were explored using a semi-structured interview which was constructed to cover seven particular areas: type of benzodiazepine used, length of use and pattern of taking; social support; reasons for first using these tablets and current reasons; perception of doctor attitude and prescribing behaviour; wishes and efforts to stop taking the tablets; and general sleep quality. The interviews took an average of 75 minutes (range 50-120 minutes) and were conducted by the same interviewer. Notes were taken and each interview was audio-taped and later transcribed by the researcher. All interviews were conducted in the participants homes, although participants had a choice of having the interviews at the general practice. Throughout the course of data collection, it emerged that a comparison group of the same age who did not necessarily take tablets to help with sleep was needed in order to determine whether any of the findings from the interviews were unique to the particular sample or representative of this population age-group. Interviews lasting 2 minutes were conducted on 20

Study	Barter 1996[67]
	elderly people (12F/8M) in a local high street, approached at random. A brief interview was designed to collect comparative data on sleep pattern, subjective quality of sleep, social support and whether something with perceived or actual sleep-inducing properties was taken at night.
Findings	**Return of original symptoms** Three participants had tried to stop using their sleeping tablet but had had to resume the same night due to insomnia: 'I have tried to stop, but….I am still wide awake at 2 or 3 o'clock in the morning'. A participant who had stopped for 1 month: 'I could not sleep. I was getting up at night and wandering around'
	Lack of withdrawal symptoms Some participants reported no issues with stopping their medication. Three participants had stopped using sleeping tablets and receiving prescriptions for several months or periods at a time over the years. No reports of disturbed sleep or illness were mentioned upon discontinuation.
	Experiences of withdrawal effects Some participants experienced withdrawal symptoms. A participant who had stopped using sleeping tablets for 5 days: 'I went without them…it was awful, my chest, I was in pain' and another said, 'When the drug was taken away it nearly killed me.' A participant who had stopped for 1 month: 'if I don't take a tablet then, well it is just nasty dreams, very disturbed'
	Effect on daily life Withdrawal effects could also interfere with daily life by causing disturbing dreams to the extent that a participant who had stopped for 1 month found: 'it leaves me a bit upset and shattered the next morning'.
	Lack of confidence in stopping Some participants can find the idea of stopping to be difficult: 'I couldn't possibly put myself through the problem of trying to give them up whilst I had all this worry'.
Funding	Not stated

Study	**Barter 1996[67]**
Limitations and applicability of evidence	Overall CASP rating: Minor concerns (due to limited information and quotes to support the findings and the interviewer qualification being unclear). No concerns over applicability

Study	**Bayliss 2015[69]**
Aim	To develop a preliminary model of the experiences of people undergoing combined treatment with antidepressant medication and cognitive-behavioural therapy (CBT) for depression.
Population	Participants were 12 adults who had received treatment with antidepressant medication and CBT for depression. Participants engaged in a semi structured interview about their experiences. Interviews were transcribed and analysed using components of grounded theory methodology.
Country, Setting	UK
Study design	The study used a qualitative methodology informed by grounded theory.
Methods and analysis	Seven participants were interviewed in the setting where they saw their therapist, three in the Trust's psychology department, one in a hospital ward and one at home. Before each interview, participants were given a short briefing concerning the purpose of the study and ethical issues. Interviews lasted from 35 min to 2 hr. They were recorded in full. After each interview participants were debriefed and offered further support. All interviews were later transcribed. The complete data corpus comprised over 300 pages of transcripts. Analysis drew on the approach described by Strauss and Corbin (1998). This involved constant comparison of data and emerging concepts in an iterative process of open, axial, and selective coding. This began with detailed line-by-line microanalysis (Strauss & Corbin, 1998) aimed at identifying categories within the data. Analysis then progressed to exploring these categories, their properties, and the relationships between them. Later stages of analysis involved broader theoretical integration. Wherever possible, data analysis took place after each interview.

Study	**Bayliss 2015[69]**
Findings	*Dilemmas about dependency* Several participants reported feeling dependent on medication, and a fear that discontinuation could cause a crisis. Participants tended to feel dependent on medication when they had survived a period of extreme distress through taking medication, when they saw themselves as fragile, and when they had experienced resurgences of distress after stopping or changing medication, or missing doses: 'It's always been really difficult coming off one...really uncomfortable and really feeling like you're losing your mind and getting really depressed...and so you have to put a bit of faith in the tablets'. 'I don't want to rely on drugs because I see it as an artificial control'. Such dilemmas often contributed to participants wishing to stop medication'. 'I felt very dependent on [my amitriptyline tablets] and I didn't want to be dependent on them, and so that made me want to. . .stop taking them'.
Funding	Not stated
Limitations and applicability of evidence	Overall CASP rating: Minor concerns (due to concerns over data richness (n=12)) No concerns about applicability.

Study	**Cartwright 2018[117]**
Aim	To understand how the experiences of using antidepressants and engaging in other activities and practices promote or diminish women's sense of agency in regard to their recovery.
Population	Women who had been prescribed and used antidepressants in the previous five years; who had taken part in a large anonymous online survey about antidepressant use and volunteered for an interview about their experiences of antidepressants; Including a range of women from the three groups: positive, negative and mixed experiences, including participants who had been on antidepressants in the short, medium and long term. N=50; mean age (range): 44.5 (27 to 62 years); n=35 were still using antidepressants at the time of the interview and n=15 were not. They were estimated to be on antidepressants between four months and 25 years (mean: 7 years); n=17 had used

Study	Cartwright 2018[117]
	antidepressants for less than two years, n=17 for two to five years, n=9 for 5-10 years and n=7 for more than 10 years. N=23 reported positive experiences of antidepressants, 22 reported mixed, and 4 reported negative.
Setting	University of Auckland, New Zealand
Study design	Qualitative interview study
Methods and analysis	Telephone interviews were conducted using an interview guide, developed to encourage participants to talk about their experience of using antidepressants and any other activities or practices they engaged in to support their recovery. Interviewers were clinical psychology doctoral trainees trained in the interview method. Participants were initially encouraged to talk about their experiences to a depth with which they felt comfortable. They were asked to talk about what was happening in their lives prior to using antidepressants, about their experiences of antidepressants and any positive and problematic aspects. The interview then continued with a series of questions designed to engage them in reflective and interpretive activity with regard to their experiences of any alternative treatments and other activities they engaged to assist recovery. Interviews lasted 40 minutes on average varying from shorter interviews with women who had brief positive experiences of antidepressants to longer interviews that lasted up to an hour. Thematic analysis was used to analyse the data. Interview transcripts were initially examined and coded by the first author. Coded data were examined and grouped into sets of related data. This process led to the development of five potential themes examined by the second and third authors, examining areas of disagreement and establishing the final themes.
Findings	**Fear of discontinuation**
	Some expressed fear of attempting to discontinue because of previous experiences of doing so and losing their stability. One participant in particular described this as a 'really horrible, very frightening thought' and that despite being a very capable person who would like to think she could manage without antidepressants she reported to 'lose sight of reality' and starting to 'get overwhelmed by fears and worries.'
	Intensity of withdrawal symptoms
	Participants described previous experiences of severe withdrawal symptoms that led them to feel out of control. One participants talked about a 2–3-week period between prescriptions (Mirtazapine or Venlafaxine) that was 'just horrible' when she was 'feeling really like, almost aggro and really anxious and tearful. Severe withdrawal symptoms often led women to

Study	Cartwright 2018[117]
	recontinue antidepressants with one woman on Fluoxetine reporting stopping was a 'big mistake' as 'you get depressed again and then you start taking it again and you get all the side effects…so the trick is not to just stop taking it'
	Inability to manage emotions
	Unsuccessful attempts to withdraw diminished women's sense of agency in relation to managing their own well-being and increased feelings of dependency on the medication. This contributed to negative feelings about themselves and an inability to regulate emotions without them, which led to a fear of coming off them because of that.
	Something 'not quite right in the brain'
	Relying on antidepressants increased feelings of abnormality with one patient reporting being on medication and when coming off them always feeling that there is 'something not quite right in my brain- that I just need to keep taking them'
Funding	Not stated
Limitations and applicability of evidence	Overall CASP rating: Minor concerns (due to the potential influence of the researcher on the findings not being discussed). Minor concerns over applicability due to the all-female sample.

Study	Eveleigh 2019[188]
Aim	To explore the attitudes of patients, who are using antidepressants long term without a proper current indication, towards the discontinuation of these drugs, and to explore their attitudes towards the discontinuation advice they received when participating in an RCT.
Population	A purposive sample of participants from the intervention group of a cluster-RCT of patients on long-term antidepressant use (defined as 9 months or longer) without a current indication (no psychiatric diagnosis); as part of the intervention group, they had been provided advice to stop antidepressants. n= 16; male/female: 5/11; mean age (range) 57 (women: 31-76; men: 51-79) years, using a variety of antidepressants including various types of SSRIs, Tricyclics and other antidepressants; n=7 participants intended to comply with the discontinuation advice during the RCT and n=5 of these actually discontinued during or after the RCT.
Setting	General practice
Study design	Qualitative study

Study	**Eveleigh 2019[188]**
Methods and analysis	In-depth semi-structured interviews conducted via telephone lasted 15-20min; were performed by a physician who was a trained interviewer; were audio-recorded and transcribed verbatim. Interviews were analysed using thematic analysis which was carried out inductively using a qualitative software package. Analysis began once data collection commenced as an iterative process based on the 'constant comparative method'. Coding was carried out independently by two of the authors. When consensus was not reached a third author was consulted
Findings	**Fear of discontinuation: recurrence**
	Fears were sometimes fuelled by experiences during prior discontinuation attempts. Because of this difficulty tapering and discontinuation symptoms, attributions concerning lifelong need and anticipation fear were reconfirmed. The confidence a participant had beforehand in the success of a discontinuation attempt was important. If the participant could be convinced the attempt would be successful, the fear to discontinue would diminish. The GP played an important role in this, both as a 'safety net' and as a 'partner or counsellor' during the discontinuation attempt.
	Lower tolerance levels & agitation
	One patient who had made a prior attempt to tapper but did not discontinue, reported that, during that time, his tolerance level lowered, and he became agitated.
	Increased feelings: Loneliness (psychological/mood changes)
	One patient who had made a prior attempt to tapper but did not discontinue, reported that, during that time, he had more feelings of loneliness and abandonment, didn't feel well at all and didn't know what to do. He reported that kept coming back and he started to question why he should stop and restarted the medication.
Funding	ZonMW (a government organisation for grants for studies in the medical field)
Limitations and applicability of evidence	Overall CASP rating: Moderate concerns (due to the potential impact of the researcher on the findings not being explored and issues with data richness with themes mostly supported by limited information and single quotes). No concerns over applicability.

Study	**Goesling 2019[235]**
Aim	To identify themes pertaining to former opioid user's experiences before, during, and after opioid cessation

Study	Goesling 2019[235]
Population	Included adults between 18 and 70 years of age, a history of taking opioids every day for 3 months or longer and no current opioid use. Exclusion criteria: non-English speaking, current medical or psychiatric condition that would prevent meaningful participation, a history of recreational opioid use, involvement in litigation relating to current pain condition, prior use of opioid medication was for surgery related pain only and most recent opioid use was over 10 years ago. Patients were also excluded if tramadol was the type of opioid they previously used, suboxone or buprenorphine was used as replacement opioids when transitioned off opioids or they stopped because the prescription ran out. N=24 (formed 4 focus groups); time of focus groups: average = 98 (range 88-107) minutes Mean age (SD) for participants forming the focus groups is not provided; mean age (SD) of n=49 participants included in the wider mixed-method study was 49.3 (10.2) years; male/female: 17/32; primary pain: n=25 (51%) neck or back pain, n=6 (12.2%) fibromyalgia, n=5 (10.2%) other musculoskeletal pain, n=4 (8.2%) complex regional pain syndrome, n=1 (2%) headache/migraine, n=8 (16.3%) other pain. Length of pain for the majority (n=20 (59.2%) was more than 5 years.
Setting	Back and Pain Center (Department of Anaesthesiology, University of Michigan) and fibromyalgia Patient Education Workshop (University of Michigan)
Study design	Mixed methods study (including qualitative focus group data)
Methods and analysis	Focus groups of at least 5 participants; time between 1 and 2 hours. All participants completed a 20-minute online Qualtrics survey 1 week before ethe focus group. Focus groups were conducted in person by 2 trained interviewers. The number in each group ranged from 5 to 6. A semi-structured focus group protocol was developed and refined and used broad open-ended questions with follow up probes. Questions included both individual responses and more extended group discussion. Focus groups were recorded and transcribed verbatim. Analysed using an inductive thematic analysis. Transcripts read and discussed by 2 researchers to assess overall themes in the data immediately following each focus group. These initial discussions were used to formulate a list of codes to apply across transcripts. Codes were eliminated, added, and modified based on the content of focus groups. Emergent themes were compared across individuals, within groups, and across focus groups.
Findings	**Worsening of pain**

Study	Goesling 2019[235]
	Most participants experienced worsening pain symptoms when they tapered their opioid use. One participant stated, "My pain was much worse because they really did work for me pain wise". More time was spent on trying different procedures, surgeries or medications when an effective treatment could not be found. Worsening of pain without an alternative treatment impacted mood for some people.
	Leg cramps and anxiety
	Some participants had withdrawal symptoms that made it hard to quit: "I [had withdrawal] even though I tapered. Probably because I'd been taking it for so long and so much. It's like skin crawling. Leg cramps can't stop moving them, and it lasted a long time. I ended up with anxiety attacks, still have them I have to take medications for it".
	Cold and hot sweats
	All participant who experienced withdrawal symptoms during cessation reported that they stopped on their own without guidance. They also indicated that they were unsure what would happen when quitting or that they should taper to reduce withdrawal symptoms. "I didn't have any fears, but when I stopped, I had like 3 days of cold seats, hot swats, stuff like that. It was a pretty coming down thing. But you know, you got through it but you just don't know that you're gonna have that stuff happening".
Funding	National Institute on Drug Abuse (NIDA)
Limitations and applicability of evidence	Overall CASP rating: Very minor concerns (due to the potential influence of the researchers on the findings not being discussed). No concerns over applicability.

Study	Henry 2019[272]
Aim	To gain insight into patient experiences with opioid tapering by conducting focus groups and individual interviews with patients suffering from chronic neck and/or back pain.

Study	**Henry 2019[272]**
Population	Patients ≥ 35 years of age with chronic neck or back pain who were either taking long-term opioids (defined as ≥ 1 dose per day for ≥ 3 months) or had taken long-term opioids and had tapered down or off within the past year, identified through an electronic health record screening algorithm. N=21; male/female:10/11; mean age: 58 years; n=14 (67%) had recently completed an opioid taper (with 4 no longer taking opioids), n=4 (19%) were in the process of tapering and n=3 (14%) had discussed tapering but had not made changes **Of the n=7 patients who completed interviews, n=4 had completed tapering, n=2 were currently tapering and n=1 had been recommended to tapper.**
Setting	13 primary care clinics within the University of California, Davis
Study design	Focus group and qualitative interview study
Methods and analysis	Focus groups were conducted by the same investigator (while another investigator was taking notes), using a guide with topics derived from the Health Belief Model. Major topics included perceived barriers and benefits to tapering, strategies for communicating with clinician's, strategies for managing pain and opioids and sources of support. The most compelling storytellers (i.e., patients who investigators judged were best at engaging and opening other patients to the possibility of tapering) were identified based on group dynamics, audio recordings and transcripts. These patients were invited for 30-minute interviews. Individualised interview guides were used to prompt interviewees to recount and elaborate on the stories they told during their focus group. Interview transcripts were iteratively reviewed by four investigators to identify themes in patients' accounts of their tapering experiences. Investigators met every 2 weeks for 6 months to discuss and compare their interpretations of findings and to resolve differences among investigators. They summarised the key themes and concepts that emerged from the data and used them to develop a conceptual model of patients' tapering experiences.
Findings	**View on tapering**
	Several patients had tapered down or off opioids more than once. Patients who understood tapering to mean a gradual or partial reduction in opioid medication were generally more receptive to tapering than those who understood it to mean stopping 'cold turkey' or stopping opioid completely. Those who used the terms 'taper' and 'detox' interchangeably tended to associate tapering with withdrawal symptoms.
	Fear of worse pain, withdrawal and loss of function

Study	Henry 2019[272]
	Fear emerged as a uniquely powerful emotion affecting both patients' willingness to taper and their overall tapering experience. Most patient fears involved the possibility of worse pain and withdrawal owing to decreased opioids. One patient was so afraid of withdrawal that she would only attempt tapering in an inpatient facility**.** For most patients the prospect of tapering evoked fears involving a mix of pain, withdrawal and loss of function: 'I have that fear that if I stop, things are going to go to hell. I don't want to be in that situation again'. One patient described inchoate fear after a clinician refused to refill her oxycodone. Fears of addiction and overdose were less prominent than fears of pain and withdrawal. Managing emotions during tapering mostly entailed managing the fears of pain and loss of function. One patient noted that having fewer pills heightened the fears of uncontrollable pain which required her to expend more energy controlling these fears. 'I have the side effect of obsessing about how many (pills) I have'. Failure to control one's fear often made pain worse. 'I would start to feel the pain coming on and it would be like my mind would say, 'Oh my god, you're going to… it's like this fear of the worst pain you ever had, and it literally almost makes it manifest'
	Variability of withdrawal symptoms (pain)
	Patients' experiences tapering as dynamic because their pain and perceived need for opioids varied from day to day and because their pain was frequently affected (either positively or negatively) by changes in their social relationships and emotional state. Patients repeatedly emphasised that tapering requires planning and sustained effort, that 'it's a process' and involves going through a lot of different changes', that requires patients to adjust and recalibrate in response to these changes. When asked how she would advise others about tapering, one patient said, 'it's just that pain changes, it doesn't stay the same, there's constant change. It may take a while for it to change, it may get worse, it may get better'.
	Actively working to avoid withdrawal symptoms: stomach sickness, physical discomfort, headaches
	Patients continually adjusted opioid use based on their planned activities with tapering often requiring patients to expend more effort adjusting their habits and opioid consumption to maintain functionality. Nearly all noted that managing opioids became more difficult as tapering progressed. They worked to avoid withdrawal. One patient reported: 'If I'm an hour late on my dose, I get sick to my stomach.' Patients had to continuously exert self-control to balance their immediate desire for pain relief against their fear of worse pain or withdrawal if they ran out of opioids in the future. 2 patients quoted below made different decisions about these trade-offs: 1) 'If I'm careful and follow the plan of taking a pill every six hours or every eight hours I'm going to be ok… I may be somewhat physically uncomfortable but I'm not in screaming pain. I'm in screaming pain when I've taken too much medication one day and don't have enough for the next day.' 2) I can either feel like 80% my normal self for the whole months, or I can feel like I used to feel good for 3 weeks, and the last week, I don't take any

Study	Henry 2019[272]
	because it's all gone. Then you get the headaches and that kind of stuff. It's worth it for me to do that to be able to live the first 3 weeks.' Even patients who realized that their fear of uncontrolled pain was unfounded admitted that had to tolerate greater discomfort to 'get by' with fewer opioids.
	Worsening of symptoms for which medication was prescribed: back pain
	It was reported that for several patients, tapering discussions were precipitated by clinical retirement, with patients noting they had trouble finding primary care clinicians willing to prescribe opioids when they needed to change clinicians. One patient reported 'my back got worse, the pain was getting worse, and my doctor hadn't really sent me for more diagnostics, I just sent him an email and I said ''can I have another prescription of opioids?''…they're prescriptions I've had, why do I have to (come in and talk about the problem again)?'
	Duration of withdrawal symptoms
	Patients who tapered off opioids noted that withdrawal symptoms lasted weeks to months; 1 patient still experienced withdrawal symptoms 1 year after stopping oxycodone.
Funding	Not stated
Limitations and applicability of evidence	Overall CASP rating: Minor concerns (due to the potential influence of the researcher not being discussed and minor possibility of selection bias in patients interviewed (selected by the researchers: 10/21 of those who participated in focus groups were invited for individual interviews based on group dynamics and data review)). No concerns over applicability.

Study	Frank 2016[216]
Aim	To explore patients' perspectives on opioid tapering.
Population	Adult primary care patients who were currently or had previously been, on chronic opioid therapy (COT) n=24; 11 male, 13 female; mean age 52 years (range 31-73). Six participants (25%) were on COT and not tapering, 12 (50%) were currently tapering COT, and 6 (25%) had discontinued COT. The mean duration of opioid therapy was 7.7 years (SD 5.9). All participants were English-speaking.

Study	**Frank 2016[216]**
Setting	Three Colorado health care systems (Academic medical centre, Safety net hospital and a Veterans Affairs medical centre)
Study design	Qualitative study using in-person, semi-structured interviews.
Methods and analysis	Interviews were audio recorded, transcribed and analysed in ATLAS.ti. A team-based, mixed inductive and deductive approach was used, guided by the Health Belief Model. Emergent themes were iteratively refined with input from a multidisciplinary team.
	Fear & anxiety about withdrawal
	Past experiences of opioid withdrawal produced fear and anxiety about future opioid tapering or discontinuation.
	58-year-old male, on opioid medication without tapering: 'I don't think they're aware of how bad withdrawals are. **I mean there's vomiting bile, there's stomach cramps, there's the cold shakes and fever…I mean it's pretty bad'**
	53-year-old female, tapering opioid mediations: 'I also had lots of fears about let's say there was an apocalypse in our society, what would happen to me? Where would I get my medication from? What was going to happen, you know? I would get so sick not having those drugs 'cause I was physically dependent on these drugs, you know. It's a very insecure feeling.
	Little or no withdrawal symptoms
	In contrast, there were several disconfirming cases in patients who described little or no opioid withdrawal symptoms during tapering.
	60-year-old male discontinued opioid medications: 'I didn't stop under doctor's orders or discussion or anything, I just got up one day and I'm done. Instead of taking four, I took three and I did that for a couple of weeks and then I took two and I took one. I never felt any discomfort or anxiety or anything so… it worked for me.'
Funding	Small Grants Program at the Division of General Internal Medicine, University of Colorado School of Medicine.
Limitations and applicability of evidence	Overall CASP rating: No concerns. No concerns over applicability.

Study	**Leydon 2007[386]**
Aim	To explore patient experiences of and beliefs about their long-standing SSRI use and understand the barriers and facilitators to discontinuation.
Population	People taking selective serotonin reuptake inhibitors (SSRIs). N=17; M:F 7:10; age range 28 to 64 years. Length of time taking their current SSRI ranged from 1 to 11 years (mean 4 years). Seven described this as their first and only episode of depression. Of the rest, six talked in terms of previous distinct episodes, while four described their depression as 'ongoing' or 'long term'. Stratification: Currently taking/stopping; Antidepressants (SSRIs)
Setting	One group general practice in Southampton, UK.
Study design	Face-to-face semi-structured qualitative interviews with thematic analysis
Methods and analysis	Patients were recruited from one group practice within Southampton City Primary Care Trust (PCT). All participants receiving prescriptions for an SSRI for 12 months or more were identified from computer records by a clerical member of the practice staff. Only those patients deemed well enough by their GP were contacted by a letter from their GP about the study. A single research conducted the semi-structured qualitative interviews. Interviews lasted for an average of 1 hour. Participants were invited to tell their 'story' of SSRI use and in this way many of the issues of interest were raised spontaneously by patients. Interviews were audiotaped and transcribed verbatim. Thematic analysis was carried out both by hand and with the use of a word processor. Analysis began once data collection commenced and followed an iterative process derived from the 'constant comparative method'. Independent coding of a sample of transcripts was carried out by two of the authors. This was followed by a series of 'data sessions' between all authors to derive a consensus-coding framework.
Findings	**Fear of discontinuation and consequences of stopping**
	Participants described uncertainty about the potential for bad consequences when stopping, as well as uncertainty about the process itself, which could invoke fear. In addition to anticipated problems, actual problems encountered during past attempts to stop instilled trepidation about future attempts to stop. Nine interviewees expressed concern that stopping the medication could precipitate a relapse of depression and fear that stopping may leave them back in the initial distressing phase of depression.

Study	Leydon 2007[386]
	Severity of discontinuation symptoms
	Some participants had experienced quite severe problems associated with discontinuation. Eleven of the participants who had tried stopping reported bad experiences with one reporting a relapse experience so bad that he regretted ever trying. Experiences of withdrawal led one participant to restart their medication after 1 week. Another participant described how it was difficult to say which was worse, the experience of withdrawal effects or the initial depressive symptoms. Problems of withdrawal on previous occasions could become a conscious key driver for continuing to take medication and could forestall attempts to discontinue. One participant reported 'the major factor' driving sustained antidepressant use was the side effects of coming off them, saying: ' I don't think I take them to sustain my mood but purely to stop the side effects.'
	Bodily symptoms
	When asked 'how long did you stop for', one participant replied: 'a week, not because of the moods… this wasn't a moods situation. It was my body…was reacting, not how I expected it to react. It had the shakes…um…bit like a junkie' (43-year-old female)
	Onset
	One participant who had tried stopping and had relapsed, reported: 'I didn't turn into a blubbering mess straight away, it was about 4-5 days afterwards. (48-years old male)
Funding	Not stated
Limitations and applicability of evidence	Overall CASP rating: Minor concerns (due to participants only recruited from one group practice within one primary care trust) No concerns over applicability.

Study	North 1995[471]
Aim	To gain an understanding of the reasons benzodiazepines continue to be used, and the relationships users have formed with their medication using in-depth interviews.
Population	Two distinct groups of long-term benzodiazepine users were selected to participate in the study: **n-=22 total**

Study	North 1995[471]
	1. A group of community-based BZD users from three group practices located in middle- class areas : n=15. The participants from two of the group practices were invited by the GPs to participate in the study when they were prescribed BZDs during a defined two-week period. A third practice was asked to generate a list of current BZD users from their computerised age-sex register. Patients were excluded by their GP if they had (i) been prescribed BZDs for less than one year, (ii) significant social problems at the time of the study and were unable to cope with the stress of an interview (as assessed by their practitioner),(iii) significant medical problems that would prevent them from participating in the study, such as dementia or CVA affecting speech, (iv) been diagnosed as having an organic mental disorder, schizophrenia, a delusional paranoid disorder or a bipolar disorder; (v) a current prescription for other psychotropic medication (with the exception of antidepressants). Hypnotics: 5, anxiolytics: 7, combination: 3 2. A group of BZD users from TRANX, a tranquilliser self-help group for those wanting to withdraw from BZDs; n=7 The same exclusion criteria as above did not apply as they were contacted directly, and it would have been inappropriate to identify and exclude given the nature of the dynamic within the support group. Hypnotics: 1, anxiolytics: 2, combination: 4 5 had used BZDs continuously for an average of 21 years, range 10-28 years. **3 had withdrawn from BZDs at the time of the interview, 4 were on reduced doses of diazepam.** Characteristics (all patients): mean age (range): 61 (34-82); male/female: 11/11; all were anxiolytic and/or hypnotic users; ethnicity: European; **8 participants had experienced or were experiencing withdrawal under supervision (7 of these were members of TRANX)**; **8 were prescribed other psychotropic medication simultaneously, 7 of these were prescribed antidepressants, 3 non-BZD hypnotics and 1 TRANX member was prescribed lithium carbonate for bipolar disorder.**
Setting	Three group practices in middle class areas plus a self-help group.
Study design	Qualitative study using a questionnaire plus an in-depth semi-structured interview.
Methods and analysis	A short-written questionnaire was used to elicit socio-demographic data and a drug history. In the questionnaire, information was sought on what BZDs were taken and patterns of use (including duration and dosage). The in-depth semi-structured interviews (carried out by either a medical practitioner or a researcher with a psychology degree) were designed to cover four main areas: (1) the role of BZDs in their lives; (2) issues of dependence, control and withdrawal; (3) the doctor-patient relationship; (4) the social context. Each interview lasted 2-3 hours.

Study	North 1995[471]
	Interviews took place in the participant's home, at the medical school and in the participant's office at work. All participants were given the opportunity to review their transcripts and a second interview was arranged if they wished to discuss the transcript further with the researchers. Only minor changes were made to the transcripts and some points were re-emphasised by participants.
Findings	**Return of original symptoms** The majority of community- based participants had attempted to withdraw/ reduce their medication at some stage. They soon found their original symptoms of anxiety or insomnia had returned and were only suppressed by restoring the initial dosage.
	Lack of withdrawal symptoms Several participants had withdrawn from their medication with ease, experiencing no problems as they slowly reduced the medication over months.
	Experiences of withdrawal effects In contrast to those slowly reducing their medication, those on rapid withdrawal described the experience as 'a journey to hell', or 'the most horrific time of my life'.
	Lack of confidence in stopping Employed men who took anxiolytics during the working week tended not to have attempted to stop or reduce their medication. Each described how they wanted to stop but realised that full cessation was unlikely without a major lifestyle or career change.
Funding	Not reported
Limitations and applicability of evidence	Overall CASP rating: Minor concerns (due to data analysis not being described fully). No concerns over applicability.

Study	Papp 2018[508]
Aim	To gather information as reported spontaneously by internet users about the specific symptoms experiences while having brain zaps.
Population	N=595 posts, generated between December 2014 and December 2016, made anonymously and with no discernible demographic information.

Study	Papp 2018[508]
	9 most frequently prescribed drugs: Other antidepressants: Venlafaxine contributed to 23.3% of the posts; Desvenlafaxine contributed to 3.1% of the reports, Duloxetine to 10.7%, SSRIs: Fluoxetine (SSRI) was mentioned in 3.1% of the posts; Sertaline was mentioned in 19.6%, Paroxetine in 14.7%, Citaroplam 13.4%, Escitalopram 9.2% Drugs not included in guideline medicine list: Bupropion was mentioned in 2.7% of the posts analysed. Strata: mixed/unclear antidepressants: SSRIs & other antidepressants; 60% SSRI's; 37.1% other antidepressants; 2.7% bupropion not meeting guideline medicine list (the numbers don't add up to 100% but extracted as reported in the paper) The most frequently reported action preceding brain zaps was abrupt stopping (39.9%), followed by tapering (25.7%), skipping doses (12.5%). The duration of taking antidepressants before the onset of brain zaps ranged from 2 days to 25 years, with 2 years or more reported in a little over half the cases; <60 days: 7.8%; 60 days to <2 years: 36.4%; 2 years to <5 years: 16.2%; 5 years to <10 years: 26.6%; ≥10 years 9.7%
Setting	Not specified
Study design	Qualitative analysis of unsolicited posts on mental health website
Methods and analysis	Qualitative analysis of unsolicited posts on mental health website; Mental Health Daily. This is a sprawling and popular website devoted to a myriad of mental health issues, that contains a forum dedicated to posting about brain zaps. The posts were made anonymously and with no discernible demographic information. The study examined 595 posts, which were analysed into 648 statements. They were entered into a large spreadsheet where rows represented the individual posts and the columns the various pieces of information extracted such as the name of the medication and the symptoms described. Posts were generated between December 13, 2014 and December 12, 2016.
Findings	**Brain zap**

Study	Papp 2018[508]
	The subjective experience of the 'brain zap' was most often linked to an electric shock felt inside the skull with several reporting experiences that seem like momentary dissociations. The zap experience was most often accompanied by vertigo as well as hearing a sound, including people reporting 'hearing their eyes move'.
	Onset/time-lag
	The most frequently reported time lags between the last dose of antidepressants and the first instance of a brain zap were 'immediate' and 'while taking', followed by '1-2 weeks' and '20-36 hours'
	Length and duration of symptoms
	Very few posters made specific statements about the length of brain zap, with most frequent descriptions being: 'a split second' and other descriptions including a few seconds, 2 seconds, one-half to 5 seconds and 2-30 seconds with the higher numbers described as rare extremes. Most patients experienced brain zaps for less than a year with many experiencing them for a month or less. There was a smaller number of people experienced brain zaps between 5 and 30 years.
	Severity
	In only a small number of reports, brain zap resulted in significant disability
Funding	Not applicable/not specified
Limitations and applicability of evidence	Overall CASP rating: Serious concerns (due to potential selection bias as the method used to select posts was not specified, lack of sufficient detail on the data analysis). Moderate concerns about applicability due to a lack of sufficient information on the characteristics of peopled from which the information emerged and the data being unverified due to the nature of the source (anonymous posts on mental health website).

Study	Parr 2006[514]
Aim	To gain more detailed understanding of perceptions relating to starting, continuing and stopping BZD use.
Population	GPs and users of BZDs that had at some time been prescribed daily BZDs for 3 months or more, were recruited. In line with the protocol, only findings from BZD users are extracted for this review.

Study	Parr 2006[514]
	Users of BZDs: n=23; male/female:9/14; mean age (range): 50 (25-79) years; mean duration of use: 11 years (range: 6 months to 28 years); 36% were prescribed BZDs for more than one mental health condition including panic disorder, depression, anxiety and post-traumatic stress disorder; other reasons included inability to sleep (20%); medical conditions (16%); withdrawal from alcohol or other drugs (12%); stress (12%) and coping with domestic violence (4%). 52% reported they had stayed on the dose originally prescribed by their doctor; six (26%) were currently prescribed BZDs for panic attacks, nerves, sleeping problems, anxiety, obsessive compulsive behaviour or because they were addicted to them; For those who had ceased, mean length of time since cessation was 8 years (<1 year to 25 years)
Setting	Tropical holiday and regional centre of Cairns, Australia and surrounding rural districts.
Study design	Qualitative interview study
Methods and analysis	Semi-structured face to face interviews were conducted with GPs and users in the tropical holiday and regional centre of Cairns, Australia and surrounding rural districts. GPs were interviewed in their surgeries using a 15-30 min semi-structured interview adapted from smoking cessation in general practice project (Young et al 2000). Interviewed commenced by asking GPs about their experience with BZD prescriptions, exploring factors that influenced their decision to prescribe and their approach to cessation. Interviews with users were conducted in their homes or another mutually agreed site, using a 30-60 min semi-structured interview, exploring initial reason for BZD use, reasons for continued use and beneficial and harmful effects of using BZDs. If they had attempted to cease, they were asked the reasons for doing so, how they went about it and what helped or hindered the process. All interviews were conducted by the first author and included questions such as 'What do you usually do to help people who are dependent on benzodiazepines to stop taking them?' for GPs and 'What information were you given about benzodiazepines' for users. Interviews were audio taped, with notes being taken concurrently and audiotapes were later transcribed verbatim by the first author. The primary research team (the first three authors) independently reviewed the first three GP and user interviews and developed a preliminary list of domains and categories, referring these at a face-to-face meeting. The first author applied these domains and categories to remaining interviews. The fourth author audited all interviews to verify that the ascription to domains and categories adequately reflected the information in the transcripts. The research team agreed on domain amalgamations. Assessments of representativeness of categories involved assigning a rating of 'general' if raised by all participants, 'typical' if raised by more than half of them or 'variant' if raised by 15-50% of participants. Further corroboration of categorization was achieved through verification of the results by three GPs and four users who were asked for feedback on whether they reflected their thoughts and experiences or those of other potential informants.

Study	**Parr 2006[514]**
Findings	**Adverse symptoms**
	Participants typically found within a short period of time of commencing, they felt addicted because of adverse symptoms when they tried to stop them. They endured 'hang-over' effects in the morning; or took other medication to cope with withdrawal symptoms.
	Intensity of withdrawal symptoms as a barrier to ceasing benzodiazepine use
	The intensity of withdrawal symptoms associated with previous attempts to cut down was identified as contributing to an inability to cease benzodiazepine use.
	Sleep problems, loss of function, inability to cope with mental health problems
	People found they could not sleep, function or cope with ongoing mental health problems. BZDs also helped them keep emotions and thoughts under control, feel less burdened and worried and cope with adverse life circumstances and distressing symptoms associated with their medical conditions.
Funding	Not stated
Limitations and applicability of evidence	Overall CASP rating: Minor concerns (due to the potential influence of the researcher not being discussed and themes occasionally illustrated by single quotes). No concerns over applicability.

Study	**Pestello, 2008[532]**
Aim	The paper examines the experience of taking antidepressant medications and its impact on the sense of self.
Population	N=227 postings on a health-related website
Country, Setting	Country not specified
Study design	Analysis of postings on a health-related website
Methods and analysis	Internet message board postings on a popular medical internet site to see how people talked about and responded to the most popular and commonly used antidepressant medications: Sertraline, Fluoxetine, Paroxetine, Citalopram, and Venlafaxine. All of the postings on the discussion site were thematically based. Postings addressed general side effects, sexual side effects, giving medical advice and frustration with physicians. The actual themes for analysis were derived inductively through a grounded

Study	Pestello, 2008[532]
	theory approach. Analytic categories were identified as they arose. Constant comparison method was then used in which each narrative posting was systematically compared and combined, further refining and reducing the themes.
	Impact of withdrawal A number of posting were devoted to the physical and mental side effects that occur when discontinuing antidepressant use.'' '' I am currently trying to wean myself off of Venlafaxine, which honestly is the most awful thing I have ever done. I have horrible dizzy spells and nausea whenever I lower my dose of Venlafaxine''. ''I can't move my neck or eyes without feeling dizzy and like the room is spinning. My lips sometimes feel numb. It seems like I'm about five times as anxious/depressed as I was pre-Paroxetine.'' ''It took me almost 2 years to get off Paroxetine and the side effects were horrendous. I even had to quit my job because I felt sick all the time. Even now that I am off it, I still feel electric shocks in my brain and can't deal with rapid movements.''
	Frustration with physicians Respondents repeatedly talked about not being listened to by their physicians or not being taken seriously. '' I myself went from doctor to doctor. It seemed like no one took me seriously. They would just nod and give me that ''she may be crazy'' look''. ''May be new doctor will be in better tune to what you really are needing. Doctors get so busy trying to diagnose and treat so many patients that I feel like I am definitely a number and not a name. Now, how can you treat a number? ''It makes me angry when someone says, ''I think that your depression is giving you physical symptoms... let's pump you up with more happy drugs''. The only reason I have for being depressed or anxious is that doctors can't seem to help me with my problem''.
Funding	Not stated
Limitations and applicability of evidence	Overall CASP rating: Serious concerns (due to limitations around research design/methods, data collection method and analysis (postings on health website)). Moderate concerns about applicability due to a lack of sufficient information on the characteristics of people from which the information emerged and the data being unverified due to the nature of the source (anonymous posts on health website).

Study	Scott 2020[633]
Aim	To evaluate a one-to-one pain review service (based in two GP practices) and its potential impact on opioid use, health and wellbeing outcomes and quality of life (QoL), and to help inform future service provision.
Population	Patients receiving ≥3 opioid painkiller prescriptions in a 3-month period, who had taken opioids ≥3 months (long-term opioid use) and were not using illicit drugs or receiving end-of-life care were identified by GPs for service participation using the opioid risk assessment tool (ORAT). The service involved an individually tailored pain management plan including setting goals, developing a relaxation plan, introducing gentle exercise, dealing with low mood and improved sleep, access to alternative care and support options including physiotherapy and relaxation groups. All service users who enrolled between September 2016 and December 2017 were included in the quantitative analysis and a convenience sample provided qualitative interview data. Project workers facilitated recruitment of 18 service users for semi-structured interview; interviews were also conducted with the service providers; project workers (n=2), the project worker's manager (n=1); and GPs in participating GP practices (n=4). For the purpose of this review only information relating to service users is extracted. Characteristics: n=34; female: 22/34 (64.7%); mean age (SD): 51 (10) years; 100% white ethnicity; 19.4% employed, 74.2% unemployed, 6.5% retired; disability: 20/27 (74.1%); baseline medications excluding opioids: benzodiazepine 12/34 (35.3%), amitriptyline 12/34 (35.3%), SSRI antidepressants 8/34 (23.5%), gabapentin 7/34 (20.6%), other antidepressants 6/34 (17.6%), pregabalin 4/34 (11.8%), SNRI antidepressants 1/34 (2.9%), zopiclone 1/34 (2.9%); psychological comorbidities: sleep issues 17/30 (56/7%), depression 13/29 (44.8%), anxiety/panic attacks 9/29 (31%), experience of child abuse 9/30 (30%) , social isolation 7/29 (24.1%), experience of domestic abuse 5/29 (17.2%), substance misuse 3/29 (10.3%), alcohol misuse 2/29 (6.9%), other mental health issues 2/29 (6.9%), eating disorder 1/29 (3.4%), PTSD 1/29 (3.4%), shelf harm 1/29 (3.4%), negative self-talk thoughts 1/29 (3.4%). Denominators less than 34 indicate missing data. Reason for original prescription: back pain 9/32 (28.1%); arthritis 5/32 (15.6%); spinal or disc degeneration/deformities 5/32 (15.6%); Fibromyalgia 4/32 (12.5%); other 9/32 (28.1%); median opioid dose (IQR): 90 (60 to 240); Opioid drug: codeine 17/34 (50%); tramadol 10/34 29.4%; Morphine 9/34 (26.5%) oxycodone family 7/34 (20.6%); Fentanyl 5/34 (14.7); Buprenorphine 3/34 (8.8%); Methadone 1/34 (2.9%); multiple opioid drugs 16/34 (47.1%) In patients still using the service when data collection finished (n=17; 50%), the median duration of service use 7.7 months (IQR 3.2 to 13.3) and the median number of attended appointments was 12 (IQR 6 to 20); in patients who were discharged/lost to

Study	**Scott 2020[633]**
	follow-up (n=17; 50%), the median duration was 3.8 months (IQR 1.1 to 9.1) and the median number of attended appointments was 6 (IQR 1 to 11). Reasons for discharge from service no longer taking opioids (3/17; 17.6%); reduction in opioid dose (4/17; 23.6%); happy as is (2/17; 11.8%); no time (1/17; 5.8%) and fears that reduced pain may lead to reduced disability benefits (1/17, 5.8%).
Setting	Two GP practices in South Gloucestershire, England
Study design	Mixed-methods study
Methods and analysis	Semi-structured interviews were conducted with n=18 service users and n=7 service providers. Interviews were conducted face-to-face or by telephone depending on interviewee preference. Service user interviews explored experiences of the service and service acceptability was also discussed. Interviews were audio-recorder and transcribed verbatim, anonymised, and analysed thematically. Quantitative and qualitative data were analysed independently by two researchers and integrated using the' following a thread' technique (a method of integration at the analysis stage) through discussion of the key findings and themes in both datasets.
Findings	**Withdrawal symptoms when reducing opioids: sweating and headaches** A small number of service users reported increased pain levels and withdrawal side effects, for example, sweating and headaches, as a result of reducing opioids.
Funding	National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West (NIHR CLAHRC West); University Hospitals Bristol NHS Foundation Trust; postdoctoral fellowship award (grant reference: PDF-2017-10-068)
Limitations and applicability of evidence	Overall CASP rating: Moderate concerns (due to role of the researcher not being discussed and limited relevance of the study aim to the review topic with very limited information to contribute to the review). Moderate concerns over relevance with participants being pain service users whose experience of withdrawal may differ to that of people with no access to similar support.

Study	**Van Hout 2017[705]**
Aim	To gain an understanding of unique individual and collective experiences of trajectories of codeine misuse and dependence in South Africa.
Population	A purposive sample of adult individuals in South African treatment centres with experience of codeine misuse and/or dependence; excluding participants under 18 years, non-S-A residents, individuals reporting codeine use within accepted medical guidelines, suffering from serious mental health problems and individuals with a known history of violence or aggressions. Characteristics: n=25 ; male/female 16/9; mean age (range) 43 (21 to 74) with 67% (n=15) aged between 30-49 years; n=20 admitted misusing codeine within the last 12 months and the majority (n=13; 52%) scored 10 or above on the severity of dependence screener (SDS), a five-item questionnaire, with scores of over five indicating dependence use in the past 12 months. 32% reported codeine tablets as their primary drug of use, 20% reported codeine syrup and 12% reported consuming both. A number of participants had a history of illicit drug use such as heroin, cannabis, cocaine and ecstasy. Some used codeine in combination with alcohol with a small number of female participants combining with diet pills. Many reported taking codeine-based medications to manage physical pain as a result of chronic condition such as arthritis and severe headaches or to relieve pain (acute or chronic) following surgical interventions. 'Many' experienced psychological issues such as depression, anxiety and stress related conditions and used codeine to suppress their symptoms.
Setting	Clinics and treatments centres participating on the South African Council for Alcoholism and Drug Dependence
Study design	Qualitative interview study
Methods and analysis	In-depth interviews were conducted face-to-face or by telephone by one researcher, with a note taker, were conducted in English, were audio-taped with permission and lasted between 30-90 minutes. Audio recordings were transcribed and analysed using the Empirical Phenomenological Psychological)EPP) five step method.
Findings	**Withdrawal symptoms**
	Participants described experiences of unpleasant withdrawal symptoms such as pain (physical including headaches and psychological), fear, crying, self-pity, irritability, anxiety, aggression, disturbed sleep patterns, perspiration, 'the turkey skin and shivering' and shock down my body'. These contributed to sustained misuse.

Study	Van Hout 2017[705]
	Cravings
	Most participants described strong cravings. Some participants resorted to other illicit drugs such as cannabis (smoking weed) or engaging a hobby as a means for managing the cravings for codeine.
	Little or no cravings and withdrawal symptoms
	While most participants described strong craving and withdrawal effects, one young male participant reported how he successfully managed to reduce his misuse of codeine. He reported tapering down gradually on his own using 'fewer and fewer' and that 'there were still a little bit of withdrawal symptoms, but it wasn't as bad as what it could have been if I stopped immediately'
Funding	The European Community's Seventh Framework programme; grant agreement no 611736
Limitations and applicability of evidence	Overall CASP rating: Minor concerns (due potential influence of the researcher on the findings not being discussed). Moderate concerns over applicability due to some participants combining codeine with illicit drug use and currently. Study included as all (100%) participants were current or past codeine users regardless of any other drugs they used.

Study	Van Hout 2018[704]
Aim	To gain an understanding of individual and collective experiences of codeine use, pathways to misuse and dependence and experiences of treatment services in Ireland following the introduction of such guidelines for the safe supply of over-the-counter codeine-based products.
Population	A purposive sample of adult codeine misusers and dependents (n=21), both actively using, in treatment and in recovery. Recruitment was facilitated by selected gatekeepers (specialist medical doctors) within the National Drug Treatment Reporting System. These gatekeepers assisted in the recruitment of individuals in the centres by identifying codeine misusers and dependent patients. To distinguish between dependent and non-dependent use, participants completed the severity of dependence screener (SDS) (Gossop et al 1995), a five-item questionnaire, with scores of over five indicating dependence use in the past 12 months.

Study	**Van Hout 2018[704]**
	Characteristics: n=21 ; male/female: 12/9; mean age (range): 39 (26 to 62); n=15 admitted using codeine within the last 12 months with majority scoring 10 or above (80%, n=12) in the SDS (score over 5 indicating dependence use in the past 12 months**); 18 (86%) participants reported codeine-based medications** (e.g. Solpadol, Nurofen Plus or Solpadeine) with n=1 reporting heroin and n=1 reporting distalgesic; n=13 (62%) reported Nurofen plus was their primary drug of use, n=3 (14%) were on Suboxone and n=14 (67%) reporting they were currently on methadone maintenance treatment. Some participants had prior experience of illicit drugs such as heroin, cannabis, cocaine and ecstasy with many combining codeine with alcohol, particularly at night-time.
Setting	Specialist centres; The National Drug Treatment Reporting System
Study design	Qualitative interview study
Methods and analysis	In-depth semi-structured interviews lasted between 30 and 90 minutes and were audio-recorded with permission, transcribed and transferred to a Word document that was password-protected and analysed in accordance with the Empirical Phenomenological Psychological (EPP) five-step method.
Findings	**Difficulties ceasing**
	1) **Withdrawal symptoms** Craving and unpleasant withdrawal symptoms were described as supporting continued use. Symptoms of withdrawal centred on emesis, diarrhoea, sweating, agitation, insomnia, seizures, and cramps. One participant reported: 'I'd get withdrawals, I'd get very, very agitated and pain in my legs and my arms and my stomach. I'd get blinding headaches and loss of appetite, restlessness, couldn't sleep, I wasn't eating, complete shutdown. Codeine was reported to cause 'horrible dependence, physical and mental dependence' and destroy ones live. The necessity to develop a new daily routine and in many instances alternate coping mechanisms underpinned difficulties in self-detoxing.
	2) **Fears of pain exacerbation:** Despite becoming aware of habit-forming use and harm, while actively misusing, participants described they were unable to stop. Fears around existing pain conditions underpinned difficulties in ceasing use for some participants.
	Attempts to cope with withdrawal symptoms

Study	Van Hout 2018[704]
	Many tried to consume sufficient codeine to keep withdrawals at bay in order to sustain normal social functioning and employment. One participant reported: I was taking it almost to work because of the withdrawal symptoms. One participant described sourcing street methadone to assist withdrawal.
	Unsuccessful cessation attempts: cravings, feeling down and sleepy
	For a minority of participants with experience (all unsuccessful of codeine phosphate withdrawal, the sedative effects of codeine phosphate tapering treatment form contrasted with Nurofen Plus energising effects, which patients found complicated their successful detox; with one participant reporting: 'there is a huge difference. The over-the-counter codeine phosphate makes you feel down and sleepy, Nurofen Plus makes you the opposite, gives you uplift. Relapse with codeine phosphate tapering was universal due to lack of effect on cravings and instances of 'topping up' with Nurofen Plus. On the other hand, Suboxone in particular was viewed very positively in removal of craving and withdrawal effects. Participant: 'from the very first day I put Suboxone in my body, I have no jitter, I have no side effects, I never took a codeine since the first day I took Suboxone.' Another stated: it was a miracle, I was able to function, I was on no codeine'.
Funding	The European Community's Seventh framework Programme FP7/2007-2013 under grand agreement no 611736
Limitations and applicability of evidence	Overall CASP rating: Minor concerns (due potential influence of the researcher on the findings not being discussed). Moderate concerns over applicability due to some participants combining codeine with illicit drug use and currently being on methadone maintenance potentially for withdrawal of other medicines which could influence their experience of codeine withdrawal or whose experience may differ from that of people not on methadone maintenance. Study included as all (100%) participants were current or past codeine users regardless of any other drugs they used.

Study	Vilhelmsson 2012[716]
Aim	To qualitatively analyse the free text comments appended to consumer reports on antidepressant medication.
Population	People reporting adverse drug reactions to antidepressant medications n=181 consumer reports; 135 from women, 38 from men; The antidepressants most reported for a diagnosis of depression were Sertraline (23.8%), Citalopram (23.8%), Venlafaxine (23.2%), Mirtazapine (10.5%), Paroxetine (7.7%), Escitalopram (6.1%) and Fluoxetine (5.0%)

Study	**Vilhelmsson 2012[716]**
	Stratification: Currently taking/stopping; Antidepressants (mixed SSRI's and other antidepressants)
Setting	Sweden
Study design	Content analysis of free text comments from consumer reports
Methods and analysis	All reports of suspected adverse reactions regarding antidepressant medications submitted from January 2002 to April 2009 to KILEN's Internet-based reporting system in Sweden were analysed according to reported narrative experience(s). Content analysis was used to interpret the content of 181 reports with free text comments.
Findings	**Psychiatric adverse reactions: fear, anxiety, panic attacks**
	According to patient narratives it was especially during discontinuation of antidepressant drugs that psychiatric adverse reactions were experienced. One female patient (aged 35 years; SSRI: Sertaline) following doctor's orders to discontinue antidepressants in four days, going 'from normal dosage of 50mg to 25 mg in four days and then nothing' reported experiencing 'a fear of dying and extreme anxiety' after 3 days and having 'several panic attacks; 'I woke up and found myself standing with a knife towards my stomach on one occasion and on another with the bathrobe belt in my hand. I no longer tolerate any stress at all, which makes me panic and experience dizziness. Have been without antidepressant medication for nine days and experience hell on earth'
	Discontinuation symptoms rather than relapse/re-emergence of symptoms for which the medication was prescribed
	Conflicting accounts between patients and doctors of either drug-induced reactions or initial illness symptoms were especially present during discontinuation. Since the psychiatric events reported may often also occur as a symptom of the illness for which the antidepressant had been prescribed, their (re) appearance may easily suggest that the patient is having a relapse and needs continued treatment. According to several patient reports, there were sometimes problems of separating the symptoms related to the diagnosed depression from the suspected adverse reactions, where patients almost always interpreted negative experiences as belonging to the drug while the doctor construed them as evidence of the initial depression recurring. A female patients (aged 35 years; SSRI: Sertaline) reported that the doctor 'ignores discontinuation symptoms from the drug and wants me to start medicating again after I have been through ten days of hell. She (the doctor) believes that my depression had returned…It is totally wrong'
	Fear of discontinuation

Study	Vilhelmsson 2012[716]
	Fear of discontinuation symptoms made some patients afraid of ending their treatment; these patients often continued to take antidepressants, despite the fact that they did not want to be dependent on them. The suspected adverse reactions were not just perceived as unpleasant but also created a fear of stopping taking the antidepressant drug. A concern that the depression might return was one common feeling that was expressed; A female participant (aged 42; SSRI: Citalopram) reported: 'And when the death wish comes, I become so afraid that I start again'
	Prolonged duration of discontinuation symptoms
	Some patients reported that they perceived discontinuation symptoms over a longer period of time which they perceived as being dismissed by their doctor
Funding	Individual sponsors: Stistelsen Kempe-Carlgrenska Fonden, Folksams Forskningsstiftelse, Stiftelsen Clae Groschinskys Minnesfond Stiftelsen Lars Hiertas Minne and Elsa Lundberg och Greta Flerons fund for studies of adverse drug reactions.
Limitations and applicability of evidence	Overall CASP rating: Serious concerns (due to research aim, design and data collection (retrospective analysis of independently submitted free text feedback from consumers), study design dictated by the data/consumer feedback process; results (themes) were reported interspersed with references and insights from other studies, making it unclear what conclusions were based on this study alone). Minor concerns over applicability due to the sample being limited to people who experienced adverse drug reactions from antidepressants.

Study	Voyer, 2004[722]
Aim	To elicit descriptions of dependence from elderly long-term users of BZDs that might reveal potential indicators of dependence other than long-term use (defined as six months or longer).
Population	People from resident houses who had volunteered to participate in an activity programme, were <65, were long-terms users of prescribed psychotropic (Benzodiazepines) drugs; long term use described as minimum of 6 months and maximum of 40 year. N=45; 89% female; mean age (SD): 79 (7.1); n=36 were prescribed only BZDs and 9 received concomitant antidepressants; mean duration of use (SD): 9 (9.1) years; median: 6.5 years of BZD use. 75% were prescribed BZDs on an 'as needed' basis. Benzodiazepines included: clonazepam, lorazepam, oxazepam, temazepam which met the protocol but also alprazolam, bromazepam, flurazepam which were not part of the agreed guideline medicine

Study	Voyer, 2004[722]
	list, but percentage people prescribed each drug is not given. In line with the protocol the study is included and downgraded for indirectness of the population. It is reported that n=18 were prescribed lorazepam.
Setting	Two retirement residences for ambulatory seniors in the city of Laval (Quebec, Canada)
Study design	Qualitative interview study
Methods and analysis	Participants' medication containers were inspected. Medications were classified using the Compendium of Pharmaceuticals and Specialties (Canadian Pharmaceutical Association 1998). To estimate the amount of BZD drug used in one week, the number of pills in containers was subtracted from the number counted one week earlier allowing for renewals, and average milligram daily consumption was calculated. All participants were interviewed in person by the first investigator. Interviews were directive and included 20 questions on reasons, duration and effects of BZD drug use and withdrawal experiences, attitudes and reactions from health professionals and relatives. Interviews lasted about 25 minutes and answers were written down by the interviewer and interview notes were reviewed by three investigators. A sub-sample of 11 participants showing heterogenous profiles and drug use patterns-duration of use, health status, polypharmacy were selected for a second interview, to enrich the quality of data. These participants were asked the same questions as previously, but these questions were more open-ended; they lasted approximately 60 minutes, were audio-recorded and then transcribed verbatim. All notes and transcripts were coded and analysed using Atlas-Ti software version 4. During an iterative coding process, participants' comments were abridged and grouped into three major categories:1) reliance on BZDs, 2) descriptions of BZDs and 3) desirability of stopping BZDs. These data were used to understand patterns of BZD use.
Findings	**Undesirability of stopping due to past experience of withdrawal: anxiety & sleep problems**
	Nearly half of the respondents reported continuing to consume a BZD despite the belief that quitting would be desirable and having attempted to quit. A slight majority felt that quitting was undesirable, and experience of withdrawal could contribute to this attitude. 23 (51%) explained why stopping was not desirable, with some expressing fear that symptoms of anxiety would return if the drug were stopped. Some participants reported that stopping was not desirable because they were dependent with some evoking withdrawal symptoms. One particularly reported ' it is impossible to stop…I should probably have a placebo, because it's all in the head…It's not feasible really. After stopping I went crazy. Why make such a fuss about two little pills to sleep? At least let me sleep at night, let me be calm during the day.' Some indicated a desire to stop but that at the

Study	**Voyer, 2004[722]**
	same time they did not want to distance themselves from the drugs completely, reporting: ; 'I could stop but I would keep the pills that are left over in case', 'If I stop completely and something happens and I don't sleep, at least I have them at hand, it's a relief to know that I have some' and 'let's say that I fall sick, something happens to me, it's the nerves, so that makes keeping the pills a contingency
Funding	Not stated
Limitations and applicability of evidence	Overall CASP rating: Serious concerns (due to the role of the researcher not being explored, the recruitment strategy with participants selected for a different project, the data analysis being unclear). Moderate concerns over applicability with at least some participants prescribed benzodiazepines that did not meet protocol

Appendix F GRADE tables

F.1 Quantitative evidence

F.1.1 Opioids

F.1.1.1 Withdrawal from opioids vs continuation on opioids

No evidence identified for comparison

F.1.1.2 Withdrawal from opioids vs withdrawal from placebo

Table 22: Clinical evidence profile: withdrawal from opioids vs withdrawal from placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Withdrawal from opioids	withdrawal from placebo	Relative (95% CI)	Absolute (95% CI)		
Any withdrawal symptom (at week 5 = follow-up: 1 week-post last dose) (assessed with: assessed at appointment with psychiatrist to screen for possible withdrawal symptoms)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	0/57 (0.0%)	0/31 (0.0%) [c]	not estimable	**0 fewer per 1,000** (from 50 fewer to 50 more) [c]	⨁◯◯◯ VERY LOW	CRITICAL
Moderate or severe aches and pains on the short opiate withdrawal scale (protocol outcome: specific withdrawal symptom; at follow-up 3-days after last patch removed) (assessed with: short opiate withdrawal scale consisted of 10 items rated on a 4-point Likert scale (0-3, none to severe).)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	125/202 (61.9%)	122/197 (61.9%)	RR 1.00 (0.86 to 1.17)	**0 fewer per 1,000** (from 87 fewer to 105 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Mild or moderate problems sleeping on the short opiate withdrawal scale (protocol outcome: specific withdrawal symptom; at follow-up 3-days after last patch removed) (assessed with: short opiate withdrawal scale consisted of 10 items rated on a 4-point Likert scale (0-3, none to severe).)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Withdrawal from opioids	withdrawal from placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	73/202 (36.1%)	73/197 (37.1%)	RR 0.98 (0.75 to 1.26)	**7 fewer per 1,000** (from 93 fewer to 96 more)	⨁◯◯◯ VERY LOW	CRITICAL
Severe insomnia on the short opiate withdrawal scale (protocol outcome: specific withdrawal symptom; at follow-up 3-days after last patch removed) (assessed with: short opiate withdrawal scale consisted of 10 items rated on a 4-point Likert scale (0-3, none to severe).)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	44/202 (21.8%)	16/197 (8.1%)	RR 2.68 (1.57 to 4.59)	**136 more per 1,000** (from 46 more to 292 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Short opiate withdrawal scale score (protocol outcome: intensity of withdrawal symptoms; at follow-up 3 days after last patch removed) (assessed with: short opiate withdrawal scale consisted of 10 items rated on a 4-point Likert scale (0-3, none to severe). Total score range of possible scores 0-3 (top=poor outcome))												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	202	197	-	MD **0.27 final value higher** (0.18 higher to 0.36 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Mild opioid withdrawal as assessed on COWS (protocol outcome: intensity of withdrawal symptoms; at follow-up 2 - <5 days after last dose) (assessed with: COWS based on 11 items of opioid withdrawal symptoms, each rated 0-5, higher values being worse. 5-12 is mild, 13-24 is moderate, 25-36 is moderately severe, > or equal to 36 is severe)[d]												
1	randomised trials	serious [a]	not serious	serious f	serious [b]	none	11/72 (15.3%)	0/23 (0.0%) [c]	Peto OR 4.38 (1.02 to 18.84)	**150 more per 1,000** (from 50 more to 250 more) [c]	⨁◯◯◯ VERY LOW	CRITICAL
Moderate opioid withdrawal as assessed on COWS (protocol outcome: intensity of withdrawal symptoms; at follow-up 2 - <5 days after last dose) (assessed with: COWS based on 11 items of opioid withdrawal symptoms, each rated 0-5, higher values being worse. 5-12 is mild, 13-24 is moderate, 25-36 is moderately severe, > or equal to 36 is severe)[de]												
1	randomised trials	serious [a]	not serious	serious f	serious [b]	none	0/72 (0.0%)	0/23 (0.0%) [c]	not estimable	**0 fewer per 1,000** (from 60 fewer to 60 more) [c]	⨁◯◯◯ VERY LOW	CRITICAL
Mild opioid withdrawal as assessed on COWS (protocol outcome: intensity of withdrawal symptoms; at follow-up ≥5 days after last dose) (assessed with: COWS based on 11 items of opioid withdrawal symptoms, each rated 0-5, higher values being worse. 5-12 is mild, 13-24 is moderate, 25-36 is moderately severe, > or equal to 36 is severe)[d]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Withdrawal from opioids	withdrawal from placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious f	very serious [b]	none	11/154 (7.1%)	5/59 (8.5%)	RR 0.84 (0.31 to 2.32)	**14 fewer per 1,000** (from 58 fewer to 112 more)	⨁◯◯◯ VERY LOW	CRITICAL

Moderate opioid withdrawal as assessed on COWS (protocol outcome: intensity of withdrawal symptoms; at follow-up ≥5 days after last dose) (assessed with: COWS based on 11 items of opioid withdrawal symptoms, each rated 0-5, higher values being worse. 5-12 is mild, 13-24 is moderate, 25-36 is moderately severe, > or equal to 36 is severe)[d]

1	randomised trials	serious [a]	not serious	serious f	very serious [b]	none	2/154 (1.3%)	0/59 (0.0%) [c]	Peto OR 4.01 (0.18 to 89.47)	**10 more per 1,000** (from 20 fewer to 40 more) [c]	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
*b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control groups for continuous outcomes). For studies with zero events in both arms: no imprecision (sample size >350); serious imprecision (sample size >70<350); very serious imprecision (sample size <70). Continuous outcome MIDS were as follows: for short opiate withdrawal scale score: 0.14 (0.5*SD for the final value for the control group used (as baseline values not available)*
c. Absolute effect calculated from the risk difference due to zero events in one or both arms
d. Study also reported the number of people with 'no withdrawal' as assessed on COWS. This was not analysed as it is the 'opposite' outcome and would be double counting. The COWS score was dichotomised: 5-12 is mild, 13-24 is moderate, 25-36 is moderately severe, > or equal to 36 is severe. Presumably no-one had moderately severe or severe withdrawal, as the numbers in the other 3 categories add up to the total number of people in the study.
e. Reviewer determined that no one had 'moderate withdrawal' at this timepoint due to number of people with 'no withdrawal' or 'mild withdrawal' adding up to the total number of participants
f. It was unclear whether the placebo group were withdrawn from study medication during the taper phase.

F.1.2 Benzodiazepines

F.1.2.1 Withdrawal from benzodiazepines vs continuation on benzodiazepines

Table 23: Clinical evidence profile: withdrawal from benzodiazepines vs continuation on benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	withdrawal from BZDs	continuation with BZDs	Relative (95% CI)	Absolute (95% CI)		
Intensity of withdrawal (protocol outcome: intensity of withdrawal symptoms at 3 weeks after discontinuation)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	48	43	-	MD **2.1 higher** (5.49 lower to 9.69 higher)	⨁⨁◯◯ LOW	CRITICAL
Intensity of withdrawal (protocol outcome: intensity of withdrawal symptoms at 4 weeks after discontinuation)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	15	15	-	MD **49 higher** (82.51 lower to 180.51 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Total BWC score (protocol outcome: intensity of withdrawal symptoms at the end of the taper period)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	19	17	-	MD **1.8 higher** (4.11 lower to 7.71 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 if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDs. For continuous outcomes the MID was calculated as 3.0 for BWC, 8.1 for BSWQ and 68.3 for Withdrawal Symptom scale (0.5 median baseline SDs of intervention and control groups).*

F.1.2.2 Withdrawal from benzodiazepines vs withdrawal from placebo

Table 24: Clinical evidence profile: withdrawal from benzodiazepines vs withdrawal from placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	withdrawal from BZDs	withdrawal from placebo	Relative (95% CI)	Absolute (95% CI)		
Patients with anxiety as a discontinuation emergent sign and symptom (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))e												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	withdrawal from BZDs	withdrawal from placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [c]	very serious [b]	none	8/100 (8.0%)	0/30 (0.0%)	Peto OR 3.95 (0.73 to 21.45)	**80 more per 1,000** (from 10 more to 150 more) d	⨁◯◯◯ VERY LOW	CRITICAL
Patients with headache as a discontinuation emergent sign and symptom (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))[e]												
1	randomised trials	serious [a]	not serious	serious [c]	very serious [b]	none	2/100 (2.0%)	0/30 (0.0%)	Peto OR 3.71 (0.14 to 100.72)	**20 more per 1,000** (from 30 fewer to 70 more)**d**	⨁◯◯◯ VERY LOW	CRITICAL
Patients with insomnia as a discontinuation emergent sign and symptom (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))e												
1	randomised trials	serious [a]	not serious	serious [c]	very serious [b]	none	6/100 (6.0%)	2/30 (6.7%)	**RR 0.90** (0.19 to 4.23)	**7 fewer per 1,000** (from 54 fewer to 215 more)	⨁◯◯◯ VERY LOW	CRITICAL
Rebound- increase in anxiety of ≥50% as measured with Hamilton anxiety scale compared with baseline (protocol outcome; specific withdrawal symptom during the discontinuation period)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	3/19 (15.8%)	0/6 (0.0%)	Peto OR 4.20 (0.26 to 66.87)	**160 more per 1,000** (from 100 fewer to 410 more**)** d	⨁◯◯◯ VERY LOW	CRITICAL
Rebound- increase in panic attacks of ≥100% compared with baseline (protocol outcome; specific withdrawal symptom during the discontinuation period)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	4/19 (21.1%)	1/6 (16.7%)	**RR 1.26** (0.17 to 9.24)	**43 more per 1,000** (from 138 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	withdrawal from BZDs	withdrawal from placebo	Relative (95% CI)	Absolute (95% CI)		
Rebound- Global Improvement Score ≤3 (indicating symptoms worse than at baseline) (protocol outcome; specific withdrawal symptom during the discontinuation period)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	4/19 (21.1%)	0/6 (0.0%)	Peto OR 4.50 (0.39 to 52.29)	**210 more per 1,000** (from 50 fewer to 470 more) d	⨁◯◯◯ VERY LOW	CRITICAL
Rebound- increase in anxiety of ≥10% as measured with Hamilton anxiety scale compared with baseline (protocol outcome; specific withdrawal symptom during the discontinuation period)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	7/19 (36.8%)	1/6 (16.7%)	**RR 2.21** (0.34 to 14.54)	**202 more per 1,000** (from 110 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Patients with any discontinuation emergent sign and symptom defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks(protocol outcome: any withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [b]	none	28/100 (28.0%)	4/30 (13.3%)	**RR 2.10** (0.80 to 5.51)	**147 more per 1,000** (from 27 fewer to 601 more)	⨁◯◯◯ VERY LOW	CRITICAL
Development of new symptoms (protocol outcome: any withdrawal symptom during discontinuation period)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	12/19 (63.2%)	2/6 (33.3%)	**RR 1.89** (0.58 to 6.18)	**297 more per 1,000** (from 140 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
PWC score (protocol outcome: intensity of withdrawal symptoms; at post-intervention (immediately after 1 week taper))												
2	randomised trials	serious [a]	not serious	serious	serious [c]	none	87	93	-	MD **3.8 higher** (1.92 higher to 5.69 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	withdrawal from BZDs	withdrawal from placebo	Relative (95% CI)	Absolute (95% CI)		
Increase in withdrawal symptoms of ≥100% (protocol outcome: intensity of withdrawal symptoms during the discontinuation period))												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	1/19 (5.3%)	1/6 (16.7%)	**RR 0.32** (0.02 to 4.32)	**113 fewer per 1,000** (from 163 fewer to 553 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 0.5 * median of baseline SD of the intervention and control groups. Continuous outcome MIDS were as follows: for PWC score: 2.97 (0.5*SD for the change score for the control group used (as baseline or final values not available; change score control group SD only available for Feltner).*
c. Participants in the placebo groups had previously been taking active medication; some participants leaving the study early also underwent the taper
d. Absolute effect calculated from the risk difference due to zero events in one or both arms
e. Specific discontinuation emergent signs and symptoms only reported in paper for those events which occurred in at least 5% of people
f. for the placebo group, it was unclear whether medication was stopped during the taper phase in both studies

F.1.3 Gabapentinoids

F.1.3.1 Withdrawal from gabapentinoids vs continuation on gabapentinoids

No evidence identified for comparison

F.1.3.2 Withdrawal from gabapentinoids vs withdrawal from placebo

Evidence identified for pregabalin for comparison. No evidence identified for gabapentin.

Table 25: Clinical evidence profile: withdrawal from gabapentinoids vs withdrawal from placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Withdrawal from Pregabalin	withdrawal from placebo	Relative (95% CI)	Absolute (95% CI)		
Patients with any discontinuation emergent sign and symptom defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks (protocol outcome: any withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))												
1 [a]	randomised trials	serious [b]	not serious	serious [c]	very serious [d]	none	55/203 (27.1%)	13/59 (22.0%)	RR 1.23 (0.72 to 2.09)	**51 more per 1,000** (from 62 fewer to 240 more)	⨁◯◯◯ VERY LOW	CRITICAL
Patients with anxiety as a discontinuation emergent sign and symptom defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))[e]												
1 [a]	randomised trials	serious [b]	not serious	serious [c]	very serious [d]	none	7/203 (3.4%)	1/59 (1.7%)	RR 2.03 (0.26 to 16.21)	**17 more per 1,000** (from 13 fewer to 258 more)	⨁◯◯◯ VERY LOW	CRITICAL
Patients with headache as a discontinuation emergent sign and symptom defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))[e]												
1 [a]	randomised trials	serious [b]	not serious	serious [c]	very serious [d]	none	8/203 (3.9%)	2/59 (3.4%)	RR 1.16 (0.25 to 5.33)	**5 more per 1,000** (from 25 fewer to 147 more)	⨁◯◯◯ VERY LOW	CRITICAL
Patients with insomnia as a discontinuation emergent sign and symptom defined as a spontaneously reported adverse event (newly developed or worsening of existing adverse event) occurring during the discontinuation weeks (protocol outcome: specific withdrawal symptom; at 25-26 weeks (1 week during taper and 1 week-post last dose))[e]												
1 [a]	randomised trials	serious [b]	not serious	serious [c]	very serious [d]	none	21/203 (10.3%)	3/59 (5.1%)	RR 2.03 (0.63 to 6.58)	**52 more per 1,000** (from 19 fewer to 284 more)	⨁◯◯◯ VERY LOW	CRITICAL
PWC score (protocol outcome: intensity of withdrawal symptoms; at post-intervention (immediately after 1 week taper))												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Withdrawal from Pregabalin	withdrawal from placebo	Relative (95% CI)	Absolute (95% CI)		
4 [f]	randomised trials	serious [b]	not serious	serious g	serious [d]	none	212	93	-	MD **2.58 change score higher** (1.04 higher to 4.13 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Withdrawal from low (150-300mg/day) and withdrawal from high (450-600mg/day) dose pregabalin arms combined for analysis as per protocol (no stratification by dose). Study also had 2 separate withdrawal from placebo arms, these were also combined for analysis. For dichotomous outcomes the number of events and number of people for the 2 arms were added together. For continuous outcomes, the mean and SD for the 2 arms combined was calculated.
b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
c. Participants in the placebo groups had previously been taking active medication; some participants leaving the study early also underwent the taper
*d. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control groups for continuous outcomes). Continuous outcome MIDS were as follows: for PWC score: 2.97 (0.5*SD for the change score for the control group used (as baseline or final values not available; change score control group SD only available for Feltner)*
e. Specific discontinuation emergent signs and symptoms only reported in paper for those events which occurred in at least 5% of people
f. 2 studies, each with 2 comparisons (high dose vs placebo and low dose vs placebo). Results from high and low dose not combined, as studies reported mean differences. Therefore, each study appears as 2 comparisons: problem with the placebo arm being repeated twice addressed by halving the n in each of the repeated placebo arms to counteract the gain in statistical power from effectively double counting the placebo arm (this calculates a greater SE for the MD, conferring an appropriate reduction in precision to compensate for the placebo arm being used twice)
g. for the placebo group, it was unclear whether medication was stopped during the taper phase in both studies

F.1.4 Z-drugs

F.1.4.1 Withdrawal from Z-drugs vs continuation on Z-drugs

No evidence identified for comparison

F.1.4.2 Withdrawal from Z-drugs vs withdrawal from placebo

Table 26: Clinical evidence profile: withdrawal from Z-drugs vs withdrawal from placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	withdrawal from Z-drugs	withdrawal from placebo	Relative (95% CI)	Absolute (95% CI)		
Rebound insomnia (protocol outcome: specific withdrawal symptom at 14 days following abrupt taper). Overall rebound-was a deterioration below individual mean pre-treatment values of the scores given on the visual analogue scales during the discontinuation period. A patient was counted as having rebound according to the following: deterioration in at least one of the three sleep quality parameters (a) sleep latency, (b) total sleep time,or (c) number of nocturnal awakenings; or deterioration in at least one parameter of daytime well-being defined as (d) a feeling of being refreshed on awakening in the morning, or as an impairment in daytime well-being as a result of (e) tiredness or (f)anxiety												
1	randomised trials	not serious	not serious	not serious	not serious	none	282/612 (46.1%)	145/298 (48.7%)	**RR 0.95** (0.82 to 1.09)	**24 fewer per 1,000** (from 88 fewer to 44 more)	⨁⨁⨁⨁ HIGH	CRITICAL

F.1.5 Antidepressants

F.1.5.1 Withdrawal from antidepressants vs continuation on antidepressants

Table 27: Clinical evidence profile: withdrawal from other antidepressants vs continuation on other antidepressants

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	discontinuation of other ADs	continuation of other ADs	Relative (95% CI)	Absolute (95% CI)		
Total no. of emergent DESS symptoms (protocol outcome: intensity of withdrawal symptoms) during first 2 weeks of discontinuation												
2	randomised trials	serious [a]	serious [b]	not serious	Not serious	none	312	133	-	MD **0.14 lower** (1.2 lower to 0.91 higher)	⨁⨁◯◯ LOW	CRITICAL

Rebound: return to a MADRS score equal to or higher than the original score at the entry of the acute treatment study (protocol outcome: specific withdrawal symptom during week 1 of discontinuation)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	discontinuation of other ADs	continuation of other ADs	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [c]	none	0/27 (0.0%)	1/61 (1.6%)	**Peto OR 0.24** (0.00 to 16.57)	**20 fewer per 1,000** (from 80 fewer to 50 more) [d]	⨁⨁◯◯ LOW	CRITICAL
Rebound: return to a MADRS score equal to or higher than the original score at the entry of the acute treatment study (protocol outcome: specific withdrawal symptom during week 2 of discontinuation)												
1	randomised trials	not serious	not serious	not serious	very serious [c]	none	0/27 (0.0%)	1/61 (1.6%)	**Peto OR 0.24** (0.00 to 16.57)	**20 fewer per 1,000** (from 80 fewer to 50 more) [d]	⨁⨁◯◯ LOW	CRITICAL
Nervousness/ anxiety (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	93/285 (32.6%)	19/72 (26.4%)	**RR 1.24** (0.81 to 1.88)	**63 more per 1,000** (from 50 fewer to 232 more)	⨁◯◯◯ VERY LOW	CRITICAL
Elevated mood, feeling high (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	9/285 (3.2%)	2/72 (2.8%)	**RR 1.14** (0.25 to 5.15)	**4 more per 1,000** (from 21 fewer to 115 more)	⨁◯◯◯ VERY LOW	CRITICAL
Irritability (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	134/285 (47.0%)	17/72 (23.6%)	**RR 1.99** (1.29 to 3.07)	**234 more per 1,000** (from 68 more to 489 more)	⨁⨁◯◯ LOW	CRITICAL
Sudden worsening of mood (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	discontinuation of other ADs	continuation of other ADs	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	69/285 (24.2%)	12/72 (16.7%)	**RR 1.45** (0.83 to 2.53)	**75 more per 1,000** (from 28 fewer to 255 more)	⨁◯◯◯ VERY LOW	CRITICAL
Sudden outbursts of anger (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	49/285 (17.2%)	10/72 (13.9%)	**RR 1.24** (0.66 to 2.32)	**33 more per 1,000** (from 47 fewer to 183 more)	⨁◯◯◯ VERY LOW	CRITICAL
Sudden panic or anxiety attacks (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	21/285 (7.4%)	6/72 (8.3%)	**RR 0.88** (0.37 to 2.11)	**10 fewer per 1,000** (from 53 fewer to 92 more)	⨁◯◯◯ VERY LOW	CRITICAL
Bouts of crying or tearfulness (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	89/285 (31.2%)	12/72 (16.7%)	**RR 1.87** (1.09 to 3.23)	**145 more per 1,000** (from 15 more to 372 more)	⨁◯◯◯ VERY LOW	CRITICAL
Agitation (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	77/285 (27.0%)	17/72 (23.6%)	**RR 1.14** (0.72 to 1.81)	**33 more per 1,000** (from 66 fewer to 191 more)	⨁◯◯◯ VERY LOW	CRITICAL
Feeling unreal or detached (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	discontinuation of other ADs	continuation of other ADs	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	29/285 (10.2%)	8/72 (11.1%)	**RR 0.92** (0.44 to 1.92)	**9 fewer per 1,000** (from 62 fewer to 102 more)	⨁◯◯◯ VERY LOW	CRITICAL
Confusion or trouble concentrating (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	81/285 (28.4%)	15/72 (20.8%)	**RR 1.36** (0.84 to 2.22)	**75 more per 1,000** (from 33 fewer to 254 more)	⨁◯◯◯ VERY LOW	CRITICAL
Forgetfulness or problems with memory (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	61/285 (21.4%)	7/72 (9.7%)	**RR 2.20** (1.05 to 4.61)	**117 more per 1,000** (from 5 more to 351 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mood swings (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	48/285 (16.8%)	9/72 (12.5%)	**RR 1.35** (0.69 to 2.62)	**44 more per 1,000** (from 39 fewer to 203 more)	⨁◯◯◯ VERY LOW	CRITICAL
Trouble sleeping, insomnia (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	108/285 (37.9%)	29/72 (40.3%)	**RR 0.94** (0.68 to 1.29)	**24 fewer per 1,000** (from 129 fewer to 117 more)	⨁◯◯◯ VERY LOW	CRITICAL
Increased dreaming, nightmares (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	discontinuation of other ADs	continuation of other ADs	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	72/285 (25.3%)	15/72 (20.8%)	**RR 1.21** (0.74 to 1.98)	**44 more per 1,000** (from 54 fewer to 204 more)	⨁◯◯◯ VERY LOW	CRITICAL
Sweating more than usual (protocol outcome : specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	33/285 (11.6%)	10/72 (13.9%)	**RR 0.83** (0.43 to 1.61)	**24 fewer per 1,000** (from 79 fewer to 85 more)	⨁◯◯◯ VERY LOW	CRITICAL
Shaking, trembling (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	18/285 (6.3%)	6/72 (8.3%)	**RR 0.76** (0.31 to 1.84)	**20 fewer per 1,000** (from 57 fewer to 70 more)	⨁◯◯◯ VERY LOW	CRITICAL
Muscle tension or stiffness (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	51/285 (17.9%)	6/72 (8.3%)	**RR 2.15** (0.96 to 4.81)	**96 more per 1,000** (from 3 fewer to 317 more)	⨁◯◯◯ VERY LOW	CRITICAL
Muscle aches or pains (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	60/285 (21.1%)	7/72 (9.7%)	**RR 2.17** (1.03 to 4.53)	**114 more per 1,000** (from 3 more to 343 more)	⨁◯◯◯ VERY LOW	CRITICAL
Restless feeling in legs (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	discontinuation of other ADs	continuation of other ADs	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	29/285 (10.2%)	6/72 (8.3%)	**RR 1.22** (0.53 to 2.83)	**18 more per 1,000** (from 39 fewer to 153 more)	⨁◯◯◯ VERY LOW	CRITICAL
Muscle cramps, spasms, twitching (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	37/285 (13.0%)	8/72 (11.1%)	**RR 1.17** (0.57 to 2.40)	**19 more per 1,000** (from 48 fewer to 156 more)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue, tiredness (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	109/285 (38.2%)	24/72 (33.3%)	**RR 1.15** (0.80 to 1.64)	**50 more per 1,000** (from 67 fewer to 213 more)	⨁◯◯◯ VERY LOW	CRITICAL
Unsteady gait or incoordination (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	29/285 (10.2%)	2/72 (2.8%)	**RR 3.66** (0.89 to 14.99)	**74 more per 1,000** (from 3 fewer to 389 more)	⨁◯◯◯ VERY LOW	CRITICAL
Blurred vision (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	19/285 (6.7%)	6/72 (8.3%)	**RR 0.80** (0.33 to 1.93)	**17 fewer per 1,000** (from 56 fewer to 77 more)	⨁◯◯◯ VERY LOW	CRITICAL
Sore eyes (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	discontinuation of other ADs	continuation of other ADs	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	19/285 (6.7%)	3/72 (4.2%)	**RR 1.60** (0.49 to 5.26)	**25 more per 1,000** (from 21 fewer to 178 more)	⨁◯◯◯ VERY LOW	CRITICAL
Uncontrolled mouth/ tongue movements (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [c]	not serious	not serious	very serious [c]	none	2/285 (0.7%)	2/72 (2.8%)	**RR 0.25** (0.04 to 1.76)	**21 fewer per 1,000** (from 27 fewer to 21 more)	⨁◯◯◯ VERY LOW	CRITICAL
Problems with speech or speaking clearly (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	13/285 (4.6%)	3/72 (4.2%)	**RR 1.09** (0.32 to 3.74)	**4 more per 1,000** (from 28 fewer to 114 more)	⨁◯◯◯ VERY LOW	CRITICAL
Headache (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	0/285 (0.0%)	0/72 (0.0%)	not estimable	**0 more per 1,000** (from 20 fewer to 20 more) [d]	⨁⨁◯◯ LOW	CRITICAL
Increased saliva in mouth (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	7/285 (2.5%)	0/72 (0.0%)	**Peto OP 3.58** (0.56 to 23.01)	**20 more per 1,000** (from 0 fewer to 50 more) [d]	⨁◯◯◯ VERY LOW	CRITICAL
Dizziness, light headedness or sensation of spinning (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	discontinuation of other ADs	continuation of other ADs	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	77/285 (27.0%)	6/72 (8.3%)	**RR 3.24** (1.47 to 7.14)	**187 more per 1,000** (from 39 more to 512 more)	⨁⨁◯◯ LOW	CRITICAL
Nose running (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	43/285 (15.1%)	10/72 (13.9%)	**RR 1.09** (0.57 to 2.06)	**13 more per 1,000** (from 60 fewer to 147 more)	⨁◯◯◯ VERY LOW	CRITICAL
Shortness of breath (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	16/285 (5.6%)	3/72 (4.2%)	**RR 1.35** (0.40 to 4.50)	**15 more per 1,000** (from 25 fewer to 146 more)	⨁◯◯◯ VERY LOW	CRITICAL
Chills (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	15/285 (5.3%)	6/72 (8.3%)	**RR 0.63** (0.25 to 1.57)	**31 fewer per 1,000** (from 63 fewer to 48 more)	⨁◯◯◯ VERY LOW	CRITICAL
Fever (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	8/285 (2.8%)	6/72 (8.3%)	**RR 0.34** (0.12 to 0.94)	**55 fewer per 1,000** (from 73 fewer to 5 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Vomiting (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	discontinuation of other ADs	continuation of other ADs	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	7/285 (2.5%)	3/72 (4.2%)	**RR 0.59** (0.16 to 2.22)	**17 fewer per 1,000** (from 35 fewer to 51 more)	⨁◯◯◯ VERY LOW	CRITICAL
Nausea (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	40/285 (14.0%)	12/72 (16.7%)	**RR 0.84** (0.47 to 1.52)	**27 fewer per 1,000** (from 88 fewer to 87 more)	⨁◯◯◯ VERY LOW	CRITICAL
Diarrhoea (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	31/285 (10.9%)	5/72 (6.9%)	**RR 1.57** (0.63 to 3.89)	**40 more per 1,000** (from 26 fewer to 201 more)	⨁◯◯◯ VERY LOW	CRITICAL
Stomach cramps (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	26/285 (9.1%)	5/72 (6.9%)	**RR 1.31** (0.52 to 3.30)	**22 more per 1,000** (from 33 fewer to 160 more)	⨁◯◯◯ VERY LOW	CRITICAL
Stomach bloating (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	30/285 (10.5%)	5/72 (6.9%)	**RR 1.52** (0.61 to 3.77)	**36 more per 1,000** (from 27 fewer to 192 more)	⨁◯◯◯ VERY LOW	CRITICAL
Unusual visual sensations (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	discontinuation of other ADs	continuation of other ADs	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	12/285 (4.2%)	5/72 (6.9%)	**RR 0.61** (0.22 to 1.67)	**27 fewer per 1,000** (from 54 fewer to 47 more)	⨁◯◯◯ VERY LOW	CRITICAL
Burning, numbness (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	19/285 (6.7%)	2/72 (2.8%)	**RR 2.40** (0.57 to 10.07)	**39 more per 1,000** (from 12 fewer to 252 more)	⨁◯◯◯ VERY LOW	CRITICAL
Unusual sensitivity to sound (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	11/285 (3.9%)	7/72 (9.7%)	**RR 0.40** (0.16 to 0.99)	**58 fewer per 1,000** (from 82 fewer to 1 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Ringing or noises in the ears (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	18/285 (6.3%)	5/72 (6.9%)	**RR 0.91** (0.35 to 2.37)	**6 fewer per 1,000** (from 45 fewer to 95 more)	⨁◯◯◯ VERY LOW	CRITICAL
Unusual tastes or smells (protocol outcome: specific withdrawal symptoms) during study weeks 1-4												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	9/285 (3.2%)	1/72 (1.4%)	**RR 2.27** (0.29 to 17.66)	**18 more per 1,000** (from 10 fewer to 231 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. For the total number of emergent DESS symptoms, 43.8% of the evidence was at very high risk of bias, and 56.2% of the evidence was at low risk of bias.
b. I2=69%; p=0.07
*c. 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 the number of DESS the MID was calculated as 2.63 (0.5*median final SDs of control groups).*

d. Absolute effect calculated from the risk difference due to zero events in one or both arms.

Table 28: Clinical evidence profile: withdrawal from SSRI antidepressants vs continuation on SSRI antidepressants

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	discontinuation of SSRIs	no withdrawal of SSRIs	Relative (95% CI)	Absolute (95% CI)		
Total no. of emergent DESS symptoms (protocol outcome: intensity of withdrawal symptoms at 2 weeks post-abrupt discontinuation)												
2	randomised trials	very serious [a]	not serious	not serious	none	none	43	61	-	MD **0.69 higher** (0.16 higher to 1.22 higher)	⨁⨁◯◯ LOW	CRITICAL
Rebound: return to a MADRS score equal to or higher than the original score at the entry of the acute treatment study (protocol outcome: specific withdrawal symptom 2 weeks post-abrupt discontinuation)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	1/43 (2.3%)	2/61 (3.3%)	**RR 0.71** (0.07 to 7.58)	**10 fewer per 1,000** (from 30 fewer to 216 more)	⨁⨁◯◯ LOW	CRITICAL
Discontinuation Emergent Signs and Symptoms (DESS) score of ≥4 (protocol outcome: intensity of withdrawal symptoms at 2 weeks post-abrupt discontinuation)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	29/181 (16.0%)	15/190 (7.9%)	**RR 2.03** (1.13 to 3.66)	**81 more per 1,000** (from 10 more to 210 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 (DESS score): 1.75 (0.5*SD for the final value score for the control group used (as baseline values not available; final value control group SD only available for Montgomery 2004)).*

F.1.5.2 Withdrawal from antidepressants vs withdrawal from placebo

Table 29: Clinical evidence profile: withdrawal from other antidepressants vs withdrawal from placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	withdrawal from ADs	withdrawal from placebo	Relative (95% CI)	Absolute (95% CI)		
Withdrawal symptoms during discontinuation (protocol outcome: any withdrawal symptom during the discontinuation period))												
6	randomised trials	very serious [a]	not serious	serious d	not serious	none	207/1029 (20.1%)	116/799 (14.5%)	**RR 1.53** (1.26 to 1.87)	**77 more per 1,000** (from 38 more to 126 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms (protocol outcome: any withdrawal symptom at 3 days after discontinuation of treatment)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	7/9 (77.8%)	2/9 (22.2%)	**RR 3.50** (0.98 to 12.48)	**556 more per 1,000** (from 4 fewer to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL
Headache as a DEAE (protocol outcome: specific withdrawal symptom during the discontinuation period)												
1	randomised trials	serious [a]	not serious	serious	serious [b]	none	23/190 (12.1%)	13/185 (7.0%)	**RR 1.72** (0.90 to 3.30)	**51 more per 1,000** (from 7 fewer to 162 more)	⨁◯◯◯ VERY LOW	CRITICAL
Insomnia as a DEAE (protocol outcome: specific withdrawal symptom during the discontinuation period)												
1	randomised trials	serious [a]	not serious	serious	very serious [b]	none	13/190 (6.8%)	11/185 (5.9%)	**RR 1.15** (0.53 to 2.50)	**9 more per 1,000** (from 28 fewer to 89 more)	⨁◯◯◯ VERY LOW	CRITICAL
Nausea as a DEAE (protocol outcome: specific withdrawal symptom during the discontinuation period)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	withdrawal from ADs	withdrawal from placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious	not serious	none	27/190 (14.2%)	9/185 (4.9%)	**RR 2.92** (1.41 to 6.04)	**93 more per 1,000** (from 20 more to 245 more)	⨁⨁◯◯ LOW	CRITICAL
Dizziness as a DEAE (protocol outcome: specific withdrawal symptom during the discontinuation period)												
1	randomised trials	very serious [a]	not serious	serious c	very serious [b]	none	6/95 (6.3%)	3/110 (2.7%)	**RR 2.32** (0.60 to 9.01)	**36 more per 1,000** (from 11 fewer to 218 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mild adverse events (protocol outcome: intensity of withdrawal symptoms at mean 5 days after discontinuation of treatment)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	9	9	-	MD **1.5 higher** (0.49 higher to 2.51 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Moderate adverse events (protocol outcome: intensity of withdrawal symptoms at mean 5 days after discontinuation of treatment)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	9	9	-	MD **0.9 higher** (0.55 lower to 2.35 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. For the withdrawal symptoms during discontinuation outcome, the majority of 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 0.2 for number of mild adverse events and 0.35 number of mild adverse events (0.5 control group SD final value).*
c. unclear if placebo was withdrawn or not during the taper phase
d. in 3/6 studies, participants in the placebo groups had previously been taking active medication; in 4/6 studies it was unclear if placebo was withdrawn or not during the taper phase
e. participants in the placebo groups had previously been taking active medication

F.2 Qualitative evidence

F.2.1 Opioids

Table 30: Summary of evidence: Opioids: Review finding 1

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Worsening of symptoms for which the medication was prescribed					
2	Focus groups and interviews (1 study); semi-structured focus groups (1 study)	People experienced worsening pain symptoms with original symptoms such as back pain getting worse with tapering.	Limitations	Minor limitations [a]	LOW
			Coherence	No concerns about coherence	
			Relevance	No concerns about relevance	
			Adequacy	Serious concerns about adequacy	

(a) Two studies with very minor to minor limitations; minor concerns over methodological limitations due to the potential influence of the researcher not being discussed in both studies[235, 272] and minor possibility of selection bias in patients interviewed in one study[272]; no concerns about coherence; no concerns over relevance; serious concerns about adequacy with the finding emerging from two studies with limited information.

Table 31: Summary of evidence: Opioids: Review finding 2

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Fluctuations/Variability in withdrawal symptoms					
1	Focus groups and interviews (1 study)	Symptoms experienced during tapering such as pain and the need for opioids fluctuated from day to day, getting better or worse.	Limitations	Minor limitations [a]	MODERATE
			Coherence	No concerns about coherence	
			Relevance	No concerns about relevance	
			Adequacy	Minor concerns about adequacy	

(a) One study with minor limitations; minor concerns over methodological limitations due to the potential influence of the researcher not being discussed and minor possibility of selection bias in patients interviewed[272]; no concerns about coherence; no concerns over relevance; minor concerns about adequacy with sufficient information to support the finding but coming from one study.

Table 32: Summary of evidence: Opioids: Review finding 3

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Fear of pain exacerbation and withdrawal					
3	Semi-structured interviews (1 study); Focus groups and interviews (1 study); In-depth interviews (1 study)	The experience of fear of worse pain and loss of function associated with past opioid withdrawal was central in the experience of tapering and warranted management as it could lead to an exacerbation of pain or prevent future tapering attempts.	Limitations	Minor limitations [a]	LOW
			Coherence	No concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	No concerns about adequacy	

(a) *Three studies with minor limitations; minor concerns over methodological limitations with nothing to lower our confidence in one study[216], minor concerns in one study due to the potential influence of the researcher not being discussed and minor possibility of selection bias in patients interviewed[272], due to the influence of the researcher not being discussed in one study[704]; no concerns about coherence; serious concerns over relevance with no concerns in two studies[216, 272] but moderate concerns in one study due to some participants combining codeine with illicit drug use and currently being on methadone maintenance potentially for withdrawal of other medicines which could influence their experience of codeine withdrawal or whose experience may differ from that of people not on methadone maintenance[704] and due to fear over withdrawal potentially not being an actual withdrawal symptom despite having been explicitly reported as such in one study[272]; no concerns about adequacy with sufficient information to support the theme.*

Table 33: Summary of evidence: Opioids: Review finding 4

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Increased pain levels and headaches					
4	Focus groups and interviews (1 study); Mixed method study involving qualitative interviews (1 study) In-depth interviews (2 studies)	Increased physical pain including headaches, cramps, pain in the legs and arms were experienced by people as a result of opioid (including codeine) reduction, the intensity of which could often vary from physical discomfort to 'screaming pain' depending on adherence to the tapering plan.	Limitations	Minor limitations [a]	LOW
			Coherence	No concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	No concerns about adequacy	

(a) *Four studies with minor to moderate limitations; minor concerns over methodological limitations with moderate concerns in one study due to role of the researcher not being discussed and limited relevance of the study aim to the review topic with very limited information to contribute to the review[633] but minor concerns in the other three contributing studies due to the potential influence of the researcher on the findings not being discussed[272, 704, 705] and also minor possibility of selection bias in patients interviewed in one[272]; no concerns about coherence; moderate concerns over relevance due to moderate concerns across the majority of contributing studies due to some participants combining codeine with illicit drug use in two studies[704, 705] and with participants in one study being pain service users receiving an individually tailored one-to-one tapering program whose experience of withdrawal may differ to that of people with no access to similar support[633]; no concerns about adequacy with sufficient information from four studies to support the theme.*

Table 34: Summary of evidence: Opioids: Review finding 5

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Gastrointestinal problems					
3	Focus groups and interviews (1 study); In-depth interviews (1 study); semi-structured interviews (1 study)	People tapering off opioids and codeine misusers and dependents reported withdrawal symptoms including stomach sickness or pain, emesis, vomiting, diarrhoea and loss of appetite which were described as very unpleasant and, in some cases, supported continued use.	Limitations	Minor limitations [a]	MODERATE
			Coherence	No concerns about coherence	
			Relevance	No concerns about relevance	
			Adequacy	Minor concerns about adequacy	

(a) *Three studies with minor limitations; minor concerns over methodological limitations due to the potential influence of the researcher on the findings not being discussed in two studies[272, 704] and also minor possibility of selection bias in patients interviewed in one study[272] and nothing to lower our confidence in one study[216]; no concerns about coherence; no concerns over relevance with moderate concerns in one study due to some participants combining codeine with illicit drug use[704] but no concerns in the other two contributing studies; minor concerns about adequacy with the theme supported by three studies but with relatively limited information from each study.*

Table 35: Summary of evidence: Opioids: Review finding 6

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Sweating, 'cold shakes', fever					
5	In-depth interviews (2 studies); semi-structured interviews (1 study); mixed method study involving qualitative interviews (1 study); semi-structured focus groups (1 study)	People tapering off opioids including codeine experienced sweating, 'cold shakes', cold and hot sweats and fever.	Limitations	Minor limitations [a]	VERY LOW
			Coherence	Minor concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	Minor concerns about adequacy	

(a) *Five studies with no to moderate limitations; minor concerns over methodological limitations with moderate concerns in one study due to role of the researcher not being discussed and limited relevance of the study aim to the review topic with very limited information to contribute to the review[633] but nothing to lower our confidence in one study[216] and minor concerns in three studies due to the potential influence of the researcher on the findings not being discussed[235, 704, 705]; minor concerns about coherence with participants across contributing studies reporting those similar-nature symptoms but with not all symptoms reported across the four studies; moderate concerns over relevance due to moderate concerns in the majority of contributing studies due to some participants combining codeine with illicit drug use in two studies[704, 705] and with participants in one study being pain service users receiving an individually tailored one-to-one tapering program whose experience of withdrawal may differ to that of people with no access to similar support[633]; minor concerns about adequacy with the theme supported by five studies but with relatively limited information from each study.*

Table 36: Summary of evidence: Opioids: Review finding 7

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Sleep problems					
2	In-depth interviews (2 studies)	Experiencing insomnia and disturbed sleep patterns were barriers to stopping codeine misuse.	Limitations	Minor limitations [a]	VERY LOW
			Coherence	No concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	Serious concerns about adequacy	

(a) *Two studies with minor limitations; minor concerns over methodological limitations due to the potential influence of the researcher on the findings not being discussed in both contributing studies[704, 705] and no further concerns to lower our confidence; no concerns about coherence; moderate concerns over applicability due to some participants in both contributing studies combining codeine with illicit drug use and participants of one study also currently being on methadone maintenance potentially for withdrawal of other medicines which could influence their experience of codeine withdrawal or whose experience may differ from that of people not on methadone maintenance[704]; serious concerns about adequacy with very limited information to support the theme.*

Table 37: Summary of evidence: Opioids: Review finding 8

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Mood problems					
3	In-depth interviews (2 studies); semi-structured focus groups (1 study)	Long-term opioid users and codeine misusers and dependents reported psychological pain, fear, crying, self-pity, irritability, anxiety attacks, aggression and feeling very agitated, which appeared to contribute to sustained misuse or needed separate management with medication.	Limitations	Minor limitations [a]	VERY LOW
			Coherence	No concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	Serious concerns about adequacy	

(a) *Three studies with minor limitations; minor concerns over methodological limitations due to the potential influence of the researcher on the findings not being discussed across contributing studies[235, 704, 705] and no further concerns to lower our confidence; no concerns about coherence; moderate concerns over applicability due to some participants in two contributing studies[704, 705] combining codeine with illicit drug use and participants of one study also currently being on methadone maintenance potentially for withdrawal of other medicines which could influence their experience of codeine withdrawal or whose experience may differ from that of people not on methadone maintenance[704]; serious concerns about adequacy with very limited information to support the theme.*

Table 38: Summary of evidence: Opioids: Review finding 9

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Cravings					
2	In-depth interviews (2 studies)	Codeine misusers and dependents experienced strong cravings, with some resorting to illicit drugs (cannabis) to manage them, which often led to relapses whereas using drugs that acted on cravings to treat dependence (suboxone) were reported to lead to instant stopping.	Limitations	Minor limitations [a]	VERY LOW
			Coherence	No concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	Serious concerns about adequacy	

(a) *Two studies with minor limitations; minor concerns over methodological limitations due to the potential influence of the researcher on the findings not being discussed in both contributing studies[704, 705] and no further concerns to lower our confidence; no concerns about coherence; moderate concerns over applicability due to some participants in both contributing studies combining codeine with illicit drug use and participants of one study also currently being on methadone maintenance potentially for withdrawal of other medicines which could influence their experience of codeine withdrawal or whose experience may differ from that of people not on methadone maintenance[704]; serious concerns about adequacy with very limited information to support the theme.*

Table 39: Summary of evidence: Opioids: Review finding 10

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Duration of withdrawal symptoms					
1	Focus groups and interviews (1 study)	Withdrawal symptoms could last from weeks to months or persist a year after stopping opioids.	Limitations	Minor limitations [a]	LOW
			Coherence	No concerns about coherence	
			Relevance	No concerns about relevance	
			Adequacy	Serious concerns about adequacy	

(a) One study with minor limitations; minor concerns over methodological limitations due to the potential influence of the researcher not being discussed and minor possibility of selection bias in patients interviewed[272]; no concerns about coherence; moderate concerns over relevance due to lack of information on which opioids were prescribed; serious concerns about adequacy very limited information from one study to support the theme.

Table 40: Summary of evidence: Opioids: Review finding 11

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Little or no withdrawal symptoms					
2	Semi-structured interviews (1 study); In-depth interviews (1 study)	Some people described little or no opioid withdrawal symptoms during tapering.	Limitations	Very minor limitations	LOW
			Coherence	Minor about coherence [a]	
			Relevance	Minor concerns about relevance	
			Adequacy	Moderate concerns about adequacy	

Two studies with no or minor concerns; very minor concerns about methodological limitations with nothing to lower our confidence in one study[216] and minor concerns in the other contributing study due to the potential influence of the researcher on the findings not being discussed[705]; minor concerns about coherence with information being in contrast with the experience of most participants in both contributing studies but emerging from two separate studies; minor concerns over relevance with moderate concerns in one study due to some participants combining codeine with illicit drug use in one study[705] but no concerns in the other contributing study; moderate concerns about adequacy with relatively limited information from two studies to support the theme.

F.2.2 Benzodiazepines

Table 41: Summary of evidence: Benzodiazepines: Review finding 1

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Return of the original symptoms for which the medication was prescribed					
4	Semi-structured interviews (3 studies) directive interviews and inspection of medication containers (1 study)	Participants reported a return of their original symptoms of insomnia or anxiety following attempts to reduce or stop their benzodiazepine use, that persisted a month after stopping or were relieved only by restoring the initial dose or made stopping undesirable, an inability to function or cope with their ongoing mental health problems.	Limitations	Minor limitations [a]	MODERATE
			Coherence	No concerns about coherence	
			Relevance	Minor concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy [a]	

(a) Three studies with minor limitations and one study with serious limitations; minor concerns about methodological limitations in the majority of studies due to limited information and quotes to support the study findings and the Interviewer qualification being unclear[67], lack of details on the analysis[471] and the role of the researcher not being discussed and themes supported by single quotes[514] and serious limitations in one study due to the role of the researcher not being explored, the recruitment strategy with participants selected for a different project, the data analysis being unclear[722]; no concerns about coherence; minor concerns over relevance with no concerns in three studies[67, 471, 514] but moderate concerns in one study with at least some participants taking benzodiazepines that did not meet the protocol[722]; minor concerns about adequacy with four studies supporting the theme but with information in each study being limited.

Table 42: Summary of evidence: Benzodiazepines: Review finding 2

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Findings**	**Criteria**	**Rating**	**Overall assessment of confidence**
Worry as part of withdrawal					

Study design and sample size		Findings	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
3	Semi-structured interviews (2 studies); directive interviews and inspection of medication containers (1 study)	Benzodiazepine withdrawal evoked feelings of worry and burden with people wishing to keep some benzodiazepines for psychological reasons, to have just in case.	Limitations	Moderate limitations[a]	VERY LOW
			Coherence	No concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	Moderate concerns about adequacy	

(a) *Two studies with minor limitations and one study with serious limitations; moderate concerns about methodological with minor concerns in two studies due to limited information and quotes to support the study findings and the Interviewer qualification being unclear[67] and the role of the researcher not being discussed and themes supported by single quotes[514] but serious limitations in one study contributing the majority of the information for this theme, due to the role of the researcher not being explored, the recruitment strategy with participants selected for a different project, the data analysis being unclear[722]; no concerns about coherence; moderate concerns over relevance with no concerns in two studies but moderate concerns in one study with at least some participants taking benzodiazepines that did not meet the protocol[722] and due to the feeling of worry caused before and not necessarily as a result of withdrawal; moderate concerns about adequacy with three studies supporting the theme but with information in each study being very limited.*

Table 43: Summary of evidence: Benzodiazepines: Review finding 3

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Findings**	**Criteria**	**Rating**	**Overall assessment of confidence**
Intensity of withdrawal symptoms					
3	Semi-structured interviews (3 studies)	Several, particularly those on rapid withdrawal experienced adverse withdrawal symptoms including chest pain and hang-over effects, with the intensity of the symptoms during past attempts to reduce use, leading to an inability to cease benzodiazepines or to taking other medication to cope.	Limitations	Minor limitations [a]	MODERATE
			Coherence	No concerns about coherence	
			Relevance	No concerns about relevance	
			Adequacy	Minor concerns about adequacy	

(a) *Three studies with minor limitations; minor concerns about methodological limitations due to limited information and quotes to support the study findings and the Interviewer qualification being unclear[67] lack of details on the analysis[471], the role of the researcher not being discussed and findings illustrated by single quotes[514]; no concerns about coherence; no concerns over relevance;; minor concerns about adequacy with information from two studies being relatively limited.*

Table 44: Summary of evidence: Benzodiazepines: Review finding 4

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Findings**	**Criteria**	**Rating**	**Overall assessment of confidence**
Disturbed dreams					
1	Semi-structured interviews	A number of elderly participants experienced what they called 'disturbed dreams' after stopping benzodiazepines which appeared to impact their daily life.	Limitations	Minor limitations [a]	VERY LOW
			Coherence	No concerns about coherence	
			Relevance	Minor concerns about relevance	
			Adequacy	Serious concerns about adequacy	

(a) *One study with minor limitations; minor concerns about methodological limitations due to limited information and quotes to support the study findings and the Interviewer qualification being unclear[67]; no concerns about coherence; minor concerns over relevance due to the population contributing to the finding being limited to elderly people; serious concerns about adequacy with limited information from one study supporting the finding.*

Table 45: Summary of evidence: Benzodiazepines: Review finding 5

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Lack of withdrawal symptoms					
2	Semi-structured interviews (2 studies)	Several people prescribed hypnotic and/or anxiolytic benzodiazepines, including people who had stopped receiving prescriptions for several months or periods at a time over the years, did not experience problems when stopping or slowly reducing their medicines.	Limitations	Minor limitations [a]	MODERATE
			Coherence	No concerns about coherence	
			Relevance	No concerns about relevance	
			Adequacy	No concerns about adequacy	

(a) Two studies with minor limitations; minor concerns about methodological limitations due to limited information and quotes to support the study findings and the Interviewer qualification being unclear[67] lack of details on the analysis[471]; no concerns about coherence; no concerns over relevance; no concerns about adequacy.

F.2.3 Antidepressants (mixed/unclear)

Table 46: Summary of evidence: Antidepressants: Review finding 1

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Severity of withdrawal symptoms					
3	Mixed method (HTA) involving qualitative analysis of yellow card reports (1 study); qualitative analysis of unsolicited posts on mental health website (1 study); Telephone interviews (1 study)	People experienced severe withdrawal symptoms, also in the period between prescriptions, which were sometimes experienced as debilitating, resulted in feeling out of control, regretting stopping and recontinuing antidepressants.	Limitations	Minor limitations [a]	LOW
			Coherence	No concerns about coherence	
			Relevance	Minor concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy [a]	

(a) *Three studies with no notable issues, minor and serious issues; minor concerns about methodological limitations with no notable limitations identified for one study[46], serious limitations in one study making a minor contribution to the theme, due to potential selection bias as the method used to select website posts was not specified and lack of sufficient detail on the data analysis[508], but minor methodological limitations due to the potential influence of the researcher on the findings not being discussed in the study contributing the majority of the information to this theme[117]; minor concerns over relevance with moderate concerns over one study with the information emerging being specifically about 'brain zaps' and due to a lack of sufficient information on the characteristics of peopled from which the information emerged and the data being unverified due to the nature of the source (anonymous posts on mental health website), but the study contributing limited information to the theme[508], no concerns in one study[46] and minor concerns in the study contributing the most information to the theme due to the all-female sample included[117]; minor concerns about adequacy with information emerging from three studies but being very limited in two out of three contributing studies*.

Table 47: Summary of evidence: Antidepressants: Review finding 2

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Fear of discontinuation					
3	Semi-structured interviews (2 studies); structured or semi-structured telephone interviews (1 study)	People became overwhelmed by fears and worries as a result of antidepressant discontinuation, that were fuelled by past negative experiences of discontinuation attempts and contributed to attributions about their lifelong need for medication despite wanting to discontinue.	Limitations	Moderate limitations [a]	LOW
			Coherence	No concerns about coherence	
			Relevance	Moderate concerns about relevance [a]	
			Adequacy	No concerns about adequacy	

(a) *Three studies with minor to moderate issues; moderate methodological limitations due to the potential influence of the researcher on the findings not being discussed in two studies[117, 188] and issues with data richness in two studies with themes mostly supported by limited information in one study[188] and with a very small sample included in one study[69]; moderate concerns over applicability due to fear not necessarily experienced during withdrawal by all participants raising it and due to the all-female sample of one study[117].*

Table 48: Summary of evidence: Antidepressants: Review finding 3

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Dizziness, nausea and loss of appetite					
2	Mixed method (HTA) involving qualitative analysis of yellow card reports (1 study); qualitative analysis of postings on a health-related website. (1 study)	People on venlafaxine experienced nausea and dizziness during discontinuations and after stopping, accompanied by loss of appetite and abdominal pain in one person	Limitations	Moderate limitations [a]	VERY LOW
			Coherence	Minor concerns about coherence [a]	
			Relevance	Minor concerns about relevance [a]	
			Adequacy	Moderate concerns about adequacy [a]	

(a) Two studies: one with no notable issues and one with serious issues; moderate concerns over methodological limitations with no notable limitations in one study[46] but serious limitation in the other study[532] due to the research design/methods, data collection method and analysis (postings on health website); minor concerns about coherence with loss of appetite reported in only one person in one study; minor concerns over relevance with moderate concerns in one study[532] due to a lack of sufficient information on the characteristics of people from which the information emerged and the data being unverified due to the nature of the source (anonymous posts on health website) but no concerns in the other study; moderate concerns about adequacy with information only emerging from a small people in two studies.

Table 49: Summary of evidence: Antidepressants: Review finding 4

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Increase in negative emotions					
3	Semi-structured interviews (2 studies); structured or semi-structured telephone interviews (1 study)	People reported an inability to regulate emotions without the medicine, feeling depressed, anxious, tearful, increased feelings of loneliness and abandonment during discontinuation, which sometimes led to restarting the medicines, contributing to further negative feelings about themselves.	Limitations	Minor limitations [a]	VERY LOW
			Coherence	Moderate concerns about coherence [a]	
			Relevance	Moderate concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy [a]	

(a) Three studies with minor to moderate issues; minor concerns over methodological limitations with moderate concerns in one study due to the potential impact of the researcher on the findings not being explored and issues with data richness with themes mostly supported by limited information and single quotes but minor limitations in two studies again due to the potential influence of the researcher on the findings not being discussed in one study[117] and due to concerns over data richness with a very small sample (n=12) included in one study[69]; moderate concerns about coherence with negative feelings varying across participants; moderate concerns over applicability with minor concerns in one study due to the all-female sample[117] but also due to concerns over some negative feelings described being related to recurrence of depression rather than being withdrawal symptoms; minor concerns about adequacy with relatively limited information from three studies supporting the theme.

Table 50: Summary of evidence: Antidepressants: Review finding 5

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Strange sensation in the head					
5	Secondary analysis of narrative interviews (1 study); mixed methods (HTA) involving qualitative analysis of yellow card reports (1 study); telephone interviews (1 study); qualitative analysis of posts on health website (2 studies)	People reported experiencing strange withdrawal symptoms that included 'electric shock-like sensations' in the brain, a head buzz or 'brain zap' that often persisted after stopping the medicine and were sometimes accompanied by vertigo or associated with making a rapid mascle movement.	Limitations	Moderate limitations [a]	LOW
			Coherence	No concerns about coherence	
			Relevance	Moderate concerns about relevance [a]	
			Adequacy	No concerns about adequacy	

(a) Five studies with no notable issues to serious issues; moderate concerns over methodological limitations with no notable limitation in one study[46], minor limitations in two studies due to the potential influence of the researchers on the findings not being discussed[31, 117] and very minor concerns over potential bias in recruitment with participants having already been selected for a different project[31] but serious limitations in two studies in one study[532] due to the research design/methods, data collection method and analysis (postings on health website), and due to potential selection bias as the method used to select posts was not specified, lack of sufficient detail on the data analysis in the other study [508]; moderate concerns over relevance with moderate concerns in two studies due to a lack of sufficient information on the characteristics of people from which the information emerged and the data being unverified due to the nature of the source (anonymous posts on health websites)[508, 532], minor concerns in one study due to the all-female sample included[117] and no concerns in two studies[31, 46].

F.2.4 Antidepressants (SSRIs)

Table 51: Summary of evidence: Antidepressants: Review finding 6

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Severity of withdrawal symptoms					
3	Mixed method (HTA) involving qualitative analysis of yellow card reports (1 study); semi-structured interviews (1 study); qualitative analysis of postings on a health-related website. (1 study)	People experienced severe withdrawal symptoms, the unpleasantness of which was comparable to the initial depressive symptoms, often led to feelings of regret about trying to stop, relapse and prevented future discontinuation attempts contributing to sustained use.	Limitations	Moderate limitations [a]	LOW
			Coherence	No concerns about coherence	
			Relevance	Minor concerns about relevance	
			Adequacy	No concerns about adequacy	

(a) Two studies with no and minor issues and one study with serious issues; moderate concerns over methodological limitations with no concerns in one study[46], minor concerns in one contributing study where participants were only recruited from one group practice within one primary care trust[386] and serious concerns in one study[532] due to the research design/methods, data collection method and analysis (postings on health website); minor concerns over relevance with moderate concerns in one study[532] due to a lack of sufficient information on the characteristics of people from which the information emerged and the data being unverified due to the nature of the source (anonymous posts on health website) but no similar concerns in the other contributing studies.

Table 52: Summary of evidence: Antidepressants: Review finding 7

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Fear of discontinuation and relapse					
2	Semi-structured interviews (1 study); content analysis of free text comments from consumer reports (1 study)	People experienced fear about the process of discontinuation, about discontinuation symptoms and the consequences of stopping which was thought to potentially lead to relapse of depression and was often driven by past attempts to stop; this fear sometimes ultimately prevented discontinuation.	Limitations	Moderate limitations [a]	LOW
			Coherence	No concerns about coherence	
			Relevance	Moderate concerns about relevance [a]	
			Adequacy	No concerns about adequacy	

(a) Two studies with minor and serious issues; moderate concerns about methodological limitations with minor concerns in one study where participants were only recruited from one group practice within one primary care trust[386], but serious concerns in the other contributing study due to the study design and data collection (retrospective analysis of independently submitted free text feedback from consumers), study design dictated by the data/consumer feedback process, results (themes) were reported interspersed with references and insights from other studies, making it unclear what conclusions were based on this study alone[716]; moderate concerns about relevance with fear potentially not emerging as a result of discontinuation but preceding it in some participants in both studies and due to participants in one study being limited to people experiencing adverse drug reactions[716].

Table 53: Summary of evidence: Antidepressants: Review finding 8

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Suicidal thoughts					
1	Mixed method (HTA) involving qualitative analysis of yellow card reports	Both paroxetine and citalopram users experienced persistent suicidal thoughts during withdrawal from antidepressants with some having made multiple suicide attempts; these were also experienced during dose reductions.	Limitations	No limitations	LOW
			Coherence	No concerns about coherence	
			Relevance	No concerns about relevance	
			Adequacy	Serious concerns about adequacy [a]	

(a) One study with no notable issues; serious concerns about adequacy with information from a very small number of participants in one study supporting the theme[46].

Table 54: Summary of evidence: Antidepressants: Review finding 9

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Nausea and dizziness					
2	Mixed method (HTA) involving qualitative analysis of yellow card reports (1 study); qualitative analysis of postings on a health-related website. (1 study)	People coming off paroxetine experience nausea and dizziness.	Limitations	Moderate limitations [a]	VERY LOW
			Coherence	No concerns about coherence	
			Relevance	Minor concerns about relevance [a]	
			Adequacy	Serious concerns about adequacy [a]	

(a) Two studies: one with no notable issues and one with serious issues; moderate concerns over methodological limitations with no notable limitations in one study[46] but serious limitation in the other study[532] due to the research design/methods, data collection method and analysis (postings on health website); minor concerns over relevance with moderate concerns in one study[532] due to a lack of sufficient information on the characteristics of people from which the information emerged and the data being unverified due to the nature of the source (anonymous posts on health website) but no concerns in the other study; serious concerns about adequacy with limited information emerging from a very small people in two studies

Table 55: Summary of evidence: Antidepressants: Review finding 10

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Insomnia					
1	Mixed method (HTA) involving qualitative analysis of yellow card reports	Insomnia was one of the withdrawal symptoms experienced since starting to reduce antidepressants.	Limitations	No limitations	VERY LOW
			Coherence	No concerns about coherence	
			Relevance	No concerns about relevance	
			Adequacy	Serious concerns about adequacy [a]	

(a) One study with no notable issues[46]; serious concerns about adequacy with very limited information from one participant emerging from one study.

Table 56: Summary of evidence: Antidepressants: Review finding 11

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Psychiatric adverse reactions					
3	Mixed method (HTA) involving qualitative analysis of yellow card reports; qualitative analysis of postings on a health-related website. (1 study); content analysis of free text comments from consumer reports (1 study)	People experienced unmanageable stress, excessive anxiety that were much higher to pre-antidepressant levels, irrational fears (e.g., fear of dying), panic attacks, became violent towards the self or others since beginning discontinuation or particularly after a significant dose reduction (e.g., to 10mg) which were interpreted as withdrawal symptoms by patients but often as relapse/recurrence of depression. indicating the need for continued treatment by doctors.	Limitations	Serious limitations [a]	LOW
			Coherence	No concerns about coherence	
			Relevance	Moderate concerns about relevance [a]	
			Adequacy	No concerns about adequacy	

(a) *Two studies with serious issues and one study with no notable issues; serious concerns about methodological limitations with no concerns in one study[46] but serious concerns in two studies, in one study due to the study design and data collection (retrospective analysis of independently submitted free text feedback from consumers), study design dictated by the data/consumer feedback process, results (themes) were reported interspersed with references and insights from other studies, making it unclear what conclusions were based on the study alone[716] and in the other study due to the research design/methods, data collection method and analysis (postings on health website)[532]; moderate concerns about relevance with no concerns in one study but minor concerns in another contributing study due to participants in one study being limited to people experiencing adverse drug reactions[716] and moderate concerns in the third contributing study due to a lack of sufficient information on the characteristics of people from which the information emerged and the data being unverified due to the nature of the source (anonymous posts on health website).*

Table 57: Summary of evidence: Antidepressants: Review finding 12

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Changes in mood					
1	Mixed method (HTA) involving qualitative analysis of yellow card reports	Sudden changes in mood and crying were experienced since beginning to reduce the medicine but also after a significant reduction in dose.	Limitations	No limitations	VERY LOW
			Coherence	No concerns about coherence	
			Relevance	No concerns about relevance	
			Adequacy	Serious concerns about adequacy [a]	

(a) One study with no notable issues[46]; serious concerns about adequacy with very limited information from two participants emerging from one study.

Table 58: Summary of evidence: Antidepressants: Review finding 13

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Other bodily symptoms					
2	Mixed method (HTA) involving qualitative analysis of yellow card reports (1 study); semi-structured interviews (1 study)	Since beginning to reduce their medicine people experienced symptoms including agitation, sweating and palpitations but also flu-like symptoms including debilitating tiredness, headaches, aching joints and muscles particularly (5 weeks) after dropping the antidepressant dose.	Limitations	Minor limitations [a]	VERY LOW
			Coherence	No concerns about coherence	
			Relevance	No concerns about relevance	
			Adequacy	Serious concerns about adequacy [a]	

(a) Two studies with no to minor notable issues; minor methodological limitations associated with one study with participants only recruited from one group practice within one primary care trust[386] and no concerns in the other study[46]; serious concerns about adequacy with very limited information from two studies.

Table 59: Summary of evidence: Antidepressants: Review finding 14

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Onset of withdrawal symptoms					
2	Semi-structured interviews (1 study); content analysis of free text comments from consumer reports (1 study)	The onset of withdrawal symptoms was not until 3-5 days after the discontinuation attempt (involving reducing and stopping antidepressants)	Limitations	Moderate limitations [a]	VERY LOW
			Coherence	Minor concerns about coherence [a]	
			Relevance	Minor concerns about relevance [a]	
			Adequacy	Moderate concerns about adequacy [a]	

(b) Two studies with minor and serious issues; moderate concerns about methodological limitations with minor concerns in one study where participants were only recruited from one group practice within one primary care trust[386], but serious concerns in the other contributing study due to the study design and data collection (retrospective analysis of independently submitted free text feedback from consumers), study design dictated by the data/consumer feedback process, results (themes) were reported interspersed with references and insights from other studies, making it unclear what conclusions were based on this study alone[716]; minor concerns about coherence with slightly different days of onset reported and it was not always clear if these were relevant to the start of reduction or complete discontinuation; minor concerns about relevance due to participants in one study being limited to people experiencing adverse drug reactions[716]; moderate concerns about adequacy with limited information from two studies supporting the theme.

Appendix G Economic evidence tables

None.

Appendix H Health economic model

This question was not prioritised for health economic modelling.

Appendix I Excluded studies

I.1 Studies excluded from the quantitative review

Study	Exclusion reason
Lewis 2008[384]	HTA/study protocol
Alexopoulos 2000[15]	No usable outcomes (assess relapse of depression in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Allgulander 2001[22]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Allgulander 2006[21]	Incorrect study design (escitalopram for GAD, some withdrawal symptoms reported but no comparison)
Altshuler 2001[23]	Incorrect study design (retrospective chart review)
Altshuler 2003[24]	Incorrect study design (non-randomised study)
Alvarez 2012[25]	No usable outcomes (efficacy and safety study, withdrawal symptoms not reported)
Ancoli-Israel 2005[28]	Incorrect study design (non-comparative withdrawal from zaleplon)
Andersch 1991[29]	Population does not match protocol (>20% of population were on a benzodiazepine not included on the guideline medicine list)
Andrade 2004[34]	Systematic review of articles describing aetiology, nosology, mechanisms etc
Anonymous 1998[41]	Short narrative review article, no includable RCTs described
Ansseau 1990[42]	Intervention and comparator do not match protocol (buspirone vs oxazepam arms, no placebo or withdrawal comparator)
Babul 2004[49]	No usable outcomes (efficacy study, withdrawal symptoms not reported)
Bainum 2017[51]	Incorrect study design (observational cohort study)
Baldwin 2016[56]	Secondary analysis of RCTs (included studies checked for references)
Baldwin 2007[58]	Secondary analysis of comparative studies (included studies checked for references)
Baldwin 2012[57]	Intervention and comparator do not match protocol (efficacy study, no withdrawal period)
Balmer 1981[59]	Incorrect study design (prospective cohort)
Barker 2004[63]	Systematic review (protocol does not match current review protocol)
Baron 2010[64]	No usable outcomes (no withdrawal outcomes)
Belleville 2008[74]	Intervention and comparator do not match protocol (hypnotic taper intervention with or without self-help treatment for insomnia)
Bergh 2012[77]	No usable outcomes (depressive symptoms score reported for continuation vs discontinuation, withdrawal symptoms or rebound symptoms not reported)
Bialos 1982[82]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms only reported for one arm)
Bidzan 2012[83]	Intervention and comparator do not match protocol (efficacy study, no withdrawal period)
Bieling 2012[84]	No usable outcomes (no withdrawal outcomes)
Biondi 1994[85]	Comparator does not match protocol (no withdrawal comparator)

Study	Exclusion reason
Bixler 1985[86]	Incorrect study design (non-randomised study)
Black 2000[88]	Incorrect study design (review of case reports to establish diagnostic criteria for SSRI discontinuation syndrome)
Boulenger 2014[92]	No usable outcome data (DESS total scores reported, but no variance reported and P values for calculation of variance not reported for all arms of trial)
Bowden 1980[94]	No usable outcomes (diazepam withdrawal; withdrawal symptoms not reported in a way that can be used)
Boyer 2008[96]	Comparator does not match protocol (3 arm trial, one arm discontinues antidepressants during taper phase, but the placebo treatment arm continues taking placebo during the taper phase (no withdrawal from placebo) and the other antidepressant continues but reduces dose during the taper phase)
Busto 1986[103]	Intervention does not match protocol (both arms discontinued benzodiazepines, taper vs abrupt discontinuation)
Busto 1989 [108]	No usable outcomes (no withdrawal outcomes)
Busto 1998[104]	Population does not match protocol (healthy volunteers)
Busto 1998[105]	Systematic review (protocol does not match current review protocol)
Cappell 1987[116]	No usable outcomes
Cantopher 1990[114]	Incorrect comparator (both groups withdraw from benzodiazepines, not compared to a 'no withdrawal' group)
Choy 2007[125]	No usable outcomes (no withdrawal outcome; change in MADRS or HAM-A scores after three years on or off medication)
Cohen 2004[132]	Incorrect study type (before and after study)
Cohen 2019[131]	Systematic review (protocol does not match current review protocol)
Cohen-Mansfield 1999[129]	Population does not match protocol (people on psychotropic medication: only 33% were on lorazepam, the others were on haloperidol or thioridazine)
Cook 1986[135]	No usable outcomes
Coppen 1978[140]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Covi 1973[143]	No usable outcomes (no extractable withdrawal symptom outcomes)
Cowan 2005[144]	Intervention does not match (crossover, morphine-placebo over 60 hours)
Crowe 2018[148]	Meta-analysis of long-term cognitive effects of benzo use
Cutler 1993[151]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Cutler 2009[150]	Comparator does not match protocol (efficacy study, during the discontinuation phase, the arm taking medication taper to no pills, where-as the placebo arm continues taking placebo: no withdrawal in placebo arm)
Da 2014[152]	Systematic review (protocol does not match current review protocol: review of efficacy studies, 3 trials reported to have withdrawal symptom outcomes: these 3 studies checked for inclusion in the current review).
Dallal 1998[153]	Incorrect study type (non-comparative study)

Study	Exclusion reason
Dannon 2004[155]	Incorrect study design (non-randomised study). No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Davidson 1984[156]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Davies 2019[159]	Systematic review (protocol does not match current review protocol)
Davis 2006[160]	Narrative review
Dell'Osso 2008[165]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Detke 2002[166]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Detke 2002[167]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Doogan 1992[171]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Duffy 2019[175]	Study protocol
Elie 1990[181]	Population does not match protocol (benzodiazepine not included on the guideline medicine list). No usable outcomes.
Elie 1990[182]	No usable outcomes (no withdrawal symptom outcomes)
Elie 1999[183]	No usable outcomes (numerical data not reported for rebound insomnia or withdrawal symptoms)
Eveleigh 2018[187]	No usable outcomes (no withdrawal symptom outcomes; focussed on successful cessation)
Fahy 1992[190]	No usable outcomes (relapse symptom outcomes, no withdrawal outcomes)
Fallon 2008[191]	No comparator (out of the original randomised groups, no people were left in the placebo group for the discontinuation phase)
Fava 2018[194]	Systematic review (protocol does not match current review protocol)
Fava 2015[195]	Systematic review (protocol does not match current review protocol)
Fava 2006[196]	Narrative review
Feet 1988[198]	No usable outcomes (assesses change in condition in people continued on benzodiazepines vs those discontinued; withdrawal symptoms or rebound symptoms not specifically reported)
Feiger 1999[199]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Fontaine 1984[213]	Population does not match protocol (>20% of population were on a benzodiazepine not included on the guideline medicine list)
Fontaine 1984[214]	Population does not match protocol (>20% of population were on a benzodiazepine not included on the guideline medicine list)
Fontaine 1985[211]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)

Study	Exclusion reason
Fontaine1987[212]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Fixsen 2017[206]	Incorrect study design (qualitative study)
Frank 1990[215]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Frost 1979[217]	Incorrect study design (crossover, no comparative arm)
Fry 2000[218]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Gahr 2013[220]	Systematic review (protocol does not match current review protocol)
Gardos 1977[222]	Incorrect study design (case study)
Garner 1993[224]	Systematic review (protocol does not match current review protocol)
Gastpar 2017[225]	Intervention and comparator do not match protocol (paroxetine arm is not withdrawn during the taper phase, placebo arm continue taking placebo during taper phase)
Geddes 2003[226]	Systematic review (protocol does not match current review protocol)
Georgotas 1989[227]	No usable outcomes (assesses recurrence in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Ghaemi 2010[228]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Giller 1985[231]	Incorrect study design (unclear if randomised)
Glen1984[233]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Goldstein 2002[237]	No usable outcomes (narrative report of discontinuation-emergent adverse event only available for one arm)
Goldstein 2004[236]	No usable outcomes (efficacy study with placebo lead-out phase: discontinuation-emergent adverse events were reported but only for one arm, or narratively as no significant difference between groups)
Goodwin 2009[239]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Grant 2006[242]	No usable outcomes (assesses relapse; withdrawal symptoms or rebound symptoms not reported)
Greist 2004[246]	Pooled analysis of multiple studies (some primary studies unpublished; for those published, usable references checked for inclusion in review)
Habraken 1997[252]	No usable outcomes (withdrawal outcome results not extractable)
Hajak 2009[255]	No usable outcomes (BWSQ outcome reported for withdrawal (zolpidem-placebo arm) vs continuation (zolpidem-zolpidem arm), but only percentage reported – calculations from the number completing the run-out phase do not match up with percentages provided).

Study	Exclusion reason
Harrison 1986[259]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Hartelius 1978[260]	No usable outcomes (withdrawal outcome results not extractable)
Hartford 2007[261]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Hartmann 1983[262]	No usable outcomes
Hedner 2000[267]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Henigsberg 2012[271]	Intervention and comparator do not match protocol (efficacy study, no withdrawal period)
Henssler 2019[273]	Systematic review (protocol does not match current review protocol)
Hindmarch 2000[274]	Comparator does not match protocol (no placebo arm)
Hitzeman 2010[275]	Incorrect study design (case study)
Hochstrasser 2001[276]	No usable outcomes (assess relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Hollander 2003[277]	No usable outcomes (withdrawal symptom outcomes not reported)
Huijbers 2016[280]	No usable outcomes (assess relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Jacobsen 2015[292]	No usable outcomes (DESS scores reported but only narratively as not significant between the antidepressant and placebo arms, during the 2-week discontinuation period)
Jamison 1998[299]	Comparator does not match protocol (no placebo arm)
Jenkins 1990[306]	Population does not match protocol (people on a medicine not included in this guideline)
Johnson 2011[310]	Secondary analysis of three biokinetic/bioavailability studies
Judge 2002[312]	Intervention does not match protocol (assessing antidepressant treatment interruption for 3-5 days, not withdrawal/stopping the medicine)
Kales 1988[315]	No usable outcomes
Kales 1971[316]	No usable outcomes
Kales 1991[314]	No usable outcomes (sleep time and latency measures reported as continuous outcomes after withdrawal of benzodiazepines, dichotomous outcomes of rebound symptoms only reported narratively for one temazepam group (not for placebo))
Kane 1982[317]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Katona 2012[321]	Intervention and comparator do not match protocol (efficacy study, no withdrawal period)
Katz 2010[323]	No usable outcomes (withdrawal symptom scores not reported for overall groups, description of individual participants only)
Katz 2007[324]	Population does not match protocol (people on an opioid not included in this guideline (oxymorphone))
Kaufman 2003[325]	Intervention does not match protocol (assessing antidepressant treatment interruption for 3-5 days, not withdrawal/stopping the medicine)

Study	Exclusion reason
Keller 2005[327]	Population does not match protocol (people on a medicine not included in this guideline)
Keller 1998[326]	No usable outcomes (assess relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Kishimoto 1994[341]	No usable outcomes (assesses recurrence in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Koponen 2007[349]	No usable outcomes (discontinuation-emergent adverse events only reported in results as percentages - calculations suggest ITT analysis was not used for the DEAEs outcome (i.e., excludes dropouts during treatment phase), however the total number used for analysis is only reported for the placebo arm. Analysed numbers for 60mg and 120mg arms not reported separately, in order to calculate dichotomous outcomes from percentages in results).
Klerman 1974[343]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Klysner 2002[344]	No usable outcomes (assess relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Kocsis 1996[346]	Population does not match protocol (people on an antidepressant not included on the guideline medicine list)
Kocsis 2002[347]	No usable outcomes (assesses recurrence in people continued vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Koran 2007[350]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Koran 2007[351]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Koran 2003[352]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Koran 2005[353]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Krystal 2011[359]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Krystal 2007[358]	Population does not match protocol (population were on a z-drug not included on the guideline medicine list)
Kupfer 1992[360]	No usable outcomes (assesses recurrence in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Kurita 2018[361]	No usable outcomes (no withdrawal outcomes)
Laakman 1995[362]	Incorrect study design (crossover, no comparative arm)
Laakmann 1997[363]	Not in English
Lader 2004[365]	No usable outcomes (efficacy trial: included a discontinuation phase but DESS results only reported narratively)
Lader 1984[364]	Comparator does not match protocol (both arms tapered off drug)

Study	Exclusion reason
Laughren 1982[377]	No usable outcomes (withdrawal outcome results not extractable)
Lemoine 1997[380]	Comparator does not match protocol (both arms tapered off drug)
Leppik 1997[383]	No usable outcomes (no usable withdrawal outcomes)
Liebowitz 2008[388]	No usable outcomes (no withdrawal period or outcomes)
Liebowitz 2009[387]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Lôo 1991[392]	Not in English
Ma 2008[395]	No usable outcomes (no withdrawal outcomes)
Ma 2019[394]	Systematic review, protocol only
Mahableshwarkar 2013[397]	Intervention and comparator do not match protocol (efficacy study, no withdrawal period)
Mahableshwarkar 2015[398]	Intervention and comparator do not match protocol (efficacy study, no withdrawal period)
Mahableshwarkar 2014[399]	Intervention and comparator do not match protocol (efficacy study, no withdrawal period)
Mahableshwarkar 2014[400]	Intervention and comparator do not match protocol (efficacy study, no withdrawal period)
Mahableshwarkar 2015[401]	Intervention and comparator do not match protocol (efficacy study, no withdrawal period)
Maidment 2001[403]	Meta-analysis of zaleplon efficacy studies
Markowitz 2000[408]	No usable outcomes (assess relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Mavissakalian 1999[417]	No usable outcomes (assess relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Mavissakalian 2001[416]	No usable outcomes (assess relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Mayur 2000[419]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
McIntyre 2014[424]	No usable outcomes (efficacy study, withdrawal symptoms not reported)
Michelson 2000[428]	Incorrect study design (non-randomised study)
Mindham 1972[430]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Mitler 1984[433]	No usable outcomes (no useful extractable withdrawal outcomes)
Molenaar 2016[437]	Study protocol
Montgomery 2006[438]	Narrative review
Montgomery 1988[439]	No usable outcomes (assesses recurrence in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Montgomery 1992[444]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Montgomery 1993[440]	No usable outcomes (assesses relapse/recurrence in people continued on antidepressants vs those discontinued; some side

Study	Exclusion reason
	effects reported but withdrawal symptoms or rebound symptoms not reported)
Montgomery 2009[441]	Secondary analysis of RCTs (checked references for inclusion)
Monti 1994[445]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Monti 1996[446]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Moroz 1999[448]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Murphy 1985[451]	Comparator does not match protocol (no placebo arm)
Nakao 2006[454]	Population does not match protocol (>20% of population were on a benzodiazepine not included on the guideline medicine list)
Ninan[468]	Subsidiary paper of Khan 2014 (already included in this review) with no additional outcomes
Nishimura 2018[469]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Oehrberg 1995[486]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Old age depression interest group 1993[295]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Oswald 1985[497]	Letter to editor/comment
Pato 1988[518]	Incorrect study design (crossover, no comparative arm)
Pauer 2012[519]	No usable outcomes (assesses loss of therapeutic response in people continued on pregabalin vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Pecknold 1982[523]	Comparator does not match protocol (drug vs drug comparison, no ‘no withdrawal’ arm)
Pecknold 1982[524]	Comparator does not match protocol (drug vs drug comparison, no ‘no withdrawal’ arm)
Perahia 2005[526]	Pooled analysis of RCTs (checked references of primary studies for inclusion)
Perahia 2008[528]	Intervention and comparison does not match protocol (both groups received antidepressants, assessing effectiveness of telephone intervention)
Petursson 1983[533]	Incorrect study design (not a randomised controlled trial)
Petursson 1981[534]	Incorrect study design (non-comparative study, all people withdrawn from benzodiazepines)
Pourmotabbed 1996[542]	No usable outcomes (withdrawal outcome results not extractable)
Power 1985[543]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Power 1990[544]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)

Study	Exclusion reason
Prien 1984[552]	No usable outcomes (assesses recurrence in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Pujalte 1994[554]	No usable outcomes (withdrawal outcomes not reported)
Pundiak 2008[555]	Incorrect study design (allocation to continuation or discontinuation not randomised)
Rapaport 2001[559]	No usable outcomes (some adverse events reported but not withdrawal symptoms)
Rauck 2015[564]	Population does not match protocol (population were on an opioid not included on the guideline medicine list (oxycodone with naltrexone))
Ravizza 1996[567]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Read 2018[575]	Incorrect study design (online survey study)
Reimherr 1998[577]	No usable outcomes (assess relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Reynolds 1999[578]	No usable outcomes (assess relapse in people continued on antidepressants vs those discontinued (placebo); withdrawal symptoms or rebound symptoms not reported)
Rickels 1983[580]	Population does not match protocol (>20% of population were on a benzodiazepine not included on the guideline medicine list)
Rickels 1988[583]	No usable outcomes (rebound outcome only reported for discontinuation arm)
Rickels 1990[585]	No usable outcomes (withdrawal outcomes not reported)
Rickels 2000[581]	Comparator does not match protocol (during the interruption periods the placebo arm continues taking placebo: no withdrawal in placebo arm)
Rickels 1997[586]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Rickels 2010[582]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Ristanovic 2009[590]	Incorrect study design (not randomised to intervention and comparison arms)
Robert 1995[591]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Robinson 1991[592]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Roehrs 2012[594]	Comparator does not match protocol (during the interruption periods the placebo arm continues taking placebo: no withdrawal in placebo arm)
Rosenbaum 1998[598]	Comparator does not match protocol (placebo interruption of treatment but no placebo/withdrawal comparator group)
Rosenbaum 1997[599]	No usable outcomes (withdrawal outcome results not extractable)
Rosenthal 2013[602]	No usable outcomes (assess relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)

Study	Exclusion reason
Roth 2006[604]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Rouillon 2000[605]	Population does not match protocol (people on an antidepressant not included on the guideline medicine list)
Salzman 1992[621]	Incorrect study design (not a randomised controlled trial)
Sambunaris 2014[622]	Population does not match protocol (population were on an antidepressant not included on the guideline medicine list (Levomilnacipran))
Saxe 2012[626]	Population does not match protocol (people on an antidepressant not included on the guideline medicine list)
Schagen van Leeuwen 2008[628]	No usable outcomes (only narrative report of no significant difference in adverse events between withdrawal from antidepressants vs withdrawal from placebo arms)
Schmidt 2002[631]	No usable outcomes (withdrawal symptoms or rebound symptoms not reported)
Segal 2010[635]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Shadeck 1996[627]	Not in English
Shaw 1992[637]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Sindrup 1990[639]	Comparator does not match protocol (withdrawal symptoms reported for drug vs drug comparison, not for placebo group)
Stein 1980[650]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Stein 2008[648]	No usable outcomes (no withdrawal period or outcomes)
Stein 1996[649]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Stein 2012[647]	No usable outcomes (reports mean+SD DESS for both arms at the end of the discontinuation phase, but the number re-randomised to the withdrawal arm (placebo) and the continuation arm for the discontinuation phase not reported)
Stip 1999[651]	Comparator does not match protocol (during the discontinuation phase the placebo arm continues taking placebo: no withdrawal in placebo arm)
Stocchi 2003[652]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Sunder 2004[656]	No usable outcomes (discontinuation symptoms only reported narratively as no significant difference between groups)
Terra 1998[666]	No usable outcomes (assesses recurrence in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Tourian 2009[674]	Comparator does not match protocol (3 arm trial, one arm discontinues antidepressants during taper phase, but the placebo treatment arm continues taking placebo during the taper phase (no withdrawal from placebo) and the other antidepressant arm continues but reduces dose during the taper phase)

Study	Exclusion reason
Tyrer 1983[690]	No usable outcomes (total number reporting withdrawal symptoms reported, no breakdown per group)
Ulfvarson 2003[693]	No usable outcomes (assess symptoms in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported: symptom scores provided are stated in the methods to look at symptoms of side effects of SSRIs. Narrative comment that 'the responsible physicians recorded no withdrawal symptoms', but unclear if this was assessed in both arms)
van Geffen 2005[702]	Incorrect study design (qualitative study)
Van 2021[706]	Systematic review (protocol does not match current review protocol)
Vandel 2004[707]	Letter to editor
Versiani 1999[713]	No usable outcomes (assesses relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Vöhringer 2015[718]	No usable outcomes (assess relapse in people continued on antidepressants vs those discontinued; withdrawal symptoms or rebound symptoms not reported)
Voshaar 2003[499]	Comparison does not match protocol (people in the comparison arm received usual care and 'did not receive any help with benzodiazepine reduction' but did not specifically continue on benzodiazepines).
Walsh 1983[728]	Incorrect study design (crossover, no comparative arm)
Wardle 1994[730]	No usable outcomes (withdrawal outcomes not reported)
Ware 1997[731]	No usable outcomes (insomnia rebound not reported as dichotomous outcome, only as symptom score)
Wilson 2020[751]	Pooled analysis of 2 RCTs
Yonkers 2015[764]	Intervention and comparison do not match protocol (antidepressants vs placebo for treatment of premenstrual dysphoric disorder: both groups took the antidepressant/placebo for a few days each menstrual cycle, for 6 cycles. Although withdrawal symptoms were assessed in the 3 days after the last pill was taken in each cycle, this was a break in treatment rather than withdrawal)
Young 2018[773]	Intervention and comparator do not match protocol (online peer education vs Facebook control to support chronic pain patients on opioid therapy)
Zajecha 1998[777]	No usable outcomes (reports new or worsened adverse events in people continued on antidepressants vs those discontinued, but unclear whether they are withdrawal symptoms; withdrawal symptoms or rebound symptoms not reported)
Zitman 2001[783]	Comparison does not match protocol (people in both arms of the trial discontinued from benzodiazepines)

I.2 Studies excluded from the qualitative review

Reference	Reason for exclusion
Abagiu 2014[1]	Incorrect study design and topic: Review on MAT programmes rather; Not qualitative.
Abbasi-Ghahramanloo 2018[2]	No relevant themes
Abdellaoui 2018[3]	No relevant themes

Reference	Reason for exclusion
Abiodun 1991[4]	Incorrect medications: mixture of prescribed, non-prescribed and illicit drug use.
Abood 2018[5]	Incorrect population: prescription medication abuse with the use of KHAT
Abouyanni 2000[6]	No relevant themes
Adams 1993[7]	No relevant themes
Adams 2018[8]	No relevant themes
Agyapong 2009[11]	Analysis does not meet protocol: quantitative analysis with qualitatively reported numerical findings
Al-Amri 2002[12]	No relevant themes
Al-Husseini[13]	Incorrect population: Illicit use of pregabalin; use for addiction treatment
Albright 2010[14]	No relevant themes
Alghofaily 2019[16]	Incorrect study design: quantitative survey
Alishashi 2021[17]	Incorrect study design: closed question survey
Alkhamis 2009[18]	Incorrect population: non-prescribed drug misuse
Allcock 2003[19]	Incorrect population: student nurses
Alley 2020[20]	Quantitative analysis; no relevant themes
Alves 2011[26]	No relevant themes
Alvidrez 2004[27]	Incorrect population: illicit drug use
Anderson 2015[30]	No relevant themes
Anderson 2014[32]	Systematic review with different aim; incorrect topic: prescribers' views on minimising potentially inappropriate medication; no relevant themes; incorrect population: prescribers.
Anderson 2020[33]	Relevant to substitution treatment for illicit drug use
Andrews 2005[37]	Incorrect study design: quantitative survey
Andrews 2013[36]	No relevant themes
Andrews-Cooper 2019[35]	Review: references checked
Andrilla 2018[38]	Quantitative analysis; no extractable themes
Andrilla 2019[40]	No relevant themes
Andrilla 2020[39]	Incorrect population: prescribers of buprenorphine for OUD
Anonymous 2009[548]	No relevant themes
Anonymous 2010[9]	Incorrect study design: Summary of research into addiction
Anonymous 2010[547]	Incorrect age population: adolescents, alcohol and drug use
Anonymous 2017[186]	Incorrect population: opium dependence/active methadone treatment
Anonymous 2020[184]	Incorrect setting: emergency departments; no relevant themes
Anthierens 2007[43]	Non-English language paper: French; full-text not available
Armstrong 2016[44]	Full paper not available
Attiullah 2004[45]	No relevant qualitative information
Ayakta 2021[47]	No relevant themes
Ayres 2012[48]	Incorrect population: Illicit substance abuse
Badger 2002[50]	No relevant qualitative information
Baker[52]	Quantitative analysis; no relevant themes
Baldacchino 2005[54]	No relevant qualitative information
Baldacchino 2010[53]	No relevant qualitative information
Baldwin 2012[55]	No relevant qualitative information
Balough 2019[60]	No relevant qualitative information

Reference	Reason for exclusion
Banta-Green 2010[61]	Analysis does not meet protocol: quantitative
Bargon 2019[62]	No relevant qualitative information
Barrett 2018[65]	No relevant qualitative information
Barry 2010[66]	No relevant themes
Basu 2005[68]	Incorrect study design: Overview of drug and alcohol abuse
Bech, 2005[70]	No relevant qualitative information
Becker 2007[71]	No relevant themes
Belaise 2012[72]	Grey literature: Letter; identified through PHE search
Bell 1990[73]	Analysis does not meet protocol: Quantitative analysis of a survey
Bendtsen 1999[75]	No relevant themes
Bennet 2019[76]	Incorrect study design: pharmacists opinions based on one case report of perceived responsibility for medicines
Bergman 2013[78]	No relevant themes
Bergstein 2021[79]	Incorrect population: 95% heroin use
Bessen 2019[80]	No relevant themes
Bhamb 2006[81]	No relevant qualitative information
Black 2020[87]	Quantitative analysis; no extractable themes
Blake 2007[89]	No relevant themes
Blanck 2015[90]	Incorrect study design: quantitative with no open-ended questions; incorrect population - nurses frequency of prescribing (any prescribing not only for pain).
Bornstein 2020[91]	No relevant themes
Bounthavong 2020[93]	No relevant themes
Bowls 2021[95]	Incorrect population: non-prescription use; no relevant themes
Brinkley-Rubinstein[97]	No relevant themes
British Medical Association 2015[98]	Call for evidence report; no relevant themes.
Broekmans 2004[99]	Incorrect study design: Survey that did not contain open ended free text answers
Brown 2020[100]	Quantitative analysis; no extractable themes
Bunbury 1980[101]	Unable to obtain paper
Bunting 2021[102]	No relevant themes
Busto 1998[107]	Analysis does not meet protocol: Quantitative data; no relevant information
Busto 2001[106]	No relevant information: says respondents had side effects but not much beyond that.
Buttram 2019[109]	Incorrect population/ topic: Gabapentin as treatment for substance abuse alternative
Calcaterra 2016[110]	No relevant themes
Canham 2015[113]	No relevant themes
Canfield 2010[111]	No relevant qualitative information
Canfield 2011[112]	erratum statement
Caplehorn 1996[115]	Opinions on methadone treatment; no extractable themes
Castañeda 2020[118]	No relevant themes
Chang 2016[119]	Doctors' views about Canadian opioid guidelines; no extractable themes
Chatterjee 2021[120]	No relevant themes

Reference	Reason for exclusion
Chau 2021[121]	Incorrect population - acting representatives from local and regional drug use, community and advocacy organisations
Chen 2011[122]	Doctors' opinions and practices; no relevant themes
Choi 2021[123]	No relevant themes
Chouinard 2018[124]	Quantitatively analysed survey; no extractable themes
Cleveland 2020[126]	Mixed sample of illicit and prescription opioids also obtained for non-medical use ; no relevant themes
Click 2018[127]	No relevant themes
Cochran 2013[128]	Opinions on screening and intervention for opioid abuse; quantitative results from questionnaire
Cohen 1983[130]	A list of symptoms of withdrawal experienced but without qualitative data
Conrardy 2016[134]	Incorrect opioid drug combination: hydrocodone-acetaminophen; no relevant themes
Cook 2007[136]	Incorrect drugs: only 60% taking a benzodiazepine listed in the guideline
Cooper 2007[137]	Incorrect study design: Questionnaire that did not contain open ended free text answers
Cooper 2013[138]	No relevant themes
Cooper 2016[139]	Review of qualitative studies: references checked
Cossette 2020[141]	Incorrect drugs: antipsychotics; no relevant themes
Coupland 2021[142]	Incorrect intervention - prescriber views of a service for pregnant women with substance use disorders (alcohol and drugs); no mention of prescription or illicit or type of drug.
Coyne 2021[145]	Quantitatively analysed survey; no extractable themes
Coyne 2021[146]	Quantitatively analysed survey; no extractable themes
Crime 1983[147]	No relevant information
Dankert 2008[154]	Irrelevant topic: opinions on implantable psychotropic meds
Davies 1997[157]	No relevant themes
Davies 2018[158]	APPG report identified from PHE review; not eligible for inclusion as grey literature
Davis 2018[161]	Paper not available
Dawson 2002[163]	Irrelevant topic: Inadequate pain relief for cancer patients
Dawson 2005[162]	No relevant qualitative information
De Sola 2020[164]	No relevant themes
Dickinson 2010[168]	Identified from PHE report; no relevant themes
Donald 2021[169]	No relevant themes
Donner 1988[170]	No relevant qualitative information
Doucette 1997[172]	Irrelevant topic: pharmacists views on opioids for cancer pain
Drazdowski 2016[173]	Incorrect study design & topic: Rationale for non-medical prescription abuse
Droege 2007[174]	No relevant qualitative information
Dunn 2016[177]	No relevant qualitative information
Dunn 2017[176]	No relevant qualitative information
Dyas 2010[178]	Unclear if drugs met protocol: 'prescribed or over-the-counter' hypnotics that were not specified
Dybwad 1997[179]	No relevant themes

Reference	Reason for exclusion
Ebbert 2018[180]	No relevant qualitative information
Esquibel 2014[185]	No relevant themes
Eveleigh 2019[188]	Duplicate of paper already extracted in the review
Fagerlin 2010[189]	Incorrect study design: quantitative survey
Farrugia 2020[192]	Incorrect population - illicit; intervention - take home naloxone for overdose
Fatani 2021[193]	Incorrect population: mixed sample of people using prescription and illicit substances reported to be taking them for non-medical use
Fernandez 2018[202]	Doctors survey; some useful info about prescribing decisions
Fernandez 2021[201]	Incorrect population: illicit and tobacco use
Feroni 2005[203]	Analysis does not meet protocol: Quantitative analysis of a survey
Fingleton 2019[204]	No relevant themes
Fisher 1995[205]	Analysis does not meet protocol: quantitatively analysed investigation
Fixsen 2017[206]	Incorrect study design: narrative investigation of publicly available online accounts of benzodiazepine use and withdrawal (e.g., including internet blogs and YouTube videos); no distinction between prescribed and illicit use made
Fleming 2017[207]	Abstract only
Foley 2017[208]	No relevant qualitative information
Foley 2018[209]	No relevant qualitative information
Foley 2016[210]	No relevant themes
Fulton 2012[219]	Qualitative study but concentrating on initial use of a drug that may or may not be prescribed at the time.
Galland 2017[221]	Unable to obtain paper
Garfield 2003[223]	No relevant themes
Giannitrapani 2018[229]	No relevant themes
Gibson 2014[230]	Incorrect study design: narrative view
Glanz 1986[232]	No relevant qualitative information
Godbole 2011[234]	Incorrect topic: psychotropic medication in pregnancy
Gooberman-Hill 2011[238]	No relevant themes; incorrect populations: GPs
Gottlieb 1978[240]	Incorrect study design: Questionnaire that did not contain open ended free text answers
Grahmann[241]	No relevant themes
Grazzi 2008[243]	No relevant qualitative information
Greaves 2015[244]	No relevant themes
Green 2017[245]	No relevant themes
Griffoen 2017[247]	No relevant themes
Group 2015[248]	Incorrect topic: management of cancer pain
Gruss 2019[249]	No relevant themes
Guillaumie 2015[250]	Incorrect population: views of pharmacists
Guy 2018[251]	APPG report identified from PHE review; not eligible for inclusion as grey literature
Hadlandsmyth 2019[253]	No relevant themes
Hamilton 2021[256]	Incorrect population (GPs) and no relevant themes
Harmark 2011[257]	No relevant qualitative information
Harmark 2013[258]	No relevant qualitative information

Reference	Reason for exclusion
Haskell 1986[263]	Incorrect study design: Quantitative data from survey on benzodiazepines
Haslam 2004[264]	No relevant themes
Hassan 2021[265]	No relevant themes
Heinemann 2017[268]	No relevant qualitative information
Hellewell 2002[269]	No relevant qualitative information
Hooten 2011[278]	Survey with no relevant themes
Howell 2015[279]	No relevant themes
Huijbers 2020[281]	No relevant themes
Hurstak 2017[282]	No relevant themes
Hwang 2016[283]	No relevant themes
Ike 2019[284]	No relevant themes
Imtiaz 2014[285]	No relevant themes
Inciardi 2009[286]	Incorrect population: Illicit substance abuse program users and dealers' interviews to better understand drug diversion
Iqbal 2000[287]	no relevant themes
Isacson 1993[288]	Analysis does not meet protocol: Quantitative analysis of a survey
Isacsson, 1999[290]	Incorrect study design: Quantitative survey data on parasuicide
Isacson 2008[289]	No relevant qualitative information
Isenberg 2017[291]	Incorrect population: HIV patients with chronic pain and a history of substance abuse; no relevant themes
Jacobson 2019[293]	No relevant themes
Jacoby 2003[294]	No relevant themes
Jaiteh 2019[297]	Incorrect population: IVDU users
James 2009[298]	Incorrect drug types: second generation antipsychotics & mood stabilizers not meeting protocol
Jamison 2014[300]	Incorrect study design: Closed questionnaire surveys that does not contain open ended free text answers
Jarbrink 1999[301]	Incorrect study design: closed questionnaire surveys that does not contain open ended free text answers
Jarernsiripornkul 2002[302]	Incorrect study design: no open-ended questions; no extractable themes
Jarernsiripornkul 2003[303]	no qualitative information to be used
Jariangprasert 2007[304]	No open-ended free text answers
Jauhar 2009[305]	Not a qualitative research study
Jeske 2019[307]	Unclear if participants were on methadone maintenance due to raking prescribed or illicit opioids; no relevant themes
Jiao 2018[308]	No extractable themes
Johnson 2017[309]	No relevant themes
Joranson 2001[311]	No relevant themes
Kahan 2011[313]	No relevant themes
Kang 2019[318]	No relevant themes: information needs of physicians and pharmacists
Kapadia 2007[319]	Incorrect population: not limited to prescribed medicine and cannot distinguish in the paper where attitudes were about prescribed or illicit drug use
Kattail 2019[322]	No relevant themes
Keller 2021[328]	Incorrect population (clinicians)

Reference	Reason for exclusion
Kelly 2021[329]	Incorrect population: GPs; no relevant themes
Kennedy-Martin 2017[330]	Incorrect study design: Conference abstract
Kennedy-Martin 2017[331]	Incorrect study design: Conference abstract
Kesten 2019[333]	No relevant themes
Kesselheim 2017[332]	No relevant themes
Khetta 2017[335]	Paper not available
Kilaru 2014[336]	No relevant themes
Kim 2019[337]	No relevant information
Kim 2020[338]	No qualitative analysis
King 1983[339]	Incorrect study design: Questionnaire that did not contain open ended free text answers
Kinnaird 2019[340]	No relevant themes
Kissin 2006[342]	Incorrect study design: Survey data presented in a quantitative fashion
Knolan 2001[345]	Incorrect study design: No open-ended free text answers
Kohlbeck 2018[348]	Incorrect study design: Review of prescribing practices after an education intervention; no relevant themes
Kosteniuk 2020[354]	No relevant themes
Kraus 2015[355]	Incorrect study design: quantitative survey
Krawczyk 2018[356]	No relevant themes
Kring 2014[357]	Unable to obtain paper
Lafferty[366]	Incorrect study design: survey with no open-ended free text answers
Lahteenmaki 2019[367]	Incorrect study design: RCT
Lai 2021[368]	Incorrect population: people with a history on non-medical opioid use
Lal 2019[369]	No relevant themes
Langford 2021[370]	No relevant themes
Langford 2021[371]	Incorrect population: care providers
Lapshin 2006[373]	Incorrect study design: development of questionnaire
Larson 2018[374]	No relevant themes
Lau 2008[375]	Limited free text answers and nothing related to protocols
Lau 2016[376]	Incorrect medication: paracetamol
Leece 2015[378]	Qualitative study concentrating on prescribing practices; no relevant themes
Lefebvre-Durel 2021[379]	Incorrect population (health care professionals); no relevant themes
Leonardi 2016[381]	Buprenorphine usage for replacement treatment; no relevant themes
Leong[382]	No relevant themes
Lewis 2016[385]	Incorrect study design: gabapeptin intervention for pain; very briefly reported qualitative findings; no extractable themes
Liebrenz 2015[389]	Mixed population of prescribed and illicit medication. Outcomes do not directly relate to a clinical question.
Lin 2007[390]	Incorrect study design: statement responses with quantitative results
Linn 1971[391]	Incorrect study design: Opinions based on specific situations with anti-depressive medication
Lopez 2018[393]	No qualitative information: about adherence to guidance
Magee 2021[396]	No relevant themes
Mahtani-Chugani 2011[402]	Narrative review: references checked
Malewski 2018[404]	Unable to obtain paper

Reference	Reason for exclusion
Manubay 2015[405]	Incorrect study design: quantitative questionnaire
Marazziti 2014[406]	Incorrect study design: Questionnaire survey
Markocic 2016[407]	Questionnaire that did not contain open ended free text answers
Martin 2018[410]	No relevant themes
Martirosyan 2012[411]	Incorrect drugs: drugs for Type 2 diabetes
Marquez 2021[409]	Incorrect population (health care providers); no relevant themes
Mathis, 2020[413]	No relevant themes
Mathis 2020[412]	No relevant themes
Matthias 2013[414]	No relevant themes
Matthias 2020[415]	No relevant themes
Mayock 2021[418]	Incorrect population: long-term methadone maintenance treatment; no relevant themes
Mazurenko 2020[420]	No relevant themes; incorrect setting: acute care hospital
McCaffery 1990[421]	Incorrect study design: Assessment of nurses' knowledge of opioid drugs, no qualitative data
McCaffery 1992[422]	No relevant themes
McCarthy 2014[423]	Very briefly stated themes; not extractable as no information to support them
McKeganey 2004[425]	Incorrect topic: Non-prescribed illegal drug use; no relevant qualitative info
McMullen 2009[426]	No relevant themes
McNeil 2016[427]	No relevant themes
Miller 1991[429]	No relevant themes
Mishriky 2019[431]	No relevant themes
Mitchell 2006[432]	Need to check relevant references
Mol 2005[434]	Incorrect design: quantitative; No open-ended free text answers
Mol 2006[435]	No relevant themes
Mol 2007[436]	Incorrect study design: Quantitative trial
Moore 2002[447]	Incorrect study design: Survey of prescribing practices
Mueller 2017[449]	Qualitative study without relevant information
Muller-Schwefe 2014[450]	Incorrect population: mixed population with cancer pain; no relevant information
Nabovati 2017[452]	Incorrect study design: closed question survey
Nagel 2018[453]	No relevant themes
Nardini 2019[455]	Incorrect study design: quantitative survey
Narsin 2012[456]	Incorrect study design: quantitative survey
Navis 2019[458]	Incorrect population: HCPs; no relevant themes
Neo 2001[459]	Incorrect study design: quantitative survey
Nerlekar 2019[460]	Incorrect study design: quantitative questionnaire
Nielsen 2011[462]	Incorrect study design: closed-question survey, no qualitative analysis
Nielsen 2013[463]	No relevant themes
Nielsen 2013[461]	Incorrect population: illicit drug use; quantitative measures
Nielsen 2016[466]	Incorrect study design: quantitative survey
Nielsen 2018[467]	Analysis does not meet protocol: quantitative analysis
Nielsen 2018[465]	Partially incorrect population: illicitly obtained opioids for the majority
Nielsen 2019[464]	No relevant themes

Reference	Reason for exclusion
Nolan 2005[470]	No relevant themes
Nunn 2011[473]	Correction to existing paper; no extractable themes
Nwokeji, 2007[474]	Incorrect study design: closed question survey
Nygaard 2004[475]	Incorrect study design: quantitative survey
Nystrom 2005[476]	Incorrect study design: quantitative questionnaires
O'Brien 2012[477]	Analysis does not meet protocol: quantitative
O'Byrne 2019[478]	Incorrect population: illicit drug users
O'Connor 2004[479]	Analysis did not meet protocol: quantitative measures and analysis
O'Mullan 2014[480]	No relevant themes (information on side-effects not withdrawal symptoms)
O'Mullan 2015[481]	No relevant themes
O'Rourke 2019[482]	Incorrect study design: Secondary analysis of quantitative survey
O'Shea 1991[483]	Analysis does not meet protocol: quantitative analysis
O'Sullivan 2016[484]	Analysis does not meet protocol: quantitative analysis
Oberleitner 2011[485]	Paper not ordered: dissertation
Okoro 2018[487]	Incorrect study design: closed-question questionnaire
Oldfield 2019[488]	Analysis does not meet protocol: quantitatively analysed results of workshop with medical students
Olsen 2009[490]	Incorrect study design: quantitative survey
Olsen 2018[491]	Incorrect study design: closed question survey; quantitative analysis
Olsen 2019[492]	Incorrect study design: closed question questionnaire; quantitative analysis
Olsen 2019[489]	No relevant themes
Oppong 2016[493]	No relevant themes
Oros 2021[494]	Incorrect population: care providers
Ostrach 2019[495]	No relevant themes
Ostrow 2017[496]	Incorrect study design: results of closed-question survey
Ott 2012[498]	Unclear if drugs met protocol and unclear if survey included open-ended questions
Overton 2018[500]	Incorrect study design: not a qualitative study; Delphi method involving a multidisciplinary expert panel
Owen 2012[501]	Incorrect study design: quantitative survey
Oxman 2000[502]	Incorrect study design: quantitatively analysed survey
Oyler 2018[503]	Incorrect study design: closed question survey with 1 open-ended optional question and no qualitative analysis
Padmanathan 2014[504]	Incorrect study design: appraisal of accessing psychotropic medicines in India
Palacios-Cena 2017[505]	No relevant themes
Paparella 2018[507]	Incorrect study design: review of practice guidelines
Parchman 2017[509]	No relevant themes
Pareira 2017[529]	Incorrect population: illicit drug users
Park 2013[510]	No relevant themes
Park 2014[511]	Analysis does not meet protocol: quantitative
Park 2021[512]	Incorrect population: 30.8% benzodiazepines that were not prescribed
Parks 2018[513]	Paper not ordered: dissertation

Reference	Reason for exclusion
Parran 2000[515]	Incorrect study design: quantitative survey
Parry 2017[516]	Incorrect population: health professionals treating codeine misusers, majority of which was intentional use for intoxication
Paterson 2016[517]	No relevant themes
Peacey[520]	Incorrect study design: quantitative survey
Peacock-Chambers 2020[521]	No relevant themes: about early intervention child development services for mothers in recovery of opioid use disorder
Pearace 2019[522]	Incorrect population: illicit opioid use
Penm 2019[525]	No relevant themes
Pérodeau 2016[530]	No relevant themes
Perrone 2012[531]	Incorrect study design: closed question questionnaire
Pinsker 1984[535]	Unclear analysis; quantitatively stated results
Pohjanoksa-Mantyla, 2009[536]	No relevant themes
Pomerleau 2017[537]	Incorrect design: closed question survey
Poon 2016[538]	Incorrect study design: review of a monitoring system not relevant to the protocols
Porucznik 2013[539]	Incorrect study design & analysis: web-based questionnaire; quantitative analysis
Pottegard 2014[540]	Analysis does not meet protocol: quantitative analysis
Potter 2001[541]	Incorrect study design: Closed question survey
Prathivadi 2021[546]	No relevant themes
Prathivadi 2021[545]	Incorrect population: care providers; no relevant themes
Price 2012[549]	Study testing validity & reliability of questionnaire developed using qualitative data, qualitative data or analysis not reported; no relevant themes
Prien 1978[551]	Incorrect design: secondary examination of existing surveys; no qualitative analysis
Price 2009[550]	No relevant themes
Qureshi 2015[556]	Incorrect study design: quantitative survey
Raban 2016[557]	Incorrect study design: Website content evaluation; available qualitative results not likely to relate to drugs meeting protocol
Radomski 2018[558]	No relevant themes
Rash 2018[560]	Incorrect study design: systematic review protocol
Rath 2012[563]	Paper not ordered: dissertation
Rauck 2017[565]	Incorrect study design: quantitative survey
Rausch 2012[566]	Incorrect study design: Article
Razouki 2018[568]	Incorrect study design: closed-question survey
Read 2014[569]	Analysis does not meet protocol: quantitative analysis
Read 2015[570]	Analysis does not meet protocol: quantitative analysis
Read 2016[573]	Incorrect study design: quantitative survey
Read 2017[571]	Incorrect study design: quantitative questionnaires
Read 2017[571]	Identified from PHE review; no relevant themes
Read 2018[575]	Incorrect study design: Quantitatively analysed survey
Read 2019[572]	Incorrect study design: closed question survey; reports some qualitative comments but not sufficient to extract themes
Read 2019[572]	Incorrect study design: quantitative survey

Reference	Reason for exclusion
Reeve 2013[576]	Systematic review: references checked
Richards 2004[579]	Incorrect study design: quantitative questionnaires
Rifkin 2010[587]	Drugs not meeting protocol
Riley 2018[588]	Paper not ordered: dissertation
Riley 2019[589]	Incorrect study design: quantitative survey
Robinson 2015[593]	Incorrect study design: quantitative
Rolman 2019[595]	Incorrect study design: quantitative review
Roman 2011[596]	Analysis and topic does not meet protocol: quantitative analysis exploring the use of medication for substance-use disorder
Rosen 2014[597]	Incorrect study design: quantitative survey
Rosenberg 2003[600]	Incorrect study design: quantitatively analysed closed question survey
Rosenblat 2018[601]	Incorrect study design: quantitatively analysed survey
Roth 2008[603]	Incorrect study design: quantitative survey
Roux 2011[606]	Incorrect study design: quantitative questionnaire
Rubio 2016[607]	Incorrect population: relevant to illicit drug use
Runci 2012[608]	Analysis does not meet protocol: quantitative analysis
Russel 2000[609]	Incorrect drugs: not dependence forming
Rutkow 2015[610]	Incorrect study design: quantitative survey
Ryan 2007[611]	Analysis does not meet protocol: quantitative measures and analysis
Saad 2018[613]	Incorrect study design: quantitative survey; partially incorrect population: only 3/9 most commonly reported medication met protocol
Saeed 2019[614]	Incorrect study design: closed question survey
Saigal 2019[615]	Incorrect study design: literature review
Sake 2018[570]	Incorrect study design: quantitative survey
Salazar-Fraile 2015[616]	No relevant themes
Salimi 2014[617]	Incorrect study design: prospective study on opioid detoxification efficacy; unclear if relevant to prescribed opioids
Salinas 2012[618]	Incorrect study design: quantitative survey
Salinas 2012[619]	Incorrect study design: quantitative survey
Salvato 2003[620]	Analysis does not meet protocol: quantitatively analysed questionnaires; cancer pain management
Samples 2015[623]	Analysis does not meet protocol: quantitative analysis
Sanchez-Ramirez 2019[624]	Closed question survey
Satterwhite 2019[625]	No relevant themes
Schieffe 2005[629]	Incorrect study design: quantitatively analysed questionnaire data and medical records
Schmalstieg-Bahr, 2019[630]	No relevant themes
Schofield 2011[632]	Identified through PHE review; no relevant themes
Seamark 2013[634]	No relevant themes
Shader 1968[636]	Incorrect study design: quantitative questionnaire
Simmonds 2015[638]	No relevant themes
Sirdifield 2013[640]	Systematic review: references checked
Sirdifield 2013[640]	Systematic review: references checked
Sirdifield 2017[641]	Systematic review: references checked
Sirdifield 2019[641]	Systematic review: references checked

Reference	Reason for exclusion
Sirey 2001[642]	Incorrect study design; quantitatively analysed questionnaire
Sirley 1999[643]	Analysis does not meet protocol: quantitatively analysed interviews
Slat 2021[644]	No relevant themes
Slevin 2011[645]	Incorrect study design: closed question survey analysed qualitatively
Slingsby 2007[646]	No relevant themes
Stockman 2018[653]	Identified through PHE review; no relevant themes
Stumbo 2016[654]	Incorrect population: majority was illicit or non-prescribed opioids; no relevant themes
Subelj 2010[655]	No relevant themes
Takaesu 2014[657]	Incorrect study design: quantitative questionnaire
Tan 1999[658]	Incorrect study design: closed question questionnaire
Tanguay Bernard 2018[659]	Analysis did not meet protocol: quantitative analysis
Tannoury 2019[660]	Incorrect study design: quantitative survey
Taverner 2000[661]	Analysis does not meet protocol: quantitative analysis
Taylor 2006[662]	Incorrect study design: quantitative survey
Taylor 2015[663]	Incorrect setting: administration of controlled drugs in acute setting; no relevant themes
Tepper 2004[665]	Incorrect study design: quantitative questionnaire; full-text not available
Thakur 2020[667]	No relevant themes
Togighi 2019[668]	Incorrect population: opioid dependence obtained without prescription
Tong 2019[669]	No relevant themes
Torabi 2019[670]	Analysis does not meet protocol: quantitative analysis
Torberg 2019[680]	Incorrect study design: quantitative questionnaire
Tordoff 2010[671]	Unable to obtain paper
Tormohlen 2019[672]	Incorrect study design: quantitatively analysed survey
Torrens 2016[673]	Non-English language paper: Spanish
Townsend 2003[675]	No relevant themes
Towsley 2013[676]	Paper not ordered: dissertation
Toye 2017[677]	Review: references checked
Trafton 2011[678]	Incorrect study design: quantitative
Tran 2015[679]	Incorrect study design: quantitative survey; methadone maintenance for illicit drug use
Trujols 2017[681]	Incorrect study design: secondary analysis of quantitative survey; relevant to illicit drug use
Turk 1994[684]	Incorrect study design: closed question questionnaire; quantitative analysis
Turk 1995[685]	Incorrect study design: quantitative survey
Turk 1996[683]	Incorrect study design: article reviewing literature and quantitative survey results
Turk 1997[686]	Incorrect study design: quantitatively analysed questionnaire
Turminello 2019[682]	Incorrect study design: short article including quantitative survey results
Turner 2005[687]	Incorrect study design: quantitative survey; Incorrect drugs: methadone and buprenorphine maintenance for drug misuse
Turner 2008[688]	No relevant themes
Tylee 1999[689]	Analysis does not meet protocol: quantitative analysis

Reference	Reason for exclusion
Uebelacker 2011[691]	No relevant themes
Ueberall 2015[692]	Incorrect study design: quantitative survey
Ulmer 2017[694]	Incorrect study design: closed questionnaire; no qualitative analysis
Uosukainen 2013[695]	Incorrect study design: quantitatively analysed questionnaires
Upshur 2006[696]	Incorrect study design: quantitative survey
Urru 2015[697]	Incorrect study design: quantitative survey
Vader 2003[698]	Population does not meet protocol: illicit drug use; Incorrect study design: quantitative analysis of expert panel results
Vallerand 2009[699]	No relevant themes
Vallerand 2010[700]	No relevant themes
Van Eijk 2002[701]	Unable to obtain paper
Van Geffen 2005[702]	Incorrect study design: Quantitatively analysed questionnaire
Van Hout 2018[703]	Opioid agonist treatment for both prescription and illicit opioids; views reported mostly relevant to illicit opioid use.
Vanderplasschen 2015[708]	Population does not meet protocol: illicit drug use
Varley 2019[710]	Paper not ordered: dissertation
Vargas 2015[709]	No relevant themes
Verbeek-Heida 2006[711]	No relevant themes
Verdoux 2014[712]	Incorrect study design: quantitative survey
Vignau 2001[714]	Incorrect study design: quantitative
Vilhelmsson 2011[717]	No relevant themes
Vijayaraghavan 2012[715]	Incorrect study design: quantitative questionnaire
Von Korff 1995[719]	Analysis does not meet protocol: interviews analysed quantitatively; no extractable themes.
Von Korff 2016[720]	Quantitatively analysed interviews
Voon 2018[721]	No relevant themes
Voyer 2007[723]	Incorrect study design: article
Waddington 2015[724]	Incorrect design and irrelevant topic: qualitatively analysed food interviews.
Wagner 2014[726]	Population does not meet protocol: illicit drug use
Wagner 2016[725]	No relevant themes
Wallace 2014[727]	No relevant themes
Walter 2018[729]	Views on mixed prescription and non-prescription opioids explored; former also likely to be illicitly obtained; unclear if emerging themes were relevant to prescription opioids
Webster 2019[732]	No relevant themes; incorrect population: Physicians
Weiss 2001[733]	No relevant themes; incorrect population: GPs
Wells 2005[735]	Population does not meet protocol: cancer-related pain; quantitative results
Wells 2019[734]	Incorrect study design: quantitative questionnaire
Wentik 2019[736]	Unable to obtain paper
Wergeland Sorbye 2019[737]	Incorrect study design: single nurse interview relevant to palliative care; no themes reported
Wettermark 2003[738]	Incorrect study design: quantitative data obtained from national register
Wettermark 2009[739]	No relevant themes
Wheatley 1993[740]	Incorrect design: single case history and quantitative survey results

Reference	Reason for exclusion
White 2015[741]	Population does not meet protocol: people who inject opioids intended for oral/ sublingual consumption, not dependent on prescribed medicines.
Whiteside 2018[742]	Incorrect study design: secondary analysis of quantitative measures
Wilcox 1994[746]	Incorrect study design: quantitatively analysed survey
Wilder 2016[743]	Analysis does not meet protocol: quantitative analysis
Wilkinson 2016[745]	Incorrect study design: article, includes presentation of individual cases but no qualitative analysis
Williams 1999[747]	Incorrect study design: quantitative survey
Williams 2018[748]	Incorrect study design: quantitative survey
Wilson 2015[752]	No relevant themes
Wilson 2018[750]	Incorrect study design: quantitative survey
Wilson 2020[749]	No relevant themes
Winstock 2009[753]	Quantitative survey
Wolfe 2008[755]	Incorrect study design: quantitative survey
Wolf 2011[754]	Analysis did not meet protocol: quantitative
Wood 2019[756]	No relevant themes: majority were most likely illicit drug users
Wyse 2019[758]	No relevant themes
Wyse 2019[757]	Incorrect population: clinicians
Yadav 2019[759]	Population does not meet protocol: pharmacist views for opioid substitution of non-prescribed opioids
Yarborough 2016[760]	Population does not meet protocol: mixed population of people with illicit and prescribed drug use with data not analysed separately and not being possible to separate out information reported by people with illicit or prescribed drug use
Yedinak 2016[761]	Incorrect population: non-medical use of prescription opioids
Yeo 1994[762]	Analysis does not meet protocol: views of GPs following interview briefly presented but no evidence of qualitative analysis
Yildirim 2014[763]	Incorrect study design: Article
Yorkgitis 2019[765]	Incorrect study design: closed-question survey; quantitative analysis
Yoshida 2006[766]	Incorrect study design: review of drug product information; no qualitative data
Young 1997[768]	Incorrect study design: quantitative survey
Young 2005[770]	Population does not meet protocol: not specifically linked to any of the drugs included in the review protocol.
Young 2006[774]	Incorrect study design: Results of three quantitative studies
Young 2009[769]	Incorrect study design: intervention study; quantitative measures
Young 2012[767]	Incorrect study design: quantitative survey
Young 2017[772]	Incorrect study design: longitudinal study with quantitative measures
Young 2017[771]	Incorrect study design: quantitative survey
Yuanhong Lai 2019[776]	No relevant themes
Zerzan 2011[778]	Population did not meet protocol" physicians prescribing for end-of-life care
Zgierska 2012[779]	No relevant themes
Zgierska 2014[780]	No relevant themes
Zhang 2018[781]	Incorrect study design: quantitative measures; relevant to non-prescribed opioids
Zhou 2017[782]	Incorrect population: illicit drug use; quantitative measures

Table 60: Studies identified but not included in the qualitative review due to saturation being reached

Reference
Read 2020[574]
Wiles 2018[744]
Teal 2009[664]

I.3 Health Economic studies excluded

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 J Research recommendation

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

Drug class (for this analysis)	BNF chapter	Drugs included
		Nitrazepam
		Temazepam
	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

Drug class (for this analysis)	BNF chapter	Drugs included
		Paroxetine
		Sertraline
	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.[553]

* 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.