THE LANCET
Psychiatry

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Marsden J, White M, Annand F, et al. Medicines associated with dependence or withdrawal: a mixed-methods public health review and national database study in England. *Lancet Psychiatry* 2019; published online Oct 3. https://doi.org/10.1016/S2215-0366(19)30331-1.

SUPPLEMENTARY APPENDIX

Contents

Appendix Table S1: NICE mapping of medicines for study (27 April 2018)

BNF Cat	Drug class	Drug	Legal category	Indications	Usual dose	Additional notes on drug and/or dose	Index events - i.e. when in a patient's condition or journey they might be prescribed, or reviewed, or dose increased/decreased/ceased				Recommended limits (on duration of prescribing)		
							SPC	BNF	NICE	Opioids aware	SPC	BNF	NICE
4.1.1	Benzodiazepines	Nitrazepam	CD 4.1	Insomnia (short-term use)	Adult 5–10 mg daily Elderly 2.5–5mg daily			Short-term insomnia is usually related to an emotional problem or serious medical illness. It may last for a few weeks and may recur; a hypnotic can be useful but should not be given for more than 3 weeks (preferably only 1 week). Intermittent use is desirable with omission of some doses. A short-acting drug is usually appropriate.	CKS: Use the lowest effective dose for the shortest period possible. The exact duration will depend on the underlying cause but should not continue for longer than 2 weeks. Up to 4 weeks' use may occasionally be required, but continued use should always be re-assessed after 2 weeks. https://cks.nice.org.uk/insomnia#!scenario:1		Generally the duration of treatment varies from a few days to two weeks, with a maximum of four weeks; including the tapering off process	Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.1	Benzodiazepines	Flurazepam	CD 4.1	Insomnia (short-term use)	Adult 15–30 mg once daily Elderly 15 mg once daily			Short-term insomnia is usually related to an emotional problem or serious medical illness. It may last for a few weeks and may recur; a hypnotic can be useful but should not be given for more than 3 weeks (preferably only 1 week). Intermittent use is desirable with omission of some doses. A short-acting drug is usually appropriate.	CKS: Use the lowest effective dose for the shortest period possible. The exact duration will depend on the underlying cause but should not continue for longer than 2 weeks. Up to 4 weeks' use may occasionally be required, but continued use should always be re-assessed after 2 weeks. https://cks.nice.org.uk/insomnia#!scenario:1		Treatment should, if possible, be on an intermittent basis. Treatment should be as short as possible and should be started with the lowest recommended dose. The maximum dose should not be exceeded. Generally the duration of treatment varies from a few days to two weeks with a maximum of four weeks, including the tapering off process. In certain cases, extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status. Long-term chronic use is not recommended. Treatment should not normally be continued beyond 4 weeks.	Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.1	Benzodiazepines	Loprazolam	CD 4.1	Insomnia (short-term use)	Adult 1 mg once daily, increased to 1.5–2 mg once daily if required Elderly 0.5–1 mg once daily			Short-term insomnia is usually related to an emotional problem or serious medical illness. It may last for a few weeks and may recur; a hypnotic can be useful but should not be given for more than 3 weeks (preferably only 1 week). Intermittent use is desirable with omission of some doses. A short-acting drug is usually appropriate.	CKS: Use the lowest effective dose for the shortest period possible. The exact duration will depend on the underlying cause but should not continue for longer than 2 weeks. Up to 4 weeks' use may occasionally be required, but continued use should always be re-assessed after 2 weeks.				

4.1.1	Benzodiazepines	**Lormetazepam**	CD 4.1	Insomnia (short-term use)	Adult 0.5–1.5 mg once daily Elderly 500 micrograms once daily		Short-term insomnia is usually related to an emotional problem or serious medical illness. It may last for a few weeks and may recur; a hypnotic can be useful but should not be given for more than 3 weeks (preferably only 1 week). Intermittent use is desirable with omission of some doses. A short-acting drug is usually appropriate.	https://cks.nice.org.uk/insomnia#!scenario:1 CKS: Use the lowest effective dose for the shortest period possible. The exact duration will depend on the underlying cause but should not continue for longer than 2 weeks. Up to 4 weeks' use may occasionally be required, but continued use should always be re-assessed after 2 weeks.	Generally, the duration of treatment varies from a few days to 2 weeks, with a maximum of 4 weeks including the tapering off process. Extension of the treatment period should not take place without re-evaluation of the need for continued therapy.	Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.1	Benzodiazepines	Temazepam	CD 3	Insomnia (short-term use)	Adult 10–20 mg once daily Elderly 10 mg once daily	Dosage should be checked regularly at the start of treatment in order to decrease, if necessary, the dose or frequency of administration to prevent overdose due to accumulation.	Short-term insomnia is usually related to an emotional problem or serious medical illness. It may last for a few weeks and may recur; a hypnotic can be useful but should not be given for more than 3 weeks (preferably only 1 week). Intermittent use is desirable with omission of some doses. A short-acting drug is usually appropriate.	https://cks.nice.org.uk/insomnia#!scenario:1 CKS: Use the lowest effective dose for the shortest period possible. The exact duration will depend on the underlying cause but should not continue for longer than 2 weeks. Up to 4 weeks' use may occasionally be required, but continued use should always be re-assessed after 2 weeks. https://cks.nice.org.uk/insomnia#!scenario:1	Treatment should be as short as possible. Generally the duration of treatment varies from a few days to two weeks with a maximum, including tapering-off, of four weeks. The tapering-off process should be tailored to the individual. In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status.	Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.1	Benzodiazepines	Temazepam	CD 3	Conscious sedation for dental procedures	Adult 15–30 mg before procedure					
4.1.1	Benzodiazepines	Temazepam	CD 3	Premedication before surgery or investigatory procedures	Adult 10–20 mg before procedure Elderly 10 mg before procedure					
4.1.1	Z-drugs	Zaleplon	CD 4.1	Insomnia (short-term use)	By mouth Adult 10 mg daily for up to 2 weeks, dose to be taken at bedtime or after going to bed if difficulty falling asleep. Elderly 5 mg daily for up to 2 weeks, dose to be taken at bedtime or after going to bed if difficulty falling asleep.		Short-term insomnia is usually related to an emotional problem or serious medical illness. It may last for a few weeks and may recur; a hypnotic can be useful but should not be given for more than 3 weeks (preferably only 1 week). Intermittent use is desirable with omission of some doses. A short-acting drug is usually appropriate.	CKS: Use the lowest effective dose for the shortest period possible. The exact duration will depend on the underlying cause but should not continue for longer than 2 weeks. Up to 4 weeks' use may occasionally be required, but continued use should always be re-assessed after 2 weeks. https://cks.nice.org.uk/insomnia#!scenario:1		Up to 2 weeks Avoid prolonged use (risk of tolerance and withdrawal symptoms)	... it is recommended that hypnotics should be prescribed for short periods of time only, in strict accordance with their licensed indications. NICE TA77 https://www.nice.org.uk/guidance/ta77/chapter/1-Guidance
4.1.1	Z-drugs	Zolpidem	CD 4.1	Insomnia (short-term use)	By mouth Adult 10 mg daily for up		Short-term insomnia is usually related to an emotional problem or	CKS: Use the lowest effective dose for the shortest period	The duration of treatment should usually vary from a	Up to 4 weeks Avoid prolonged use (and	... it is recommended that hypnotics should be prescribed for

					to 4 weeks, dose to be taken at bedtime, for debilitated patients, use elderly dose. Elderly 5 mg daily for up to 4 weeks, dose to be taken at bedtime.	serious medical illness. It may last for a few weeks and may recur; a hypnotic can be useful but should not be given for more than 3 weeks (preferably only 1 week). Intermittent use is desirable with omission of some doses. A short-acting drug is usually appropriate.	possible. The exact duration will depend on the underlying cause but should not continue for longer than 2 weeks. Up to 4 weeks' use may occasionally be required, but continued use should always be re-assessed after 2 weeks. https://cks.nice.org.uk/insomnia#!scenario:1	few days to two weeks with a maximum of four weeks including tapering off where clinically appropriate. As with all hypnotics, long-term use is not recommended and a course of treatment should not exceed four weeks.	abrupt withdrawal thereafter)	short periods of time only, in strict accordance with their licensed indications. NICE TA77 https://www.nice.org.uk/guidance/ta77/chapter/1-Guidance
4.1.1	Z-drugs	Zopiclone	CD 4.1	Insomnia (short-term use)	Adult 7.5 mg daily Elderly 3.75mg daily, increasing to 7.5mg daily	Short-term insomnia is usually related to an emotional problem or serious medical illness. It may last for a few weeks and may recur; a hypnotic can be useful but should not be given for more than 3 weeks (preferably only 1 week). Intermittent use is desirable with omission of some doses. A short-acting drug is usually appropriate.	CKS: Use the lowest effective dose for the shortest period possible. The exact duration will depend on the underlying cause but should not continue for longer than 2 weeks. Up to 4 weeks' use may occasionally be required, but continued use should always be re-assessed after 2 weeks. https://cks.nice.org.uk/insomnia#!scenario:1	As with all hypnotics, long-term use is not recommended and a course of treatment should not exceed four weeks.	Up to 4 weeks Avoid prolonged use (risk of tolerance and withdrawal symptoms)	... it is recommended that hypnotics should be prescribed for short periods of time only, in strict accordance with their licensed indications. NICE TA77 https://www.nice.org.uk/guidance/ta77/chapter/1-Guidance
4.1.1	Z-drugs	Zopiclone	CD 4.1	Insomnia (short-term use) in patients with chronic pulmonary insufficiency	Adult 3.75mg once daily for up to 4weeks, dose to taken at bedtime, increased if necessary to 7.5mg daily	Short-term insomnia is usually related to an emotional problem or serious medical illness. It may last for a few weeks and may recur; a hypnotic can be useful but should not be given for more than 3 weeks (preferably only 1 week). Intermittent use is desirable with omission of some doses. A short-acting drug is usually appropriate.	CKS: Use the lowest effective dose for the shortest period possible. The exact duration will depend on the underlying cause but should not continue for longer than 2 weeks. Up to 4 weeks' use may occasionally be required, but continued use should always be re-assessed after 2 weeks. https://cks.nice.org.uk/insomnia#!scenario:1	Transient insomnia 2 - 5 days. Short term insomnia 2 - 3 weeks. A single course of treatment should not continue for longer than 4 weeks including any tapering off. Extension beyond the maximum treatment period should not take place without re-evaluation of the patient's status.	Up to 4 weeks Avoid prolonged use (risk of tolerance and withdrawal symptoms)	... it is recommended that hypnotics should be prescribed for short periods of time only, in strict accordance with their licensed indications. NICE TA77 https://www.nice.org.uk/guidance/ta77/chapter/1-Guidance
4.1.1	Chloral and derivatives	**Chloral hydrate**	POM	Insomnia (short-term use)	Chloral Mixture, BP 2000 0.5–2 g daily Chloral hydrate 143.3 mg/5 mL oral solution 430–860 mg once daily (max. per dose 2 g) Chloral betaine 707 mg (≡ 414 mg chloral hydrate) tablets 1–2 tablets, alternatively 414–828 mg once daily; maximum 2 g per day				Avoid prolonged use (and abrupt withdrawal thereafter)	

4.1.1	Clomethiazole	**Clomethiazole**	POM	Severe insomnia (short-term use)	Capsules Elderly 192–384 mg once daily Oral solution Elderly 5–10 mL once daily	As with all psychotropic drugs, treatment should be kept to a minimum, reviewed regularly and discontinued as soon as possible.		As with all psychotropic drugs, treatment should be kept to a minimum, reviewed regularly and discontinued as soon as possible.	Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.1	Clomethiazole	**Clomethiazole**	POM	Restlessness and agitation	Capsules Elderly 192 mg 3 times a day Oral solution Elderly 5 mL 3 times a day				Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.1	Clomethiazole	**Clomethiazole**	POM	Alcohol withdrawal	~~Capsules~~ ~~192 mg 3 times a day~~ ~~Oral solution~~ ~~5 mL 3 times a day~~				Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Muscle spasm of varied aetiology	2–15 mg daily in divided doses, then increased if necessary to 60 mg daily				Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Acute muscle spasm	IM or IV 10 mg, then 10 mg after 4 hours if required				Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Tetanus	IV injection 100–300 micrograms/kg every 1–4 hours IV infusion or nasoduodenal tube 3–10 mg/kg over 24 hours				Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Muscle spasm in cerebral spasticity or in postoperative skeletal muscle spasm	Child dose only				Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Anxiety	Adult 2 mg 3 times a day, then increased if necessary to 15–30 mg daily in divided doses Elderly 1 mg 3 times a day, then increased if necessary to 7.5–15 mg daily in divided doses.	The patient must be evaluated after a period of no more than 4 weeks and then regularly thereafter in order to assess the need for continued treatment, especially if the patient is free of symptoms.	Benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling, or causing the patient unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic, or psychotic illness	As an anxiolytic, the lowest effective dose should be employed; dosage regimes should not exceed beyond 4 weeks and treatment should be gradually withdrawn. Patients who have received benzodiazepines for a long time may require an extended withdrawal period. Long-term chronic use is not recommended.	Avoid prolonged use (and abrupt withdrawal thereafter)	Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises. Follow the advice in the 'British national formulary' on the use of a benzodiazepine in this context. https://www.nice.org.uk/guidance/cg113

4.1.2	Benzodiazepines	Diazepam	CD 4.1	Insomnia associated with anxiety	Adult 5–15 mg daily		CKS: Use the lowest effective dose for the shortest period possible. The exact duration will depend on the underlying cause but should not continue for longer than 2 weeks. Up to 4 weeks' use may occasionally be required, but continued use should always be re-assessed after 2 weeks. https://cks.nice.org.uk/insomnia#!scenario:1	Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Severe acute anxiety	By intramuscular injection, or by slow intravenous injection Adult 10 mg, then 10 mg after at least 4 hours if required, intravenous injection to be administered into a large vein, at a rate of not more than 5 mg/minute.			Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Control of acute panic attacks	By intramuscular injection, or by slow intravenous injection Adult 10 mg, then 10 mg after at least 4 hours if required, intravenous injection to be administered into a large vein, at a rate of not more than 5 mg/minute.			Avoid prolonged use (and abrupt withdrawal thereafter)	Benzodiazepines are associated with a less good outcome in the long term and should not be prescribed for the treatment of individuals with panic disorder Rec 1.4.7 NICE CG 113
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Acute alcohol withdrawal	By intramuscular injection, or by slow intravenous injection Adult 10 mg, then 10 mg after at least 4 hours if required, intravenous injection to be administered into a large vein, at a rate of not more than 5 mg/minute.			Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Acute drug-induced dystonic reactions	By intravenous injection Adult 5–10 mg, then 5–10 mg after at least 10 minutes as required, to be			Avoid prolonged use (and abrupt withdrawal thereafter)	

					administered into a large vein, at a rate of not more than 5 mg/minute.			
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Acute anxiety and agitation	By rectum Adult 500 micrograms/kg, then 500 micrograms/kg after 12 hours as required. Elderly 250 micrograms/kg, then 250 micrograms/kg after 12 hours as required.			Avoid prolonged use (and abrupt withdrawal thereafter)
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Premedication	By mouth Adult 5–10 mg, to be given 1–2 hours before procedure, for debilitated patients, use elderly dose. Elderly 2.5–5 mg, to be given 1–2 hours before procedure. By intravenous injection Adult 100–200 micrograms/kg, to be administered into a large vein at a rate of not more than 5 mg/minute, immediately before procedure.			Avoid prolonged use (and abrupt withdrawal thereafter)
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Sedation in dental procedures carried out in hospital	By mouth Adult Up to 20 mg, to be given 1–2 hours before procedure.			Avoid prolonged use (and abrupt withdrawal thereafter)
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Conscious sedation for procedures, and in conjunction with local anaesthesia	By mouth Adult 5–10 mg, to be given 1–2 hours before procedure, for debilitated patients, use elderly dose. Elderly 2.5–5 mg, to be given 1–2 hours before procedure.			Avoid prolonged use (and abrupt withdrawal thereafter)
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Sedative cover for minor surgical and	By intravenous injection Adult 10–20 mg, to be			Avoid prolonged use (and abrupt withdrawal thereafter)

				medical procedures	administered into a large vein over 2–4 minutes, immediately before procedure.			
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Status epilepticus	By intravenous injection Adult 10 mg, then 10 mg after 10 minutes if required, administered at a rate of 1 mL (5 mg) per minute. By rectum Adult 10–20 mg, then 10–20 mg after 10–15 minutes if required. Elderly 10 mg, then 10 mg after 10–15 minutes if required.			Avoid prolonged use (and abrupt withdrawal thereafter)
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Febrile convulsions	By intravenous injection Adult 10 mg, then 10 mg after 10 minutes if required, administered at a rate of 1 mL (5 mg) per minute. By rectum Adult 10–20 mg, then 10–20 mg after 10–15 minutes if required. Elderly 10 mg, then 10 mg after 10–15 minutes if required.			Avoid prolonged use (and abrupt withdrawal thereafter)
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Convulsions due to poisoning	By intravenous injection Adult 10 mg, then 10 mg after 10 minutes if required, administered at a rate of 1 mL (5 mg) per minute. By rectum Adult 10–20 mg, then 10–20 mg after 10–15 minutes if required. Elderly 10 mg, then 10 mg after 10–15			Avoid prolonged use (and abrupt withdrawal thereafter)

					minutes if required.					
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Life-threatening acute drug-induced dystonic reactions	Child dose only				Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Dyspnoea associated with anxiety in palliative care	By mouth Adult 5–10 mg daily				Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.2	Benzodiazepines	Diazepam	CD 4.1	Pain of muscle spasm in palliative care	By mouth Adult 5–10 mg daily				Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.2	Benzodiazepines	Alprazolam	CD 4.1	Short-term use in anxiety	Adult 250–500 micrograms 3 times a day, increased if necessary up to 3 mg daily Elderly 250 micrograms 2–3 times a day, increased if necessary up to 3 mg daily	It is recommended that the patient be reassessed at the end of no longer than 4 weeks' treatment and the need for continued treatment established, especially in case the patient is symptom free. Dosage should be reassessed at intervals of no more than 4 weeks.			The overall duration of treatment should not be more than 8-12 weeks, including a tapering off process.	Avoid prolonged use (and abrupt withdrawal thereafter)	Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises. Follow the advice in the 'British national formulary' on the use of a benzodiazepine in this context. https://www.nice.org.uk/guidance/cg113
4.1.2	Benzodiazepines	Chlordiazepoxide HCl	CD 4.1	Short-term use in anxiety	Adult 10 mg 3 times a day, increased if necessary to 60–100 mg daily in divided doses Elderly 5mg 3 times a day, increased if necessary to 30–50mg daily in divided doses	The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free. Extension of use should not take place without further clinical evaluation. Chronic use is not recommended (little is known of the long term safety and efficacy: potential for dependence)			For short term use (2 – 4 weeks only) Treatment should not continue as full dose for more than 4 weeks including 2 week tapering off process	Avoid prolonged use (and abrupt withdrawal thereafter)	Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises. Follow the advice in the 'British national formulary' on the use of a benzodiazepine in this context. https://www.nice.org.uk/guidance/cg113
4.1.2	Benzodiazepines	Chlordiazepoxide HCl	CD 4.1	Treatment of alcohol withdrawal in moderate dependence	By mouth Adult 10–30 mg 4 times a day, dose to be gradually reduced over 5–7 days, consult local protocols for titration regimens		Gradually reduce the dose of the benzodiazepine over 7–10 days to avoid alcohol withdrawal recurring.(part of rec 1.3.5.4 in CG 115) Co-existing benzodiazepine and alcohol dependence: When withdrawal is managed in the community, and/or where there is a high level of benzodiazepine dependence, the regimen should last for longer than 3 weeks, tailored to the service user's symptoms and discomfort (Part fo rec 1.3.5.11 CG 115)		Avoid prolonged use (and abrupt withdrawal thereafter)	When managing alcohol withdrawal in the community, avoid giving people who misuse alcohol large quantities of medication to take home to prevent overdose or diversion[11]. Prescribe for installment dispensing, with no more than 2 days' medication supplied at any time. From NICE CG 115 Rec 1.3.5.5

4.1.2	Benzodiazepines	Chlordiazepoxide HCl	CD 4.1	Treatment of alcohol withdrawal in severe dependence	By mouth Adult 10–50 mg 4 times a day and 10–40 mg as required for the first 2 days, dose to be gradually reduced over 7–10 days, consult local protocols for titration regimens; maximum 250 mg per day	Gradually reduce the dose of the benzodiazepine over 7–10 days to avoid alcohol withdrawal recurring.(part of rec 1.3.5.4 in CG 115) Co-existing benzodiazepine and alcohol dependence: When withdrawal is managed in the community, and/or where there is a high level of benzodiazepine dependence, the regimen should last for longer than 3 weeks, tailored to the service user's symptoms and discomfort (Part fo rec 1.3.5.11 CG 115)		Avoid prolonged use (and abrupt withdrawal thereafter)	When managing alcohol withdrawal in the community, avoid giving people who misuse alcohol large quantities of medication to take home to prevent overdose or diversion[11]. Prescribe for installment dispensing, with no more than 2 days' medication supplied at any time. From NICE CG 115 Rec 1.3.5.5
4.1.2	Benzodiazepines	Lorazepam	CD 4.1	Short-term use in anxiety	Adult 1–4 mg daily in divided doses. Elderly 0.5–2 mg daily in divided doses		2-4 weeks only	Avoid prolonged use (and abrupt withdrawal thereafter)	Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises. Follow the advice in the 'British national formulary' on the use of a benzodiazepine in this context. https://www.nice.org.uk/guidance/cg113
4.1.2	Benzodiazepines	Lorazepam	CD 4.1	Short-term use in insomnia associated with anxiety	Adult 1–2 mg daily	CKS: Use the lowest effective dose for the shortest period possible. The exact duration will depend on the underlying cause but should not continue for longer than 2 weeks. Up to 4 weeks' use may occasionally be required, but continued use should always be re-assessed after 2 weeks. https://cks.nice.org.uk/insomnia#!scenario:1	2-4 weeks only	Avoid prolonged use (and abrupt withdrawal thereafter)	Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises. Follow the advice in the 'British national formulary' on the use of a benzodiazepine in this context. https://www.nice.org.uk/guidance/cg113
4.1.2	Benzodiazepines	Lorazepam	CD 4.1	Acute panic attacks	By intramuscular injection, or by slow intravenous injection Adult Usual dose 1.5–2.5 mg every 6 hours if required			Avoid prolonged use (and abrupt withdrawal thereafter)	Benzodiazepines are associated with a less good outcome in the long term and should not be prescribed for the treatment of individuals with panic disorder Rec 1.4.7 NICE CG 113
4.1.2	Benzodiazepines	Lorazepam	CD 4.1	Conscious sedation for procedures	By mouth Adult 2–3 mg, to be taken the night before operation; 2–4 mg, to be taken 1–2 hours before operation.			Avoid prolonged use (and abrupt withdrawal thereafter)	

					By slow intravenous injection Adult 50 micrograms/kg, to be administered 30–45 minutes before operation. By intramuscular injection Adult 50 micrograms/kg, to be administered 60–90 minutes before operation.			
4.1.2	Benzodiazepines	Lorazepam	CD 4.1	Premedication	By mouth Adult 2–3 mg, to be taken the night before operation; 2–4 mg, to be taken 1–2 hours before operation. By slow intravenous injection Adult 50 micrograms/kg, to be administered 30–45 minutes before operation. By intramuscular injection Adult 50 micrograms/kg, to be administered 60–90 minutes before operation.			Avoid prolonged use (and abrupt withdrawal thereafter)
4.1.2	Benzodiazepines	Lorazepam	CD 4.1	Status epilepticus	By slow intravenous injection Adult 4 mg for 1 dose, then 4 mg after 10 minutes if required for 1 dose, to be administered into a large vein.			Avoid prolonged use (and abrupt withdrawal thereafter)
4.1.2	Benzodiazepines	Lorazepam	CD 4.1	Febrile convulsions	By slow intravenous injection Adult 4 mg for 1 dose, then 4 mg after 10 minutes if required for 1 dose, to be			Avoid prolonged use (and abrupt withdrawal thereafter)

					administered into a large vein.					
4.1.2	Benzodiazepines	Lorazepam	CD 4.1	Convulsions caused by poisoning	By slow intravenous injection Adult 4 mg for 1 dose, then 4 mg after 10 minutes if required for 1 dose, to be administered into a large vein.				Avoid prolonged use (and abrupt withdrawal thereafter)	
4.1.2	Benzodiazepines	Oxazepam	CD 4.1	Anxiety (short-term use)	Adult 15–30 mg 3–4 times a day Elderly 10–20 mg 3–4 times a day			The duration of treatment should be as short as possible depending on the indication, but should not exceed 4 weeks for insomnia and eight to twelve weeks in case of anxiety, including a tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.	Avoid prolonged use (and abrupt withdrawal thereafter)	Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises. Follow the advice in the 'British national formulary' on the use of a benzodiazepine in this context. https://www.nice.org.uk/guidance/cg113
4.1.2	Benzodiazepines	Oxazepam	CD 4.1	Insomnia associated with anxiety	Adult 15–25 mg once daily (max. per dose 50 mg)		CKS: Use the lowest effective dose for the shortest period possible. The exact duration will depend on the underlying cause but should not continue for longer than 2 weeks. Up to 4 weeks' use may occasionally be required, but continued use should always be re-assessed after 2 weeks. https://cks.nice.org.uk/insomnia#!scenario:1	The duration of treatment should be as short as possible depending on the indication, but should not exceed 4 weeks for insomnia and eight to twelve weeks in case of anxiety, including a tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.	Avoid prolonged use (and abrupt withdrawal thereafter)	Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises. Follow the advice in the 'British national formulary' on the use of a benzodiazepine in this context. https://www.nice.org.uk/guidance/cg113
4.3.1	Antidepressants	Amitriptyline	POM	Abdominal pain or discomfort (in patients who have not responded to laxatives, loperamide, or antispasmodics)	By mouth Adult Initially 5–10 mg daily, to be taken at night; increased in steps of 10 mg at least every 2 weeks as required; maximum 30 mg per day		increased in steps of 10 mg at least every 2 weeks as required			
4.3.1	Antidepressants	Amitriptyline	POM	Depressive illness (not recommended)	By mouth Adult Initially 75 mg daily in divided doses, alternatively initially 75 mg once daily, dose to be taken at bedtime, increased if necessary to 150–	Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerability.	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good.	The antidepressant effect usually sets in after 2 - 4 weeks. Treatment with antidepressants is symptomatic and must therefore be continued for an appropriate length of time usually up to 6 months after	Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with

					200 mg daily, dose to be increased gradually. Elderly Initially 30–75 mg daily in divided doses, alternatively initially 30–75 mg once daily, dose to be taken at bedtime, increased if necessary to 150–200 mg daily, dose to be increased gradually.		1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	recovery in order to prevent relapse.	or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). Following remission, antidepressant therapy should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years. If possible tricyclic and related antidepressants should be withdrawn slowly.	the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.1	Antidepressants	Amitriptyline	POM	Neuropathic pain	By mouth Adult Initially 10 mg once daily, increased if necessary to 75 mg once daily, dose to be taken at night, dose to be increased gradually, higher doses to be given on specialist advice.		After starting or changing a treatment, carry out an early clinical review of dosage titration, tolerability and adverse effects to assess the suitability of the chosen treatment. Carry out regular clinical reviews to assess and monitor the effectiveness of the treatment https://www.nice.org.uk/guidance/cg173/chapter/1-Recommendations 1.3.22: Review the need for continuing migraine prophylaxis 6 months after the start of prophylactic treatment NICE CG150 https://www.nice.org.uk/guidance/cg150/chapter/Recommendations#management-2	Treatment is symptomatic and should therefore be continued for an appropriate length of time. In many patients, therapy may be needed for several years. Regular reassessment is recommended to confirm that continuation of the treatment remains appropriate for the patient. Treatment must be continued for an appropriate length of time. Regular reassessment is recommended to confirm that continuation of the treatment remains appropriate for the patient		
4.3.1	Antidepressants	Amitriptyline	POM	Migraine prophylaxis	By mouth Adult Initially 10 mg once daily, then increased if necessary to 50–75 mg once daily (max. per dose 150 mg), dose to be taken at night.					
4.3.1	Antidepressants	Amitriptyline with Perphenazine	POM	Depression with anxiety	By mouth Adult 1 tablet 3 times a day, an additional tablet may be taken at bedtime when required.		Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good.	Following remission, antidepressant treatment should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years.	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with

4.3.1	Antidepressants	***Amoxapine***		NOT LISTED IN BNF					
4.3.1	Antidepressants	Clomipramine	POM	Depressive illness	Adult Initially 10 mg daily, then increased if necessary to 30–150 mg daily in divided doses, alternatively increased to 30–150 mg once daily; maximum 250 mg per day. Elderly Initially 10 mg daily, then increased to 30–75 mg daily	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). Following remission, antidepressant therapy should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years. If possible tricyclic and related antidepressants should be withdrawn slowly.	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90

									and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.1	Antidepressants	Clomipramine	POM	Phobic and obsessional states	Adult Initially 25 mg daily, then increased to 100–150 mg daily; maximum 250 mg per day. Elderly Initially 10 mg daily, then increased to 100–150 mg daily; maximum 250 mg per day.		After a response has been obtained, maintenance therapy should be continued at the optimum dose to avoid relapse. Patients with a history of recurrence require maintenance treatment for a longer duration. Duration of maintenance treatment and need for further treatment should be reviewed periodically.	Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.	
4.3.1	Antidepressants	Clomipramine	POM	Adjunctive treatment of cataplexy associated with narcolepsy	Adult Initially 10 mg daily; increased if necessary to 10–75 mg daily			Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.	
4.3.1	Antidepressants	Dosulepin	POM	Depressive illness, particularly where sedation is required (not recommended—increased risk of fatality in	Adult Initially 75 mg daily, increased if necessary to 150 mg daily; up to 225 mg daily in some circumstances (e.g. hospital use). Elderly Initially 50–75 mg		Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	Dosulepin should not be prescribed. 1.8.1.1.3 Do not switch to, or start, dosulepin because evidence supporting its tolerability relative to other antidepressants is outweighed by the increased cardiac risk and toxicity in overdose	Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with

				overdose) (initiated by a specialist)	daily, increased if necessary to 75–150 mg daily; up to 225 mg daily in some circumstances (e.g. hospital use).			or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). Following remission, antidepressant therapy should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years. If possible tricyclic and related antidepressants should be withdrawn slowly.	the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.1	Antidepressants	Doxepin	POM	Depressive illness (particularly where sedation is required)	Adult Initially 75 mg daily; maintenance 25–300 mg daily, doses above 100 mg given in 3 divided doses. Elderly Start with lower doses and adjust according to response.	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). Following remission, antidepressant therapy should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years. If possible tricyclic and related antidepressants should be withdrawn slowly.	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age,

4.3.1	Antidepressants	Imipramine	POM	Depressive illness	Adult Initially up to 75 mg daily, increased to 150–200 mg daily. Elderly Initially 10 mg daily, increased to 30–50 mg daily	Improvement in depression may not occur during the first two to four weeks of treatment and hence patients should be closely monitored during this period.	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90		Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). Following remission, antidepressant therapy should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years. If possible tricyclic and related antidepressants should be withdrawn slowly.	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.1	Antidepressants	Imipramine	POM	Depressive illness in hospital patients	Adult Initially up to 75 mg daily, increased to up to 300 mg daily	Improvement in depression may not occur during the first two to four weeks of treatment and hence patients should be closely monitored during this period.	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the		Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). Following	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people

							early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90		remission, antidepressant therapy should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years. If possible tricyclic and related antidepressants should be withdrawn slowly.	with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.1	Antidepressants	Lofepramine	POM	Depressive illness	Adult 140–210 mg daily in divided doses. Elderly May respond to lower doses	Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90		Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). Following remission, antidepressant therapy should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years. If possible tricyclic and related antidepressants should be withdrawn slowly.	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.1	Antidepressants	Nortriptyline	POM	Depressive illness	Adult To be initiated at a low dose, then increased if necessary to 75–100 mg daily;	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly	The antidepressive effect usually sets in after 2-4 weeks. Treatment with antidepressants is symptomatic and	Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication

					maximum 150 mg per day. Elderly To be initiated at a low dose, then increased if necessary to 30–50 mg daily					
4.3.1	Antidepressants	Nortriptyline	POM	Neuropathic pain	Adult Initially 10 mg once daily, increased if necessary to 75 mg daily; higher doses to be given under specialist supervision.					
4.3.1	Antidepressants	Trimipramine	POM	Depressive illness (particularly where sedation required)	Adult Initially 50–75 mg daily, increased if necessary to 150–300 mg daily. Elderly	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.	Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). Following remission, antidepressant therapy should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years. If possible tricyclic and related antidepressants should be withdrawn slowly.	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90

					Initially 10–25 mg 3 times a day, maintenance 75–150 mg daily					
4.3.1	Antidepressants	Mianserin	POM	Depressive illness (particularly where sedation is required)	Adult Initially 30–40 mg daily in divided doses; usual dose 30–90 mg. Elderly Initially 30 mg daily; usual dose 30–90 mg.	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	It is often advantageous to maintain antidepressant treatment for several months after clinical improvement has occurred. In order to ensure an optimal antidepressant effect the dosage of mianserin should not be reduced. https://www.medicines.org.uk/emc/product/8476/smpc	Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). Following remission, antidepressant therapy should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years. If possible tricyclic and related antidepressants	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with

							should be withdrawn slowly.	depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.1	Antidepressants	Trazodone	POM	Depressive illness (particularly where sedation is required)	Adult Initially 150 mg daily, increased if necessary to 300 mg daily; increased if necessary to 600 mg daily in divided doses, higher dose for use in hospital patients only. Elderly Initially 100 mg daily, increased if necessary to 300 mg daily; increased if necessary to 600 mg daily in divided doses, higher dose for use in hospital patients only.	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). Following remission, antidepressant therapy should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years. If possible tricyclic and related antidepressants should be withdrawn slowly.	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.1	Antidepressants	Trazodone	POM	Anxiety	Adult 75mg daily, increased if necessary to 300mg daily			Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on

									long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.	
4.3.1	Antidepressants	***Maprotiline***	Not in BNF							
4.3.1	Antidepressants	***Protriptyline***	Not in BNF							
4.3.2	Antidepressants	Phenelzine	Depressive illness	Adult Initially 15 mg 3 times a day, dose may be increased if necessary after 2 weeks if response not evident, increased if necessary to 15 mg 4 times a day, doses up to 30 mg three times a day may be used in hospital patients; once satisfactory response has been achieved, reduce dose gradually to lowest suitable maintenance dose (15 mg on alternate days may be adequate).	The effectiveness of the drug may not become apparent in less than 4 weeks therapy	Response is usually seen within first week; response may not become apparent for up to 4 weeks	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	Due to the possibility of patients undergoing "Withdrawal Syndrome" abrupt withdrawal of phenelzine should be avoided where possible	If possible avoid abrupt withdrawal. MAOIs are associated with withdrawal symptoms on cessation of therapy. If possible MAOIs should be withdrawn slowly. Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). Following remission, antidepressant therapy should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years.	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.2	Antidepressants	Isocarboxazid	Depressive illness	Adult Initially 30 mg daily, dose may be increased if necessary after 4 weeks, increased to 60 mg daily for 4–6 weeks, then reduced to 10–20 mg daily, usual maintenance dose, but up to 40 mg daily may be required. Elderly 5–10 mg daily		Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years		If possible avoid abrupt withdrawal. MAOIs are associated with withdrawal symptoms on cessation of therapy. If possible MAOIs should be withdrawn slowly. Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after

							(because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). Following remission, antidepressant therapy should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years.	remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.2	Antidepressants	Tranylcypromine	Depressive illness	Adult Initially 10 mg twice daily, dose may be increased if necessary after 1 week, increased if necessary to 10 mg daily, dose to be taken in the morning and 20 mg daily, dose to be taken in the afternoon, doses above 30 mg daily, under close supervision only; maintenance 10 mg daily.	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	Tranylcypromine therapy should be withdrawn gradually	If possible avoid abrupt withdrawal. MAOIs are associated with withdrawal symptoms on cessation of therapy. If possible MAOIs should be withdrawn slowly. Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). Following remission, antidepressant therapy should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years.	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.2	Antidepressants	Moclobemide	Depressive illness	Usual dose 150–600 mg daily	Patients should be reviewed every 1–2 weeks	1.5.2.6 For people started on antidepressants who are not considered to be at		Withdrawal effects may occur within 5 days of stopping treatment with	1.9.1.1 Support and encourage a person who has benefited

				at the start of antidepressant treatment	increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). Following remission, antidepressant treatment should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years.	from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90 1.3.24 If the person's symptoms of social anxiety disorder have responded well to a pharmacological intervention in the first 3 months, continue it for at least a further 6 months. 1.3.25 When stopping a pharmacological intervention, reduce the dose of the drug gradually. If symptoms reappear after the dose is lowered or the drug is stopped, consider increasing the dose, reintroducing the drug or offering individual CBT. https://www.nice.org.uk/guidance/cg159/chapter/1-Recommendations#interventions-for-
4.3.2	Antidepressants	Moclobemide	Social anxiety disorder	Initially 300 mg daily for 3 days, then increased to 600 mg daily in 2 divided doses continued for 8–12 weeks to assess efficacy			

4.3.3	Antidepressants	Citalopram	Depressive illness	Tablets Adult 20 mg once daily, maximum 40 mg per day. Elderly 10–20 mg once daily; maximum 20 mg per day. Oral drops Adult 16 mg once daily, maximum 32 mg per day. Elderly 8–16 mg daily; maximum 16 mg per day.	As with all antidepressant medicinal products, dosage should be reviewed and adjusted, if necessary, within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms	Following remission, antidepressant treatment should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years. Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).	adults-with-social-anxiety-disorder-2 1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.3	Antidepressants	Citalopram	Panic disorder	By mouth using tablets Adult Usual dose 20–30 mg daily; maximum 40 mg per day. Elderly Initially 10 mg daily, increased in steps of 10 mg daily if required, dose to be increased gradually; maximum 20 mg per day. By mouth using oral drops Adult Usual dose 16–24 mg daily; maximum 32 mg per day.			1.4.25 If there is no improvement after a 12-week course, an antidepressant from the alternative class (if another medication is appropriate) or another form of therapy (see 1.4.9) should be offered NICE CG113	Patients with panic disorder should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months or even longer.		Long-term treatment may be necessary for some people and should be offered if needed •If the person is showing improvement on treatment with an antidepressant, the medication should be continued for at least 6 months after the optimal dose is reached, after which the dose can be tapered From NICE CG113

					Elderly Initially 8 mg once daily, increased in steps of 8 mg if required, dose to be increased gradually; maximum 16 mg per day.				
4.3.1	Antidepressants	Escitalopram	POM	Depressive illness	By mouth Adult 10 mg once daily; increased if necessary up to 20 mg daily. Elderly Initially 5 mg once daily; maximum 10 mg per day.	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	Following remission, antidepressant treatment should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years. Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90 If the drug is effective, advise the person to continue taking it for at least a year as the likelihood of relapse is high. https://www.nice.org.uk/guidance/cg113
4.3.0	Antidepressants	Escitalopram	POM	Generalised anxiety disorder	By mouth Adult 10 mg once daily; increased if necessary up to 20 mg daily. Elderly Initially 5 mg once daily; maximum 10 mg per day.		Review the effectiveness and side effects of the drug every 2–4 weeks during the first 3 months of treatment and every 3 months thereafter. https://www.nice.org.uk/guidance/cg113		
4.3.1	Antidepressants	Escitalopram	POM	Obsessive-compulsive disorder	By mouth Adult 10 mg once daily; increased if necessary up to 20 mg daily. Elderly Initially 5 mg once				

					daily; maximum 10 mg per day.			
4.3.2	Antidepressants	Escitalopram	POM	Panic disorder	By mouth Adult Initially 5 mg once daily for 7 days, then increased to 10 mg daily; maximum 20 mg per day. Elderly Initially 2.5 mg once daily; maximum 10 mg per day.		1.4.25 If there is no improvement after a 12-week course, an antidepressant from the alternative class (if another medication is appropriate) or another form of therapy (see 1.4.9) should be offered NICE CG113	Long-term treatment may be necessary for some people and should be offered if needed •If the person is showing improvement on treatment with an antidepressant, the medication should be continued for at least 6 months after the optimal dose is reached, after which the dose can be tapered From NICE CG113
4.3.3	Antidepressants	Escitalopram	POM	Social anxiety disorder	By mouth Adult Initially 10 mg once daily for 2–4 weeks, dose to be adjusted after 2-4 weeks of treatment; usual dose 5–20 mg daily.			
4.3.3	Antidepressants	Fluoxetine	POM	Major depression	Adult Initially 20 mg daily, maxiumum 60mg daily Elderly Initially 20 mg daily, usual maximum 40mg daily but dose upto 60mg can be used	Dose is increased after 3–4 weeks if necessary, and at appropriate intervals thereafter.	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions

									and other risk factors https://www.nice.org.uk/guidance/cg90	
4.3.3	Antidepressants	Fluoxetine	POM	Bulimia nervosa	Adult 60 mg daily Elderly Up to 40 mg daily, usual maximum 40mg daily but dose upto 60mg can be used				Long-term efficacy (more than 3 months) has not been demonstrated in bulimia nervosa.	
4.3.3	Antidepressants	Fluoxetine	POM	Obsessive-compulsive disorder	Adult 20 mg daily, increased if necessary up to 60mg daily Elderly 20mg, increased if necessary up to 40mg daily	Dose to be increased gradually, review treatment if inadequate response after 10 weeks	If no improvement is observed within 10 weeks, treatment with fluoxetine should be reconsidered. The need for treatment should be reassessed periodically.		While there are no systematic studies to answer the question of how long to continue fluoxetine treatment, OCD is a chronic condition and it is reasonable to consider continuation beyond 10 weeks in responding patients. Long-term efficacy (more than 24 weeks) has not been demonstrated in OCD.	
4.3.3	Antidepressants	Fluoxetine	POM	Menopausal symptoms, particularly hot flushes, in women with breast cancer (except those taking tamoxifen)	20mg daily					
4.3.3	Antidepressants	Fluvoxamine	POM	Depressive illness	Maintenance 100 mg daily	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically	Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.	Following remission, antidepressant treatment should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years.	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to

								important. https://www.nice.org.uk/guidance/cg90			continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.3	Antidepressants	Fluvoxamine	POM	Obsessive-compulsive disorder	Maintenance 100–300 mg daily,	Dosage adjustments should be made carefully on an individual patient basis, to maintain the patients at the lowest effective dose. The need for treatment should be reassessed periodically.	If no improvement in obsessive-compulsive disorder within 10 weeks, treatment should be reconsidered		While there are no systematic studies to answer the question of how long to continue fluvoxamine treatment, OCD is a chronic condition and it is reasonable to consider continuation beyond 10 weeks in responding patients. Long-term efficacy (more than 24 weeks) has not been demonstrated in OCD.		
4.3.3	Antidepressants	Paroxetine	POM	Major depression	Adult 20 mg daily, maximum 50 mg per day. Elderly 20 mg daily; maximum 40 mg per day.		Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.	Following remission, antidepressant treatment should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years.	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors

										https://www.nice.org.uk/guidance/cg90
4.3.3	Antidepressants	Paroxetine	POM	Social anxiety disorder	Adult 20 mg daily, maximum 50 mg per day. Elderly 20 mg daily; maximum 40 mg per day.	Long-term use should be regularly evaluated				
4.3.3	Antidepressants	Paroxetine	POM	Post-traumatic stress disorder	Adult 20 mg daily, maximum 50 mg per day. Elderly 20 mg daily; maximum 40 mg per day.	Long-term use should be regularly evaluated				
4.3.3	Antidepressants	Paroxetine	POM	Generalised anxiety disorder	Adult 20 mg daily, maximum 50 mg per day. Elderly 20 mg daily; maximum 40 mg per day.	Long-term use should be regularly evaluated	Review the effectiveness and side effects of the drug every 2–4 weeks during the first 3 months of treatment and every 3 months thereafter. https://www.nice.org.uk/guidance/cg113			If the drug is effective, advise the person to continue taking it for at least a year as the likelihood of relapse is high. https://www.nice.org.uk/guidance/cg113
4.3.3	Antidepressants	Paroxetine	POM	Obsessive-compulsive disorder	Adult Initially 20 mg daily, increased to 40 mg daily, no evidence of greater efficacy at higher doses; maximum 60 mg per day. Elderly Initially 20 mg daily; maximum 40 mg per day.			Patients with OCD should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months or even longer		
4.3.3	Antidepressants	Paroxetine	POM	Panic disorder	Adult Initially 10 mg daily, increased to 40 mg daily; maximum 60 mg per day. Elderly Initially 10 mg daily; maximum 40 mg per day.			Patients with panic disorder should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months or even longer		
4.3.3	Antidepressants	Paroxetine	POM	Menopausal symptoms, particularly hot flushes, in women with breast cancer (except those taking tamoxifen).	Adult 10 mg once daily					
4.3.3	Antidepressants	Sertraline	POM	Depressive illness	Maintenance 50 mg daily		Patients should be reviewed every 1–2 weeks	1.5.2.6 For people started on antidepressants who are not considered to be at	Longer-term treatment may also be appropriate for	Following remission, antidepressant treatment should be continued at the	1.9.1.1 Support and encourage a person who has benefited

						at the start of antidepressant treatment	increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90			
4.3.3	Antidepressants	Sertraline	POM	Obsessive-compulsive disorder	Initially 50 mg daily, then increased in steps of 50 mg at intervals of at least 1 week if required; maximum 200 mg per day			Continued treatment in panic disorder and OCD should be evaluated regularly, as relapse prevention has not been shown for these disorders.		
4.3.3	Antidepressants	Sertraline	POM	Panic disorder	Initially 25 mg daily for 1 week, then increased to 50 mg daily, then increased in steps of 50 mg at intervals of at least 1 week if required; maximum 200 mg per day	Therapy should be initiated at 25 mg/day. After one week, the dose should be increased to 50 mg once daily. This dosage regimen has been shown to reduce the frequency of early treatment emergent side effects characteristic of panic disorder.		Continued treatment in panic disorder and OCD should be evaluated regularly, as relapse prevention has not been shown for these disorders.		
4.3.3	Antidepressants	Sertraline	POM	Post-traumatic stress disorder	Initially 25 mg daily for 1 week, then increased to 50 mg daily, then increased in steps of 50 mg at intervals of at least 1 week if required;	Therapy should be initiated at 25 mg/day. After one week, the dose should be increased to 50 mg once daily. This dosage regimen has been shown to reduce the frequency of early treatment emergent side				
								prevention of recurrence of major depressive episodes (MDE). In most of the cases, the recommended dose in prevention of recurrence of MDE is the same as the one used during current episode. Patients with depression should be treated for a sufficient period of time of at least 6 months to ensure they are free from symptoms.	same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years.	from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90

					maximum 200 mg per day	effects characteristic of panic disorder.				
4.3.3	Antidepressants	Sertraline	POM	Social anxiety disorder	Initially 25 mg daily for 1 week, then increased to 50 mg daily, then increased in steps of 50 mg at intervals of at least 1 week if required; maximum 200 mg per day	Therapy should be initiated at 25 mg/day. After one week, the dose should be increased to 50 mg once daily. This dosage regimen has been shown to reduce the frequency of early treatment emergent side effects characteristic of panic disorder.				
4.3.4	Antidepressants	Agomelatine	POM	Major depression	Adult 25 mg daily, increased if necessary to 50 mg daily	During treatment transaminases should be monitored periodically after around three weeks, six weeks (end of acute phase), twelve weeks and twenty four weeks (end of maintenance phase) and thereafter when clinically indicated (see also section 4.4). Treatment should be discontinued if transaminases exceed 3 X upper limit of normal (see sections 4.3 and 4.4).	Test liver function before treatment and after 3, 6, 12 and 24 weeks of treatment, and then regularly thereafter when clinically indicated (restart monitoring schedule if dose increased); discontinue if serum transaminases exceed 3 times the upper limit of reference range or symptoms of liver disorder.		Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free of symptoms.	
4.3.4	Antidepressants	Duloxetine	POM	Major depression	Adult 60mg once daily			1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	After consolidation of the antidepressive response, it is recommended to continue treatment for several months, in order to avoid relapse. In patients responding to duloxetine, and with a history of repeated episodes of major depression, further long-term treatment at a dose of 60 to 120 mg/day could be considered.	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors

4.3.4	Antidepressants	Duloxetine	POM	Generalised anxiety disorder	Adult Initially 30 mg once daily, increased if necessary to 60 mg once daily; maximum 120 mg per day.		Review the effectiveness and side effects of the drug every 2–4 weeks during the first 3 months of treatment and every 3 months thereafter. https://www.nice.org.uk/guidance/cg113		https://www.nice.org.uk/guidance/cg90 If the drug is effective, advise the person to continue taking it for at least a year as the likelihood of relapse is high. https://www.nice.org.uk/guidance/cg113
4.3.4	Antidepressants	Duloxetine	POM	Diabetic neuropathy	Adult 60 mg once daily; maximum 120 mg per day.	Review treatment at least every 3 months	After starting or changing a treatment, carry out an early clinical review of dosage titration, tolerability and adverse effects to assess the suitability of the chosen treatment. Carry out regular clinical reviews to assess and monitor the effectiveness of the treatment https://www.nice.org.uk/guidance/cg173/chapter/1-Recommendations	Discontinue if inadequate response after 2 months	
4.3.4	Antidepressants	Duloxetine	POM	Moderate to severe stress urinary incontinence	Adult (female) 40 mg twice daily	Patient should be assessed for benefit and tolerability after 2–4 weeks			
4.3.4	Antidepressants	Flupentixol	POM	Schizophrenia and other psychoses, particularly with apathy and withdrawal but not mania or psychomotor hyperactivity	Adult Initially 3–9 mg twice daily; maximum 18 mg per day. Elderly Initially 0.75–4.5 mg twice daily				
4.3.4	Antidepressants	Flupentixol	POM	Depressive illness	Adult Initially 1 mg once daily, increased if necessary to 2 mg after 1 week; maximum 3 mg per day. Elderly Initially 500 micrograms daily, then increased if necessary to 1 mg after 1 week; maximum 1.5 mg per day.	Discontinue if no response after 1 week at maximum dosage	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of		1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to

							antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90		continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.4	Antidepressants	Mirtazapine	POM	Major depression	Adult Initially 15–30 mg daily, to up to 45 mg once daily	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	Following remission, antidepressant treatment should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years.	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.4	Antidepressants	Reboxetine	POM	Major depression	Adult 4 mg twice daily for 3–4 weeks, then increased if necessary to 10 mg daily in divided doses;	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at		1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months

				maximum 12 mg per day	
4.3.4	Antidepressants	Tryptophan	POM	Treatment-resistant depression (used alone or as adjunct to other antidepressant drugs) (initiated under direction of hospital consultant)	1 g 3 times a day; maximum 6 g per day

intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good.

1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important.

https://www.nice.org.uk/guidance/cg90

1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good.

1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important.

https://www.nice.org.uk/guidance/cg90

after remission of an episode of depression.

1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission.

1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse

1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors

https://www.nice.org.uk/guidance/cg90

1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression.

1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission.

1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse

1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with

4.3.4	Antidepressants	Venlafaxine	POM	Major depression	Immediate-release Initially 75 mg daily in 2 divided doses, then increased if necessary up to 375 mg daily Modified-release Initially 75 mg once daily, increased if necessary up to 375 mg once daily	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	Following remission, antidepressant treatment should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years.	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.4	Antidepressants	Venlafaxine	POM	Generalised anxiety disorder	Modified-release 75 mg once daily, increased if necessary up to 225 mg once daily		Review the effectiveness and side effects of the drug every 2–4 weeks during the first 3 months of treatment and every 3 months thereafter. https://www.nice.org.uk/guidance/cg113		If the drug is effective, advise the person to continue taking it for at least a year as the likelihood of relapse is high. https://www.nice.org.uk/guidance/cg113
4.3.4	Antidepressants	Venlafaxine	POM	Social anxiety disorder	Modified-release medicines 75 mg once daily, increased if necessary up to 225 mg once daily				
4.3.4	Antidepressants	Venlafaxine	POM	Menopausal symptoms, particularly hot flushes,	Modified-release 37.5 mg once daily for one week, then				

				in women with breast cancer	increased if necessary to 75 mg once daily.				
4.3.4	Antidepressants	Vortioxetine	POM	Major depression	Adult Initially 10 mg once daily; adjusted according to response to 5–20 mg once daily. Elderly Initially 5 mg once daily; increased if necessary up to 20 mg once daily.	Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment	1.5.2.6 For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good. 1.5.2.7 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important. https://www.nice.org.uk/guidance/cg90	After the depressive symptoms resolve, treatment for at least 6 months is recommended for consolidation of the antidepressive response.	Manufacturer advises treatment can be stopped abruptly, without need for gradual dose reduction.	1.9.1.1 Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. 1.9.1.2 Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission. 1.9.1.4Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse 1.9.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors https://www.nice.org.uk/guidance/cg90
4.3.4	Antidepressants	***Nefazodone***		Not in BNF					
4.3.4	Antidepressants	***Oxitriptan***		Not in BNF					
4.7.2	Opioid pain medicines	Buprenorphine	CD3	Moderate to severe pain	By sublingual administration Adult 200–400 micrograms every 6–8 hours. By intramuscular injection, or by slow intravenous injection Adult 300–600 micrograms every 6–8 hours.	Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/ 24hours.	Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.	

4.7.2	Opioid pain medicines	Buprenorphine	CD3	Premedication	By sublingual administration Adult 400 micrograms. By intramuscular injection Adult 300 micrograms.					Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Buprenorphine	CD3	Intra-operative analgesia	Slow intravenous injection Adult 300–450 micrograms					Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Buprenorphine	CD3	Adjunct in the treatment of opioid dependence	Sublingual tablets Adult Usual dose 12–24 mg daily; maximum 32 mg per day. Oral lyophilisate Adult Maximum 18 mg per day.					Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Buprenorphine	CD3	For Bupeaze®: Moderate to severe chronic cancer pain in patients who have not previously received strong opioid analgesic	By transdermal application using patches Adult Initially 35 micrograms/hour up to every 96 hours, if necessary, dose should be adjusted at intervals of no longer than 96 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time.	Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/ 24hours.	Analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)	Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Buprenorphine	CD3	For Bupeaze®: Severe pain unresponsive to non-opioid analgesics in patients who have not previously received strong opioid analgesic	By transdermal application using patches Adult Initially 35 micrograms/hour up to every 96 hours, if necessary, dose should be adjusted at intervals of no longer than 96 hours using a patch of the next strength or using 2 patches of the same strength (applied at same	Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/ 24hours.	Analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)	Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

					time to avoid confusion). Maximum 2 patches can be used at any one time.				prescriber) When stable, review every 6 months.	
4.7.2	Opioid pain medicines	Buprenorphine	CD3	For Bupeaze®: Moderate to severe chronic cancer pain in patients who have previously received strong opioid analgesic	The initial dose should be based on previous 24-hour opioid requirement, consult product literature	Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/ 24hours.		Analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)	Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.	Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Buprenorphine	CD3	For Bupeaze®: Severe pain unresponsive to non-opioid analgesics in patients who have previously received strong opioid analgesic	The initial dose should be based on previous 24-hour opioid requirement, consult product literature	Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/ 24hours.		Analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)	Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.	Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Codeine	Tablet - CD5 Soln Inj- CD2 Oral soln- CD5	Acute diarrhoea	Usual dose 15–60 mg 3–4 times a day					Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Codeine	Tablet - CD5 Soln Inj- CD2 Oral soln- CD5	Mild to moderate pain	By mouth Adult 30–60 mg every 4 hours if required; maximum 240 mg per day. By intramuscular injection Adult		The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.			Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

					30–60 mg every 4 hours if required.		
4.7.2	Opioid pain medicines	Codeine	Tablet - CD5 Soln Inj- CD2 Oral soln- CD5	Short-term treatment of acute moderate pain	Child dose only		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Codeine	Tablet - CD5 Soln Inj- CD2 Oral soln- CD5	Dry or painful cough	By mouth using linctus Adult 15–30 mg 3–4 times a day.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Co-codamol	CD5	Mild to moderate pain (using co-codamol 8/500 preparations only)	8/500–16/1000 mg every 4–6 hours as required; maximum 64/4000 mg per day.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Co-codamol	CD5	Mild to moderate pain (using co-codamol 15/500 preparations only)	15/500–30/1000 mg every 4–6 hours as required; maximum 120/4000 mg per day.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Co-codamol	CD5	Severe pain (using co-codamol 30/500 preparations only)	30/500–60/1000 mg every 4–6 hours as required; maximum 240/4000 mg per day.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Diamorphine	CD2	Acute pain	By intramuscular injection, or by subcutaneous injection Adult 5 mg every 4 hours if required. By slow intravenous injection Adult 1.25–2.5 mg every 4 hours if required.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Diamorphine	CD2	Acute pain (heavier, well-muscled patients)	By intramuscular injection, or by subcutaneous injection Adult Up to 10 mg every 4 hours if required. By slow intravenous injection Adult 2.5–5 mg every 4 hours if required.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

4.7.2	Opioid pain medicines	Diamorphine	CD2	Chronic pain not currently treated with a strong opioid analgesic	By subcutaneous injection, or by intramuscular injection Adult Initially 2.5–5 mg every 4 hours, adjusted according to response. By subcutaneous infusion Adult Initially 5–10 mg, adjusted according to response, dose to be administered over 24 hours.	Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/ 24hours. .		Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.	Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Diamorphine	CD2	Acute pulmonary oedema	By slow intravenous injection Adult 2.5–5 mg, dose to be administered at a rate of 1 mg/minute.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Diamorphine	CD2	Myocardial infarction	By slow intravenous injection Adult 5 mg, followed by 2.5–5 mg if required, dose to be administered at a rate of 1–2 mg/minute. Elderly 2.5 mg, followed by 1.25–2.5 mg if required, dose to be administered at a rate of 1–2 mg/minute.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Diamorphine	CD2	Myocardial infarction (frail patients)	By slow intravenous injection Adult 2.5 mg, followed by 1.25–2.5 mg if required, dose to be administered at a rate of 1–2 mg/minute.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Dihydrocodeine	MR tablet-CD5 Tablet - CD5 Soln inj-CD2 Oral soln-CD5	Moderate to severe pain	By mouth using immediate-release medicines Adult 30 mg every 4–6 hours as required. By deep subcutaneous injection, or by intramuscular injection				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

					Adult Up to 50 mg every 4–6 hours if required.				
4.7.2	Opioid pain medicines	Dihydrocodeine	MR tablet-CD5 Tablet - CD5 Soln inj-CD2 Oral soln-CD5	Chronic severe pain	By mouth using modified-release medicines Adult 60–120 mg every 12 hours.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Dihydrocodeine	MR tablet-CD5 Tablet - CD5 Soln inj-CD2 Oral soln-CD5	For DF118 Forte®: Severe pain	Adult 40–80 mg 3 times a day; maximum 240 mg per day.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Co-dydramol	CD5	Mild to moderate pain (using 10/500 preparations only)	By mouth Adult 10/500–20/1000 mg every 4–6 hours as required; maximum 80/4000 mg per day.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Co-dydramol	CD5	Severe pain (using 20/500 preparations only)	By mouth Adult 20/500–40/1000 mg every 4–6 hours as required; maximum 160/4000 mg per day.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Co-dydramol	CD5	Severe pain (using 30/500 preparations only)	By mouth Adult 30/500–60/1000 mg every 4–6 hours as required; maximum 240/4000 mg per day.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Dipipanone (with cyclizine)	CD2	Acute pain	By mouth Adult Initially 1 tablet every 6 hours, then increased if necessary up to 3 tablets every 6 hours, dose to be increased gradually.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Fentanyl	CD2	Chronic intractable pain not currently treated with a strong opioid analgesic	By transdermal application Adult Initially 12 micrograms/hour every 72 hours, alternatively initially 25 micrograms/hour	Opioid Aware states that the dose of opioids above which harms outweigh	Evaluation of the analgesic effect should not be made before the system has been worn for 24 hours (to allow for the gradual increase in plasma-fentanyl concentration)—previous analgesic therapy should be phased out gradually from	Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3	Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

					every 72 hours. Dose should be adjusted at 48–72 hour intervals in steps of 12–25 micrograms/hour if necessary, more than one patch may be used at a time (but applied at the same time to avoid confusion)—consider additional or alternative analgesic therapy if dose required exceeds 300 micrograms/hour	benefits is 120mg oral morphine equivalent/ 24hours.	time of first patch application	weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.		
4.7.2	Opioid pain medicines	Fentanyl	CD2	Chronic intractable pain currently treated with a strong opioid analgesic	By transdermal application Adult Initial dose based on previous 24-hour opioid requirement (consult product literature)	Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/ 24hours.		Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Fentanyl	CD2	Spontaneous respiration: analgesia and enhancement of anaesthesia, during operation	By slow intravenous injection Adult Initially 50–100 micrograms (max. per dose 200 micrograms), dose maximum on specialist advice, then 25–50 micrograms as required. By intravenous infusion Adult 3–4.8 micrograms/kg/hour, adjusted according to response.					Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Fentanyl	CD2	Assisted ventilation: analgesia and enhanceme	By slow intravenous injection Adult Initially 300–3500					Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

				nt of anaesthesia during operation	micrograms, then 100–200 micrograms as required. By intravenous infusion Adult Initially 10 micrograms/kg, dose to be given over 10 minutes, then 6 micrograms/kg/hour, adjusted according to response, may require up to 180 micrograms/kg/hour during cardiac surgery.			
4.7.2	Opioid pain medicines	Fentanyl	CD2	Assisted ventilation: analgesia and respiratory depression in intensive care	By slow intravenous injection Adult Initially 300–3500 micrograms, then 100–200 micrograms as required. By intravenous infusion Adult Initially 10 micrograms/kg, dose to be given over 10 minutes, then 6 micrograms/kg/hour, adjusted according to response, may require up to 180 micrograms/kg/hour during cardiac surgery.			Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Fentanyl	CD2	Breakthrough pain in patients receiving opioid therapy for chronic cancer pain	By buccal administration using lozenges Adult Initially 200 micrograms, dose to be given over 15 minutes, then 200 micrograms after 15 minutes if required, no more than 2 dose units for each pain episode; if adequate pain relief not achieved with 1 dose unit for consecutive breakthrough pain episodes, increase the			Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

					strength of the dose unit until adequate pain relief achieved with 4 lozenges or less daily, if more than 4 episodes of breakthrough pain each day, adjust background analgesia By buccal administration using buccal films Adult Initially 200 micrograms, adjusted according to response, consult product literature for information on dose adjustments, maximum 1.2 mg per episode of breakthrough pain; leave at least 4 hours between treatment of episodes of breakthrough pain, if more than 4 episodes of breakthrough pain each day occur on more than 4 consecutive days, adjust background analgesia.					
4.7.2	Opioid pain medicines	Hydromorphone	CD2	Severe pain in cancer	By mouth using immediate-release medicines Adult 1.3 mg every 4 hours, dose to be increased if necessary according to severity of pain. By mouth using modified-release medicines Adult 4 mg every 12 hours, dose to be increased if necessary according to severity of pain.	Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/ 24hours.		Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Meptazinol	POM	Moderate to severe	By mouth Adult					Avoid abrupt withdrawal after long-term treatment;

				pain, including post-operative pain and renal colic	200 mg every 3–6 hours as required. By intramuscular injection Adult 75–100 mg every 2–4 hours if required. By slow intravenous injection Adult 50–100 mg every 2–4 hours if required.				they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Meptazinol	POM	Obstetric analgesia	By intramuscular injection Adult 2 mg/kg, usual dose 100–150 mg.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Methadone	CD2	Severe pain	By mouth, or by subcutaneous injection, or by intramuscular injection Adult 5–10 mg every 6–8 hours, adjusted according to response, on prolonged use not to be given more frequently than every 12 hours.	The relative potency of methadone depends on the starting dose and the duration of administration. Conversions to and from methadone should always be undertaken with specialist advice	Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Methadone	CD2	Adjunct in treatment of opioid dependence	By mouth using oral solution Adult Usual dose 60–120 mg daily.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Methadone	CD2	Adjunct in treatment of opioid dependence if tolerance low or not known	By mouth using oral solution Adult Usual dose 60–120 mg daily.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Methadone	CD2	Adjunct in treatment of opioid dependence if tolerance high (under expert supervision)	By mouth using oral solution Adult Usual dose 60–120 mg daily.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Methadone	CD2	Cough in terminal disease	Initially by mouth using linctus Adult 1–2 mg every 4–6 hours, (by mouth)				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

					reduced to 1–2 mg twice daily, use twice daily frequency if prolonged use.				
4.7.2	Opioid pain medicines	Morphine	CD 2	Pain	Child dose only				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Morphine	CD 2	Acute pain	By mouth, or by subcutaneous injection, or by intramuscular injection Adult Initially 10 mg every 4 hours, adjusted according to response, subcutaneous injection not suitable for oedematous patients, dose can be given more frequently during titration, use dose for elderly in frail patients. Elderly Initially 5 mg every 4 hours, adjusted according to response, subcutaneous injection not suitable for oedematous patients, dose can be given more frequently during titration. By slow intravenous injection Adult Initially 5 mg every 4 hours, adjusted according to response, dose can be adjusted more frequently during titration, reduced dose recommended in frail and elderly patients.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Morphine	CD 2	Chronic pain	By mouth, or by subcutaneous injection, or by intramuscular injection Adult Initially 5–10 mg	Opioid Aware states that the dose of opioids above which		Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified	Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

					every 4 hours, adjusted according to response, subcutaneous injection not suitable for oedematous patients. By rectum Adult Initially 15–30 mg every 4 hours, adjusted according to response.	harms outweigh benefits is 120mg oral morphine equivalent/ 24hours.		release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.	
4.7.2	Opioid pain medicines	Morphine	CD 2	Pain (with modified-release 12-hourly preparations)	By mouth using modified-release medicines Adult Every 12 hours, dose adjusted according to daily morphine requirements, dosage requirements should be reviewed if the brand is altered	Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/ 24hours.		Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.	Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Morphine	CD 2	Pain (with modified-release 24-hourly preparations)	By mouth using modified-release medicines Adult Every 24 hours, dose adjusted according to daily morphine requirements, dosage requirements should be reviewed if the brand is altered.	Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/ 24hours.		Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.	Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Morphine	CD 2	Pain management in palliative care (starting dose for	By mouth Adult 20–30 mg daily in divided doses, using immediate-release preparation 4-hourly or a 12-	Opioid Aware states that the dose of opioids above which harms		Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations	Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

				opioid-naïve patients)	hourly modified-release preparation	outweigh benefits is 120mg oral morphine equivalent/ 24hours.		may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.	
4.7.2	Opioid pain medicines	Morphine	CD 2	Pain management in palliative care (starting dose for patients being switched from a regular weak opioid)	By mouth Adult 40–60 mg daily in divided doses, using immediate-release preparation 4-hourly or 12-hourly modified-release preparation				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Morphine	CD 2	Pain in palliative care (following initial titration)	By mouth using immediate-release medicines Adult Usual dose 30 mg every 4 hours; up to 200 mg every 4 hours By mouth using modified-release medicines Adult Usual dose 100 mg every 12 hours; up to 600 mg every 12 hours				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Morphine	CD 2	Cough in terminal disease	By mouth Adult Initially 5 mg every 4 hours.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Morphine	CD 2	Premedication	By subcutaneous injection, or by intramuscular injection Adult Up to 10 mg, dose to be administered 60–90 minutes before operation.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Morphine	CD 2	Patient controlled analgesia (PCA)	Consult local protocol	Opioid Aware states that the dose of opioids above which harms		Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations	Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

						outweigh benefits is 120mg oral morphine equivalent/ 24hours.			
4.7.2	Opioid pain medicines	Morphine	CD 2	Myocardial infarction	By slow intravenous injection Adult 5–10 mg, followed by 5–10 mg if required, dose to be administered at a rate of 1–2 mg/minute, use dose for elderly in frail patients. Elderly 2.5–5 mg, followed by 2.5–5 mg if required, dose to be administered at a rate of 1–2 mg/minute.			may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.	Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Morphine	CD 2	Acute pulmonary oedema	By slow intravenous injection Adult 5–10 mg, dose to be administered at a rate of 2 mg/minute, use dose for elderly in frail patients. Elderly 2.5–5 mg, dose to be administered at a rate of 2 mg/minute.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Morphine	CD 2	Dyspnoea at rest in palliative care	By mouth Adult Initially 5 mg every 4 hours, to be given in carefully titrated doses.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Morphine plus cyclizine	CD2	For Cyclimorph-15®: Moderate to severe pain (short-term use only)	By subcutaneous injection, or by intramuscular injection, or by intravenous injection Adult 1 mL, do not repeat dose more often than every 4 hours;				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

					maximum 3 doses per day.		
4.7.2	Opioid pain medicines	Morphine plus cyclizine	CD2	For Cyclimorph-10®: Moderate to severe pain (short-term use only)	By subcutaneous injection, or by intramuscular injection, or by intravenous injection Adult 1 mL, do not repeat dose more often than every 4 hours; maximum 3 doses per day.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Oxycodone	CD2	Postoperative pain	By mouth using immediate-release medicines Adult Initially 5 mg every 4–6 hours, dose to be increased if necessary according to severity of pain, some patients may require higher doses than the maximum daily dose; maximum 400 mg per day. By mouth using modified-release medicines Adult Initially 10 mg every 12 hours (max. per dose 200 mg every 12 hours), dose to be increased if necessary according to severity of pain, some patients might require higher doses than the maximum daily dose. By slow intravenous injection Adult 1–10 mg every 4 hours as required. By intravenous infusion Adult Initially 2 mg/hour, adjusted according to response.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

					By subcutaneous injection Adult Initially 5 mg every 4 hours as required. By subcutaneous infusion Adult Initially 7.5 mg/24 hours, adjusted according to response.					
4.7.2	Opioid pain medicines	Oxycodone	CD2	Severe pain	By mouth using immediate-release medicines Adult Initially 5 mg every 4–6 hours, dose to be increased if necessary according to severity of pain, some patients may require higher doses than the maximum daily dose; maximum 400 mg per day. By mouth using modified-release medicines Adult Initially 10 mg every 12 hours (max. per dose 200 mg every 12 hours), dose to be increased if necessary according to severity of pain, some patients might require higher doses than the maximum daily dose. By slow intravenous injection Adult 1–10 mg every 4 hours as required. By intravenous infusion Adult Initially 2 mg/hour, adjusted according to response. By subcutaneous	Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/ 24hours.		Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

					injection Adult Initially 5 mg every 4 hours as required. By subcutaneous infusion Adult Initially 7.5 mg/24 hours, adjusted according to response.		
4.7.2	Opioid pain medicines	Oxycodone	CD2	Moderate to severe pain in palliative care	By mouth using immediate-release medicines Adult Initially 5 mg every 4–6 hours, dose to be increased if necessary according to severity of pain, some patients may require higher doses than the maximum daily dose; maximum 400 mg per day. By mouth using modified-release medicines Adult Initially 10 mg every 12 hours (max. per dose 200 mg every 12 hours), dose to be increased if necessary according to severity of pain, some patients might require higher doses than the maximum daily dose. By slow intravenous injection Adult 1–10 mg every 4 hours as required. By intravenous infusion Adult Initially 2 mg/hour, adjusted according to response. By subcutaneous injection		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

					Adult Initially 5 mg every 4 hours as required. By subcutaneous infusion Adult Initially 7.5 mg/24 hours, adjusted according to response.					
4.7.2	Opioid pain medicines	Oxycodone	CD2	Patient controlled analgesia (PCA)	Consult local protocol	Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/ 24hours.		Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Oxycodone (Onexila XL®)	CD2	Severe pain	By mouth Adult Initially 10 mg every 24 hours, dose to be increased if necessary according to severity of pain, some patients may require higher doses than the maximum daily dose; maximum 400 mg per day.	Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/ 24hours.		Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Oxycodone with naloxone	CD2	Severe pain requiring opioid analgesia in patients not currently treated with opioid analgesics	By mouth Adult Initially 10/5 mg every 12 hours (max. per dose 40/20 mg every 12 hours), dose to be increased according to response; patients already receiving opioid analgesics can	Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine		Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

					start with a higher dose.	equivalent/ 24hours.			
4.7.2	Opioid pain medicines	Oxycodone with naloxone	CD2	Second-line treatment of symptomatic severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy	By mouth Adult Initially 5/2.5 mg every 12 hours, adjusted weekly according to response, usual dose 10/5 mg every 12 hours; maximum 60/30 mg per day.	Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/ 24hours.	Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	**Papaveretum**	CD2	Postoperative analgesia	By subcutaneous injection, or by intramuscular injection Adult 7.7–15.4 mg every 4 hours if required. Elderly Initially 7.7 mg every 4 hours if required. By intravenous injection Adult Use 25 to 50% of the corresponding subcutaneous/intramuscular dose.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	**Papaveretum**	CD2	Severe chronic pain	By subcutaneous injection, or by intramuscular injection Adult 7.7–15.4 mg every 4 hours if required. Elderly Initially 7.7 mg every 4 hours if required. By intravenous injection Adult Use 25 to 50% of the corresponding subcutaneous/intramuscular dose.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	**Papaveretum**	CD2	Premedication	By subcutaneous injection, or by intramuscular injection Adult 7.7–15.4 mg				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

					Elderly 7.7 mg		
4.7.2	Opioid pain medicines	Pentazocine	CD3	Moderate to severe pain	By mouth Usual dose 25–100 mg every 3–4 hours; maximum 600 mg per day		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Pentazocine	CD3	Moderate pain	By subcutaneous injection, or by intramuscular injection, or by intravenous injection Adult 30 mg every 3–4 hours as required; maximum 360 mg per day.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Pentazocine	CD3	Severe pain	By subcutaneous injection, or by intramuscular injection, or by intravenous injection Adult 45–60 mg every 3–4 hours as required; maximum 360 mg per day.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Pethidine	CD2	Acute pain	By mouth Adult 50–150 mg every 4 hours. By subcutaneous injection, or by intramuscular injection Adult 25–100 mg, then 25–100 mg after 4 hours, for debilitated patients use dose described for elderly patients. Elderly Initially 25 mg, then 25–100 mg after 4 hours. By slow intravenous injection Adult 25–50 mg, then 25–50 mg after 4 hours, for debilitated patients use dose described for elderly patients. Elderly		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

					Initially 25 mg, then 25–50 mg after 4 hours.					
4.7.2	Opioid pain medicines	Pethidine	CD2	Obstetric analgesia	By subcutaneous injection, or by intramuscular injection Adult 50–100 mg, then 50–100 mg after 1–3 hours if required; maximum 400 mg per day.					Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Pethidine	CD2	Premedication	By intramuscular injection Adult 25–100 mg, dose to be given 1 hour before operation, for debilitated patients use dose described for elderly patients. Elderly 25 mg, dose to be given 1 hour before operation.					Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Pethidine	CD2	Postoperative pain	By subcutaneous injection, or by intramuscular injection Adult 25–100 mg every 2–3 hours if required, for debilitated patients use dose described for elderly patients. Elderly Initially 25 mg every 2–3 hours if required.					Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Tapentadol	CD2	Moderate to severe acute pain which can be managed only with opioid analgesics	By mouth using immediate release medicines: Initially 50 mg every 4–6 hours, adjusted according to response, maximum 700 mg in the first 24 hours, during the first 24 hours of treatment, an additional dose of 50 mg may be taken 1 hour after the initial dose, if pain control not achieved; maximum 600 mg per day.	Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/ 24hours.	The dosing regimen should be individualised according to the severity of pain being treated, the previous treatment experience and the ability to monitor the patient.	Opioid trial If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Tapentadol	CD2	Severe chronic pain	By mouth, using modified-release	Opioid Aware	After initiation of therapy the dose should be	Opioid trial If possible, use		Avoid abrupt withdrawal after long-term treatment;

					medicines: Initially 50 mg every 12 hours, adjusted according to response; maximum 500 mg per day.	states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/ 24hours. Doses of tapentadol above 300mg/day may increase the risk of adverse events	titrated individually to a level that provides adequate analgesia and minimises undesirable effects under the close supervision of the prescribing physician.	immediate release morphine (tablets or liquid), prescribed for 1-2 weeks A trial using modified release preparations may take longer (3 weeks or more) to allow for dose adjustments Long-term prescribing Oral morphine is 1st choice Patient should be reviewed within 4 weeks (by the initiating prescriber) When stable, review every 6 months.	they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Tramadol	CD3	Moderate to severe pain	Intramuscular injection, or by intravenous injection, or by intravenous infusion Adult 50–100 mg every 4–6 hours, intravenous injection to be given over 2–3 minutes.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Tramadol	CD3	Moderate to severe acute pain	By mouth using immediate-release medicines Adult Initially 100 mg, then 50–100 mg every 4–6 hours; Usual maximum 400 mg/24 hours.				Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Tramadol	CD3	Moderate to severe chronic pain	By mouth using immediate-release medicines Adult Initially 50 mg, then, adjusted according to response; Usual maximum 400 mg/24 hours.		The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported. Tramadol should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with tramadol is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether and to what extent further treatment is necessary.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Tramadol	CD3	Postoperati ve pain	By intravenous injection				Avoid abrupt withdrawal after long-term treatment;

					Adult Initially 100 mg, then 50 mg every 10–20 minutes if required up to total maximum 250 mg (including initial dose) in first hour, then 50–100 mg every 4–6 hours, intravenous injection to be given over 2–3 minutes; maximum 600 mg per day.			they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Tramadol	CD3	Moderate to severe pain (with modified-release 12-hourly preparations)	By mouth using modified-release medicines Adult 50–100 mg twice daily, increased if necessary to 150–200 mg twice daily, doses exceeding the usual maximum not generally required; Usual maximum 400 mg/24 hours.	The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported. Tramadol should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with tramadol is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether and to what extent further treatment is necessary.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Tramadol	CD3	Moderate to severe pain (with modified-release 24-hourly preparations)	By mouth using modified-release medicines Adult Initially 100–150 mg once daily, increased if necessary up to 400 mg once daily; Usual maximum 400 mg/24 hours.	The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported. Tramadol should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with tramadol is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether and to what extent further treatment is necessary.		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	Tramadol (Zydol® XL)	CD3	Moderate to severe pain	By mouth using modified-release tablets Adult	The need for continued treatment should be assessed at regular intervals as withdrawal		Avoid abrupt withdrawal after long-term treatment; they should be withdrawn

					Initially 150 mg once daily, increased if necessary up to 400 mg once daily.	symptoms and dependence have been reported. Tramadol should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with tramadol is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether and to what extent further treatment is necessary.	gradually to avoid abstinence symptoms.
4.7.2	Opioid pain medicines	*Dextromoramide*		Not in BNF			
4.8.1	Gabapentinoids	Gabapentin	POM	Adjunctive treatment of focal seizures with or without secondary generalisation	Usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day)		
4.8.1	Gabapentinoids	Gabapentin	POM	Monotherapy for focal seizures with or without secondary generalisation	Usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day)		
4.8.1	Gabapentinoids	Gabapentin	POM	Peripheral neuropathic pain	Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; maximum 3.6 g per day	After starting or changing a treatment, carry out an early clinical review of dosage titration, tolerability and adverse effects to assess the suitability of the chosen treatment. Carry out regular clinical reviews to assess and monitor the effectiveness of the treatment https://www.nice.org.uk/guidance/cg173/chapter/1-Recommendations	
4.8.1	Gabapentinoids	Gabapentin	POM	Migraine prophylaxis	Initially 300 mg daily, then increased to up to 2.4 g daily in divided doses, adjusted according to response		
4.8.1	Gabapentinoids	Gabapentin	POM	Menopausal symptoms,	300 mg 3 times a day, initial dose		

				particularly hot flushes, in women with breast cancer	should be lower and titrated up over three days			
4.8.1	Gabapentinoids	Pregabalin	POM	Peripheral and central neuropathic pain	150mg to 600mg daily	During dose titration the initial dose can be increased after3-7 days, and then again after 7 days	After starting or changing a treatment, carry out an early clinical review of dosage titration, tolerability and adverse effects to assess the suitability of the chosen treatment. Carry out regular clinical reviews to assess and monitor the effectiveness of the treatment https://www.nice.org.uk/guidance/cg173/chapter/1-Recommendations	
4.8.1	Gabapentinoids	Pregabalin	POM	Adjunctive therapy for focal seizures with or without secondary generalisation	Initially 25 mg twice daily, then increased in steps of 50 mg daily, dose to be increased at 7 day intervals, increased to 300 mg daily in 2–3 divided doses for 7 days, then increased if necessary up to 600 mg daily in 2–3 divided doses (150mg to 600mg daily)	During dose titration the dose should to be increased at 7 day intervals	N/A	
4.8.1	Gabapentinoids	Pregabalin	POM	Generalised anxiety disorder	150mg to 600mg daily	During dose titraione the dose can to be increased at 7 day intervals	Review the effectiveness and side effects of the drug every 2–4 weeks during the first 3 months of treatment and every 3 months thereafter. https://www.nice.org.uk/guidance/cg113/chapter/1-Guidance	If the drug is effective, advise the person to continue taking it for at least a year as the likelihood of relapse is high. https://www.nice.org.uk/guidance/cg113/chapter/1-Guidance

Notes:

1. Drugs listed in Appendix A of the spec for this mapping exercise were checked against BNF 68 (sections 4.1, 4.3, 4.7 and 4.8).
2. Some drugs listed in appendix A of the spec are no longer listed in the BNF because they have been discontinued:

- Amoxapine
- Maprotiline
- Protriptyline
- Nefazodone
- Oxitriptan
- Dextromoramide

These are included in the Excel spreadsheet in green font.

3. A small number of drugs listed in these sections of the BNF did to not appear in appendix A. These have been added to the spreadsheet if they seemed to fall within the scope of the review. They are marked in red font in the spreadsheet:

- Lormetazepam
- Chloral hydrate
- Clomethiazole
- Papaveretum

4. Index dates and recommended limits have been taken from the BNF, SPC and NICE guidance (or NICE advice if no NICE guidance exists; Clinical Knowledge Summaries). These sources often give the same information and no major contradictions were identified.

5. Doses are taken from the BNF, given as 'usual dose' if available in the BNF. If no usual dose is stated in the BNF a range is provided. For many of the opioids a dose range is not stated in the BNF- in these cases an initial dose is provided. The Opioids Aware site states that doses above 120mg/day morphine equivalent increase the risk of harm without additional benefits to patients (this same dose if referenced in the recent Cochrane review of opioids in non-cancer pain). When a drug can be used above this dose this is noted in the spreadsheet- this may help to identify potentially inappropriate long-term opioid prescribing.

Appendix Table S2. Medicines included in the database analysis

Drug class	BNF chapter	Drugs included
Antidepressants	4.3.1 (Tricyclics)	Amitriptyline (including with perphenazine)
		Amoxapine
		Clomipramine
		Dosulepin
		Doxepin
		Imipramine
		Lofepramine
		Maprotiline
		Mianserin
		Nortriptyline
		Protriptyline
		Trazodone
		Trimipramine
	4.3.2 (MAOIs)	Isocarboxazid
		Moclobemide
		Phenelzine
		Tranylcypromine
	4.3.3 (SSRIs)	Citalopram
		Escitalopram
		Fluoxetine
		Fluvoxamine
		Paroxetine
		Sertraline
	4.3.4 (Other antidepressants)	Agomelatine
		Duloxetine
		Flupentixol
		Mirtazapine
		Nefazodone
		Oxitriptan
		Reboxetine
		Tryptophan
		Venlafaxine
		Vortioxetine
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
		Pethidine
		Tapentadol
		Tramadol (including with paracetamol)
	4.7.1	Codeine with paracetamol = co-codamol*
		Dihydrocodeine with paracetamol = co-dydramol**
		Lormetazepam
		Nitrazepam
		Temazepam

Cont…/

Appendix Table S2. Medicines included in the analysis, cont…/

Drug class	BNF chapter	Drugs included
Gabapentinoids	4.7.3	Gabapentin
	4.8.1	Pregabalin
Benzodiazepines	4.1.1 (insomnia)	Flurazepam
		Loprazolam
		Lormetazepam
		Nitrazepam
		Temazepam
	4.1.2 (anxiety)	Diazepam
		Chlordiazepoxide
		Lorazepam
		Oxazepam
Z-drugs	4.1.1	Zaleplon
		Zopiclone
		Zolpidem

BNF, British National Formulary version 68

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

Appendix Table S3. REA search strategy

A.1 Databases date parameters and filters used

A.1.1 Step 1: Existing systematic reviews

Database	Dates searched	Search filter used
Cochrane Database of Systematic Reviews (The Cochrane Library -Wiley)	All years to Issue 9 of 12, September 2018	None
Epistemonikos	All years to 24 September 2018	Systematic review studies
Database of promoting health effectiveness reviews (DoPHER)	All years to 19 September 2018	None
HealthEvidence	All years to 19 September 2018	None

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Substance-Related Disorders] explode all trees
#2.	MeSH descriptor: [Substance Withdrawal Syndrome] explode all trees
#3.	MeSH descriptor: [Inappropriate Prescribing] explode all trees
#4.	MeSH descriptor: [Medical Overuse] explode all trees
#5.	MeSH descriptor: [Deprescriptions] explode all trees
#6.	(abstinen* or abstain* or cessat* or detox* or discontinu* or reduc* or stop* or taper* or withdraw* or substitut* or depend* or addict* or abuse* or abusing or chronic or long* term or longterm or short* term or short term or misus* or overus* or deprescrib*):ti,ab
#7.	(over* near/3 use* or using or utlisat* or utilizat*) near/3 (prescription* or prescrib* or drug* or medicine* or medication* or pharm*):ti,ab
#8.	inappropriate near/3 (prescription or prescrib*):ti,ab
#9.	(OR #1-#8)
#10.	MeSH descriptor: [Narcotics] explode all trees
#11.	MeSH descriptor: [Analgesics, Opioid] explode all trees
#12.	(analgesic* near/3 opioid* or narcotic near/3 agent*):ti,ab
#13.	MeSH descriptor: [Buprenorphine] explode all trees
#14.	MeSH descriptor: [Codeine] explode all trees
#15.	MeSH descriptor: [Dextromoramide] explode all trees
#16.	MeSH descriptor: [Heroin] explode all trees
#17.	MeSH descriptor: [Fentanyl] explode all trees
#18.	MeSH descriptor: [Hydromorphone] explode all trees
#19.	MeSH descriptor: [Meptazinol] explode all trees
#20.	MeSH descriptor: [Methadone] explode all trees
#21.	MeSH descriptor: [Morphine] explode all trees
#22.	MeSH descriptor: [Oxycodone] explode all trees
#23.	MeSH descriptor: [Opium] explode all trees
#24.	MeSH descriptor: [Pentazocine] explode all trees

#25.	MeSH descriptor: [Meperidine] explode all trees
#26.	MeSH descriptor: [Tramadol] explode all trees
#27.	(buprenorphine* or codeine* or dextromoramide* or diamorphine* or dihydrocodeine* or dipipanone* or fentanyl or hydromorphone* or meptazinol or methadone* or morphine* or oxycodone or papaveretum or pentazocine or pethidine or tapentadol or tramadol or heroin):ti,ab
#28.	(z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or zaleplon or zopiclone or zolpidem):ti,ab
#29.	(generation near/3 hypnotic*):ti,ab
#30.	MeSH descriptor: [Benzodiazepines] explode all trees
#31.	(benzodiazepin* or bzd or flurazepam or loprazolam or lormetazepam or nitrazepam or temazepam or diazepam or chlordiazepoxide or lorazepam or oxazepam):ti,ab
#32.	MeSH descriptor: [Pregabalin] explode all trees
#33.	(gabapentin* or pregabalin*):ti,ab
#34.	MeSH descriptor: [Antidepressive Agents] explode all trees
#35.	(antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or RIMA* or tricyclic* or SSRI* or SNRI* or SNORI*):ti,ab
#36.	MeSH descriptor: [Amitriptyline] explode all trees
#37.	MeSH descriptor: [Amoxapine] explode all trees
#38.	MeSH descriptor: [Clomipramine] explode all trees
#39.	MeSH descriptor: [Dothiepin] explode all trees
#40.	MeSH descriptor: [Doxepin] explode all trees
#41.	MeSH descriptor: [Imipramine] explode all trees
#42.	MeSH descriptor: [Lofepramine] explode all trees
#43.	MeSH descriptor: [Maprotiline] explode all trees
#44.	MeSH descriptor: [Mianserin] explode all trees
#45.	MeSH descriptor: [Nortriptyline] explode all trees
#46.	MeSH descriptor: [Protriptyline] explode all trees
#47.	MeSH descriptor: [Trazodone] explode all trees
#48.	MeSH descriptor: [Trimipramine] explode all trees
#49.	MeSH descriptor: [Isocarboxazid] explode all trees
#50.	MeSH descriptor: [Moclobemide] explode all trees
#51.	MeSH descriptor: [Phenelzine] explode all trees
#52.	MeSH descriptor: [Tranylcypromine] explode all trees
#53.	MeSH descriptor: [Citalopram] explode all trees
#54.	MeSH descriptor: [Fluoxetine] explode all trees
#55.	MeSH descriptor: [Fluvoxamine] explode all trees
#56.	MeSH descriptor: [Paroxetine] explode all trees
#57.	MeSH descriptor: [Sertraline] explode all trees
#58.	MeSH descriptor: [5-Hydroxytryptophan] explode all trees
#59.	MeSH descriptor: [Duloxetine Hydrochloride] explode all trees
#60.	MeSH descriptor: [Flupenthixol] explode all trees
#61.	MeSH descriptor: [Tryptophan] explode all trees
#62.	MeSH descriptor: [Venlafaxine Hydrochloride] explode all trees
#63.	(amitriptyline or amoxapine or clomipramine or dosulepin or doxepin or imipramine or lofepramine or maprotiline or mianserin or nortriptyline or protriptyline or trazodone or trimipramine or isocarboxazid or moclobemide or phenelzine or tranylcypromine or citalopram or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline or agomelatine or duloxetine or flupentixol or mirtazapine or nefazodone or oxitriptan or reboxetine or tryptophan or venlafaxine or vortioxetine):ti,ab
#64.	(OR #10-#63)

#65.	#9 and #64

Epistemonikos search terms

1.	"substance-related disorders" OR "substance withdrawal syndrome" OR "inappropriate prescribing" OR "medical overuse" OR "deprescriptions" OR "abstinen*" or "abstain*" or "cessat*" or "detox*" or "discontinu*" or "reduc*" or "stop*" or "taper*" or "withdraw*" or "substitut*" or "depend*" or "addict*" or "abuse*" or "abusing" or "chronic" or "long* term" or "longterm" or "short* term" or "short term" or "misus*" or "overus*" OR "deprescrib*" OR "inappropriate prescription"
2.	"buprenorphine*" or "codeine*" or "dextromoramide*" or "diamorphine*" or "dihydrocodeine*" or "dipipanone*" or "fentanyl" or "hydromorphone*" or "meptazinol" or "methadone*" or "morphine*" or "oxycodone" or "papaveretum" or "pentazocine" or "pethidine" or "tapentadol" or "tramadol" or "heroin" OR "z drug*" or "z hypnotic*" or "non-benzodiazepin*" or "nonbenzodiazepin*" or "zaleplon" or "zopiclone" or "zolpidem" OR "generation hypnotic" OR "benzodiazepin*" or "bzd" or "flurazepam" or "loprazolam" or "lormetazepam" or "nitrazepam" or "temazepam" or "diazepam" or "chlordiazepoxide" or "lorazepam" or "oxazepam" OR "gabapentin*" or "pregabalin*" OR "antidepress*" or "anti depress*" or "thymoanaleptic*" or "thymoleptic*" or "MAOI*" or "monoamine oxidase inhibit*" or "RIMA*" or "tricyclic*" or "SSRI*" or "SNRI*" or "SNORI*" OR "amitriptyline" or "amoxapine" or "clomipramine" or "dosulepin" or "doxepin" or "imipramine" or "lofepramine" or "maprotiline" or "mianserin" or "nortriptyline" or "protriptyline" or "trazodone" or "trimipramine" or "isocarboxazid" or "moclobemide" or "phenelzine" or "tranylcypromine" or "citalopram" or "escitalopram" or "fluoxetine" or "fluvoxamine" or "paroxetine" or "sertraline" or "agomelatine" or "duloxetine" or "flupentixol" or "mirtazapine" or "nefazodone" or "oxitriptan" or "reboxetine" or "tryptophan" or "venlafaxine" or "vortioxetine"
3.	(title:("substance-related disorders" OR "substance withdrawal syndrome" OR "inappropriate prescribing" OR "medical overuse" OR "deprescriptions" OR "abstinen*" OR "abstain*" OR "cessat*" OR "detox*" OR "discontinu*" OR "reduc*" OR "stop*" OR "taper*" OR "withdraw*" OR "substitut*" OR "depend*" OR "addict*" OR "abuse*" OR "abusing" OR "chronic" OR "long* term" OR "longterm" OR "short* term" OR "short term" OR "misus*" OR "overus*" OR "deprescrib*" OR "inappropriate prescription") OR abstract:("substance-related disorders" OR "substance withdrawal syndrome" OR "inappropriate prescribing" OR "medical overuse" OR "deprescriptions" OR "abstinen*" OR "abstain*" OR "cessat*" OR "detox*" OR "discontinu*" OR "reduc*" OR "stop*" OR "taper*" OR "withdraw*" OR "substitut*" OR "depend*" OR "addict*" OR "abuse*" OR "abusing" OR "chronic" OR "long* term" OR "longterm" OR "short* term" OR "short term" OR "misus*" OR "overus*" OR "deprescrib*" OR "inappropriate prescription")) AND (title:("buprenorphine*" OR "codeine*" OR "dextromoramide*" OR "diamorphine*" OR "dihydrocodeine*" OR "dipipanone*" OR "fentanyl" OR "hydromorphone*" OR "meptazinol" OR "methadone*" OR "morphine*" OR "oxycodone" OR "papaveretum" OR "pentazocine" OR "pethidine" OR "tapentadol" OR "tramadol" OR "heroin" OR "z drug*" OR "z hypnotic*" OR "non-benzodiazepin*" OR "nonbenzodiazepin*" OR "zaleplon" OR "zopiclone" OR "zolpidem" OR "generation hypnotic" OR "benzodiazepin*" OR "bzd" OR "flurazepam" OR "loprazolam" OR "lormetazepam" OR "nitrazepam" OR "temazepam" OR "diazepam" OR "chlordiazepoxide" OR "lorazepam" OR "oxazepam" OR "gabapentin*" OR "pregabalin*" OR "antidepress*" OR "anti depress*" OR "thymoanaleptic*" OR "thymoleptic*" OR "MAOI*" OR "monoamine oxidase inhibit*" OR "RIMA*" OR "tricyclic*" OR "SSRI*" OR "SNRI*" OR "SNORI*" OR "amitriptyline" OR "amoxapine" OR "clomipramine" OR "dosulepin" OR "doxepin" OR "imipramine" OR "lofepramine" OR "maprotiline" OR "mianserin" OR "nortriptyline" OR "protriptyline" OR "trazodone" OR "trimipramine" OR "isocarboxazid" OR "moclobemide" OR "phenelzine" OR "tranylcypromine" OR "citalopram" OR "escitalopram" OR "fluoxetine" OR "fluvoxamine" OR "paroxetine" OR "sertraline" OR "agomelatine" OR "duloxetine" OR "flupentixol" OR "mirtazapine" OR "nefazodone" OR "oxitriptan" OR "reboxetine" OR "tryptophan" OR "venlafaxine" OR "vortioxetine") OR abstract:("buprenorphine*" OR "codeine*" OR "dextromoramide*" OR "diamorphine*" OR "dihydrocodeine*" OR "dipipanone*" OR "fentanyl" OR "hydromorphone*" OR "meptazinol" OR "methadone*" OR "morphine*" OR "oxycodone" OR "papaveretum" OR "pentazocine" OR "pethidine" OR "tapentadol" OR "tramadol" OR "heroin" OR "z

	drug*" OR "z hypnotic*" OR "non-benzodiazepin*" OR "nonbenzodiazepin*" OR "zaleplon" OR "zopiclone" OR "zolpidem" OR "generation hypnotic" OR "benzodiazepin*" OR "bzd" OR "flurazepam" OR "loprazolam" OR "lormetazepam" OR "nitrazepam" OR "temazepam" OR "diazepam" OR "chlordiazepoxide" OR "lorazepam" OR "oxazepam" OR "gabapentin*" OR "pregabalin*" OR "antidepress*" OR "anti depress*" OR "thymoanaleptic*" OR "thymoleptic*" OR "MAOI*" OR "monoamine oxidase inhibit*" OR "RIMA*" OR "tricyclic*" OR "SSRI*" OR "SNRI*" OR "SNORI*" OR "amitriptyline" OR "amoxapine" OR "clomipramine" OR "dosulepin" OR "doxepin" OR "imipramine" OR "lofepramine" OR "maprotiline" OR "mianserin" OR "nortriptyline" OR "protriptyline" OR "trazodone" OR "trimipramine" OR "isocarboxazid" OR "moclobemide" OR "phenelzine" OR "tranylcypromine" OR "citalopram" OR "escitalopram" OR "fluoxetine" OR "fluvoxamine" OR "paroxetine" OR "sertraline" OR "agomelatine" OR "duloxetine" OR "flupentixol" OR "mirtazapine" OR "nefazodone" OR "oxitriptan" OR "reboxetine" OR "tryptophan" OR "venlafaxine" OR "vortioxetine"))
4.	Limit 3 to systematic reviews

Database of promoting health effectiveness reviews (DoPHER) search terms

1.	Freetext (All but Authors): "substance-related disorders" OR "substance withdrawal syndrome" OR "inappropriate prescribing" OR "medical overuse" OR "deprescriptions" OR "abstinen*" or "abstain*" or "cessat*" or "detox*" or "discontinu*" or "reduc*" or "stop*" or "taper*" or "withdraw*" or "substitut*" or "depend*" or "addict*" or "abuse*" or "abusing" or "chronic" or "long* term" or "longterm" or "short* term" or "short term" or "misus*" or "overus*" OR "deprescrib*"
2.	Freetext (All but Authors): "over*" near "use*" near "prescri*"
3.	Freetext (All but Authors):"inappropriate" near "prescri*"
4.	1 or 2 or 3
5.	Freetext (All but Authors): "buprenorphine*" or "codeine*" or "dextromoramide*" or "diamorphine*" or "dihydrocodeine*" or "dipipanone*" or "fentanyl" or "hydromorphone*" or "meptazinol" or "methadone*" or "morphine*" or "oxycodone" or "papaveretum" or "pentazocine" or "pethidine" or "tapentadol" or "tramadol" or "heroin"
6.	Freetext (All but Authors): "z drug*" or "z hypnotic*" or "non-benzodiazepin*" or "nonbenzodiazepin*" or "zaleplon" or "zopiclone" or "zolpidem"
7.	Freetext (All but Authors): "generation" near "hypnotic"
8.	Freetext (All but Authors): "benzodiazepin*" or "bzd" or "flurazepam" or "loprazolam" or "lormetazepam" or "nitrazepam" or "temazepam" or "diazepam" or "chlordiazepoxide" or "lorazepam" or "oxazepam"
9.	Freetext (All but Authors): "gabapentin*" or "pregabalin*"
10.	Freetext (All but Authors): "antidepress*" or "anti depress*" or "thymoanaleptic*" or "thymoleptic*" or "MAOI*" or "monoamine oxidase inhibit*" or "RIMA*" or "tricyclic*" or "SSRI*" or "SNRI*" or "SNORI*"
11.	Freetext (All but Authors): "amitriptyline" or "amoxapine" or "clomipramine" or "dosulepin" or "doxepin" or "imipramine" or "lofepramine" or "maprotiline" or "mianserin" or "nortriptyline" or "protriptyline" or "trazodone" or "trimipramine" or "isocarboxazid" or "moclobemide" or "phenelzine" or "tranylcypromine" or "citalopram" or "escitalopram" or "fluoxetine" or "fluvoxamine" or "paroxetine" or "sertraline" or "agomelatine" or "duloxetine" or "flupentixol" or "mirtazapine" or "nefazodone" or "oxitriptan" or "reboxetine" or "tryptophan" or "venlafaxine" or "vortioxetine"
12.	5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11
13.	4 AND 12

HealthEvidence search terms

1.	[((substance-related disorders or substance withdrawal syndrome or inappropriate prescribing OR medical overuse OR deprescriptions or abstinen* or abstain* or cessat* or detox* or discontinu* or reduc* or stop* or taper* or withdraw* or substitut* or depend* or addict* or abuse* or abusing or chronic or long* term or longterm or short*

	term or short term or misus* or overus* or deprescrib*)) AND ((narcotics or analgesics or buprenorphine* or codeine* or dextromoramide* or diamorphine* or dihydrocodeine* or dipipanone* or fentanyl or hydromorphone* or meptazinol or methadone* or morphine* or oxycodone or papaveretum or pentazocine or pethidine or tapentadol or tramadol or heroin or z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or zaleplon or zopiclone or zolpidem or benzodiazepin* or bzd or flurazepam or loprazolam or lormetazepam or nitrazepam or temazepam or diazepam or chlordiazepoxide or lorazepam or oxazepam or gabapentin* or pregabalin* or antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or RIMA* or tricyclic* or SSRI* or SNRI* or SNORI*or amitriptyline or amoxapine or clomipramine or dosulepin or doxepin or imipramine or lofepramine or maprotiline or mianserin or nortriptyline or protriptyline or trazodone or trimipramine or isocarboxazid or moclobemide or phenelzine or tranylcypromine or citalopram or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline or agomelatine or duloxetine or flupentixol or mirtazapine or nefazodone or oxitriptan or reboxetine or tryptophan or venlafaxine or vortioxetine))]

A.1.2 Step 2: Recent evidence

Database	Dates searched	Search filter used
Medline (OVID)	1st January 2008 – 3 October 2018	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1st January 2008 – 3 October 2018	Exclusions Randomised controlled trials Systematic review studies
Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library -Wiley)	1st January 2008 to Issue 8 of 12, August 2018	None
PsycINFO (ProQuest)	1st January 2008 – 3 October 2018	Exclusions Randomised controlled trials Systematic review studies
Health Technology Appraisals (Centre for Reviews and Dissemination)	1st January 2008 – 3 October 2018	None
Trials Register of Promoting Health Interventions (TRoPHI)	All years to 3 October 2018	None
ASSIA (Proquest)	1st January 2008 – 3 October 2018	None

Medline (Ovid) search terms

1.	exp substance-related disorders/
2.	exp substance withdrawal syndrome/
3.	exp inappropriate prescribing/
4.	exp medical overuse/
5.	exp deprescriptions/

6.	(abstinen* or abstain* or cessat* or detox* or discontinu* or reduc* or stop* or taper* or withdraw* or substitut* or depend* or addict* or abuse* or abusing or chronic or long* term or longterm or short* term or short term or misus* or overus* or deprescrib*).ti,ab.
7.	(over* adj3 (use* or using or utlisat* or utilizat*) adj3 (prescription* or prescrib* or drug* or medicine* or medication* or pharm*)).ti,ab.
8.	(inappropriate adj3 (prescription or prescrib*)).ti,ab.
9.	or/1-8
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	anecdotes as topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	exp animals, laboratory/
23.	exp animal experimentation/
24.	exp models, animal/
25.	exp rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	limit 28 to English language
30.	exp narcotics/
31.	exp analgesics, opioid/
32.	(analgesic* adj3 (opioid* or narcotic) adj3 agent*).ti,ab.
33.	exp buprenorphine/
34.	exp codeine/
35.	exp dextromoramide/
36.	exp heroin/
37.	exp fentanyl/
38.	exp hydromorphone/
39.	exp meptazinol/
40.	exp methadone/
41.	exp morphine/
42.	exp oxycodone/
43.	exp opium/
44.	exp pentazocine/
45.	exp meperidine/
46.	exp tramadol/
47.	(buprenorphine* or codeine* or dextromoramide* or diamorphine* or dihydrocodeine* or dipipanone* or fentanyl or hydromorphone* or meptazinol or methadone* or morphine* or oxycodone or papaveretum or pentazocine or pethidine or tapentadol or tramadol or heroin).ti,ab.
48.	(z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or zaleplon or zopiclone or zolpidem).ti,ab.

49.	(generation adj3 hypnotic*).ti,ab.
50.	exp benzodiazepines/
51.	(benzodiazepin* or bzd or flurazepam or loprazolam or lormetazepam or nitrazepam or temazepam or diazepam or chlordiazepoxide or lorazepam or oxazepam).ti,ab.
52.	exp pregabalin/
53.	(gabapentin* or pregabalin*).ti,ab.
54.	exp antidepressive agents/
55.	(antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or maoi* or "monoamine oxidase inhibit*" or rima* or tricyclic* or ssri* or snri* or snori*).ti,ab.
56.	exp amitriptyline/
57.	exp amoxapine/
58.	exp clomipramine/
59.	exp dothiepin/
60.	exp doxepin/
61.	exp imipramine/
62.	exp lofepramine/
63.	exp maprotiline/
64.	exp mianserin/
65.	exp nortriptyline/
66.	exp protriptyline/
67.	exp trazodone/
68.	exp trimipramine/
69.	exp isocarboxazid/
70.	exp moclobemide/
71.	exp phenelzine/
72.	exp tranylcypromine/
73.	exp citalopram/
74.	exp fluoxetine/
75.	exp fluvoxamine/
76.	exp paroxetine/
77.	exp sertraline/
78.	exp 5-hydroxytryptophan/
79.	exp duloxetine hydrochloride/
80.	exp flupenthixol/
81.	exp tryptophan/
82.	exp venlafaxine hydrochloride/
83.	(amitriptyline or amoxapine or clomipramine or dosulepin or doxepin or imipramine or lofepramine or maprotiline or mianserin or nortriptyline or protriptyline or trazodone or trimipramine or isocarboxazid or moclobemide or phenelzine or tranylcypromine or citalopram or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline or agomelatine or duloxetine or flupentixol or mirtazapine or nefazodone or oxitriptan or reboxetine or tryptophan or venlafaxine or vortioxetine).ti,ab.
84.	or/30-83
85.	29 and 84
86.	randomized controlled trial.pt.
87.	controlled clinical trial.pt.
88.	randomi#ed.ab.
89.	placebo.ab.
90.	randomly.ab.
91.	clinical trials as topic.sh.

92.	trial.ti.
93.	or/86-92
94.	meta-analysis/
95.	meta-analysis as topic/
96.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
97.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
98.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
99.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
100.	(search* adj4 literature).ab.
101.	(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.
102.	cochrane.jw.
103.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
104.	or/94-103
105.	85 and (93 or 104)

Embase (Ovid) search terms

1.	*drug dependence/
2.	*withdrawal syndrome/ or *alcohol withdrawal syndrome/ or *neonatal abstinence syndrome/
3.	*inappropriate prescribing/
4.	*deprescription/
5.	(abstinen* or abstain* or cessat* or detox* or discontinu* or reduc* or stop* or taper* or withdraw* or substitut* or depend* or addict* or abuse* or abusing or chronic or long* term or longterm or short* term or short term or misus* or overus* or deprescrib*).ti,ab.
6.	(over* adj3 (use* or using or utlisat* or utilizat*) adj3 (prescription* or prescrib* or drug* or medicine* or medication* or pharm*)).ti,ab.
7.	(inappropriate adj3 (prescription or prescrib*)).ti,ab.
8.	or/1-7
9.	letter.pt. or letter/
10.	note.pt.
11.	editorial.pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/9-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice).ti.
24.	or/16-23
25.	8 not 24
26.	limit 25 to English language

27.	*narcotic agent/
28.	*narcotic analgesic agent/
29.	(analgesic* adj3 (opioid* or narcotic) adj3 agent*).ti,ab.
30.	*buprenorphine/
31.	*codeine/
32.	*dextromoramide/
33.	*diamorphine/
34.	*fentanyl/
35.	*hydromorphone/
36.	*meptazinol/
37.	*methadone/
38.	*morphine/
39.	*oxycodone/
40.	*opiate/
41.	*pentazocine/
42.	*pethidine/
43.	*tramadol/
44.	(buprenorphine* or codeine* or dextromoramide* or diamorphine* or dihydrocodeine* or dipipanone* or fentanyl or hydromorphone* or meptazinol or methadone* or morphine* or oxycodone or papaveretum or pentazocine or pethidine or tapentadol or tramadol or heroin).ti,ab.
45.	(z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or zaleplon or zopiclone or zolpidem).ti,ab.
46.	(generation adj3 hypnotic*).ti,ab.
47.	*benzodiazepine derivative/
48.	(benzodiazepin* or bzd or flurazepam or loprazolam or lormetazepam or nitrazepam or temazepam or diazepam or chlordiazepoxide or lorazepam or oxazepam).ti,ab.
49.	*pregabalin/
50.	(gabapentin* or pregabalin*).ti,ab.
51.	*antidepressant agent/
52.	(antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or RIMA* or tricyclic* or SSRI* or SNRI* or SNORI*).ti,ab.
53.	*amitriptyline/
54.	*amoxapine/
55.	*clomipramine/
56.	*dosulepin/
57.	*doxepin/
58.	*imipramine/
59.	*lofepramine/
60.	*maprotiline/
61.	*mianserin/
62.	*nortriptyline/
63.	*protriptyline/
64.	*trazodone/
65.	*trimipramine/
66.	*isocarboxazid/
67.	*moclobemide/
68.	*phenelzine/
69.	*tranylcypromine/

70.	*citalopram/
71.	*fluoxetine/
72.	*fluvoxamine/
73.	*paroxetine/
74.	*sertraline/
75.	*5 hydroxytryptophan/
76.	*duloxetine/
77.	*flupentixol/
78.	*tryptophan/
79.	*venlafaxine/
80.	(amitriptyline or amoxapine or clomipramine or dosulepin or doxepin or imipramine or lofepramine or maprotiline or mianserin or nortriptyline or protriptyline or trazodone or trimipramine or isocarboxazid or moclobemide or phenelzine or tranylcypromine or citalopram or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline or agomelatine or duloxetine or flupentixol or mirtazapine or nefazodone or oxitriptan or reboxetine or tryptophan or venlafaxine or vortioxetine).ti,ab.
81.	or/27-80
82.	26 and 81
83.	random*.ti,ab.
84.	factorial*.ti,ab.
85.	(crossover* or cross over*).ti,ab.
86.	((doubl* or singl*) adj blind*).ti,ab.
87.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
88.	crossover procedure/
89.	single blind procedure/
90.	randomized controlled trial/
91.	double blind procedure/
92.	or/83-91
93.	systematic review/
94.	Meta-Analysis/
95.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
96.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
97.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
98.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
99.	(search* adj4 literature).ab.
100.	(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.
101.	cochrane.jw.
102.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
103.	or/93-102
104.	82 and (92 or 103)

Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library -Wiley) search terms

#1.	MeSH descriptor: [Substance-Related Disorders] explode all trees
#2.	MeSH descriptor: [Substance Withdrawal Syndrome] explode all trees
#3.	MeSH descriptor: [Inappropriate Prescribing] explode all trees
#4.	MeSH descriptor: [Medical Overuse] explode all trees

#5.	MeSH descriptor: [Deprescriptions] explode all trees
#6.	(abstinen* or abstain* or cessat* or detox* or discontinu* or reduc* or stop* or taper* or withdraw* or substitut* or depend* or addict* or abuse* or abusing or chronic or long* term or longterm or short* term or short term or misus* or overus* or deprescrib*):ti,ab
#7.	(over* near/3 use* or using or utlisat* or utilizat*) near/3 (prescription* or prescrib* or drug* or medicine* or medication* or pharm*):ti,ab
#8.	inappropriate near/3 (prescription or prescrib*):ti,ab
#9.	(OR #1-#8)
#10.	MeSH descriptor: [Narcotics] explode all trees
#11.	MeSH descriptor: [Analgesics, Opioid] explode all trees
#12.	(analgesic* near/3 opioid* or narcotic near/3 agent*):ti,ab
#13.	MeSH descriptor: [Buprenorphine] explode all trees
#14.	MeSH descriptor: [Codeine] explode all trees
#15.	MeSH descriptor: [Dextromoramide] explode all trees
#16.	MeSH descriptor: [Heroin] explode all trees
#17.	MeSH descriptor: [Fentanyl] explode all trees
#18.	MeSH descriptor: [Hydromorphone] explode all trees
#19.	MeSH descriptor: [Meptazinol] explode all trees
#20.	MeSH descriptor: [Methadone] explode all trees
#21.	MeSH descriptor: [Morphine] explode all trees
#22.	MeSH descriptor: [Oxycodone] explode all trees
#23.	MeSH descriptor: [Opium] explode all trees
#24.	MeSH descriptor: [Pentazocine] explode all trees
#25.	MeSH descriptor: [Meperidine] explode all trees
#26.	MeSH descriptor: [Tramadol] explode all trees
#27.	(buprenorphine* or codeine* or dextromoramide* or diamorphine* or dihydrocodeine* or dipipanone* or fentanyl or hydromorphone* or meptazinol or methadone* or morphine* or oxycodone or papaveretum or pentazocine or pethidine or tapentadol or tramadol or heroin):ti,ab
#28.	(z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or zaleplon or zopiclone or zolpidem):ti,ab
#29.	(generation near/3 hypnotic*):ti,ab
#30.	MeSH descriptor: [Benzodiazepines] explode all trees
#31.	(benzodiazepin* or bzd or flurazepam or loprazolam or lormetazepam or nitrazepam or temazepam or diazepam or chlordiazepoxide or lorazepam or oxazepam):ti,ab
#32.	MeSH descriptor: [Pregabalin] explode all trees
#33.	(gabapentin* or pregabalin*):ti,ab
#34.	MeSH descriptor: [Antidepressive Agents] explode all trees
#35.	(antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or RIMA* or tricyclic* or SSRI* or SNRI* or SNORI*):ti,ab
#36.	MeSH descriptor: [Amitriptyline] explode all trees
#37.	MeSH descriptor: [Amoxapine] explode all trees
#38.	MeSH descriptor: [Clomipramine] explode all trees
#39.	MeSH descriptor: [Dothiepin] explode all trees
#40.	MeSH descriptor: [Doxepin] explode all trees
#41.	MeSH descriptor: [Imipramine] explode all trees
#42.	MeSH descriptor: [Lofepramine] explode all trees
#43.	MeSH descriptor: [Maprotiline] explode all trees
#44.	MeSH descriptor: [Mianserin] explode all trees
#45.	MeSH descriptor: [Nortriptyline] explode all trees

#46.	MeSH descriptor: [Protriptyline] explode all trees
#47.	MeSH descriptor: [Trazodone] explode all trees
#48.	MeSH descriptor: [Trimipramine] explode all trees
#49.	MeSH descriptor: [Isocarboxazid] explode all trees
#50.	MeSH descriptor: [Moclobemide] explode all trees
#51.	MeSH descriptor: [Phenelzine] explode all trees
#52.	MeSH descriptor: [Tranylcypromine] explode all trees
#53.	MeSH descriptor: [Citalopram] explode all trees
#54.	MeSH descriptor: [Fluoxetine] explode all trees
#55.	MeSH descriptor: [Fluvoxamine] explode all trees
#56.	MeSH descriptor: [Paroxetine] explode all trees
#57.	MeSH descriptor: [Sertraline] explode all trees
#58.	MeSH descriptor: [5-Hydroxytryptophan] explode all trees
#59.	MeSH descriptor: [Duloxetine Hydrochloride] explode all trees
#60.	MeSH descriptor: [Flupenthixol] explode all trees
#61.	MeSH descriptor: [Tryptophan] explode all trees
#62.	MeSH descriptor: [Venlafaxine Hydrochloride] explode all trees
#63.	(amitriptyline or amoxapine or clomipramine or dosulepin or doxepin or imipramine or lofepramine or maprotiline or mianserin or nortriptyline or protriptyline or trazodone or trimipramine or isocarboxazid or moclobemide or phenelzine or tranylcypromine or citalopram or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline or agomelatine or duloxetine or flupentixol or mirtazapine or nefazodone or oxitriptan or reboxetine or tryptophan or venlafaxine or vortioxetine):ti,ab
#64.	(OR #10-#63)
#65.	#9 and #64

PsycINFO (ProQuest) search terms

1.	(((((MAINSUBJECT.EXACT("Drug Withdrawal") OR MAINSUBJECT.EXACT("Substance Use Disorder")) OR ti,ab(abstinen* OR abstain* OR cessat* OR detox* OR discontinu* OR reduc* OR stop* OR taper* OR withdraw* OR substitut* OR depend* OR addict* OR abuse* OR abusing OR chronic OR long* term OR longterm OR short* term OR short term OR misus* OR overus* OR deprescrib*) OR ti,ab(over* NEAR/3 (use* OR using OR utlisat* OR utilizat*) NEAR/3 (prescription* OR prescrib* OR drug* OR medicine* OR medication* OR pharm*)) OR ti,ab(inappropriate NEAR/3 (prescription OR prescrib*))) AND ((MAINSUBJECT.EXACT.EXPLODE("Analgesic Drugs") OR MAINSUBJECT.EXACT.EXPLODE("Narcotic Drugs")) OR ti,ab(analgesic* NEAR/3 (opioid* OR narcotic) NEAR/3 agent*) OR (MAINSUBJECT.EXACT.EXPLODE("Buprenorphine") OR MAINSUBJECT.EXACT.EXPLODE("Heroin") OR MAINSUBJECT.EXACT.EXPLODE("Methadone") OR MAINSUBJECT.EXACT.EXPLODE("Pentazocine") OR MAINSUBJECT.EXACT.EXPLODE("Morphine") OR MAINSUBJECT.EXACT.EXPLODE("Tramadol") OR MAINSUBJECT.EXACT.EXPLODE("Codeine") OR MAINSUBJECT.EXACT.EXPLODE("Fentanyl") OR MAINSUBJECT.EXACT.EXPLODE("Meperidine")) OR ti,ab(buprenorphine* OR codeine* OR dextromoramide* OR diamorphine* OR dihydrocodeine* OR dipipanone* OR fentanyl OR hydromorphone* OR meptazinol OR methadone* OR morphine* OR oxycodone OR papaveretum OR pentazocine OR pethidine OR tapentadol OR tramadol OR heroin) OR ti,ab(z drug* OR z hypnotic* OR non-benzodiazepin* OR nonbenzodiazepin* OR zaleplon OR zopiclone OR zolpidem) OR ti,ab(generation NEAR/3 hypnotic*) OR MAINSUBJECT.EXACT.EXPLODE("Benzodiazepines") OR ti,ab(benzodiazepin* OR bzd OR flurazepam OR loprazolam OR lormetazepam OR nitrazepam OR temazepam OR diazepam OR chlordiazepoxide OR lorazepam OR

	oxazepam) OR (MAINSUBJECT.EXACT.EXPLODE("Pregabalin") OR MAINSUBJECT.EXACT.EXPLODE("Gabapentin")) OR ti,ab(gabapentin* OR pregabalin*) OR MAINSUBJECT.EXACT.EXPLODE("Antidepressant Drugs") OR ti,ab(antidepress* OR anti depress* OR thymoanaleptic* OR thymoleptic* OR MAOI* OR "monoamine oxidase inhibit*" OR RIMA* OR tricyclic* OR SSRI* OR SNRI* OR SNORI*) OR (MAINSUBJECT.EXACT.EXPLODE("Doxepin") OR MAINSUBJECT.EXACT.EXPLODE("Tranylcypromine") OR MAINSUBJECT.EXACT.EXPLODE("Sertraline") OR MAINSUBJECT.EXACT.EXPLODE("Isocarboxazid") OR MAINSUBJECT.EXACT.EXPLODE("Tryptophan") OR MAINSUBJECT.EXACT.EXPLODE("Fluoxetine") OR MAINSUBJECT.EXACT.EXPLODE("Hydroxytryptophan (5-)") OR MAINSUBJECT.EXACT.EXPLODE("Nortriptyline") OR MAINSUBJECT.EXACT.EXPLODE("Citalopram") OR MAINSUBJECT.EXACT.EXPLODE("Phenelzine") OR MAINSUBJECT.EXACT.EXPLODE("Imipramine") OR MAINSUBJECT.EXACT.EXPLODE("Mianserin") OR MAINSUBJECT.EXACT.EXPLODE("Paroxetine") OR MAINSUBJECT.EXACT.EXPLODE("Moclobemide") OR MAINSUBJECT.EXACT.EXPLODE("Amitriptyline") OR MAINSUBJECT.EXACT.EXPLODE("Maprotiline") OR MAINSUBJECT.EXACT.EXPLODE("Trazodone") OR MAINSUBJECT.EXACT.EXPLODE("Fluvoxamine") OR MAINSUBJECT.EXACT.EXPLODE("Chlorimipramine")) OR ti,ab(amitriptyline OR amoxapine OR clomipramine OR dosulepin OR doxepin OR imipramine OR lofepramine OR maprotiline OR mianserin OR nortriptyline OR protriptyline OR trazodone OR trimipramine OR isocarboxazid OR moclobemide OR phenelzine OR tranylcypromine OR citalopram OR escitalopram OR fluoxetine OR fluvoxamine OR paroxetine OR sertraline OR agomelatine OR duloxetine OR flupentixol OR mirtazapine OR nefazodone OR oxitriptan OR reboxetine OR tryptophan OR venlafaxine OR vortioxetine))) AND ((su.exact.explode("clinical trials") OR ti,ab((clinical OR control*) NEAR/3 trial*) OR ti,ab((singl* OR doubl* OR trebl* OR tripl*) NEAR/5 (blind* OR mask*)) OR ti,ab(volunteer* OR control-group OR controls) OR su.exact("placebo") OR ti,ab(placebo*)) OR (((SU.EXACT("Literature Review") OR RTYPE(review) OR ti(review) OR me(literature review)) AND (ti,ab(systematic OR evidence OR methodol* OR quantitative*))) OR (SU.EXACT("Meta Analysis") OR ti,ab(meta-analys* OR metanalys* OR metaanalys* OR meta analys*) OR ti,ab((systematic OR evidence* OR methodol* OR quantitative*) NEAR/3 (review* OR overview*)) OR ti,ab((pool* OR combined OR combining) NEAR/2 (data OR trials OR studies OR results)) OR RTYPE(systematic OR meta*) OR ME(meta analysis OR systematic review))))) NOT (su.exact.explode("rodents") OR su.exact.explode("mice") OR (su.exact("animals") NOT (su.exact("human males") OR su.exact("human females"))) OR ti(rat OR rats OR mouse OR mice))) AND (la.exact("English"))

Health Technology appraisals (HTA) (Centre for Reviews and Disseminations) search terms

1.	MeSH DESCRIPTOR Substance-Related Disorders EXPLODE ALL TREES
2.	(MeSH descriptor Substance Withdrawal Syndrome explode all trees)
3.	(MeSH descriptor Inappropriate Prescribing explode all trees)
4.	(MeSH descriptor Medical Overuse explode all trees)
5.	(MeSH descriptor Deprescriptions explode all trees)
6.	((abstinen* or abstain* or cessat* or detox* or discontinu* or reduc* or stop* or taper* or withdraw* or substitut* or depend* or addict* or abuse* or abusing or chronic or long* term or longterm or short* term or short term or misus* or overus* or deprescrib*))
7.	((over* adj3 (use* or using or utlisat* or utilizat*) adj3 (prescription* or prescrib* or drug* or medicine* or medication* or pharm*)))
8.	((inappropriate adj3 (prescription or prescrib*)))
9.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10.	(MeSH descriptor Narcotics explode all trees)

11.	(MeSH descriptor: [Analgesics, Opioid] explode all trees)
12.	((analgesic* adj3 (opioid* or narcotic) adj3 agent*))
13.	(MeSH descriptor: [Buprenorphine] explode all trees)
14.	(MeSH descriptor: [Codeine] explode all trees)
15.	(MeSH descriptor: [Dextromoramide] explode all trees)
16.	(MeSH descriptor: [Heroin] explode all trees)
17.	(MeSH descriptor: [Fentanyl] explode all trees)
18.	(MeSH descriptor: [Hydromorphone] explode all trees)
19.	(MeSH descriptor: [Meptazinol] explode all trees)
20.	(MeSH descriptor: [Methadone] explode all trees)
21.	(MeSH descriptor: [Morphine] explode all trees)
22.	(MeSH descriptor: [Oxycodone] explode all trees)
23.	(MeSH descriptor: [Opium] explode all trees)
24.	(MeSH descriptor: [Pentazocine] explode all trees)
25.	(MeSH descriptor: [Meperidine] explode all trees)
26.	(MeSH descriptor: [Tramadol] explode all trees)
27.	(buprenorphine* or codeine* or dextromoramide* or diamorphine* or dihydrocodeine* or dipipanone* or fentanyl or hydromorphone* or meptazinol or methadone* or morphine* or oxycodone or papaveretum or pentazocine or pethidine or tapentadol or tramadol or heroin)
28.	(z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or zaleplon or zopiclone or zolpidem)
29.	(generation adj3 hypnotic*)
30.	(MeSH descriptor: [Benzodiazepines] explode all trees)
31.	(benzodiazepin* or bzd or flurazepam or loprazolam or lormetazepam or nitrazepam or temazepam or diazepam or chlordiazepoxide or lorazepam or oxazepam)
32.	(MeSH descriptor: [Pregabalin] explode all trees)
33.	(gabapentin* or pregabalin*)
34.	(MeSH descriptor: [Antidepressive Agents] explode all trees)
35.	(antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or RIMA* or tricyclic* or SSRI* or SNRI* or SNORI*)
36.	(MeSH descriptor: [Amitriptyline] explode all trees)
37.	(MeSH descriptor: [Amoxapine] explode all trees)
38.	(MeSH descriptor: [Clomipramine] explode all trees)
39.	(MeSH descriptor: [Dothiepin] explode all trees)
40.	(MeSH descriptor: [Doxepin] explode all trees)
41.	(MeSH descriptor: [Imipramine] explode all trees)
42.	(MeSH descriptor: [Lofepramine] explode all trees)
43.	(MeSH descriptor: [Maprotiline] explode all trees)
44.	(MeSH descriptor: [Mianserin] explode all trees)
45.	(MeSH descriptor: [Nortriptyline] explode all trees)
46.	(MeSH descriptor: [Protriptyline] explode all trees)
47.	(MeSH descriptor: [Trazodone] explode all trees)
48.	(MeSH descriptor: [Trimipramine] explode all trees)
49.	(MeSH descriptor: [Isocarboxazid] explode all trees)
50.	(MeSH descriptor: [Moclobemide] explode all trees)
51.	(MeSH descriptor: [Phenelzine] explode all trees)
52.	(MeSH descriptor: [Tranylcypromine] explode all trees)
53.	(MeSH descriptor: [Citalopram] explode all trees)

54.	(MeSH descriptor: [Fluoxetine] explode all trees)
55.	(MeSH descriptor: [Fluvoxamine] explode all trees)
56.	(MeSH descriptor: [Paroxetine] explode all trees)
57.	(MeSH descriptor: [Sertraline] explode all trees)
58.	(MeSH descriptor: [5-Hydroxytryptophan] explode all trees)
59.	(MeSH descriptor: [Duloxetine Hydrochloride] explode all trees)
60.	(MeSH descriptor: [Flupenthixol] explode all trees)
61.	(MeSH descriptor: [Tryptophan] explode all trees)
62.	(MeSH descriptor: [Venlafaxine Hydrochloride] explode all trees)
63.	(amitriptyline or amoxapine or clomipramine or dosulepin or doxepin or imipramine or lofepramine or maprotiline or mianserin or nortriptyline or protriptyline or trazodone or trimipramine or isocarboxazid or moclobemide or phenelzine or tranylcypromine or citalopram or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline or agomelatine or duloxetine or flupentixol or mirtazapine or nefazodone or oxitriptan or reboxetine or tryptophan or venlafaxine or vortioxetine)
64.	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #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 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63
65.	#9 AND #64

Trials Register of Promoting Health Interventions (TRoPHI) search terms

1.	Freetext (All but Authors): "substance-related disorders" OR "substance withdrawal syndrome" OR "inappropriate prescribing" OR "medical overuse" OR "deprescriptions" OR "abstinen*" or "abstain*" or "cessat*" or "detox*" or "discontinu*" or "reduc*" or "stop*" or "taper*" or "withdraw*" or "substitut*" or "depend*" or "addict*" or "abuse*" or "abusing" or "chronic" or "long* term" or "longterm" or "short* term" or "short term" or "misus*" or "overus*" OR "deprescrib*"
2.	Freetext (All but Authors): "over*" near "use*" near "prescri*"
3.	Freetext (All but Authors): "inappropriate" near "prescri*"
4.	1 OR 2 OR 3
5.	Freetext (All but Authors): "buprenorphine*" or "codeine*" or "dextromoramide*" or "diamorphine*" or "dihydrocodeine*" or "dipipanone*" or "fentanyl" or "hydromorphone*" or "meptazinol" or "methadone*" or "morphine*" or "oxycodone" or "papaveretum" or "pentazocine" or "pethidine" or "tapentadol" or "tramadol" or "heroin"
6.	Freetext (All but Authors): "z drug*" or "z hypnotic*" or "non-benzodiazepin*" or "nonbenzodiazepin*" or "zaleplon" or "zopiclone" or "zolpidem"
7.	Freetext (All but Authors): "generation" near "hypnotic"
8.	Freetext (All but Authors): "benzodiazepin*" or "bzd" or "flurazepam" or "loprazolam" or "lormetazepam" or "nitrazepam" or "temazepam" or "diazepam" or "chlordiazepoxide" or "lorazepam" or "oxazepam"
9.	Freetext (All but Authors): "gabapentin*" or "pregabalin*"
10.	Freetext (All but Authors): "antidepress*" or "anti depress*" or "thymoanaleptic*" or "thymoleptic*" or "MAOI*" or "monoamine oxidase inhibit*" or "RIMA*" or "tricyclic*" or "SSRI*" or "SNRI*" or "SNORI*"
11.	Freetext (All but Authors): "amitriptyline" or "amoxapine" or "clomipramine" or "dosulepin" or "doxepin" or "imipramine" or "lofepramine" or "maprotiline" or "mianserin" or "nortriptyline" or "protriptyline" or "trazodone" or "trimipramine" or "isocarboxazid" or "moclobemide" or "phenelzine" or "tranylcypromine" or "citalopram" or "escitalopram" or "fluoxetine" or "fluvoxamine" or "paroxetine" or "sertraline" or "agomelatine" or "duloxetine" or "flupentixol" or "mirtazapine" or "nefazodone" or "oxitriptan" or "reboxetine" or "tryptophan" or "venlafaxine" or "vortioxetine"

12.	5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11
13.	4 AND 12

ASSIA (Proquest) search terms

1.	((MAINSUBJECT.EXACT.EXPLODE("Substance abuse disorders") OR ti,ab(abstinen* OR abstain* OR cessat* OR detox* OR discontinu* OR reduc* OR stop* OR taper* OR withdraw* OR substitut* OR depend* OR addict* OR abuse* OR abusing OR chronic OR long* term OR longterm OR short* term OR short term OR misus* OR overus* OR deprescrib*) OR ti,ab(over* NEAR/3 (use* OR using OR utlisat* OR utilizat*) NEAR/3 (prescription* OR prescrib* OR drug* OR medicine* OR medication* OR pharm*)) OR ti,ab(inappropriate NEAR/3 (prescription OR prescrib*))) AND ((MAINSUBJECT.EXACT.EXPLODE("Analgesics") OR MAINSUBJECT.EXACT.EXPLODE("Narcotics")) OR ti,ab(analgesic* NEAR/3 (opioid* or narcotic) NEAR/3 agent*) OR (MAINSUBJECT.EXACT.EXPLODE("Methadone") OR MAINSUBJECT.EXACT.EXPLODE("Heroin") OR MAINSUBJECT.EXACT.EXPLODE("Buprenorphine") OR MAINSUBJECT.EXACT.EXPLODE("Codeine") OR MAINSUBJECT.EXACT.EXPLODE("Hydromorphone") OR MAINSUBJECT.EXACT.EXPLODE("Tramadol") OR MAINSUBJECT.EXACT.EXPLODE("Morphine") OR MAINSUBJECT.EXACT.EXPLODE("Opium")) OR ti,ab(buprenorphine* or codeine* or dextromoramide* or diamorphine* or dihydrocodeine* or dipipanone* or fentanyl or hydromorphone* or meptazinol or methadone* or morphine* or oxycodone or papaveretum or pentazocine or pethidine or tapentadol or tramadol or heroin) OR ti,ab(z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or zaleplon or zopiclone or zolpidem) OR ti,ab(generation NEAR/3 hypnotic*) OR MAINSUBJECT.EXACT.EXPLODE("Benzodiazepines") OR ti,ab(benzodiazepin* OR bzd OR flurazepam OR loprazolam OR lormetazepam OR nitrazepam OR temazepam OR diazepam OR chlordiazepoxide OR lorazepam OR oxazepam) OR MAINSUBJECT.EXACT.EXPLODE("Gabapentin") OR ti,ab(gabapentin* or pregabalin*) OR MAINSUBJECT.EXACT.EXPLODE("Antidepressant drugs") OR ti,ab(antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or RIMA* or tricyclic* or SSRI* or SNRI* or SNORI*) OR (MAINSUBJECT.EXACT.EXPLODE("Imipramine") OR MAINSUBJECT.EXACT.EXPLODE("Amitriptyline") OR MAINSUBJECT.EXACT.EXPLODE("Clomipramine") OR MAINSUBJECT.EXACT.EXPLODE("Moclobemide") OR MAINSUBJECT.EXACT.EXPLODE("Sertraline") OR MAINSUBJECT.EXACT.EXPLODE("Paroxetine") OR MAINSUBJECT.EXACT.EXPLODE("Venlafaxine") OR MAINSUBJECT.EXACT.EXPLODE("Fluoxetine") OR MAINSUBJECT.EXACT.EXPLODE("Citalopram") OR MAINSUBJECT.EXACT.EXPLODE("Tryptophan")) OR ti,ab(amitriptyline OR amoxapine OR clomipramine OR dosulepin OR doxepin OR imipramine OR lofepramine OR maprotiline OR mianserin OR nortriptyline OR protriptyline OR trazodone OR trimipramine OR isocarboxazid OR moclobemide OR phenelzine OR tranylcypromine OR citalopram OR escitalopram OR fluoxetine OR fluvoxamine OR paroxetine OR sertraline OR agomelatine OR duloxetine OR flupentixol OR mirtazapine OR nefazodone OR oxitriptan OR reboxetine OR tryptophan OR venlafaxine OR vortioxetine))) AND (la.exact("English"))

A.1.3 Step 3: Grey literature

Database	Dates searched	Search filter used
King's Fund Library	All years to 11 November 2018	None
National Institute for Health Research Journals Library	All years to 29 November 2018	None

King's Fund Library search terms

1.	Prescription drug* on Annual report, journal article, journal supplement, electronic journal, King's funs publication, web publication, journal, statistical publication, web site
2.	Drug* withdrawal on Annual report, journal article, journal supplement, electronic journal, King's funs publication, web publication, journal, statistical publication, web site
3.	Drug* Dependency on Annual report, journal article, journal supplement, electronic journal, King's funs publication, web publication, journal, statistical publication, web site
4.	Drug* dependent on Annual report, journal article, journal supplement, electronic journal, King's funs publication, web publication, journal, statistical publication, web site
5.	Drug* harm on Annual report, journal article, journal supplement, electronic journal, King's funs publication, web publication, journal, statistical publication, web site

National Institute for Health Research Journals Library search terms

1.	Prescription drugs
2.	Prescription harm
3.	Prescription misuse

Table S4: Estimates of continuous receipt of a prescription duration by medicine class (latest estimated retrospective duration in months as at March 2018: 1 month; 2 to 5 months; 6 to 11 months; 12 to 34 months; and 35-36 months) by sex, age group and deprivation

Duration/characteristic	Antidepressants	Opioids	Gabapentinoids	Benzodiazepines	Z-drugs
People estimated to have been in receipt of a prescription for 1 month					
All	524,765 (11·7)	448,018 (19·1)	95,453 (11·2)	104,593 (24·9)	73,066 (20·1)
Male ¶	176,057 (11·8)	172,774 (19·8)	35,321 (10·7)	37,116 (24·9)	27,942 (20·4)
Female	346,132 (11·6)	273,077 (18·6)	59,989 (11·4)	66,972 (24·8)	44,807 (19·7)
Age (years) §					
18-24	45,199 (21·3)	13,879 (50·5)	1,853 (19·2)	4,073 (54·0)	3,411 (57·1)
25-44	170,098 (15·3)	92,053 (27·4)	18,868 (13·2)	29,899 (37·3)	18,866 (31·0)
45-64	197,504 (10·9)	160,440 (17·9)	40,324 (10·8)	36,453 (25·9)	26,411 (20·1)
65-74	59,641 (8·7)	85,832 (16·6)	17,856 (10·9)	15,999 (20·3)	11,458 (16·3)
75 ≥	49,084 (7·4)	93,468 (16·6)	16,389 (10·0)	17,637 (15·8)	12,592 (13·2)
IMD quintile †					
1 (least deprived)	119,400 (12·4)	87,381 (21·9)	18,681 (12·5)	27,992 (29·6)	19,072 (22·2)
2	117,257 (11·8)	94,709 (20·1)	19,764 (11·6)	25,174 (26·1)	17,015 (20·8)
3	111,262 (11·9)	93,627 (18·9)	20,509 (11·3)	21,693 (24·7)	14,910 (19·6)
4	100,781 (11·4)	92,527 (17·8)	19,858 (10·6)	17,459 (22·0)	12,354 (18·6)
5 (most deprived)	76,510 (10·7)	79,758 (17·2)	16,747 (10·0)	12,278 (19·8)	9,734 (17·8)

Table S4: continued .../

Duration/characteristic	Antidepressants	Opioids	Gabapentinoids	Benzodiazepines	Z-drugs
People estimated to have been in receipt of a prescription for 2 to 5 months					
All	893,279 (19·9)	424,851 (18·1)	159,644 (18·7)	63,369 (15·1)	58,159 (16·0)
Male ¶	301,056 (20·2)	162,886 (18·6)	60,800 (18·5)	23,457 (15·8)	23,217 (17·0)
Female	591,409 (19·8)	261,839 (17·8)	98,808 (18·8)	39,891 (14·8)	34,917 (15·4)
Age (years) §					
18-24	73,072 (34·4)	5,833 (21·2)	2,690 (27·9)	1,655 (21·9)	1,400 (23·5)
25-44	281,666 (25·4)	63,054 (18·8)	30,018 (21·0)	14,333 (17·9)	12,141 (19·9)
45-64	341,784 (18·9)	156,077 (17·4)	68,549 (18·4)	19,853 (14·1)	20,004 (15·2)
65-74	104,894 (15·3)	91,899 (17·8)	29,922 (18·3)	10,507 (13·3)	10,255 (14·6)
75 ≥	90,675 (13·7)	107,810 (19·1)	28,422 (17·3)	16,997 (15·3)	14,325 (15·0)
IMD quintile †					
1 (least deprived)	203,643 (21·2)	75,688 (18·9)	30,246 (20·3)	15,380 (16·3)	14,764 (17·2)
2	201,559 (20·3)	86,957 (18·5)	32,929 (19·3)	15,282 (15·8)	13,369 (16·4)
3	189,106 (20·3)	90,782 (18·4)	34,686 (19·1)	13,304 (15·2)	12,016 (15·8)
4	171,058 (19·3)	91,868 (17·6)	33,658 (18·0)	11,140 (14·0)	9,963 (15·0)
5 (most deprived)	129,002 (18·0)	80,233 (17·3)	28,416 (17·0)	8,433 (13·6)	8,167 (14·9)

Table S4: continued…/

Duration/characteristic	Antidepressants	Opioids	Gabapentinoids	Benzodiazepines	Z-drugs
People estimated to have been in receipt of a prescription for 6 to 11 months					
All	726,645 (16·2)	299,995 (12·8)	143,566 (16·8)	40,056 (9·5)	38,830 (10·7)
Male ¶	240,531 (16·1)	112,281 (12·9)	54,417 (16·5)	14,722 (9·9)	15,162 (11·1)
Female	485,993 (16·3)	187,683 (12·8)	89,129 (17·0)	25,330 (9·4)	23,664 (10·4)
Age (years) §					
18-24	42,965 (20·3)	2,839 (10·3)	1,967 (20·4)	774 (10·3)	495 (8·3)
25-44	208,821 (18·8)	40,510 (12·0)	25,629 (17·9)	7,844 (9·8)	6,883 (11·3)
45-64	286,485 (15·8)	110,415 (12·3)	61,149 (16·4)	12,466 (8·8)	13,164 (10·0)
65-74	96,909 (14·1)	66,270 (12·8)	27,272 (16·6)	6,942 (8·8)	7,112 (10·1)
75 ≥	91,366 (13·8)	79,934 (14·2)	27,535 (16·8)	12,027 (10·8)	11,175 (11·7)
IMD quintile †					
1 (least deprived)	165,982 (17·3)	51,731 (12·9)	25,955 (17·4)	9,311 (9·8)	9,643 (11·2)
2	164,069 (16·5)	60,935 (12·9)	29,468 (17·2)	9,276 (9·6)	8,819 (10·8)
3	151,409 (16·3)	63,766 (12·9)	30,682 (16·9)	8,307 (9·5)	8,067 (10·6)
4	139,280 (15·7)	66,192 (12·7)	30,850 (16·5)	7,591 (9·5)	6,797 (10·2)
5 (most deprived)	106,925 (14·9)	57,955 (12·5)	26,882 (16·1)	5,692 (9·2)	5,590 (10·2)

Table S4: continued .../

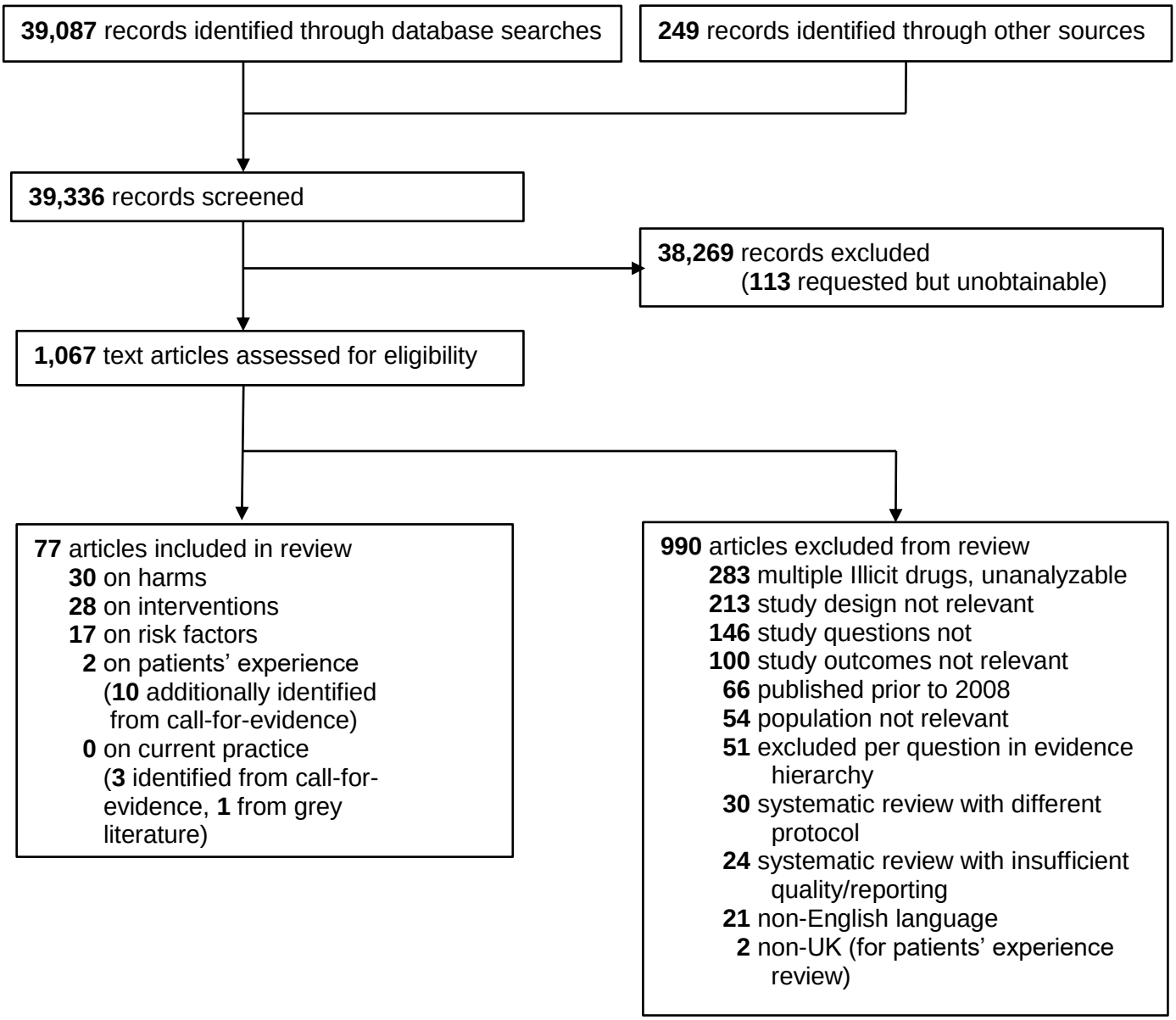
Duration/characteristic	Antidepressants	Opioids	Gabapentinoids	Benzodiazepines	Z-drugs
People estimated to have been in receipt of a prescription for 12 to 34 months					
All	1,244,978 (27·8)	551,812 (23·5)	263,480 (30·8)	79,263 (18·9)	80,178 (22·0)
Male ¶	413,304 (27·7)	200,620 (23·0)	101,310 (30·8)	28,198 (18·9)	30,199 (22·1)
Female	831,561 (27·8)	351,158 (23·9)	162,146 (30·9)	51,059 (18·9)	49,973 (22·0)
Age (years) §					
18-24	42,285 (19·9)	3,554 (12·9)	2,500 (25·9)	792 (10·5)	516 (8·6)
25-44	289,810 (26·1)	71,665 (21·3)	43,891 (30·6)	13,496 (16·8)	11,547 (18·9)
45-64	509,524 (28·2)	208,781 (23·3)	114,376 (30·7)	25,549 (18·1)	27,818 (21·2)
65-74	198,186 (28·8)	123,381 (23·9)	49,572 (30·2)	15,137 (19·2)	15,649 (22·3)
75 ≥	205,098 (31·1)	144,404 (25·6)	53,122 (32·4)	24,285 (21·8)	24,645 (25·9)
IMD quintile †					
1 (least deprived)	263,694 (27·5)	90,329 (22·6)	44,227 (29·7)	16,811 (17·8)	18,749 (21·8)
2	277,275 (27·9)	109,359 (23·2)	52,089 (30·5)	18,237 (18·9)	18,090 (22·2)
3	258,193 (27·7)	116,989 (23·7)	55,743 (30·8)	16,807 (19·1)	16,874 (22·2)
4	246,529 (27·8)	124,709 (23·9)	58,571 (31·2)	15,298 (19·2)	14,625 (22·0)
5 (most deprived)	201,450 (28·1)	111,624 (24·1)	53,494 (32·0)	12,336 (19·9)	12,022 (22·0)

Table S4: continued…/

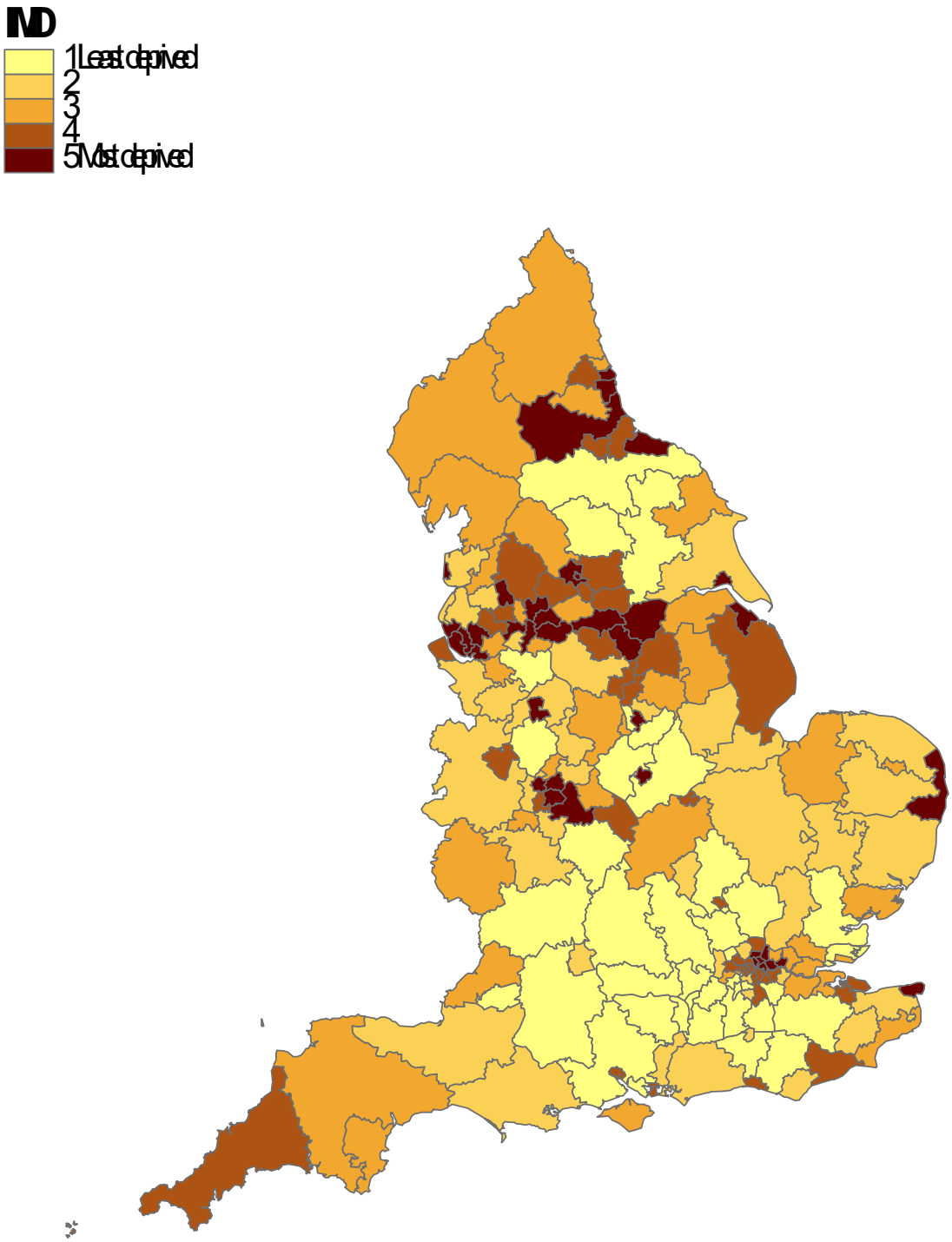
Duration/characteristic	Antidepressants	Opioids	Gabapentinoids	Benzodiazepines	Z-drugs
People estimated to have been in receipt of a prescription for 35-36 months					
All	1,090,801 (24·3)	619,501 (26·4)	192,022 (22·5)	132,283 (31·5)	114,025 (31·3)
Male ¶	358,553 (24·1)	224,902 (25·7)	77,353 (23·5)	45,430 (30·5)	40,427 (29·5)
Female	732,106 (24·5)	394,533 (26·9)	114,647 (21·8)	86,839 (32·2)	73,586 (32·4)
Age (years) §					
18-24	8,640 (4·1)	1,361 (5·0)	643 (6·7)	251 (3·3)	147 (2·5)
25-44	158,482 (14·3)	68,906 (20·5)	24,867 (17·4)	14,667 (18·3)	11,503 (18·9)
45-64	472,209 (26·1)	260,528 (29·1)	88,686 (23·8)	46,680 (33·1)	43,976 (33·5)
65-74	227,583 (33·1)	149,629 (28·9)	39,258 (24·0)	30,198 (38·3)	25,805 (36·7)
75 ≥	223,755 (33·9)	139,013 (24·6)	38,544 (23·5)	40,475 (36·3)	32,585 (34·2)
IMD quintile †					
1 (least deprived)	206,590 (21·5)	94,574 (23·7)	29,871 (20·1)	25,110 (26·5)	23,834 (27·7)
2	232,234 (23·4)	119,147 (25·3)	36,652 (21·4)	28,494 (29·5)	24,353 (29·8)
3	221,760 (23·8)	129,113 (26·1)	39,607 (21·9)	27,698 (31·5)	24,152 (31·8)
4	229,871 (25·9)	145,565 (27·9)	44,505 (23·7)	28,004 (35·2)	22,776 (34·2)
5 (most deprived)	202,723 (28·3)	132,925 (28·7)	41,853 (25·0)	23,372 (37·6)	19,236 (35·1)

IMD, Indicators of multiple deprivation
* Includes individuals who did not have a dispensed prescription reported in March 2018 yet had one reported in the months either side. ¶ Analysis of sex excludes up to 0.1% of cases overall where sex was not available.
§ Analysis of age excludes up to 0.1% where no valid age record was available.
† Analysis from GP practice data and excludes cases where no IMD score was available.
Proportions are of the total (restricted by age, sex or IMD quintile as applicable) estimated to have a prescription in that month.

Appendix Figure S1. PRISMA flowchart of study selection



Appendix Figure S2. Deprivation by CCG registered populations, England (1 April 2017)



Web-material from the REA

A master list of included studies for each section are shown at the end of this section (**W5, pages 84-100**).

Appendix web-material W1. Withdrawal symptoms

Withdrawal symptoms

For antidepressants, 17 placebo RCTs with 6,729 participants reported withdrawal symptoms including: insomnia, depression, suicidal ideation, upper respiratory tract infection, vomiting, headache, and diarrhoea (evidence rated very-low, low or moderate-quality due to risk of selection bias, attrition, incomplete outcome data and imprecision, and unexplained heterogeneity). One study of desvenlafaxine and duloxetine [1] reported more cases of withdrawal symptoms associated with these medicines than placebo (relative risk 2·2; 95% CI 1·4 to 3·46; evidence rated as high quality).

Three RCTs compared antidepressant withdrawal regimens. In the first small study of 28 participants [2], three-day versus 14-days tapers showed no significant difference in score on the Discontinuation-Emergent Signs and Symptoms scale (DESS; evidence rated as very low quality due to selection bias, lack of blinding and imprecision). In the second [3], an RCT with 285 participants contrasted abrupt withdrawal with a one-week taper reporting that tapered withdrawal was associated with the number of taper/post-therapy emergent adverse events, although there was no difference in the total score on the DESS or in cases of nausea, dizziness, suicide ideation and suicide attempts (rated very-low quality evidence).

The third trial ([4]; n=384) evaluated abrupt withdrawal versus three different methods of tapering the withdrawal from desvenlafaxine. The results suggested no significant difference in DESS score at three-week follow-up after tapering, nor any differences in adverse events reported by 5% or more of the participants in any group (evidence rated as very low quality due to selection bias of selection bias and serious imprecision around the effect between abrupt tapering and tapering on alternate days for two weeks).

One observational study comprising 398 participants evaluated rapid (1-7 days) versus gradual antidepressant withdrawal (two-weeks or more). Results suggested a benefit for gradual withdrawal in reduced time to another depressive episode within one year (evidence rated as very low quality due to selection bias, deviations from intended interventions and risk of measurement bias). For chronic non-cancer pain, one RCT [5] comprising 615 participants evaluated a withdrawal taper with higher-dose pregabalin compared to lower-dose pregabalin and lorazepam (a benzodiazepine), indicating no difference between medicines in withdrawal symptoms

measured by the Physician Withdrawal Checklist [6] and the DESS. The evidence suggested that gabapentinoids were associated with less rebound insomnia after the taper (evidence rated as very low quality due to risk of selection bias, and high attrition rates causing outcome imprecision). For insomnia, a single study of 193 participants evaluated zolpidem compared to placebo [7]. There was no difference in rebound insomnia on days two and three of a medicine "run-out" (evidence rated as low-quality evidence due to imprecision demonstrated by wide confidence intervals around the effect) **(Table S4, section 1.1 page 89-107 for the GRADE profiles**).

Interventions for prevention or treatment

Twenty-six RCTs and two non-randomised studies were identified; 12 for opioids, eight for benzodiazepines, three for antidepressants, one for Z-drugs and four reported on a range of interventions for treatment of dependence or withdrawal management. The descriptions of interventions varied considerably, and meta-analysis was not feasible, and therefore the results were reported un-pooled I GRADE profiles (**Table S4, section 1.3 page 151-191**).

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6. Rickels K, Garcia-Espana F, Mandos LA, Case GW. Physician Withdrawal Checklist (PWC-20). *J Clin Psychopharmacol*. 2008; **28**: 447–51.

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Appendix web-material W2. Risk factors

Among the 17 studies on risk factors, two studies showed higher initial opioid dosing was associated with long-term use in one study (adjusted odds ratio [AOR] 95% CI) ranging from 4·01 (95% CI 2·23 to 10·57) to 6·25 (95% CI 2·91 to 13·42) [1]; n=791) and in the other [2], from 2·02 (95% CI 1·9 to 2·15) to 3·68 (95% CI 3·34 to 4·05); n=431,963).

One study ([3]; n=1,993] reported that opioid treatment for longer than 90 days was associated with opioid overdose (hazard ratio [HR] 5·12 (95% CI 1·63 to 6·08)) and OUD (HR 2·86 [95% CI 1·54 to 5·31]).

Three studies [4,5,] reported that prior or concurrent use of benzodiazepines, history of pregabalin use or increased number of prescribed analgesics, was associated with long-term opioid use (low or very-low quality evidence due to very serious risk of bias due to attrition and unclear outcome specification). Five studies [1,2,4,5,7] reported that a mental health diagnosis was a risk factor for OUD. Among the five benzodiazepine studies, two studies [8,9] reported that non-white ethnicity was associated with a lower risk of benzodiazepine use disorder (low-quality evidence due to unclear attrition, outcome and risk factor measurement).

The second study reported that lower income was associated with more benzodiazepines prescribed. Shorter-acting benzodiazepines were associated with greater risk of long-term use. Other risk factors studied either showed inconsistent results between studies (e.g. age and gender had results in both directions of effect) or demonstrated no association.

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9. Cook B, Creedon T, Wang Y, Lu C, Carson N, Jules P, et al. Examining racial/ethnic differences in patterns of benzodiazepine prescription and misuse. Drug Alcohol Depend. 2018; **187**: 29–34.

Appendix web-material W3. Patients' experience

Twelve articles in peer-reviewed journals and other publicly available reports were identified through the literature search and the open-call (three qualitative studies; three reports; one NIHR Health Technology Assessment, and five analyses of online information).

We compiled cross-cutting and medicine-specific reports from patients about their experience of taking the medicines and their contact with medical professionals. Eleven of these reported on longer-term use of antidepressants, and one included both longer-term use of antidepressants and benzodiazepines. Table S5 summarises this thematically by harmful side-effects, medicine-attributed withdrawal symptoms following dose adjustment or cessation, and treatment services.

There was also a report on 26 patients who completed an open-ended questionnaire on several medicines [1] (evidence rated with high confidence). Most comments concerned benzodiazepines, citing harmful physical, affective, social and sexual side-effects. These patients voiced concerns about GP monitoring and cited barriers to accessing BUD treatment and support. (See Appendices S5, section 1.4 page 204-207 for GRADE CERQual profiles).

1. British Medical Association. Prescribed drugs associated with dependence and withdrawal – _building a consensus for action. Analysis report. London. 2015. https://www.drugsandalcohol.ie/24620/files/10/24620.html (accessed 14.7.19)

Appendix web-material W4. Service models and evaluations

Four reports were identified:

1. Barth KS, Ball S, Adams RS. Development and feasibility of an academic detailing intervention to improve prescription drug monitoring program use among physicians. *Journal of Continuing Education in the Health Professions*; 2017; **37**: 98–105.

2. Dann A. A novel approach to the identification, reduction and rationalisation of opiate prescribing. 2018. Royal College of General Practitioners. http://www.rcgpac.org.uk/programme-overview/2018-app/ (accessed August 14, 2019).

3. Guy A, Davies J. An analysis of four current UK service models for prescribed medication withdrawal support. 2018. All-Party Parliamentary Group for Prescribed Drug Dependence. http://www.prescribeddrug.org/wp-content/uploads/2018/11/APPG-Service-Model-Report.pdf. (accessed August 14, 2019).

4. Scott L, Kesten J, Bache K, Collins R, Redwood S, Thomas K. South Gloucestershire Pain Review Pilot (SUPPORT) Study: A mixed-methods evaluation. UK, Public Health Science, Belfast. 2018. www.ukpublichealthscience.org.

The non-comparative nature of all of the studies meant that differences between those using a service and those not using a service or using an alternative service could not be assessed.

Appendix web-material W5. References for all REA included studies

Harms of dependence and withdrawal symptoms

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Interventions for prevention or treatment

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Patient's Experience

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Current service examples

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4. Scott L, Kesten J, Bache K, Collins R, Redwood S, Thomas K. South Gloucestershire Pain Review Pilot (SUPPORT) Study: A mixed-methods evaluation. Belfast: 2018 23/11/2018. Report No.

Appendix Table S5: GRADE and GRADE CERQual profiles

1.1 Harms of dependency, withdrawal and discontinuation

1.1.1 Harms of dependency on a medication

Table 1: Evidence profile: Tapentadol vs oxycodone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tapentadol	Oxycodone	Relative (95% CI)	Absolute		
Developed shopping behaviour (follow-up 1 years)												
1	observational studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	88/42940 (0.2%)	0.9%	RR 0.24 (0.19 to 0.3) Adjusted OR[3]: 3.5 (2.84 to 4.4)	7 fewer per 1000 (from 6 fewer to 7 fewer)	⊕OOO VERY LOW	CRITICAL
Number of shopping episodes per subject (follow-up 1 years; Better indicated by lower values)												
1	observational studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	42940	112821	-	MD 0.02 lower (0.02 to 0.01 lower)	⊕OOO VERY LOW	CRITICAL

[1] 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.
[2] The majority of the evidence included an indirect population (downgrade by one increment)
[3] Adjusted odds ratio – controlling for gender, benzodiazepine use and type of payment at first opioid exposure using a conditional logistic regression.

1.1.2 Harms / side effects from stopping these medications over a short time frame

Table 2: Evidence profile: Opioids versus control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opioids	Control	Relative (95% CI)	Absolute		
Opioid vs control - no opioid withdrawal - COWS assessment 2-4 days after last intake of medication												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	61/72 (84.7%)	100%	RR 0.87 (0.77 to 0.99)	130 fewer per 1000 (from 10 fewer to 230 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Opioid vs control - no opioid withdrawal - COWS assessment at 4 days after last intake of medication												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	141/152 (92.8%)	89.8%	RR 1.04 (0.94 to 1.14)	36 more per 1000 (from 54 fewer to 126 more)	⊕⊕⊕O MODERATE	CRITICAL
Opioid vs control - no opioid withdrawal - COWS assessment 5+ days after last intake of medication												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	141/154 (91.6%)	91.6%	RR 1 (0.92 to 1.1)	0 fewer per 1000 (from 73 fewer to 92 more)	⊕⊕⊕O MODERATE	
Opioid vs control - mild or moderate opioid withdrawal - COWS assessment 2-4 days after last intake of medication												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/72 (15.3%)	0%	RR 4.04 (0.55 to 29.59)	150 more per 1000 (from 40 more to 270 more)	⊕OOO VERY LOW	CRITICAL
Opioid vs control - mild or moderate opioid withdrawal - COWS assessment at 4 days after last intake of medication												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/152 (7.2%)	10.2%	RR 0.69 (0.26 to 1.82)	32 fewer per 1000 (from 75 fewer to 82 more)	⊕OOO VERY LOW	CRITICAL
Opioid vs control - mild or moderate opioid withdrawal - COWS assessment 5+ days after last intake of medication												
1	randomised trials	serious[1]	very serious[3]	no serious indirectness	very serious[2]	none	13/154 (8.4%)	8.5%	RR 0.63 (0.05 to 8.48)	31 fewer per 1000 (from 81 fewer to 636 more)	⊕OOO VERY LOW	CRITICAL

1 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.

2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

3 Downgraded by 1 or 2 increments because of heterogeneity, I^2=75%, p=0.05.

Table 3: Evidence profile: Opioid versus opioid

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opioids	Control	Relative (95% CI)	Absolute		
Withdrawal syndrome												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/894 (1.5%)	0.9%	RR 1.62 (0.37 to 7.13)	6 more per 1000 (from 6 fewer to 55 more)	⊕OOO VERY LOW	CRITICAL
Tapentadol vs oxycodone - no opioid withdrawal - COWS assessment 2-4 days after last intake of medication												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	126/160 (78.8%)	79.6%	RR 1.01 (0.85 to 1.19)	8 more per 1000 (from 119 fewer to 151 more)	⊕⊕⊕O MODERATE	
Tapentadol vs oxycodone - no opioid withdrawal - COWS assessment at 4 days after last intake of medication												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/62 (95.2%)	91.1%	RR 1.04 (0.96 to 1.14)	36 more per 1000 (from 36 fewer to 128 more)	⊕⊕⊕O MODERATE	CRITICAL
Tapentadol vs oxycodone - no opioid withdrawal - COWS assessment 5+ days after last intake of medication												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	215/236 (91.1%)	84.9%	RR 1.1 (1.01 to 1.19)	85 more per 1000 (from 8 more to 161 more)	⊕⊕⊕O MODERATE	CRITICAL
Tapentadol vs oxycodone - mild or moderate opioid withdrawal - COWS assessment 2-4 days after last intake of medication												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	86/466 (18.5%)	27.3%	RR 0.70 (0.48 to 1.00)	82 fewer per 1000 (from 142 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
Tapentadol vs oxycodone - mild or moderate opioid withdrawal - COWS assessment 4 days after last intake of medication												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/62 (4.8%)	8.9%	RR 0.54 (0.15 to 1.97)	41 fewer per 1000 (from 76 fewer to 86 more)	⊕OOO VERY LOW	CRITICAL
Tapentadol vs oxycodone - mild or moderate opioid withdrawal - COWS assessment 5+ days after last intake of medication												
2	randomised trials	very serious[1]	very serious[4]	no serious indirectness	very serious[2]	none	21/236 (8.9%)	15.1%	RR 0.33 (0.04 to 2.72)	101 fewer per 1000 (from 145 fewer to 260 more)	⊕OOO VERY LOW	CRITICAL
Drug withdrawal syndrome												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/894 (1%)	0.5%	RR 2.24 (0.29 to 17.63)	95 fewer per 1000 (from 146 fewer to 465 more)	⊕OOO VERY LOW	CRITICAL

[1] 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.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 4: Evidence profile: Z-drugs versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Z-drugs**	**Control**	**Relative (95% CI)**	**Absolute**		
Rebound insomnia – proportion of patients with a lower self-reported total sleep time - Run out phase - day 1 (follow-up 1 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/67 (19.4%)	6.4%	RR 3.06 (1.33 to 7)	132 more per 1000 (from 21 more to 384 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Rebound insomnia - proportion of patients with a lower self-reported total sleep time - Run out phase - day 2												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/67 (7.5%)	5.6%	RR 1.34 (0.44 to 4.07)	19 more per 1000 (from 31 fewer to 172 more)	⊕⊕OO LOW	CRITICAL
Rebound insomnia - proportion of patients with a lower self-reported total sleep time - Run out phase - day 3												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/67 (7.5%)	4%	RR 1.88 (0.56 to 6.27)	35 more per 1000 (from 18 fewer to 211 more)	⊕⊕OO LOW	CRITICAL
Rebound insomnia - proportion of patients with a lower self-reported time to sleep onset - Run out phase - day 1												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	12/67 (17.9%)	6.4%	RR 2.82 (1.21 to 6.56)	116 more per 1000 (from 13 more to 356 more)	⊕⊕⊕O MODERATE	CRITICAL
Rebound insomnia – proportion of patients with a lower self-reported time to sleep onset - Run out phase - day 2												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/67 (6%)	3.2%	RR 1.88 (0.49 to 7.28)	28 more per 1000 (from 16 fewer to 201 more)	⊕⊕OO LOW	CRITICAL
Rebound insomnia -– proportion of patients with a lower self-reported time to sleep onset - Run out phase - day 3												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/67 (7.5%)	4%	RR 1.88 (0.56 to 6.27)	35 more per 1000 (from 18 fewer to 211 more)	⊕⊕OO LOW	CRITICAL

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 5: Evidence profile: Benzodiazepines versus gabapentinoids

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzodiazepines versus gabapentinoids	Control	Relative (95% CI)	Absolute		
Mean change in Physician Withdrawal Checklist (PWC) - higher dose gab - 1 week after taper (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	58	49	-	MD 0.4 lower (3.09 lower to 2.29 higher)	⊕⊕OO LOW	CRITICAL
Mean change in PWC - higher dose gab - 2 week after taper (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	44	-	MD 0.5 higher (1.92 lower to 2.92 higher)	⊕⊕OO LOW	CRITICAL
Mean change in PWC after treatment period 2 - higher dose gab - 2 week after taper (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	106	93	-	MD 0.6 higher (1.08 lower to 2.28 higher)	⊕⊕OO LOW	CRITICAL
Mean change in PWC after treatment period 2 - higher dose gab - 1 week after taper (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	109	99	-	MD 1.3 lower (2.92 lower to 0.32 higher)	⊕⊕OO LOW	CRITICAL
Discontinuation emergent signs and syndromes (DESS) after period 1												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	38/110 (34.5%)	32.7%	RR 1.06 (0.66 to 1.69)	20 more per 1000 (from 111 fewer to 226 more)	⊕OOO VERY LOW	CRITICAL
DESS after period 2												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	55/203 (27.1%)	28%	RR 0.97 (0.66 to 1.42)	8 fewer per 1000 (from 95 fewer to 118 more)	⊕OOO VERY LOW	CRITICAL
Anxiety after period 1												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/110 (2.7%)	3.9%	RR 0.71 (0.12 to 4.12)	11 fewer per 1000 (from 34 fewer to 122 more)	⊕OOO VERY LOW	CRITICAL
Anxiety after period 2												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/203 (5.4%)	8%	RR 0.68 (0.28 to 1.63)	26 fewer per 1000 (from 58 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL
Dizziness after period 1												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/110 (2.7%)	0%	Peto OR 4.44 (0.39 to 50.92)	30 more (from 10 fewer to per 1000 to 70 more)	⊕OOO VERY LOW	CRITICAL
Headache after period 1												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/110 (6.4%)	1.9%	RR 3.31 (0.42 to 26.2)	44 more per 1000 (from 11 fewer to 479 more)	⊕OOO VERY LOW	CRITICAL
Headache after period 2												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/203 (3.9%)	2%	RR 1.97 (0.43 to 9.11)	19 more per 1000 (from 11 fewer to 162 more)	⊕OOO VERY LOW	CRITICAL
Insomnia after period 1												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/110 (9.1%)	19.2%	RR 0.47 (0.21 to 1.06)	102 fewer per 1000 (from 152 fewer to 12 more)	⊕OOO VERY LOW	CRITICAL
Insomnia after period 2												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21/203 (10.3%)	6%	RR 1.72 (0.72 to 4.14)	43 more per 1000 (from 17 fewer to 188 more)	⊕OOO VERY LOW	CRITICAL
Nausea after period 1												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/110 (6.4%)	3.9%	RR 1.65 (0.36 to 7.69)	25 more per 1000 (from 25 fewer to 261 more)	⊕OOO VERY LOW	CRITICAL

Rebound anxiety after treatment period 1											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/110 (3.6%)	4.2%	RR 0.87 (0.17 to 4.6)	5 fewer per 1000 (from 35 fewer to 151 more)	⊕OOO VERY LOW	CRITICAL
Rebound anxiety after treatment period 2											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/203 (2%)	6%	RR 0.33 (0.09 to 1.14)	40 fewer per 1000 (from 55 fewer to 8 more)	⊕OOO VERY LOW	CRITICAL

1 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.
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 6: Evidence profile: Antidepressants versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antidepressants**	**Control**	**Relative (95% CI)**	**Absolute**		
Rebound insomnia (after discontinuation)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/148 (2.7%)	1.4%	RR 1.97 (0.22 to 17.34)	14 more per 1000 (from 11 fewer to 229 more)	⊕OOO VERY LOW	CRITICAL
Benzodiazepine Withdrawal symptom questionnaire criteria BWSQ												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/148 (0.68%)	1.4%	RR 0.49 (0.03 to 7.77)	7 fewer per 1000 (from 14 fewer to 95 more)	⊕OOO VERY LOW	CRITICAL
Suicide attempts (one study after discontinuation; other study time point not reported)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/605 (0.33%)	0.3%	Peto OR 1.02 (0.09 to 12.12)	0 fewer per 1000 (from 10 fewer to 10 more)[6]	⊕⊕OO LOW	CRITICAL
Depression (after discontinuation; except one study time point not reported)												
3	randomised trials	serious[1]	serious[3]	no serious indirectness	very serious[2]	none	16/1044 (1.5%)	0.6%	RR 1.16 (0.15 to 8.76)	1 more per 1000 (from 5 fewer to 47 more)	⊕OOO VERY LOW	CRITICAL

Suicide ideation (after discontinuation in two studies, one during study and other time point not reported)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/1498 (0.47%)	0%	Peto OR 4.24 (0.82 to 21.90)	0 more per 10000 (from 0 fewer to 10 more)[6]	⊕⊕OO LOW	CRITICAL
DESS - taper week 1 (Better indicated by lower values)												
3	randomised trials	serious[1]	serious[4]	no serious indirectness	serious[2]	none	793	425	-	MD 0.56 higher (0.01 lower to 1.13 higher)	⊕OOO VERY LOW	CRITICAL
DESS - taper week 2 (Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	694	359	-	MD 0.48 higher (0.18 to 0.77 higher)	⊕⊕⊕O MODERATE	CRITICAL
DESS - taper week 3 (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32	8	-	MD 6 lower (9.56 to 2.45 lower)	⊕⊕OO LOW	CRITICAL
Vertigo (after discontinuation)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/324 (3.7%)	0%	Peto OR 4.63 (1.37 to 15.6)	40 more per 1000 (from 10 more to 60 more)[6]	⊕⊕OO LOW	CRITICAL
Change after discontinuation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	14/53 (26.4%)	20.8%	RR 1.27 (0.64 to 2.54)	56 more per 1000 (from 75 fewer to 320 more)	⊕⊕OO LOW	CRITICAL
Discontinuation syndrome (after discontinuation)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	9/53 (17%)	9.4%	RR 1.8 (0.65 to 5.02)	75 more per 1000 (from 33 fewer to 378 more)	⊕⊕OO LOW	CRITICAL
Total taper/post study emergent AE												
9	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	600/1728 (34.7%)	20.5%	RR 1.63 (1.44 to 1.84)	129 more per 1000 (from 90 more to 172 more)	⊕⊕OO LOW	CRITICAL
Vomiting (after discontinuation)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/149 (0.67%)	1.9%	RR 0.35 (0.04 to 3.34)	12 fewer per 1000 (from 18 fewer to 44 more)	⊕OOO VERY LOW	CRITICAL

Dizziness (after discontinuation)											
7	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	117/1457 (8%)	2.5%	RR 4.86 (2.91 to 8.14)	97 more per 1000 (from 48 more to 179 more)	⊕⊕OO LOW	CRITICAL
Nausea (after discontinuation)											
6	randomised trials	very serious[1]	serious[5]	no serious indirectness	no serious imprecision	none	103/1454 (7.1%)	2.5%	RR 2.78 (1.36 to 5.69)	45 more per 1000 (from 9 more to 117 more)	⊕OOO VERY LOW	CRITICAL
Headache (after discontinuation)											
5	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	83/1390 (6%)	4.4%	RR 1.39 (0.96 to 2)	17 more per 1000 (from 2 fewer to 44 more)	⊕OOO VERY LOW	CRITICAL
Insomnia (after discontinuation)											
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	30/663 (4.5%)	1.9%	RR 1.37 (0.75 to 2.52)	7 more per 1000 (from 5 fewer to 29 more)	⊕OOO VERY LOW	CRITICAL
Diarrhoea (after discontinuation)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/149 (2.7%)	2.6%	RR 1.05 (0.27 to 4.14)	1 more per 1000 (from 19 fewer to 82 more)	⊕OOO VERY LOW	CRITICAL
Serious adverse events during taper											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/479 (0.21%)	0.53%	RR 0.40 (0.04 to 4.03)	0 fewer per 1000 (from 10 fewer to 10 more) [6]	⊕OOO VERY LOW	CRITICAL
Withdrawal syndrome (after discontinuation)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	117/455 (25.7%)	11.9%	RR 2.2 (1.4 to 3.46)	143 more per 1000 (from 48 more to 293 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Upper respiratory tract infection (after discontinuation)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	17/455 (3.7%)	1.3%	RR 3.17 (0.75 to 13.44)	28 more per 1000 (from 3 fewer to 162 more)	⊕⊕OO LOW	CRITICAL

1 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.

2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

3 Downgraded by one increment because heterogeneity, I^2=65%, p=0.06, unexplained by subgroup analysis.

4 Downgraded by one increment because heterogeneity, I^2=72%, p=0.01, unexplained by subgroup analysis.

5 Downgraded by one increment because heterogeneity, I^2=53%, p=0.05, unexplained by subgroup analysis.

6 Zero events in one or more arms so absolute effect calculated from risk difference.
7 One study reported suicide ideation with depression.

Table 7: Evidence profile: Antidepressants versus antidepressants

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antidepressant	Antidepressant	Relative (95% CI)	Absolute		
Suicide ideation - antidepressant v antidepressant (time point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/301 (0.66%)	1.3%	RR 0.5 (0.07 to 3.55)	6 fewer per 1000 (from 12 fewer to 33 more)	⊕OOO VERY LOW	CRITICAL

1 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.
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

1.1.3 Short versus long term opioid use

Table 8: Evidence profile: Short versus long term opioid use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long term opioid use compared to short term opioid use	Control	Relative (95% CI)	Absolute		
Depression												
1	observational studies	very serious[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	-	0%	HR 1.53 (1.29 to 1.81)	-	⊕OOO VERY LOW	CRITICAL

Alcohol abuse												
1	observational studies	very serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	-	0%	HR 1.38 (0.9 to 2.12)	-	⊕OOO VERY LOW	CRITICAL
Opioid abuse												
1	observational studies	very serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	-	0%	HR 3.97 (0.87 to 18.12)	-	⊕OOO VERY LOW	CRITICAL
Other substance abuse												
1	observational studies	very serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	-	0%	HR 1.81 (0.92 to 3.56)	-	⊕OOO VERY LOW	CRITICAL
Opioid overdose												
1	observational studies	very serious[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	-	0%	HR 5.12 (1.63 to 16.08)	-	⊕OOO VERY LOW	CRITICAL
Other substance overdose												
1	observational studies	very serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	-	0%	HR 1.82 (0.92 to 3.6)	-	⊕OOO VERY LOW	CRITICAL
Opioid dependence												
1	observational studies	very serious[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	-	0%	HR 2.85 (1.54 to 5.27)	-	⊕OOO VERY LOW	CRITICAL
Other substance dependence												
1	observational studies	very serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	-	0%	HR 1.73 (1.21 to 2.47)	-	⊕OOO VERY LOW	CRITICAL
Mortality												

1	observational studies	very serious[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	-	0%	HR 0.99 (0.84 to 1.17)	-	⊕OOO VERY LOW	CRITICAL

1 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.
2 Downgraded by 1 or 2 increments because long term use used as proxy for dependence. Short term use population includes children. Some opioids received are not available on the NHS.
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

1.1.4 Short versus long term withdrawal

Table 9: Evidence profile: 3 day taper vs 14 day taper of antidepressants

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Short taper – 3 day**	**Longer taper – 14 day**	**Relative (95% CI)**	**Absolute**		
DESS symptoms												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/15 (46.7%)	46.2%	RR 1.01 (0.46 to 2.25)	5 more per 1000 (from 249 fewer to 577 more)	⊕OOO VERY LOW	CRITICAL

1 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.
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 10: Evidence profile: abrupt vs taper of antidepressant withdrawal (managed taper of 25mg/d for one week)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Abrupt**	**Taper**	**Relative (95% CI)**	**Absolute**		
DESS score												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	31/146 (21.2%)	21.6%	RR 0.98 (0.63 to 1.54)	4 fewer per 1000 (from 80 fewer to 117 more)	⊕OOO VERY LOW	CRITICAL

Taper/post-therapy-emergent adverse events												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	75/146 (51.4%)	38.9%	RR 1.32 (1.02 to 1.72)	124 more per 1000 (from 8 more to 280 more)	⊕OOO VERY LOW	CRITICAL
Headache												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/146 (13%)	6.5%	RR 2.01 (0.94 to 4.29)	66 more per 1000 (from 4 fewer to 214 more)	⊕OOO VERY LOW	CRITICAL
Nausea												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/146 (6.2%)	4.3%	RR 1.43 (0.52 to 3.91)	18 more per 1000 (from 21 fewer to 125 more)	⊕OOO VERY LOW	CRITICAL
Dizziness												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/146 (9.6%)	5.8%	RR 1.67 (0.72 to 3.85)	39 more per 1000 (from 16 fewer to 165 more)	⊕OOO VERY LOW	CRITICAL
Suicide ideation												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/146 (0.68%)	0.7%	RR 0.95 (0.06 to 15.07)	0 fewer per 1000 (from 7 fewer to 98 more)	⊕OOO VERY LOW	CRITICAL
Suicide attempts												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/146 (0.68%)	0%	Peto OR 7.04 (0.14 to 355.37)	10 fewer per 1000 (from 10 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL

1 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.

2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 11: Evidence profile: rapid (1-7 days) versus gradual withdrawal of antidepressants (2 weeks or more)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rapid withdrawal	Gradual withdrawal	Relative (95% CI)	Absolute		
Time to first new illness												
1	observational studies	very serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	-	0%	HR 1.5 (1.14 to 1.97)	-	⊕OOO VERY LOW	CRITICAL

1 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.

2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

3 Downgraded by 1 increment because the majority of the evidence included drugs grouped together so they were not all listed and could have included drugs not listed on the included list.

Table 12: Evidence profile: Abrupt withdrawal vs tapered withdrawal of antidepressants (50 mg alternate days for two weeks)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abrupt	Taper (alternate)	Relative (95% CI)	Absolute		
DESS after taper week 3 (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	59	59	-	MD 1.44 higher (0.04 lower to 2.92 higher)	⊕⊕OO LOW	CRITICAL
Any adverse events												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	53/101 (52.5%)	52%	RR 1.01 (0.78 to 1.31)	5 more per 1000 (from 114 fewer to 161 more)	⊕⊕OO LOW	CRITICAL
Asthenia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/101 (7.9%)	4.9%	RR 1.62 (0.55 to 4.77)	30 more per 1000 (from 22 fewer to 185 more)	⊕OOO VERY LOW	CRITICAL
Diarrhoea												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/101 (5%)	5.9%	RR 0.84 (0.27 to 2.67)	9 fewer per 1000 (from 43 fewer to 99 more)	⊕OOO VERY LOW	CRITICAL
Dizziness												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/101 (14.9%)	11.8%	RR 1.26 (0.62 to 2.56)	31 more per 1000 (from 45 fewer to 184 more)	⊕OOO VERY LOW	CRITICAL
Emotional lability												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/101 (4%)	5.9%	RR 0.67 (0.2 to 2.31)	19 fewer per 1000 (from 47 fewer to 77 more)	⊕OOO VERY LOW	CRITICAL
Headache												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/101 (8.9%)	11.8%	RR 0.76 (0.33 to 1.72)	28 fewer per 1000 (from 79 fewer to 85 more)	⊕OOO VERY LOW	CRITICAL
Hypertension												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/101 (2%)	5.9%	RR 0.34 (0.07 to 1.63)	39 fewer per 1000 (from 55 fewer to 37 more)	⊕OOO VERY LOW	CRITICAL
Infection												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/101 (2%)	5.9%	RR 0.34 (0.07 to 1.63)	39 fewer per 1000 (from 55 fewer to 37 more)	⊕OOO VERY LOW	CRITICAL
Insomnia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/101 (5%)	5.9%	RR 0.84 (0.27 to 2.67)	9 fewer per 1000 (from 43 fewer to 99 more)	⊕OOO VERY LOW	CRITICAL
Nausea												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/101 (9.9%)	8.8%	RR 1.12 (0.48 to 2.65)	11 more per 1000 (from 46 fewer to 145 more)	⊕OOO VERY LOW	CRITICAL

Sweating												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/101 (3%)	6.9%	RR 0.43 (0.12 to 1.63)	39 fewer per 1000 (from 61 fewer to 43 more)	⊕OOO VERY LOW	CRITICAL
Vasodilation												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/101 (6.9%)	5.9%	RR 1.18 (0.41 to 3.38)	11 more per 1000 (from 35 fewer to 140 more)	⊕OOO VERY LOW	CRITICAL

1 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.
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 13: Evidence profile: Abrupt withdrawal vs tapered withdrawal of antidepressants (50 mg for one week and then placebo for one week)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Abrupt**	**Taper (50 then placebo)**	**Relative (95% CI)**	**Absolute**		
DESS after taper week 3 (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	47	59	-	MD 0.08 lower (1.3 lower to 1.14 higher)	⊕⊕⊕O MODERATE	CRITICAL
Any adverse events												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	43/87 (49.4%)	52%	RR 0.95 (0.72 to 1.26)	26 fewer per 1000 (from 146 fewer to 135 more)	⊕OOO VERY LOW	CRITICAL
Asthenia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/87 (2.3%)	4.9%	RR 0.47 (0.09 to 2.36)	26 fewer per 1000 (from 45 fewer to 67 more)	⊕OOO VERY LOW	CRITICAL
Diarrhoea												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/87 (5.7%)	5.9%	RR 0.98 (0.31 to 3.09)	1 fewer per 1000 (from 41 fewer to 123 more)	⊕OOO VERY LOW	CRITICAL
Dizziness												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/87 (11.5%)	11.8%	RR 0.98 (0.44 to 2.15)	2 fewer per 1000 (from 66 fewer to 136 more)	⊕OOO VERY LOW	CRITICAL
Emotional lability												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/87 (4.6%)	5.9%	RR 0.78 (0.23 to 2.68)	13 fewer per 1000 (from 45 fewer to 99 more)	⊕OOO VERY LOW	CRITICAL
Headache												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/87 (8%)	11.8%	RR 0.68 (0.28 to 1.66)	38 fewer per 1000 (from 85 fewer to 78 more)	⊕OOO VERY LOW	CRITICAL
Hypertension												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/87 (2.3%)	5.9%	RR 0.39 (0.08 to 1.89)	36 fewer per 1000 (from 54 fewer to 53 more)	⊕OOO VERY LOW	CRITICAL
Infection												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/87 (3.4%)	5.9%	RR 0.59 (0.15 to 2.28)	24 fewer per 1000 (from 50 fewer to 76 more)	⊕OOO VERY LOW	CRITICAL
Insomnia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/87 (5.7%)	5.9%	RR 0.98 (0.31 to 3.09)	1 fewer per 1000 (from 41 fewer to 123 more)	⊕OOO VERY LOW	CRITICAL
Nausea												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/87 (8%)	8.8%	RR 0.91 (0.35 to 2.35)	8 fewer per 1000 (from 57 fewer to 119 more)	⊕OOO VERY LOW	CRITICAL
Sweating												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/87 (4.6%)	6.9%	RR 0.67 (0.2 to 2.21)	23 fewer per 1000 (from 55 fewer to 83 more)	⊕OOO VERY LOW	CRITICAL
Vasodilation												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/87 (1.1%)	5.9%	RR 0.2 (0.02 to 1.59)	47 fewer per 1000 (from 58 fewer to 35 more)	⊕OOO VERY LOW	CRITICAL

1 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.

2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 14: Evidence profile: Abrupt withdrawal vs tapered withdrawal of antidepressant (50 mg for one week and then 25 mg for one week)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abrupt	Taper (50 then 25)	Relative (95% CI)	Absolute		
DESS after taper week 3 (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	57	59	-	MD 2.33 higher (0.62 to 4.04 higher)	⊕⊕OO LOW	CRITICAL
Any adverse events												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	47/94 (50%)	52%	RR 0.96 (0.73 to 1.27)	21 fewer per 1000 (from 140 fewer to 140 more)	⊕OOO VERY LOW	CRITICAL
Asthenia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/94 (0%)	4.9%	Peto OR 0.14 (0.02 to 0.83)	42 fewer per 1000 (from 8 fewer to 48 fewer) [3]	⊕⊕OO LOW	CRITICAL
Diarrhoea												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/94 (3.2%)	5.9%	RR 0.54 (0.14 to 2.11)	27 fewer per 1000 (from 51 fewer to 65 more)	⊕OOO VERY LOW	CRITICAL
Dizziness												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/94 (8.5%)	11.8%	RR 0.72 (0.31 to 1.69)	33 fewer per 1000 (from 81 fewer to 81 more)	⊕OOO VERY LOW	CRITICAL
Emotional lability												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/94 (1.1%)	5.9%	RR 0.18 (0.02 to 1.47)	48 fewer per 1000 (from 58 fewer to 28 more)	⊕OOO VERY LOW	CRITICAL
Headache												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/94 (7.4%)	11.8%	RR 0.63 (0.26 to 1.54)	44 fewer per 1000 (from 87 fewer to 64 more)	⊕OOO VERY LOW	CRITICAL
Hypertension												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/94 (0%)	5.9%	Peto OR 0.14 (0.03 to 0.7)	60 fewer per 1000 (from 110 fewer to 10 fewer) [3]	⊕⊕⊕O MODERATE	CRITICAL
Infection												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/94 (2.1%)	5.9%	RR 0.36 (0.07 to 1.75)	38 fewer per 1000 (from 55 fewer to 44 more)	⊕OOO VERY LOW	CRITICAL
Insomnia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/94 (5.3%)	5.9%	RR 0.9 (0.29 to 2.87)	6 fewer per 1000 (from 42 fewer to 110 more)	⊕OOO VERY LOW	CRITICAL
Nausea												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/94 (9.6%)	8.8%	RR 1.09 (0.45 to 2.62)	8 more per 1000 (from 48 fewer to 143 more)	⊕OOO VERY LOW	CRITICAL
Sweating												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/94 (2.1%)	6.9%	RR 0.31 (0.07 to 1.46)	48 fewer per 1000 (from 64 fewer to 32 more)	⊕OOO VERY LOW	CRITICAL
Vasodilation												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/94 (5.3%)	5.9%	RR 0.9 (0.29 to 2.87)	6 fewer per 1000 (from 42 fewer to 110 more)	⊕OOO VERY LOW	CRITICAL

1 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.

2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

3 Zero events in one or more arms so absolute effect calculated from risk difference.

1.2 Risk factors for dependence, discontinuation and short term withdrawal – Modified GRADE

1.2.1 Opioids

Table 15: Risk factor: Age (referent: 35-44) – Outcome: Long-term opioid use (12 months)

Quality assessment							Adjusted effect Age (referent: 35-44)	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	
Long-term opioid use (12 months) – Age <24 years								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 0.96 (0.36 to 2.56)	VERY LOW
Long-term opioid use (12 months) – Age 25-34 years								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 0.92 (0.5 to 1.69)	VERY LOW
Long-term opioid use (12 months) – Age 45-54 years								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 1.51 (0.87 to 2.62)	VERY LOW
Long-term opioid use (12 months) – Age ≥55 years								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 1.15 (0.51 to 2.59)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 16: Risk factor: Age <65 years – Outcome: Dependence diagnosis

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
life-time dependence diagnosis								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.8 (1.83 to 4.28)	LOW
current dependence diagnosis								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.33 (1.55 to 3.5)	LOW
Severity of lifetime dependence								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.7 (1.68 to 4.34)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 17: Risk factor: Age (referent: 18-44) – Outcome: Long-term opioid use (12 months)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long-term opioid use (12 months) - 45-54								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.65 (1.54 to 1.77)	LOW
Long-term opioid use (12 months) - 55-64								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.75 (1.63 to 1.88)	LOW

Long-term opioid use (12 months) - 65-74								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	none	OR 1.47 (1.36 to 1.59)	LOW
Long-term opioid use (12 months) - ≥75								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.45 (2.27 to 2.64)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 18: Risk factor: Sex (referent: female) – Outcome: Long-term opioid use (12 months/persistent)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long-term opioid use (12 months) - Long-term opioid use								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 1.28 (0.79 to 2.07)	VERY LOW
Long-term opioid use (12 months) - Persistent opioid use								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.04 (0.99 to 1.09)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 19: Risk factor: Ethnicity (referent: white) - – Outcome: Long-term opioid use (12 months)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long-term opioid use (12 months) – Hispanic								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 0.42 (0.19 to 0.93)	LOW
Long-term opioid use (12 months) – Other								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 0.73 (0.37 to 1.44)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 20: Risk factor: Education level (referent: High school) – Outcome: Long-term opioid use (12 months) (also reported by drinking status)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long-term opioid use (12 months) - < high school								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 0.69 (0.34 to 1.4)	VERY LOW
Long-term opioid use (12 months) - vocational/some college								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 0.9 (0.55 to 1.47)	VERY LOW
Long-term opioid use (12 months) - college graduate								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 0.58 (0.2 to 1.68)	VERY LOW

Opioid misuse (referent < high school) - Non-unhealthy drinkers								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 0.53 (0.21 to 1.34)	VERY LOW
Opioid misuse (referent < high school) - Unhealthy drinkers								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 1.39 (0.25 to 7.73)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 21: Risk factor: Rural living (referent: urban living) – Outcome: Long-term opioid use (12 months) (reported by drinking status)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Opioid misuse - Non-unhealthy drinkers								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 0.39 (0.16 to 0.95)	LOW
Opioid misuse - Unhealthy drinkers								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	none	OR 0.76 (0.12 to 4.81)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 22: Risk factor: Employment (referent: no employment) – Outcome: Long-term opioid use (12 months) (reported by drinking status)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Opioid misuse - Non-unhealthy drinkers								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 1.5 (0.53 to 4.25)	VERY LOW
Opioid misuse - Unhealthy drinkers								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 1.84 (0.31 to 10.92)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 23: Risk factor: First quarter morphine equivalent dose (referent: <1-899 mg) – Outcome: Long term opioid use (12 months)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long-term opioid use (12 months) - 900-1799 mg								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 4.01 (2.23 to 7.21)	LOW
Long-term opioid use (12 months) - 1800-3599 mg								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 5.46 (2.82 to 10.57)	LOW
Long-term opioid use (12 months) - >3600 mg								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 6.25 (2.91 to 13.42)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 24: Risk factor: Total oral morphine equivalent dose (referent: <250mg) – Outcome: Long term opioid use (12 months)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long-term opioid use (12 months) - 250-499 mg								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.02 (1.9 to 2.15)	LOW
Long-term opioid use (12 months) - 500-749 mg								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.27 (2.05 to 2.51)	LOW
Long-term opioid use (12 months) - ≥750 mg								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 3.68 (3.34 to 4.05)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 25: Risk factor: Highest quintile for opioid use (number of opioid orders over past 3 years) – Outcome: Life-time dependence diagnosis

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
life-time dependence diagnosis								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.75 (1.18 to 2.6)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 26: Risk factor: >90 days opioid treatment (Referent <90 days) – Outcome abuse / overdose

Quality assessment							Adjusted effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)		
Opioid abuse									
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	HR 3.97 (0.87 to 18.12)	VERY LOW	
Opioid overdose									
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	HR 5.12 (1.63 to 16.08)	LOW	
Opioid dependence									
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	HR 2.86 (1.54 to 5.31)	LOW	
Alcohol abuse									
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	HR 1.38 (0.9 to 2.12)	VERY LOW	
Other substance abuse									
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	HR 1.81 (0.92 to 3.56)	VERY LOW	
Non-opioid overdose									
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	HR 1.82 (0.92 to 3.6)	VERY LOW	
Other substance (non-opioid) dependence									
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	HR 1.73 (1.21 to 2.47)	LOW	
Depression									

1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	HR 1.53 (1.29 to 1.81)	LOW
Death								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	HR 0.99 (0.84 to 1.17)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 27: Risk factor: History of opioid abuse (referent: no history) – Outcome: dependence diagnosis

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
life-time dependence diagnosis								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 3.95 (2.39 to 6.53)	LOW
current dependence diagnosis								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 3.81 (2.56 to 5.67)	LOW
Severity of lifetime dependence								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 6.07 (4.05 to 9.1)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 28: Risk factor: History of high dependence severity (referent: no history) - Outcome: dependence diagnosis

Quality assessment							Adjusted effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	
life-time dependence diagnosis								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 3 (1.58 to 5.7)	LOW
current dependence diagnosis								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.85 (1.38 to 2.48)	LOW
Severity of lifetime dependence								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 3.43 (2.29 to 5.14)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 29: Risk factor: History of illicit drug use (referent: no history) - Outcome: dependence diagnosis

Quality assessment							Adjusted effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	
Severity of lifetime dependence								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 0.75 (0.59 to 0.95)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 30: Risk factor: History of illicit drug use (referent: no history) – Outcome: opioid misuse (reported by drinking status)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Opioid misuse - Non-unhealthy drinkers								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 5.2 (1.47 to 18.4)	LOW
Opioid misuse - Unhealthy drinkers								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 12.14 (1.64 to 89.87)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 31: Risk factor: History of substance use disorder (referent: no SUD) - Outcome: illicit drug use (problematic opioid use*)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Severity of lifetime dependence								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 2.50 (0.98 to 6.38)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

*Problematic opioid use was defined as a positive urine toxicology for substances not prescribed by a physician (amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, methadone, opiates phencyclidine, propoxyphene) or a current substance abuse or dependence diagnosis for any substance.

Table 32: Risk factor: History of substance use disorder (referent: no SUD) – Outcome: dependence

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Dependence - Borrowed pain medication								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 6.62 (1.4 to 31.3)	LOW
Dependence - Need to take more than prescribed								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.38 (0.6 to 3.17)	LOW
Dependence - Asked for prescription increase								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	serious [2]	None	OR 1.12 (0.5 to 2.51)	VERY LOW
Dependence - Early refill								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 3.86 (1.5 to 9.93)	LOW
Dependence - Misplaced prescription								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	serious [2]	None	OR 0.78 (0.2 to 3.04)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 33: Risk factor: History of substance abuse treatment (referent: no treatment) – Outcome: Severity of lifetime dependence

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Severity of lifetime dependence								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.93 (1.51 to 2.47)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 34: Risk factor: Alcohol dependence (referent: no alcohol dependence) – Outcome: Long term / persistent opioid use

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long-term opioid use (12 months) - Long-term opioid use (12 months)								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 2.17 (0.79 to 5.96)	VERY LOW
Long-term opioid use (12 months) - Persistent opioid use during 12 months								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.18 (0.84 to 1.66)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 35: Nicotine dependence (referent: no nicotine dependence) - Outcome: persistent opioid use during 12 months

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Persistent opioid use during 12 months								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.65 (1.48 to 1.84)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 36: Risk factor: Pain interferes with life/work – Outcome: opioid misuse

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Lifetime dependence diagnosis								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.94 (1.21 to 3.11)	LOW
Current dependence diagnosis								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	serious [2]	None	OR 1.54 (0.94 to 2.52)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 37: Risk factor: Pain interferes with life/work – Outcome: opioid misuse (reported by drinking status)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Opioid misuse - Non-unhealthy drinkers								
1	Observational studies	Very serious1	No serious inconsistency	No serious indirectness	serious 2	None	OR 1.37 (0.86 to 2.18)	VERY LOW
Opioid misuse - Unhealthy drinkers								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	serious [2]	None	OR 1.31 (0.53 to 3.24)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 38: Risk factor: Pain intensity at baseline on 0-10 scale (referent 0-4) – Outcome: Long-term opioid use (12 months)

Quality assessment							Absolute effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long-term opioid use (12 months) - 5-7								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 5.88 (1.71 to 20.22)	LOW
Long-term opioid use (12 months) - 8-10								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 9.41 (2.69 to 32.92)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 39: Risk factor: Back injury severity (referent: mild sprain) – Outcome: long term opioid use (12 months)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long-term opioid use (12 months) - severe sprain								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	OR 1.06 (0.52 to 2.16)	VERY LOW
Long-term opioid use (12 months) – radiculopathy								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 3.17 (1.83 to 5.49)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 40: Risk factor: Recovery expectations (referent: very high) – Outcome: long term opioid use (12 months)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long-term opioid use (12 months) – High								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	OR 1.33 (0.71 to 2.49)	VERY LOW
Long-term opioid use (12 months) – Low								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.88 (1.09 to 3.24)	LOW
Long-term opioid use (12 months) - Don't know								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 3.05 (1.07 to 8.69)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 41: Risk factor: Positive screen for antisocial personality (referent: negative screen) – Outcome: Dependence diagnosis / severity

Quality assessment							Adjusted effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	
life-time dependence diagnosis								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.44 (1.09 to 1.9)	LOW
Severity of lifetime dependence								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.61 (1.19 to 2.18)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 42: Risk factor: History of major depression (referent: no history) – Outcome: Current dependence diagnosis

Quality assessment							Adjusted effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	
current dependence diagnosis								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.29 (1.05 to 1.58)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 43: Risk factor: Current use of psychotropic medications (referent: no use) - Outcome: Dependence diagnosis / severity

Quality assessment							Adjusted effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	
current dependence diagnosis								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.73 (1.21 to 2.47)	LOW
Severity of lifetime dependence								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.53 (1.08 to 2.17)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 44: Risk factor: Current non-substance related psychiatric disorder (referent: no psychiatric disorder) – Outcome: illicit drug use (problematic opioid use*)

Quality assessment							Adjusted effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	
illicit drug use								
1	Observational studies	Very serious1	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 3.1 (1.5 to 6.41)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

*Problematic opioid use was defined as a positive urine toxicology for substances not prescribed by a physician (amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, methadone, opiates phencyclidine, propoxyphene) or a current substance abuse or dependence diagnosis for any substance.

Table 45: Risk factor: Mental health on short form-36 (SF-36) subscale (referent: at or above population mean) – Outcome: long term opioid use (12 months)

Quality assessment							Adjusted effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	
Long-term opioid use (12 months) - 1-2 SD below mean								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 1.33 (0.66 to 2.68)	VERY LOW
Long-term opioid use (12 months) - <2 SD below mean								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 1.37 (0.67 to 2.8)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 46: Risk factor: Mental health diagnosis (referent: no diagnosis) – Outcome: high risk opioid behaviour (early opioid refills) / concurrent sedative hypnotics

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Early opioid refills - diagnosis without PTSD								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.5 (1.39 to 1.62)	LOW
Early opioid refills - PTSD ± other diagnosis								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.64 (1.53 to 1.76)	LOW
Concurrent sedative hypnotics - diagnosis without PTSD								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 3.23 (2.87 to 3.64)	LOW
Concurrent sedative hypnotics - PTSD ± other diagnosis								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 5.46 (4.91 to 6.07)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 47: Risk factor: Mental health diagnosis (referent: no diagnosis) – Outcome: persistent use over 12 months

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Early opioid refills - diagnosis without PTSD								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.01 (1.87 to 2.16)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 48: PTSD diagnosis (referent: no PTSD diagnosis) - opioid misuse (reported by drinking status)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Opioid misuse - Non-unhealthy drinkers								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	OR 2.32 (0.88 to 6.12)	VERY LOW
Opioid misuse - Unhealthy drinkers								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 9.77 (1.7 to 56.15)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 49: Risk factor: Depression (referent: no depression) – Outcome: prescription overuse / persistent use

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Prescription overuse								
1	Observational studies	Very serious[1]	No serious inconsistency	Serious[2]	Serious [3]	None	OR 1.13 (0.98 to 1.30)	VERY LOW
Persistent use								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.59 (1.52 to 1.66)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment due to intervention indirectness as not all of the participants were receiving opioids (only 80%)
[3]Downgraded by 1 increment if the 95% CI crossed the null line

Table 50: Risk factor: Depression (referent: no depression) – Outcome: opioid misuse (reported by drinking status)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Opioid misuse - Non-unhealthy drinkers								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 3.1 (1.23 to 7.81)	LOW
Opioid misuse - Unhealthy drinkers								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	OR 0.97 (0.15 to 6.27)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 51: Risk factor: Psychological catastrophising (referent: low catastrophising) – Outcome: long term opioid use (12 months)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long-term opioid use (12 months) – Moderate								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	OR 0.98 (0.51 to 1.88)	VERY LOW
Long-term opioid use (12 months) – High								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.11 (1.11 to 4.01)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 52: Risk factor: Function (Roland Morris Disability Questionnaire) (referent 0-12) – Outcome: long term opioid use (12 months)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long-term opioid use (12 months) - 13-17								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	OR 1.8 (0.76 to 4.26)	VERY LOW
Long-term opioid use (12 months) - 18-24								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.65 (1.2 to 5.85)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 53: Risk factor: Number of prescribed analgesics (continuous variable) – Outcome: Prescription overuse

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Prescription overuse								
1	Observational studies	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	OR 1.64 (1.03 to 2.62)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment because 20% of the sample were prescribed non-opioid analgesics
[3]Downgraded [2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 54: Risk factor: Prior/current medication use (referent: no use) – Outcome: long term opioid use (12 months)

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long-term opioid use (12 months) – Benzodiazepines								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.48 (1.41 to 1.55)	LOW
Long-term opioid use (12 months) – NSAIDs								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.22 (1.17 to 1.27)	LOW
Long-term opioid use (12 months) – Pregabalin								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.96 (1.83 to 2.1)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 55: Risk factor: Smoking (referent: no smoking) – Outcome: prescription overuse / long term opioid use

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Prescription overuse								
1	Observational studies	Very serious[1]	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	OR 2.74 (1.14 to 6.63)	VERY LOW
Long-term opioid use (12 months)								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [3]	None	OR 0.95 (0.6 to 1.5)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment because 20% of the sample were prescribed non-opioid analgesics[3]Downgraded by 1 increment if the 95% CI crossed the null line

Table 56: Risk factor: Passive coping (Vanderbilt Pain Management Index, VPMI; definition and referent unclear) – Outcome: Prescription overuse

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Prescription overuse								
1	Observational studies	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	OR 0.99 (0.91 to 1.07)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment because 20% of the sample were prescribed non-opioid analgesics
[3]Downgraded by 1 increment if the 95% CI crossed the null line

Table 57: Risk factor: Previous back injury (referent: no previous injury) – Outcome: Long term opioid use

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long-term opioid use (12 months)								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.4 (1.5 to 3.84)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

1.2.2 Benzodiazepines

Table 58: Risk factor: Race (referent: white) – Outcome: Benzodiazepine dependence

Quality assessment							Adjusted effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	
Benzodiazepine dependence – Black								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	HR 0.18 (0.15 to 0.21)	LOW
Benzodiazepine dependence – Latino								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	HR 0.2 (0.17 to 0.23)	LOW
Benzodiazepine dependence – Asian								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	HR 0.43 (0.25 to 0.74)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 59: Risk factor: Ethnicity (referent: White or other) – Outcome: Chronic sedative use >275 days

Quality assessment							Adjusted effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	
Chronic sedative use >275 days – Chinese								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 0.81 (0.76 to 0.86)	LOW
Chronic sedative use >275 days - South Asian								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 0.69 (0.63 to 0.76)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 60: Risk factor: Sex (referent female) – Outcome: Benzodiazepine dependence

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Benzodiazepine dependence – Male								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	HR 1.33 (0.55 to 3.21)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 61: Risk factor: Sex (referent female) – Outcome: Long term use

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long term use								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.41 (1.12-1.78)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 62: Risk factor: Sex (referent male) – Outcome dependence, defined as per figure

Quality assessment							Absolute effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Dependence (DSM-IV-TR)								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 3.00 (1.4-6.43)	LOW
Self-rated addiction								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Only reported as non-significant – no data available[2]	NS	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment
NS = not significant

Table 63: Risk factor: Age (referent: 18-24 years) – Outcome: Benzodiazepine dependence

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Benzodiazepine dependence - 25-34 years								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	HR 1.23 (0.35 to 4.31)	VERY LOW
Benzodiazepine dependence - 35-44 years								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	HR 0.66 (0.33 to 1.31)	VERY LOW
Benzodiazepine dependence - 45-54 years								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	HR 0.87 (0.37 to 2.06)	VERY LOW
Benzodiazepine dependence - 55-64 years								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	HR 1.08 (0.37 to 3.11)	VERY LOW
Benzodiazepine dependence - 65+ years								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	HR 1.47 (0.34 to 6.27)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 64: Risk factor: Age, years (referent: below 30) – Outcome: Long term use

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long term use - 30-39								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	OR 1.24 (0.77 to 2)	VERY LOW
Long term use - 40-64								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.89 (1.95 to 4.28)	LOW
Long term use - 65 or above								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 6.36 (4.18 to 9.68)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 65: Risk factor: Age, years (referent: 50-54) – Outcome: Chronic sedative use >275 days

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Chronic sedative use >275 days - 55-59								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.03 (0.99 to 1.07)	LOW
Chronic sedative use >275 days - 60-64								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.16 (1.11 to 1.21)	LOW
Chronic sedative use >275 days - 65-69								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.29 (1.24 to 1.34)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 66: Risk factor: Age, ≥ 75 years (referent: 65-74) – Outcome: dependence/addiction

Quality assessment							Adjusted effect	
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Dependence/Addiction - Dependence (DSM-IV-TR)								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Only reported as non-significant – no data available2	NS	VERY LOW
Dependence/Addiction - Self-rated addiction								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.7 (1.1 to 2.63)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment - Only reported as non-significant
NS = not significant

Table 67: Risk factor: Relationship status (referent: marriage-like relationship) – Outcome: Chronic sedative use >275 days

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Chronic sedative use >275 days - Single								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.04 (1 to 1.08)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 68: Risk factor: Neighbourhood urbanisation (referent: urban) – Outcome: Chronic sedative use >275 days

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Chronic sedative use >275 days - Mixed urban / rural								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.11 (1.08 to 1.14)	LOW
Chronic sedative use >275 days - Rural								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.06 (1 to 1.12)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 69: Risk factor: Population income quintile (referent: fifth quintile) - Outcome: Chronic sedative use >275 days

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Chronic sedative use >275 days - Lowest								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.29 (1.23 to 1.35)	LOW
Chronic sedative use >275 days - Second								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.23 (1.18 to 1.28)	LOW
Chronic sedative use >275 days - Third								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.16 (1.11 to 1.21)	LOW
Chronic sedative use >275 days – Fourth								

1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.08 (1.04 to 1.12)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 70: Risk factor: Mental health diagnosis (vs no diagnosis) – Outcome long term use

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long term use								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.87 (1.41 to 2.48)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 71: Risk factor: Mental health disorder diagnosis (vs no diagnosis) – Outcome: Benzodiazepine dependence

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Benzodiazepine dependence – Depression								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	HR 1.43 (0.99 to 2.08)	LOW
Benzodiazepine dependence – Anxiety								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	HR 1.6 (1.02 to 2.51)	LOW
Benzodiazepine dependence – Bipolar								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	HR 1.02 (0.69 to 1.51)	VERY LOW
Benzodiazepine dependence – PTSD								

1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	HR 0.91 (0.65 to 1.27)	VERY LOW
Benzodiazepine dependence - Sleeping disturbance								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	HR 0.69 (0.53 to 0.89)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 72: Risk factor: Mental health diagnoses; panic disorder or suicidal ideation (vs no diagnosis) – Outcome: dependence or addiction

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Panic disorder - Dependence (DSM-IV-TR)								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.6 (1 to 6.76)	LOW
Panic disorder - Self-rated addiction								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.5 (1.3 to 4.81)	LOW
Suicidal ideation - Dependence (DSM-IV-TR)								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 4.5 (1.4 to 14.46)	LOW
Suicidal ideation - Self-rated addiction								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Only reported as non-significant – no data available[2]	NS	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment due to insufficient reporting of data
NS = non-significant

Table 73: Risk factor: Diagnoses (referent: not stated) – Outcome: Chronic sedative use >275 days

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Chronic sedative use >275 days - Sleep problems								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.77 (1.68 to 1.86)	LOW

Chronic sedative use >275 days - Neurologic disorders, other								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.15 (1.05 to 1.26)	LOW
Chronic sedative use >275 days - Dementia and delirium								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.11 (1.03 to 1.2)	LOW
Chronic sedative use >275 days - Anxiety, neurosis								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.09 (1.06 to 1.12)	LOW
Chronic sedative use >275 days – Depression								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.51 (1.45 to 1.57)	LOW
Chronic sedative use >275 days - Psychological signs								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious	None	OR 1.1 (0.88 to 1.38)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 74: Risk factor: Cognitive functioning (mild impairment vs intact) – Outcome: dependence or addiction

Quality assessment							Absolute effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Mild impairment vs intact - Dependence (DSM-IV-TR)								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.5 (1.1 to 5.68)	LOW
Mild impairment vs intact - Self-rated addiction								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Only reported as non-significant – no data available[2]	NS	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment due to insufficient reporting of data
NS = not significant

Table 75: Risk factor: Number of physical diseases (referent: 1 disease) – Outcome: long term use

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long term use - 2								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 0.99 (0.7 to 1.4)	VERY LOW
Long term use - 3 or more								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.56 (1.02 to 2.39)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 76: Risk factor: Count of major aggregated diagnostic groups (ADGs) as a measure of overall health status (referent: 0 ADGs) – Outcome: Chronic sedative use >275 days

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Chronic sedative use >275 days - 1-2 ADGs								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.19 (1.16 to 1.22)	LOW
Chronic sedative use >275 days - 3+ ADGs								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.34 (1.28 to 1.4)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 77: Risk factor: Count of minor ADGs (referent: 0-1 minor ADGs) – Outcome: Chronic sedative use >275 days

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Chronic sedative use >275 days - 2-3 minor ADGs								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	OR 0.99 (0.93 to 1.05)	VERY LOW
Chronic sedative use >275 days - 4-5 minor ADGs								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious [2]	None	OR 1.04 (0.98 to 1.1)	VERY LOW
Chronic sedative use >275 days - 6+minor ADGs								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.08 (1.01 to 1.15)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 78: Risk factor: Number of benzodiazepine agents (referent: 1) – Outcome: Long term use

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long term use – 2								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.32 (1.59 to 3.39)	LOW
Long term use - 3 or more								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 4.55 (2.85 to 7.26)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 79: Risk factor: Benzodiazepine half-life (referent: long acting) – Outcome: Long term use

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long term use - Short acting								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 3.02 (1.64 to 5.56)	LOW
Long term use – Both								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 3.39 (1.69 to 6.8)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 80: Risk factor: Indication of benzodiazepine (referent: anxiolytics) – Outcome: Long term use

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long term use – Hypnotics								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 1.59 (1.06 to 2.39)	LOW
Long term use – Both								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.03 (1.49 to 2.77)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

Table 81: Risk factor: Use of prescribed opioids (vs no opioids) - Outcome: Long term use

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long term use								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 0.87 (0.48 to 1.58)	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 82: Risk factor: Sedative use (referent: non-user) – Outcome: Chronic sedative use >275 days

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Chronic sedative use >275 days - Short-term user								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	OR 0.98 (0.94 to 1.02)	VERY LOW
Chronic sedative use >275 days - Moderate-term user								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.11 (2.03 to 2.19)	LOW
Chronic sedative use >275 days - Long-term user								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 14.73 (1.24 to 174.99)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 83: Risk factor: Substance use diagnosis (vs no diagnosis) – Outcome: Benzodiazepine dependence

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Benzodiazepine dependence – Alcohol								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	HR 0.77 (0.6 to 0.99)	LOW
Benzodiazepine dependence – Marijuana								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	HR 0.28 (0.2 to 0.38)	LOW
Benzodiazepine dependence – Cocaine								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	HR 1.13 (0.79 to 1.61)	VERY LOW
Benzodiazepine dependence – Opioid								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	HR 3.9 (1.18 to 12.89)	LOW
Benzodiazepine dependence – Tobacco								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	HR 2.08 (1.18 to 3.67)	LOW
Benzodiazepine dependence - Pain medications								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	HR 0.71 (0.58 to 0.86)	LOW
Benzodiazepine dependence - 2 or more substance use disorders								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	HR 2.03 (1.04 to 3.95)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the 95% CI crossed the null line

Table 84: Risk factor: Hospital level (referent: clinics only) - Outcome: Long term use

Quality assessment							Adjusted effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
Long term use - Local community hospitals only								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 2.78 (1.62 to 4.77)	LOW
Long term use - Medical centres only								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 5.87 (3.57 to 9.65)	LOW
Long term use - Metropolitan hospitals only								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 4.54 (2.78 to 7.41)	LOW
Long term use – Mixed								
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	OR 3.23 (1.96 to 5.32)	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

1.3 Interventions for prevention or treatment of dependence, withdrawal or discontinuation syndrome

1.3.1 Opioids

Table 85: Evidence profile: Managed withdrawal (tapering + Ondansetron + Naloxone) versus Managed withdrawal (tapering + placebo + Naloxone)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Managed withdrawal (tapering + Ondansetron + Naloxone) versus Managed withdrawal (tapering + placebo + Naloxone)	Control	Relative (95% CI)	Absolute		
Signs and symptoms/overall withdrawal syndrome (OOWS score) following induction of withdrawal (range of scores: 0-13; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	23	25	-	MD 0 higher (1.39 lower to 1.39 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (SOWS score) following induction of withdrawal (range of scores: 0-64; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23	25	-	MD 4.1 higher (2.78 lower to 10.98 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - psychological health (POMS score) following induction of withdrawal (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23	25	-	MD 10 higher (7.04 lower to 27.04 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - psychological health (Beck Depression Inventory change score) at 1 month of morphine treatment (range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23	25	-	MD 0.8 lower (2.41 lower to 0.81 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - physical health (Roland Morris Disability Index change score) at 1 month of morphine treatment (range of scores: 0-24; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23	25	-	MD 2.6 lower (4.7 to 0.5 lower)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 86: Evidence profile: Managed withdrawal (Ondansetron + Naloxone) versus Managed withdrawal (placebo + Naloxone)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Managed withdrawal (Ondansetron + Naloxone) versus Managed withdrawal (placebo + Naloxone)	Control	Relative (95% CI)	Absolute		
Signs and symptoms/overall withdrawal syndrome (OOWS score) (range of scores: 0-13; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33	33	-	MD 0 higher (1.11 lower to 1.11 higher)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (SOWS score) (range of scores: 0-64; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33	33	-	MD 0.3 higher (5.23 lower to 5.83 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - psychological health (POMS score) (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33	33	-	MD 1 higher (15.52 lower to 17.52 higher)	⊕⊕OO LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 87: Evidence profile: Prescriber education/skills/knowledge/support (notification of overdose letter to GP) versus Usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prescriber education/skills/knowledge/support (notification of overdose letter to GP) versus Usual care	Control	Relative (95% CI)	Absolute		
Reduction in prescribing (mean daily mg morphine equivalent) (follow-up 1-4 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	388	438	-	MD 6 lower (8.54 to 3.46 lower)	⊕⊕OO LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)

Table 88: Evidence profile: Patient advice and support (Mindfulness based recovery enhancement) versus Patient advice and support (conventional support group)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Patient advice and support (Mindfulness based recovery enhancement) versus Patient advice and support (conventional support group)	Control	Relative (95% CI)	Absolute		
Quality of life - psychological health (pain interference) post intervention (measured with: Brief Pain Inventory pain interference sub scale ; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	31	38	-	MD 1.68 lower (2.5 to 0.86 lower)	⊕OOO VERY LOW	CRITICAL
Quality of life - psychological health (pain interference) at 3 month follow up (measured with: Brief Pain Inventory pain interference sub scale ; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	23	28	-	MD 2.15 lower (3.44 to 0.86 lower)	⊕OOO VERY LOW	CRITICAL

Signs and symptoms/overall withdrawal syndrome (opioid craving) post intervention (range of scores: 1-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	31	38	-	MD 1.72 lower (2.93 to 0.51 lower)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (opioid craving) at 3 month follow up (range of scores: 1-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	23	28	-	MD 0.63 lower (2.31 lower to 1.05 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (signs of affective/sympathetic stress) post intervention - Sympathetic arousal (measured with: 56-item Calgary Symptoms of Stress Inventory ; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	31	38	-	MD 4.24 lower (7.5 to 0.98 lower)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (signs of affective/sympathetic stress) post intervention - Depression (measured with: 56-item Calgary Symptoms of Stress Inventory ; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	31	38	-	MD 2.56 lower (5.79 lower to 0.67 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (signs of affective/sympathetic stress) post intervention - Anger (measured with: 56-item Calgary Symptoms of Stress Inventory ; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	31	38	-	MD 0.81 higher (2.03 lower to 3.65 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (signs of affective/sympathetic stress) post intervention - Cognitive (measured with: 56-item Calgary Symptoms of Stress Inventory ; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	31	38	-	MD 1.75 lower (3.82 lower to 0.32 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (signs of affective/sympathetic stress) post intervention - Muscle tension (measured with: 56-item Calgary Symptoms of Stress Inventory ; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	31	38	-	MD 1.76 lower (5.16 lower to 1.64 higher)	⊕OOO VERY LOW	CRITICAL

Signs and symptoms/overall withdrawal syndrome (signs of affective/sympathetic stress) post intervention - Cardiopulmonary (measured with: 56-item Calgary Symptoms of Stress Inventory ; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	31	38	-	MD 3.68 lower (6.13 to 1.23 lower)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (signs of affective/sympathetic stress) post intervention - Neurological (measured with: 56-item Calgary Symptoms of Stress Inventory ; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	31	38	-	MD 2.78 lower (4.86 to 0.7 lower)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (signs of affective/sympathetic stress) post intervention - Upper respiratory (measured with: 56-item Calgary Symptoms of Stress Inventory ; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	31	38	-	MD 2.27 lower (4.61 lower to 0.07 higher)	⊕OOO VERY LOW	CRITICAL
Rates of lapse/relapse (Current opioid misuse measure) post treatment (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	31	38	-	MD 4.41 lower (8.48 to 0.34 lower)	⊕OOO VERY LOW	CRITICAL
Rates of lapse/relapse (Current opioid misuse measure) at 3 months follow up (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	23	28	-	MD 2.54 lower (6.71 lower to 1.63 higher)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 89: Evidence profile: Support for patients around medication management versus Usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Support for patients around medication management versus Usual care	Control	Relative (95% CI)	Absolute		
Quality of life - psychological (mood) - Depressed/discouraged (follow-up 6 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	17	21	-	MD 2.35 lower (23.13 lower to 18.43 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - psychological (mood) - Tense/anxious (follow-up 6 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	17	21	-	MD 9.34 lower (28.48 lower to 9.8 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - psychological (mood) - Irritable/angry (follow-up 6 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	17	21	-	MD 3.83 higher (15.82 lower to 23.48 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - psychological (mood) - Sleep interference (follow-up 6 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	17	21	-	MD 1.05 higher (16.84 lower to 18.94 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - physical (activity interference) - Daily routine (follow-up 6 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	17	21	-	MD 3.27 lower (20.68 lower to 14.14 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - physical (activity interference) - Sex (follow-up 6 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	17	21	-	MD 7.63 higher (16.04 lower to 31.3 higher)	⊕OOO VERY LOW	CRITICAL

Quality of life - physical (activity interference) - Appetite (follow-up 6 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	17	21	-	MD 1.54 lower (21.22 lower to 18.14 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - physical (activity interference) - Work (follow-up 6 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	17	21	-	MD 8.18 lower (26.89 lower to 10.53 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - social (activity interference) - Social (follow-up 6 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	17	21	-	MD 0.1 lower (19.21 lower to 19.01 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - social (activity interference) - Outdoor/recreation (follow-up 6 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	17	21	-	MD 0.32 higher (16.77 lower to 17.41 higher)	⊕OOO VERY LOW	CRITICAL
Rates of lapse/relapse (drug misuse) (follow-up 6 months; assessed with: Drug misuse index)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	5/19 (26.3%)	73.7%	RR 0.36 (0.16 to 0.79)	472 fewer per 1000 (from 155 fewer to 619 fewer)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Hospital Anxiety and Depression scale) - Anxiety (follow-up 6 months; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	19	19	-	MD 2.62 lower (4.9 to 0.34 lower)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Hospital Anxiety and Depression scale) - Depression (follow-up 6 months; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	19	19	-	MD 3 lower (5.44 to 0.56 lower)	⊕OOO VERY LOW	CRITICAL

[1] 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

[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)

[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 90: Evidence profile: Managed withdrawal (taper + support) versus Usual care (maintenance of treatment)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Managed withdrawal (taper + support) versus Usual care (maintenance of treatment)	Control	Relative (95% CI)	Absolute		
Reduction/cessation in prescribed drug use (daily opioid dose) (follow-up 4-6 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12	18	-	MD 74.2 lower (211.37 lower to 62.97 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Hospital anxiety and depression scale) - Anxiety (follow-up 4-6 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	11	18	-	MD 0.4 higher (2.49 lower to 3.29 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Hospital anxiety and depression scale) - Depression (follow-up 4-6 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	11	18	-	MD 0.4 higher (2.86 lower to 3.66 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (continuous reaction time) (follow-up 4-6 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	11	18	-	MD 23.6 lower (48.31 lower to 1.11 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (finger tapping test) - Dominant hand (follow-up 4-6 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12	18	-	MD 4.9 higher (2.98 lower to 12.78 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (finger tapping test) - Non-dominant hand (follow-up 4-6 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12	18	-	MD 5.3 higher (1.03 lower to 11.63 higher)	⊕OOO VERY LOW	CRITICAL

Signs and symptoms/overall withdrawal syndrome (digit span test) - Forwards (follow-up 4-6 weeks; range of scores: 0-14; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	11	18	-	MD 1 higher (0.99 lower to 2.99 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (digit span test) - Backwards (follow-up 4-6 weeks; range of scores: 0-14; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	11	18	-	MD 1.2 higher (1.19 lower to 3.59 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (trail making test B) (follow-up 4-6 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12	18	-	MD 19.1 higher (13.36 lower to 51.56 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Mini-mental state examination) (follow-up 4-6 weeks; range of scores: 0-30; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12	18	-	MD 0.3 higher (0.63 lower to 1.23 higher)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 91: Evidence profile: Prescriber education/skills/knowledge/support (nurse + registry + academic detailing + decision tools) versus Prescriber education/skills/knowledge/support (decision tools only)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prescriber education/skills/knowledge/support (nurse+registry+academic detailing+decision tools) versus Prescriber education/skills/knowledge/support (decision tools only)	Control	Relative (95% CI)	Absolute		
Cessation of medication (discontinuation of opioids) (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	0%	OR 1.5 (1 to 2.25)	-	⊕⊕OO LOW	CRITICAL
Reduction/cessation in prescribed drug use (10% reduction in opioid dose among non-discontinued patients) (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	0%	OR 1.6 (1.1 to 2.33)	-	⊕⊕OO LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 92: Prescriber education/skills/knowledge/support (ACT based training) versus Prescriber education/skills/knowledge/support (standard training)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prescriber education/skills/knowledge/support (ACT based training) versus Prescriber education/skills/knowledge/support (standard training)	Control	Relative (95% CI)	Absolute		
Client satisfaction (training evaluation) (range of scores: 0-10; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	41	38	-	MD 0 higher (1.13 lower to 1.13 higher)	⊕⊕⊕O MODERATE	CRITICAL
Reduction in prescribing (rated frequency of prescribing opioids on a 5-point scale) (range of scores: 0-5; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	serious[1]	serious[3]	none	41	38	-	MD 0.1 lower (0.53 lower to 0.33 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)
[2] 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
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 93: Evidence profile: Prescriber education/skills/knowledge/support (GP notification) versus Prescriber education/skills/knowledge/support (GP educational materials)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prescriber education/skills/knowledge/support (GP notification) versus Prescriber education/skills/knowledge/support (GP educational materials)	Control	Relative (95% CI)	Absolute		
Reduction in prescribing (opioid prescriptions per patient) at 91-270 days post intervention (Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	399	391	-	MD 11.1 lower (12.41 to 9.79 lower)	⊕OOO VERY LOW	CRITICAL
Reduction in prescribing (chronic high-dose opioid use) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	26/399 (6.5%)	4.9%	RR 1.34 (0.75 to 2.38)	17 more per 1000 (from 12 fewer to 68 more)	⊕OOO VERY LOW	CRITICAL
Uptake of psychosocial interventions (visits to mental health specialists) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	29/399 (7.3%)	6.4%	RR 1.14 (0.68 to 1.91)	9 more per 1000 (from 20 fewer to 58 more)	⊕OOO VERY LOW	CRITICAL
Lapse/relapse (diagnosis of opioid abuse) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	39/368 (10.6%)	9.5%	RR 1.12 (0.72 to 1.73)	11 more per 1000 (from 27 fewer to 69 more)	⊕OOO VERY LOW	CRITICAL
Lapse/relapse (opioid associated ED visits) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	104/399 (26.1%)	25.6%	RR 1.02 (0.8 to 1.29)	5 more per 1000 (from 51 fewer to 74 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 94: Evidence profile: Prescriber education/skills/knowledge/support (GP notification) versus Prescriber education/skills/knowledge/support (GP notification + education)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Prescriber education/skills/knowledge/support (GP notification) versus Prescriber**	**Control**	**Relative (95% CI)**	**Absolute**		

							education/skills/knowledge/support (GP notification + education)					
Reduction in prescribing (opioid prescriptions per patient) at 91-270 days post intervention (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	399	408	-	MD 11.5 lower (12.85 to 10.15 lower)	⊕OOO VERY LOW	CRITICAL
Reduction in prescribing (chronic high-dose opioid use) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	26/399 (6.5%)	6.9%	RR 0.95 (0.57 to 1.59)	3 fewer per 1000 (from 30 fewer to 41 more)	⊕OOO VERY LOW	CRITICAL
Uptake of psychosocial interventions (visits to mental health specialists) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	29/399 (7.3%)	8.8%	RR 0.82 (0.52 to 1.32)	16 fewer per 1000 (from 42 fewer to 28 more)	⊕OOO VERY LOW	CRITICAL
Lapse/relapse (diagnosis of opioid abuse) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	39/368 (10.6%)	8.3%	RR 1.28 (0.81 to 2.02)	23 more per 1000 (from 16 fewer to 85 more)	⊕OOO VERY LOW	CRITICAL
Lapse/relapse (opioid associated ED visits) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	104/399 (26.1%)	30.6%	RR 0.85 (0.68 to 1.06)	46 fewer per 1000 (from 98 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 95: Evidence profile: Prescriber education/skills/knowledge/support (GP notification) versus Usual care (no communication)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prescriber education/skills/knowledge/support (GP notification) versus Usual care (no communication)	Control	Relative (95% CI)	Absolute		
Reduction in prescribing (opioid prescriptions per patient) at 91-270 days post intervention (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	399	821	-	MD 11.6 lower (12.61 to 10.59 lower)	⊕OOO VERY LOW	CRITICAL
Reduction in prescribing (chronic high-dose opioid use) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	26/399 (6.5%)	7.2%	RR 0.91 (0.58 to 1.42)	6 fewer per 1000 (from 30 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL
Uptake of psychosocial interventions (visits to mental health specialists) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	29/399 (7.3%)	7.1%	RR 1.03 (0.67 to 1.58)	2 more per 1000 (from 23 fewer to 41 more)	⊕OOO VERY LOW	CRITICAL
Lapse/relapse (diagnosis of opioid abuse) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	39/368 (10.6%)	11.3%	RR 0.93 (0.65 to 1.34)	8 fewer per 1000 (from 40 fewer to 38 more)	⊕OOO VERY LOW	CRITICAL
Lapse/relapse (opioid associated ED visits) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	104/399 (26.1%)	28.3%	RR 0.92 (0.76 to 1.12)	23 fewer per 1000 (from 68 fewer to 34 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 96: Evidence profile: Prescriber education/skills/knowledge/support (GP education) versus Prescriber education/skills/knowledge/support (GP notification + education)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prescriber education/skills/knowledge/support (GP education) versus Prescriber education/skills/knowledge/support (GP notification + education)	Control	Relative (95% CI)	Absolute		
Reduction in prescribing (opioid prescriptions per patient) at 91-270 days post intervention (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	391	408	-	MD 0.4 lower (2.1 lower to 1.3 higher)	⊕OOO VERY LOW	CRITICAL
Reduction in prescribing (chronic high-dose opioid use) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	19/391 (4.9%)	6.9%	RR 0.71 (0.4 to 1.25)	20 fewer per 1000 (from 41 fewer to 17 more)	⊕OOO VERY LOW	CRITICAL
Uptake of psychosocial interventions (visits to mental health specialists) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	25/391 (6.4%)	8.8%	RR 0.72 (0.44 to 1.18)	25 fewer per 1000 (from 49 fewer to 16 more)	⊕OOO VERY LOW	CRITICAL
Lapse/relapse (diagnosis of opioid abuse) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	34/358 (9.5%)	8.3%	RR 1.15 (0.72 to 1.84)	12 more per 1000 (from 23 fewer to 70 more)	⊕OOO VERY LOW	CRITICAL
Lapse/relapse (opioid associated ED visits) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	100/391 (25.6%)	30.6%	RR 0.83 (0.67 to 1.04)	52 fewer per 1000 (from 101 fewer to 12 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 97: Evidence profile: Prescriber education/skills/knowledge/support (GP education) versus Usual care (no communication)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prescriber education/skills/knowledge/support (GP education) versus Usual care (no communication)	Control	Relative (95% CI)	Absolute		
Reduction in prescribing (opioid prescriptions per patient) at 91-270 days post intervention (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	391	821	-	MD 0.5 lower (1.94 lower to 0.94 higher)	⊕OOO VERY LOW	CRITICAL
Reduction in prescribing (chronic high-dose opioid use) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	19/391 (4.9%)	7.2%	RR 0.68 (0.41 to 1.12)	23 fewer per 1000 (from 42 fewer to 9 more)	⊕OOO VERY LOW	CRITICAL
Uptake of psychosocial interventions (visits to mental health specialists) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	25/391 (6.4%)	7.1%	RR 0.91 (0.58 to 1.42)	6 fewer per 1000 (from 30 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL
Lapse/relapse (diagnosis of opioid abuse) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	34/358 (9.5%)	11.3%	RR 0.84 (0.57 to 1.22)	18 fewer per 1000 (from 49 fewer to 25 more)	⊕OOO VERY LOW	CRITICAL
Lapse/relapse (opioid associated ED visits) at 91-270 days post intervention												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	100/391 (25.6%)	28.3%	RR 0.91 (0.74 to 1.11)	25 fewer per 1000 (from 74 fewer to 31 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 98: Evidence profile: Prescriber education/skills/knowledge/support (GP notification + education) versus Usual care (no communication)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Prescriber education/skills/knowledge/support (GP notification + education) versus Usual care (no communication)**	**Control**	**Relative (95% CI)**	**Absolute**		
Reduction in prescribing (opioid prescriptions per patient) at 91-270 days post intervention (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	408	821	-	MD 0.1 lower (1.58 lower to 1.38 higher)	⊕OOO VERY LOW	CRITICAL
Reduction in prescribing (chronic high-dose opioid use) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	28/409 (6.8%)	7.2%	RR 0.95 (0.62 to 1.47)	4 fewer per 1000 (from 27 fewer to 34 more)	⊕OOO VERY LOW	CRITICAL
Uptake of psychosocial interventions (visits to mental health specialists) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	36/408 (8.8%)	7.1%	RR 1.25 (0.84 to 1.86)	18 more per 1000 (from 11 fewer to 61 more)	⊕OOO VERY LOW	CRITICAL
Lapse/relapse (diagnosis of opioid abuse) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	30/363 (8.3%)	11.3%	RR 0.73 (0.49 to 1.09)	31 fewer per 1000 (from 58 fewer to 10 more)	⊕OOO VERY LOW	CRITICAL

Lapse/relapse (opioid associated ED visits) at 91-270 days post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	125/408 (30.6%)	28.3%	RR 1.08 (0.9 to 1.3)	23 more per 1000 (from 28 fewer to 85 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 99: Evidence profile: Patient advice and support (taper support) versus Usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Patient advice and support (taper support) versus Usual care	Control	Relative (95% CI)	Absolute		
Reduction/cessation in prescribed drug use (morphine equivalent dose) post intervention (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	15	-	MD 42.9 lower (92.42 lower to 6.62 higher)	⊕⊕OO LOW	CRITICAL
Reduction/cessation in prescribed drug use (morphine equivalent dose) at 3 month follow up (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 26.71 lower (83.04 lower to 29.62 higher)	⊕⊕OO LOW	CRITICAL
Cessation of medication (complete discontinuation of opioids) post intervention												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/16 (6.3%)	6.7%	RR 0.94 (0.06 to 13.68)	4 fewer per 1000 (from 63 fewer to 850 more)	⊕OOO VERY LOW	CRITICAL
Cessation of medication (complete discontinuation of opioids) at 3 month follow up												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/16 (12.5%)	12.5%	RR 1 (0.16 to 6.25)	0 fewer per 1000 (from 105 fewer to 656 more)	⊕OOO VERY LOW	CRITICAL
Quality of life (at least moderately better on Patient Global Impression of Change) post intervention												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	9/16 (56.3%)	20%	RR 2.81 (0.94 to 8.45)	362 more per 1000 (from 12 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
Quality of life (at least moderately better on Patient Global Impression of Change) at 3 month follow up												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	10/16 (62.5%)	37.5%	RR 1.67 (0.8 to 3.49)	251 more per 1000 (from 75 fewer to 934 more)	⊕⊕OO LOW	CRITICAL
Quality of life - psychological (pain interference) post intervention (range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 1.39 lower (2.78 lower to 0 higher)	⊕⊕OO LOW	CRITICAL
Quality of life - psychological (pain interference) at 3 month follow up (range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 1.21 lower (2.43 lower to 0.01 higher)	⊕⊕OO LOW	CRITICAL
Quality of life - psychological (pain self-efficacy) post intervention (range of scores: 0-60; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 7.86 higher (1.22 to 14.5 higher)	⊕⊕OO LOW	CRITICAL
Quality of life - psychological (pain self-efficacy) at 3 month follow up (range of scores: 0-60; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 7.26 higher (2.14 lower to 16.66 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (Prescription Opioids Difficulties Scale) post intervention - Problems sub scale (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 4.9 lower (8.4 to 1.4 lower)	⊕⊕OO LOW	CRITICAL
Quality of life (Prescription Opioids Difficulties Scale) post intervention - Concerns sub scale (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 0.16 higher (3.74 lower to 4.06 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (Prescription Opioids Difficulties Scale) at 3 month follow up - Problems sub scale (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 4.47 lower (10.13 lower to 1.19 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (Prescription Opioids Difficulties Scale) at 3 month follow up - Concerns sub scale (Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 1.62 higher (3.27 lower to 6.51 higher)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Patient Health Questionnaire-9 - depression) post intervention (range of scores: 0-27; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 2.21 lower (6.62 lower to 2.2 higher)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Patient Health Questionnaire-9 - depression) at 3 month follow up (range of scores: 0-27; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 1.89 lower (6.23 lower to 2.45 higher)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Generalised Anxiety Disorder-7) post intervention (range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 2.73 lower (5.99 lower to 0.53 higher)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Generalised Anxiety Disorder-7) at 3 month follow up (range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 2.39 lower (5.79 lower to 1.01 higher)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Insomnia Severity Index) post intervention (range of scores: 0-28; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 3.13 lower (7.22 lower to 0.96 higher)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Insomnia Severity Index) at 3 month follow up (range of scores: 0-28; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 1.91 lower (5.49 lower to 1.67 higher)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Patient health questionnaire-15 somatic symptoms) post intervention (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 1.47 lower (4.72 lower to 1.78 higher)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Patient health questionnaire-15 somatic symptoms) at 3 month follow up (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 0.43 lower (3.33 lower to 2.47 higher)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (opioid craving) post intervention (range of scores: 0-10; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 0.36 lower (2.42 lower to 1.7 higher)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (opioid craving) at 3 month follow up (range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 0.46 lower (1.93 lower to 1.01 higher)	⊕⊕OO LOW	CRITICAL
Rates of lapse/relapse (Prescription opioid misuse index) post intervention (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 0.08 higher (0.58 lower to 0.74 higher)	⊕⊕OO LOW	CRITICAL
Rates of lapse/relapse (Prescription opioid misuse index) at 3 month follow up (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[2]	none	16	16	-	MD 0.06 higher (0.45 lower to 0.57 higher)	⊕⊕OO LOW	CRITICAL

[1] 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
[2] Insufficient detail to assess imprecision
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 100: Evidence profile: Alternatives to prescribing (internet pain management program) versus Usual care (waiting list)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Alternatives to prescribing (internet pain management program) versus Usual care (waiting list)**	**Control**	**Relative (95% CI)**	**Absolute**		
Reduction/cessation in prescribed drug use (number of people decreasing/stopping opioids)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/43 (20.9%)	6.8%	RR 3.07 (0.89 to 10.58)	141 more per 1000 (from 7 fewer to 651 more)	⊕OOO VERY LOW	CRITICAL
Reduction/cessation in prescribed drug use (number increasing opioids)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/43 (16.3%)	19.2%	RR 0.85 (0.35 to 2.08)	29 fewer per 1000 (from 125 fewer to 207 more)	⊕OOO VERY LOW	CRITICAL

Reduction/cessation in prescribed drug use (number adding/increasing an antidepressant)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/26 (30.8%)	18%	RR 1.71 (0.71 to 4.15)	128 more per 1000 (from 52 fewer to 567 more)	⊕OOO VERY LOW	CRITICAL
Quality of life - psychological (pain interference) (measured with: Brief pain inventory ; range of scores: 0-10; Better indicated by lower values)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	45	47	-	MD 0.2 lower (1.22 lower to 0.82 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - psychological (pain self-efficacy) (range of scores: 0-60; Better indicated by higher values)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	45	47	-	MD 6.1 higher (0.73 to 11.47 higher)	⊕OOO VERY LOW	CRITICAL
Rates of lapse/relapse (Current opioid misuse measure) (Better indicated by lower values)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	45	47	-	MD 0.4 lower (3.12 lower to 2.32 higher)	⊕⊕OO LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1.3.2 Benzodiazepines

Table 101: Evidence profile: Managed withdrawal (Melatonin + taper) versus Managed withdrawal (Placebo + taper)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Managed withdrawal (Melatonin + taper) versus Managed withdrawal (Placebo + taper)**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life - psychological (sleep quality) (measured with: Northside Hospital Sleep Medicine Institute Test; range of scores: 0-8; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	18	18	-	MD 1.66 lower (3.01 to 0.31 lower)	⊕OOO VERY LOW	CRITICAL

Cessation of medication (discontinuation of hypnotic drug)											
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	10/14 (71.4%)	7.1%	RR 10 (1.47 to 68.04)	639 more per 1000 (from 33 more to 1000 more)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Geriatric Depression Scale) (range of scores: 1-30; Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	18	18	-	MD 1.45 lower (4.65 lower to 1.75 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Goldberg Anxiety Scale) (range of scores: 0-9; Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	18	18	-	MD 1 lower (2.47 lower to 0.47 higher)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 102: Evidence profile: Managed withdrawal (Melatonin+taper+support) versus Managed withdrawal (placebo+taper+support)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Managed withdrawal (Melatonin+taper+support) versus Managed withdrawal (placebo+taper+support)**	**Control**	**Relative (95% CI)**	**Absolute**		
Cessation of medication (total benzodiazepine withdrawal) post intervention												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	36/45 (80%)	91.1%	RR 0.88 (0.74 to 1.04)	109 fewer per 1000 (from 237 fewer to 36 more)	⊕⊕⊕O MODERATE	CRITICAL
Cessation of medication (total benzodiazepine withdrawal) at 3 year follow up												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious[1]	none	12/42 (28.6%)	34.2%	RR 0.84 (0.44 to 1.59)	55 fewer per 1000 (from 192	⊕⊕OO LOW	CRITICAL

		risk of bias								fewer to 202 more)		

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 103: Evidence profile: Patient advice and support (CBT + group therapy + taper) versus Patient advice and support (group therapy + taper only)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Patient advice and support (CBT + group therapy + taper) versus Patient advice and support (group therapy + taper only)	Control	Relative (95% CI)	Absolute		
Cessation of medication (cessation of benzodiazepine use)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	15/18 (83.3%)	84.6%	RR 0.98 (0.72 to 1.34)	17 fewer per 1000 (from 237 fewer to 288 more)	⊕OOO VERY LOW	CRITICAL
Rates of lapse/relapse (Relapse to benzodiazepine use) at 11 month follow up												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/10 (10%)	10%	RR 1 (0.07 to 13.87)	0 fewer per 1000 (from 93 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (number of withdrawal symptoms) post intervention (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	14	12	-	MD 1.07 lower (4.38 lower to 2.24 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (number of withdrawal symptoms) at 3 month follow up (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	11	10	-	MD 0.45 higher (3.25 lower to 4.15 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - psychological (Psychological Distress Inventory) post intervention (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	14	12	-	MD 3.07 higher (5.07 lower to 11.21 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - psychological (Psychological Distress Inventory) at 3 month follow up (range of scores: 0-100; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	11	10	-	MD 9.96 lower (20.85 lower to 0.93 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (Systematic Quality of Life Inventory - current state sub scale) at 3 month follow up (Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	11	10	-	MD 0.05 higher (1.15 lower to 1.25 higher)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 104: Evidence profile: Patient education (booklet) versus Usual care (waiting list)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Patient education (booklet) versus Usual care (waiting list)**	**Control**	**Relative (95% CI)**	**Absolute**		
Cessation of medication (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	38/123 (30.9%)	5.1%	OR 8.1 (3.34 to 19.64)	252 more per 1000 (from 101 more to 462 more)	⊕⊕OO LOW	CRITICAL
Reduction/cessation in prescribed drug use (complete cessation plus benzodiazepine reduction) (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	54/123 (43.9%)	11.60%	OR 6.73 (3.12 to 14.52)	353 more per 1000 (from 174 more to 540 more)	⊕⊕OO LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)

Table 105: Evidence profile: Patient advice and support (single tailored letter) versus Usual care (standard GP letter)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Patient advice and support (single tailored letter) versus Usual care (standard GP letter)	Control	Relative (95% CI)	Absolute		
Cessation of medication (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	0%	OR 2.3 (1.21 to 4.37)	-	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 106: Evidence profile: Patient advice and support (multiple tailored letters) versus Usual care (standard GP letter)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Patient advice and support (multiple tailored letters) versus Usual care (standard GP letter)	Control	Relative (95% CI)	Absolute		
Cessation of medication (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	0%	OR 2.1 (1.11 to 3.97)	-	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 107: Evidence profile: Prescriber education/skills/knowledge/support (education manual + educational meeting + coach) versus Prescriber education/skills/knowledge/support (education manual only)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prescriber education/skills/knowledge/support (education manual + educational meeting + coach) versus Prescriber education/skills/knowledge/support (education manual only)	Control	Relative (95% CI)	Absolute		
Cessation of medication (complete benzodiazepine discontinuation) 0-3 months post discontinuation letter												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	998/11423 (8.7%)	8.3%	RR 1.06 (0.96 to 1.16)	5 more per 1000 (from 3 fewer to 13 more)	⊕OOO VERY LOW	CRITICAL
Cessation of medication (complete benzodiazepine discontinuation) 4-6 months post discontinuation letter												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	1129/11423 (9.9%)	10.2%	RR 0.97 (0.89 to 1.06)	3 fewer per 1000 (from 11 fewer to 6 more)	⊕OOO VERY LOW	CRITICAL
Reduction/cessation in prescribed drug use (at least 50% reduction in benzodiazepine use) 0-3 months post discontinuation letter												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	1793/11423 (15.7%)	14.8%	RR 1.06 (0.99 to 1.14)	9 more per 1000 (from 1 fewer to 21 more)	⊕OOO VERY LOW	CRITICAL
Reduction/cessation in prescribed drug use (at least 50% reduction in benzodiazepine use) 4-6 months post discontinuation letter												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	1820/11423 (15.9%)	16.7%	RR 0.95 (0.89 to 1.02)	8 fewer per 1000 (from 18 fewer to 3 more)	⊕OOO VERY LOW	CRITICAL

[1] 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

[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)

Table 108: Evidence profile: Prescriber education/skills/knowledge/support (GP workshop+follow up visits) versus Prescriber education/skills/knowledge/support (GP workshop + written instructions)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prescriber education/skills/knowledge/support (GP workshop+follow up visits) versus Prescriber education/skills/knowledge/support (GP workshop + written instructions)	Control	Relative (95% CI)	Absolute		
Cessation of medication (cessation of benzodiazepine use) post intervention												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	71/191 (37.2%)	42.9%	RR 0.87 (0.67 to 1.12)	56 fewer per 1000 (from 142 fewer to 51 more)	⊕⊕OO LOW	CRITICAL
Cessation of medication (cessation of benzodiazepine use) at 36 month follow up												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	79/191 (41.4%)	39.3%	RR 1.05 (0.82 to 1.36)	20 more per 1000 (from 71 fewer to 141 more)	⊕⊕OO LOW	CRITICAL
Reduction/cessation of prescribed medication (initiation of antidepressants) at 12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	39/187 (20.9%)	12.4%	RR 1.68 (1.02 to 2.76)	84 more per 1000 (from 2 more to 218 more)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (attempted suicide by overdose) at 4 months												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/191 (0%)	0.6%	OR 0.12 (0 to 6)	5 fewer per 1000 (from 6 fewer to 29 more)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Tremor												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30/186 (16.1%)	11.3%	RR 1.42 (0.83 to 2.46)	47 more per 1000 (from	⊕⊕OO LOW	CRITICAL

										19 fewer to 165 more)		
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Irritability												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	42/186 (22.6%)	26.4%	RR 0.85 (0.59 to 1.24)	40 fewer per 1000 (from 108 fewer to 63 more)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Insomnia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	87/186 (46.8%)	52.2%	RR 0.9 (0.72 to 1.11)	52 fewer per 1000 (from 146 fewer to 57 more)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Anxiety												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	72/186 (38.7%)	40.3%	RR 0.96 (0.74 to 1.25)	16 fewer per 1000 (from 105 fewer to 101 more)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Convulsions												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/186 (1.6%)	0.6%	RR 2.56 (0.27 to 24.41)	9 more per 1000 (from 4 fewer to 140 more)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Tremor												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/184 (7.1%)	6.9%	RR 1.02 (0.47 to 2.22)	1 more per 1000 (from 37 fewer to 84 more)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Irritability												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	26/184 (14.1%)	14.5%	RR 0.98 (0.58 to 1.64)	3 fewer per 1000 (from 61 fewer to 93 more)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Insomnia												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	66/159 (41.5%)	33.3%	RR 1.25 (0.93 to 1.66)	83 more per 1000 (from 23 fewer to 220 more)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Anxiety												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48/184 (26.1%)	29.6%	RR 0.88 (0.63 to 1.24)	36 fewer per 1000 (from 110 fewer to 71 more)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Convulsions												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/184 (0%)	0%	not pooled	not pooled	⊕⊕⊕O MODERATE	CRITICAL
Rates of lapse/relapse (use of benzodiazepine at 36 months in those who stopped use at 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/86 (25.6%)	35.5%	RR 0.72 (0.45 to 1.15)	99 fewer per 1000 (from 195 fewer to 53 more)	⊕⊕OO LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 109: Evidence profile: Prescriber education/skills/knowledge/support (GP workshop + follow up) versus Usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prescriber education/skills/knowledge/support (GP workshop + follow up) versus Usual care	Control	Relative (95% CI)	Absolute		
Cessation of medication (cessation of benzodiazepine use) post intervention												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71/191 (37.2%)	14.5%	RR 2.57 (1.71 to 3.86)	228 more per 1000 (from 103 more to 415 more)	⊕⊕⊕O MODERATE	CRITICAL
Cessation of medication (cessation of benzodiazepine use) at 36 month follow up												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	79/191 (41.4%)	26%	RR 1.59 (1.17 to 2.15)	153 more per 1000 (from 44 more to 299 more)	⊕⊕OO LOW	CRITICAL
Reduction/cessation of prescribed medication (initiation of antidepressant medication) at 12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	39/187 (20.9%)	13.6%	RR 1.53 (0.96 to 2.46)	72 more per 1000 (from 5 fewer to 199 more)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (attempted suicide by overdose) at 4 months												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/191 (0%)	0%	See comment	-	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Tremor												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/186 (16.1%)	5.3%	RR 3.05 (1.49 to 6.23)	109 more per 1000 (from 26 more to 277 more)	⊕⊕⊕O MODERATE	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Irritability												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/186 (22.6%)	8.8%	RR 2.56 (1.47 to 4.44)	137 more per 1000 (from 41 more to 303 more)	⊕⊕⊕O MODERATE	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Insomnia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	87/186 (46.8%)	17.7%	RR 2.65 (1.85 to 3.8)	292 more per 1000 (from 150 more to 496 more)	⊕⊕⊕O MODERATE	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Anxiety												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	72/186 (38.7%)	12.4%	RR 3.13 (2.02 to 4.86)	264 more per 1000 (from 126 more to 479 more)	⊕⊕⊕O MODERATE	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Convulsions												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/186 (1.6%)	0.6%	RR 2.74 (0.29 to 26.11)	10 more per 1000 (from 4 fewer to 151 more)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Tremor												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/184 (7.1%)	6.7%	RR 1.05 (0.49 to 2.29)	3 more per 1000 (from 34 fewer to 86 more)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Irritability												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	26/184 (14.1%)	12.2%	RR 1.16 (0.67 to 2)	20 more per 1000 (from 40 fewer to 122 more)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Insomnia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	66/159 (41.5%)	28.7%	RR 1.45 (1.07 to 1.96)	129 more per 1000 (from 20 more to 276 more)	⊕⊕OO LOW	CRITICAL

Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Anxiety												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48/184 (26.1%)	20.1%	RR 1.3 (0.88 to 1.91)	60 more per 1000 (from 24 fewer to 183 more)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Convulsions												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/184 (0%)	0%	not pooled	not pooled	⊕⊕⊕O MODERATE	CRITICAL
Rates of lapse/relapse (benzodiazepine use at 36 months in those who stopped use at 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	22/86 (25.6%)	30.8%	RR 0.83 (0.42 to 1.64)	52 fewer per 1000 (from 179 fewer to 197 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 110: Evidence profile: Prescriber education/skills/knowledge/support (GP workshop + written instructions) versus Usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Prescriber education/skills/knowledge/support (GP workshop + written instructions) versus Usual care**	**Control**	**Relative (95% CI)**	**Absolute**		
Cessation of medication (cessation of benzodiazepine use) post intervention												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	72/168 (42.9%)	14.5%	RR 2.97 (1.98 to 4.44)	286 more per 1000 (from 142 more to 499 more)	⊕⊕⊕O MODERATE	CRITICAL
Cessation of medication (cessation of benzodiazepine use) at 36 month follow up												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	66/168 (39.3%)	26%	RR 1.51 (1.1 to 2.07)	133 more per 1000 (from 26	⊕⊕OO LOW	CRITICAL

										more to 278 more)		
Reduction/cessation of prescribed medication (initiation of antidepressants) at 12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20/161 (12.4%)	13.6%	RR 0.91 (0.52 to 1.6)	12 fewer per 1000 (from 65 fewer to 82 more)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (attempted suicide by overdose) at 4 months												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/168 (0.6%)	0%	OR 7.61 (0.15 to 383.8)	-	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Tremor												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18/159 (11.3%)	5.3%	RR 2.14 (0.99 to 4.62)	60 more per 1000 (from 1 fewer to 192 more)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Irritability												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/159 (26.4%)	8.8%	RR 2.99 (1.73 to 5.18)	175 more per 1000 (from 64 more to 368 more)	⊕⊕⊕O MODERATE	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Insomnia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	83/159 (52.2%)	17.7%	RR 2.96 (2.07 to 4.23)	347 more per 1000 (from 189 more to 572 more)	⊕⊕⊕O MODERATE	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Anxiety												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64/159 (40.3%)	12.4%	RR 3.26 (2.09 to 5.07)	280 more per 1000 (from 135 more to 505 more)	⊕⊕⊕O MODERATE	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Convulsions												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/159 (0.63%)	0.6%	RR 1.07 (0.07 to 16.95)	0 more per 1000 (from 6 fewer to 96 more)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Tremor												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/159 (6.9%)	6.7%	RR 1.03 (0.46 to 2.31)	2 more per 1000 (from 36 fewer to 88 more)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Irritability												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	23/159 (14.5%)	12.2%	RR 1.19 (0.68 to 2.07)	23 more per 1000 (from 39 fewer to 131 more)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Insomnia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	53/159 (33.3%)	28.7%	RR 1.16 (0.84 to 1.61)	46 more per 1000 (from 46 fewer to 175 more)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Anxiety												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	47/159 (29.6%)	20.1%	RR 1.47 (1 to 2.17)	94 more per 1000 (from 0 more to 235 more)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Convulsions												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/159 (0%)	0%	not pooled	not pooled	⊕⊕⊕O MODERATE	CRITICAL
Rates of lapse/relapse (benzodiazepine use at 36 months in those who stopped use at 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	27/76 (35.5%)	30.8%	RR 1.15 (0.6 to 2.21)	46 more per 1000 (from 123 fewer to 373 more)	⊕OOO VERY LOW	CRITICAL

[1] 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

[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1.3.3 Z drugs

Table 111: Evidence profile: Alternatives to prescribing (Auricular acupuncture) versus Alternatives to prescribing (CBT for insomnia)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alternatives to prescribing (Auricular acupuncture) versus Alternatives to prescribing (CBT for insomnia)	Control	Relative (95% CI)	Absolute		
Cessation of medication (discontinuation of z-drugs) post treatment												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/24 (70.8%)	84%	RR 0.84 (0.62 to 1.15)	134 fewer per 1000 (from 319 fewer to 126 more)	⊕OOO VERY LOW	CRITICAL
Reduction in prescribed drug use (in those who did not discontinue) post treatment												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/7 (100%)	100%	RR 1 (0.71 to 1.41)	0 fewer per 1000 (from 290 fewer to 410 more)	⊕OOO VERY LOW	CRITICAL
Quality of life - psychological health (sleep efficiency) post treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24	25	-	MD 16 lower (23.07 to 8.93 lower)	⊕⊕OO LOW	CRITICAL
Quality of life - psychological health (rated sleep quality) post treatment (range of scores: 0-5; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24	25	-	MD 0.6 lower (1.04 to 0.16 lower)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (insomnia) post treatment (measured with: Insomnia severity index; range of scores: 0-28; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	25	-	MD 6.89 higher (4.14 to 9.64 higher)	⊕⊕OO LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Hospital anxiety and depression scale) post treatment - Anxiety (range of scores: 0-21; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	25	-	MD 0.55 lower (2.13 lower to 1.03 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Hospital anxiety and depression scale) post treatment - Depression (range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	25	-	MD 0.35 lower (1.77 lower to 1.07 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (sleepiness) post treatment (measured with: Epworth sleepiness scale ; range of scores: 0-24; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	25	-	MD 1.1 lower (2.95 lower to 0.75 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (insomnia) at 6 months (measured with: Insomnia severity index ; range of scores: 0-28; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	23	-	MD 3.53 higher (0.47 to 6.59 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Hospital anxiety and depression scale) at 6 months - Anxiety (range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	22	23	-	MD 0.1 lower (1.82 lower to 1.62 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (Hospital anxiety and depression scale) at 6 months - Depression (range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	23	-	MD 0.15 lower (1.55 lower to 1.25 higher)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (sleepiness) at 6 months (measured with: Epworth sleepiness scale ; range of scores: 0-24; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	22	23	-	MD 0.21 lower (1.85 lower to 1.43 higher)	⊕OOO VERY LOW	CRITICAL

[1] 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

[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1.3.4 Antidepressants

Table 112: Evidence profile: Prescriber education/skills/knowledge/support (cessation advice) versus Usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prescriber education/skills/knowledge/support (cessation advice) versus Usual care	Control	Relative (95% CI)	Absolute		
Cessation of medication (discontinuation of antidepressants) at 12 months												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	4/67 (6%)	8%	RR 0.75 (0.22 to 2.53)	20 fewer per 1000 (from 62 fewer to 122 more)	⊕OOO VERY LOW	CRITICAL
Signs and symptoms/overall withdrawal syndrome (relapse of depression) at 12 months												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	18/70 (25.7%)	13.2%	RR 1.95 (0.97 to 3.94)	125 more per 1000 (from 4 fewer to 388 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1.3.5 Mixed drugs

Table 113: Evidence profile: Alternatives to prescribing (CBT+therapeutic interactive voice response) versus Alternatives to prescribing (CBT only)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alternatives to prescribing (CBT+therapeutic interactive voice response) versus Alternatives to prescribing (CBT only)	Control	Relative (95% CI)	Absolute		
Reduction/cessation in prescribed drug use (number of patients taking prescribed drugs) post intervention - Opioids												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	10/26 (38.5%)	64%	RR 0.6 (0.34 to 1.06)	256 fewer per 1000 (from 422 fewer to 38 more)	⊕OOO VERY LOW	CRITICAL
Reduction/cessation in prescribed drug use (number of patients taking prescribed drugs) post intervention - Benzodiazepines												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	9/26 (34.6%)	40%	RR 0.87 (0.42 to 1.77)	52 fewer per 1000 (from 232 fewer to 308 more)	⊕OOO VERY LOW	CRITICAL
Reduction/cessation in prescribed drug use (number of patients taking prescribed drugs) post intervention - Antidepressants												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20/26 (76.9%)	84%	RR 0.92 (0.7 to 1.2)	67 fewer per 1000 (from 252 fewer to 168 more)	⊕OOO VERY LOW	CRITICAL
Reduction/cessation in prescribed drug use (number of patients taking prescribed drugs) at 8 month follow up - Opioids												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	11/26 (42.3%)	72%	RR 0.59 (0.35 to 0.98)	295 fewer per 1000 (from 14 fewer to 468 fewer)	⊕OOO VERY LOW	CRITICAL
Reduction/cessation in prescribed drug use (number of patients taking prescribed drugs) at 8 month follow up - Benzodiazepines												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	9/26 (34.6%)	36%	RR 0.96 (0.46 to 2.02)	14 fewer per 1000 (from 194 fewer to 367 more)	⊕OOO VERY LOW	CRITICAL
Reduction/cessation in prescribed drug use (number of patients taking prescribed drugs) at 8 month follow up - Antidepressants												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	17/26 (65.4%)	76%	RR 0.86 (0.6 to 1.23)	106 fewer per 1000 (from 304 fewer to 175 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 114: Evidence profile: Patient advice and support (intensive preventative programme) versus Usual care (no changes in drug use)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Patient advice and support (intensive preventative programme) versus Usual care (no changes in drug use)**	**Control**	**Relative (95% CI)**	**Absolute**		
Reduction/cessation in prescribed drug use (regular use) at 12 months - Antidepressants												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	25/259 (9.7%)	10.8%	RR 0.9 (0.54 to 1.49)	11 fewer per 1000 (from 50 fewer to 53 more)	⊕OOO VERY LOW	CRITICAL
Reduction/cessation in prescribed drug use (regular use) at 12 months - Benzodiazepines												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	22/259 (8.5%)	17.8%	RR 0.48 (0.3 to 0.77)	93 fewer per 1000 (from 41 fewer to 125 fewer)	⊕OOO VERY LOW	CRITICAL
Reduction/cessation in prescribed drug use (regular use) at 12 months - Opioids												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	7/259 (2.7%)	2.2%	RR 1.21 (0.41 to 3.56)	5 more per 1000 (from 13 fewer to 56 more)	⊕OOO VERY LOW	CRITICAL
Reduction/cessation of prescribed medication (irregular use) at 12 months - Antidepressants												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/259 (0.39%)	1.1%	RR 0.35 (0.04 to 3.31)	7 fewer per 1000 (from 11 fewer to 25 more)	⊕OOO VERY LOW	CRITICAL
Reduction/cessation of prescribed medication (irregular use) at 12 months - Benzodiazepines												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	56/259 (21.6%)	19.7%	RR 1.1 (0.79 to 1.53)	20 more per 1000 (from 41 fewer to 104 more)	⊕OOO VERY LOW	CRITICAL
Reduction/cessation of prescribed medication (irregular use) at 12 months - Opioids												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20/259 (7.7%)	3%	RR 2.6 (1.16 to 5.79)	48 more per 1000 (from 5 more to 144 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 115: Evidence profile: Patient advice and support (motivational interviewing) versus Usual care (information booklet about prescription drugs in general)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Patient advice and support (motivational interviewing) versus Usual care (information booklet about prescription drugs in general)**	**Control**	**Relative (95% CI)**	**Absolute**		
Reduction/cessation in prescribed drug use (difference in defined daily dose) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	55	62	-	MD 0.3 higher (0.49 lower to 1.09 higher)	⊕OOO VERY LOW	CRITICAL
Cessation of medication (discontinuation) (follow-up 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	10/56 (17.9%)	8.6%	RR 2.08 (0.81 to 5.38)	93 more per 1000 (from 16 fewer to 377 more)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1.4 Patients' experience – GRADE CERQual

Table 116: Qualitative studies with thematic analysis(1-3)

Study design and sample size			Quality assessment		
No of studies contributing to the finding	**Design**	**Findings**	**Criteria**	**Rating**	**Overall assessment of confidence**
Patients experience side effects with prescribed antidepressants					
3	Qualitative	Participants expressed severe emotional/mental side effects with antidepressants. Participants often felt that they were caught in a drug loop and reported feeling dependent on medication, and a fear that discontinuation could cause a crisis.	Limitations	minor limitations	MODERATE
			Coherence	no concerns about coherence	
			Relevance	no concerns about relevance	
			Adequacy	minor concerns about adequacy	
Patients experience withdrawal symptoms with prescribed antidepressants					
1	Qualitative	Participants were reluctant to discontinue medications influenced by previous negative experiences of withdrawal from antidepressants.	Limitations	no limitations	LOW
			Coherence	minor concerns about coherence	
			Relevance	no concerns about relevance	
			Adequacy	substantial concerns about adequacy	
Patients on antidepressants experience difficulty in accessing and engaging in treatment and support					
2	Qualitative	Participants described prescribers not listening to their concerns.	Limitations	minor limitations	MODERATE
			Coherence	no concerns about coherence	
			Relevance	no concerns about relevance	
			Adequacy	minor concerns about adequacy	

Table 117: Studies based on online information(4-8)

Study design and sample size			Quality assessment		
No of studies contributing to the finding	**Design**	**Findings**	**Criteria**	**Rating**	**Overall assessment of confidence**
Patients experience side effects with prescribed antidepressants					
2	1 online survey; 1 analysis of postings on a health related website.	Participants experienced negative physical, emotional, sexual and social side effects with antidepressants.	Limitations	severe limitations	LOW
			Coherence	no concerns about coherence	
			Relevance	no concerns about relevance	
			Adequacy	no concerns about adequacy	
Patients experience withdrawal symptoms with prescribed antidepressants					
3	1 qualitative google searches of relevant websites; 1 analysis of postings on a health related website; 1 posts from an antidepressant withdrawal website.	Participants experienced a range of physical and mental side effects when discontinuing antidepressants.	Limitations	severe limitations	LOW
			Coherence	no concerns about coherence	
			Relevance	no concerns about relevance	
			Adequacy	no concerns about adequacy	
Patients on antidepressants experience difficulty in accessing and engaging in treatment and support					
3	2 online surveys; 1analysis of postings on a health related website.	Participants experience was that there was not sufficient/lack of information offered on the side effects and withdrawal associated with the antidepressants and they felt frustrated at not being listened to by their physicians or not being taken seriously.	Limitations	severe limitations	LOW
			Coherence	no concerns about coherence	
			Relevance	no concerns about relevance	
			Adequacy	no concerns about adequacy	

Table 118: Grey literature reports(9-12)

Study design and sample size			Quality assessment		
No of studies contributing to the finding	**Design**	**Findings**	**Criteria**	**Rating**	**Overall assessment of confidence**
Patients experience side effects with prescribed benzodiazepines, z-drugs, opioids and antidepressants					
3	2 reports; 1 HTA (qualitative and mixed methods)	Participants felt that there were diverse physical symptoms due to withdrawal.	Limitations	minor limitations	HIGH
			Coherence	no concerns about coherence	
			Relevance	no concerns about relevance	
			Adequacy	no concerns about adequacy	
Patients experience withdrawal symptoms with prescribed benzodiazepines, z-drugs, opioids and antidepressants					
3	2 reports; 1 HTA (qualitative and mixed methods)	Participants described withdrawal as incapacitating and disabling and experienced a negative impact on relationships and social life, occupational impact and emotional impact with prescribed drugs.	Limitations	minor limitations	HIGH
			Coherence	no concerns about coherence	
			Relevance	no concerns about relevance	
			Adequacy	no concerns about adequacy	
Patients on benzodiazepines, z-drugs, opioids and antidepressants experience difficulty in accessing and engaging in treatment and support					
3	2 reports; 1 HTA (mixed methods)	Participants felt that there was lack of access to effective management and informed medical oversight of dependence and withdrawal process.	Limitations	minor limitations	HIGH
			Coherence	no concerns about coherence	
			Relevance	no concerns about relevance	
			Adequacy	no concerns about adequacy	

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1.5 Current practice service examples

GRADE assessment was not possible for this data.

Table S6. Summary of evidence on patients' reports of antidepressant-associated side-effects, withdrawal symptoms and treatment services

			Summary of patient reports and experiences of antidepressants		
Study/date	**Design**	**Data**	**Side-effects/adverse drug reactions/concerns**	**Withdrawal symptoms following dose reduction/cessation**	**Views of treatment/services**
Avery 2011	Mixed methods	270 patient yellow card reports	(Severe) agitation, feeling stressed, nervous, mood swings, paranoia. Recurrent suicidal thinking.	Sudden change in emotion/mood, insomnia, excessive anxiety, agitation, sweating/palpitations; bouts of stomach upsets, nausea, dizziness, aching joint/flu symptoms, headache, disorientation, aggression. Irritable bowel symptoms, electric shock-like sensations, confusion. Balance problems, no appetite, stomach pain.	Many favourable comments about doctors. Small minority felt GP had not known about the risk of side-effects or had not understood them or ignored them.
Bayliss 2015	Qualitative study with thematic analysis	12 patients	Several participants felt they were dependent on medication, feeling fragile and worried that a crisis would ensue if this was discontinued.	Felt like losing you mind when coming off and getting really depressed.	One participant commented that dose adjustment and medication switches left them feeling they were: "stuck in a loop where they just prescribe [to] you". Brief consultations felt not adequate to address needs. Perception that underlying cause of illness not addressed.
Belaise 2012	Analysis of website posts	12 patients who had discontinued	Not an aim of the study.	Most frequent symptoms reported significant persistent post withdrawal emergent symptoms including anxiety, panic, insomnia, depression, mood swings, irritability, impaired concentration/memory.	Not an aim of the study.
Davies 2018	On-line survey/mixed methods	186 respondents	Not an aim of the study.	Withdrawal perceived as incapacitating and disabling which impacted on all aspects of personal, social, occupational functioning and finances. Withdrawal placing great strain on relationships, with friends lost due to isolation, and dependence on carers. Many reports of withdrawal as protracted and sometimes unbearable process, often unsuccessful causing pessimism and hopelessness.	Many reports expressing disillusionment with medicine and medical professionals due to not being adequately informed before treatment of the risk of withdrawal, and being offered no adequate withdrawal management and support.

continued …/

Table S6: continued …/

			Summary of patient reports and experiences of antidepressants		
Study/date	**Design**	**Data**	**Side-effects/adverse drug reactions/concerns**	**Withdrawal symptoms following dose reduction/cessation**	**Views of treatment/services**
Dickenson 2010	Qualitative study with semi-structured interviews	36 patients (aged over 75)	Not an aim of the study.	Reports of unsuccessful attempts to discontinue antidepressants. Anxiety about attempting to withdraw.	Belief (often with some acceptance) that antidepressant medication will be for rest of life, so adherent to prescription. Doctors believed to see depression as general condition of old age. Medication not addressed at annual clinical review.
Guy 2018	Mixed-methods	158 petition submissions People taking antidepressants or benzodiazepines	Belief that over time medication has no effect and cause anxiety, depression, suicidal thoughts and anger. Mood swings. Deteriorated mood after dose increase. Side-effects persisting for years.	Followed 4-week taper and felt "…mental and physical anguish." Suffering feels intolerable, debilitating symptoms, left bed-ridden. Unable to work. Lost all savings, risk of losing home.	Wish had been offered talking therapy 17 years ago. Doctor did not warn about side-effects. Feeling that clinicians do not agree about diagnosis and treatment. Sough second opinion; felt understood which was vital.
Pestello 2008	Analysis of online forum posts	227 posts on health-related website	Vivid nightmares, night sweats. Weight gain. Acute anxiety, Palpitations. Loss of sex drive, sexual dysfunction. Memory loss. Hallucinations.	Dizzy spells. Nausea. Lips numb. More anxious and depressed. Feel electric shocks.	Felt not listened to and taken seriously by doctors. Feel "I am a number and not a name". "…doctors can't seem to help me."
Read 2017	Analysis of an on-line survey	1,008 respondents	Medication causing drowsiness, tiredness, and fatigue causing problems with concentration and memory and negatively impacting on personal, social and occupational functioning. Blunting of affect. "…makes me totally disconnected…". No sexual desire.	Not an aim of the study.	Pros and cons of medication should have been emphasised. Risk of side-effects not explained very well, or not discussed. Had to obtain information myself.

continued …/

Table S6. continued …/

			Summary of patient reports and experiences of antidepressants		
Study/date	**Design**	**Data**	**Side-effects/adverse drug reactions/concerns**	**Withdrawal symptoms following dose reduction/cessation**	**Views of treatment/services**
Read 2018	Analysis of an on-line survey	752 respondents	Not an aim of the study.	Not an aim of the study.	Mixed: some positive reports relating to regular GP monitoring; some negative reports of receiving repeat prescriptions only with no or little monitoring and interest in doing so.
Schofield 2011	Qualitative study with thematic analysis	65 patients	Fear of addiction, stigma, cost and experience of side-effects (felt numb and abnormal) led some to experiment with timing and dosing of medication.	"…biggest side effect is every time when I stop I become a lot worse than what I was to begin with."	Felt unable to contribute to initial discussion with GP, but most expected to get better. Longer-term users reported good relationship with GP, as they became an expertise in their own treatment, some reluctant to come off.
Stockman 2018	On-line survey	174 respondents	Not an aim of the study.	SSRI/SSNI withdrawal symptoms reported were grouped by system and grouped in descending order of frequency of report: neurological, gastrointestinal, musculoskeletal and cardiovascular. psychological, respiratory, psychosexual/genitourinary, other.	Not an aim of the study.