Supplementary appendix

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

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## SUPPLEMENTARY APPENDIX

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### 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) |
|---------|------------|------|----------------|-------------|------------|-------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------|
| 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. | 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 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. | Treatment should, if possible, be on an intermittent basis. 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. | Treatment should not normally be continued beyond 4 weeks. Avoid prolonged use (and abrupt withdrawal thereafter) |

**Notes:**
- **BNF:** British National Formulary
- **Cat:** Category
- **Legal category:** Classification of drugs by legal category
- **Drug class:** Classification of drugs by therapeutic group
- **Indications:** Conditions for which the drug is prescribed
- **Usual dose:** Recommended dose for different age groups
- **Additional notes on drug and/or dose:** Additional information on the use and administration of the drug
- **Index events:** Events when the drug might be prescribed, reviewed, or the dose increased/decreased/ceased
- **Recommended limits (on duration of prescribing):** Guidelines for the duration of treatment
- **SPC:** Summary of Product Characteristics
- **BNF:** British National Formulary
- **NICE:** National Institute for Health and Care Excellence
- **Opioids aware:** Information on opioids awareness

**References:**
- [https://cks.nice.org.uk/inomnia#!scenario:1](https://cks.nice.org.uk/inomnia#!scenario:1)
| Benzodiazepines | CD | Drug | Insomnia | Dosage | Notes |
|-----------------|----|------|----------|--------|-------|
| **Benzodiazepines** | **CD 3** | Temazepam | Insomnia (short-term use) | Adult 10–20 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. 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. |
| **Benzodiazepines** | **CD 3** | Zaleplon | Insomnia (short-term use) | By mouth | 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. 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. |

**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)

**Avoid prolonged use (risk of tolerance and withdrawal symptoms)**
4.1.1 Z-drugs

**Zopiclone**

| Scenario | Adult | Elderly |
| --- | --- | --- |
| Short-term insomnia related to emotional problem or serious medical illness. 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. | 7.5 mg daily | 3.75 mg daily, increasing to 7.5 mg daily |

4.1.1 Chloral and derivatives

**Chloral hydrate**

| Scenario | Adult | Elderly |
| --- | --- | --- |
| Short-term insomnia related to an emotional problem or serious medical illness. 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. | 0.5–2 g daily | 1–2 tablets, alternatively 414–828 mg once daily, maximum 2 g per day |

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

**Use**

- 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.

Avoid prolonged use (and abrupt withdrawal thereafter)

4.1.1 Insomnia

**Chloral Mixture**

| Scenario | Adult | Elderly |
| --- | --- | --- |
| Short-term insomnia related to an emotional problem or serious medical illness. 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. | 0.5–2 g daily | 1–2 tablets, alternatively 414–828 mg once daily, maximum 2 g per day |

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

**Use**

- 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.

Avoid prolonged use (and abrupt withdrawal thereafter)

4.1.1 Insomnia

**Insomnia**

| Scenario | Adult | Elderly |
| --- | --- | --- |
| Insomnia (short-term use in patients with chronic pulmonary insufficiency) | 3.75 mg daily once daily for up to 4 weeks, dose to be taken at bedtime, increased if necessary to 7.5 mg daily | 1.875 mg daily, increasing to 3.75 mg daily |

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

**Use**

- 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.

Avoid prolonged use (and abrupt withdrawal thereafter)
### 4.1.1 Clomethiazole

#### POM

- **Severe insomnia (short-term use)**
  - Capsules: Elderly 192–384 mg once daily, Oral solution Elderly 5–10 mL once daily

#### Elderly

- **Capsules**
  - 192–384 mg once daily
- **Oral solution**
  - 5 mL 3 times a day

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)

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#### Restlessness and agitation

- Capsules: Elderly 192 mg 3 times a day, Oral solution Elderly 5 mL 3 times a day

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)

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#### 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 IM or IV

- **Acute muscle spasm**
  - 10 mg, then 10 mg after 4 hours if required

- **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)

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#### Muscle spasm in cerebral spasticity or in postoperative skeletal muscle spasm

- **Child dose only**

Avoid prolonged use (and abrupt withdrawal thereafter)

---

#### 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
### Benzodiazepines: Diazepam

#### 4.1.2 Benzodiazepines: Diazepam

| Condition                      | Route of Administration                                                                 | Dosage |
|-------------------------------|--------------------------------------------------------------------------------------------|--------|
| **Insomnia associated with anxiety** | Adult: 5–15 mg daily                                                                       |        |
| **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. |        |
| **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. |        |
| **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. |        |
| **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 |        |

**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](https://cks.nice.org.uk/insomnia#!scenario:1)

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

Avoid prolonged use (and abrupt withdrawal thereafter)
4.1.2 Benzodiazepines Diazepam

**Acute anxiety and agitation**

Administered into a large vein, at a rate of not more than 5 mg/minute.

- **By rectum**
  - **Adult**
    - 500 micromg/kg, then 500 micromg/kg after 12 hours as required.
  - **Elderly**
    - 250 micromg/kg, then 250 micromg/kg after 12 hours as required.

**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.

4.1.2 Benzodiazepines Diazepam

**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.

4.1.2 Benzodiazepines Diazepam

**Sedation in dental procedures carried out in hospital**

- **By mouth**
  - **Adult**
    - Up to 20 mg, to be given 1–2 hours before procedure.

4.1.2 Benzodiazepines Diazepam

**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.

4.1.2 Benzodiazepines Diazepam

**Sedative cover for minor surgical and diagnostic procedures**

- **By intravenous injection**
  - **Adult**
    - 10–20 mg, to be
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 minutes if required.

Avoid prolonged use (and abrupt withdrawal thereafter)
4.1.2 Benzodiazepines

Diazepam CD 4.1

- Life-threatening acute drug-induced dystonic reactions
- By mouth
  - Adult
    - 5–10 mg daily

Pain of muscle spasm in palliative care
- By mouth
  - Adult
    - 5–10 mg daily

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 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).

Chlordiazepoxide HCl

- Short-term use in anxiety
  - Adult
    - 10 mg 3 times a day, increased if necessary to 60–100 mg daily in divided doses
  - Elderly
    - 5 mg 3 times a day, increased if necessary to 30–50 mg daily in divided doses

- 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)

Chlordiazepoxide HCl

- 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

Avoid prolonged use (and abrupt withdrawal thereafter)

Avoid prolonged use (and abrupt withdrawal thereafter)

Avoid prolonged use (and abrupt withdrawal thereafter)

Avoid prolonged use (and abrupt withdrawal thereafter)

Avoid prolonged use (and abrupt withdrawal thereafter)

Avoid prolonged use (and abrupt withdrawal thereafter)

Avoid prolonged use (and abrupt withdrawal thereafter)

The overall duration of treatment should not be more than 8–12 weeks, including a tapering off process.

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

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.

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.

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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
| 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) |
|---|---|---|---|---|---|---|---|
| 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 | Avoid prolonged use (and abrupt withdrawal thereafter) |
| 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. | Avoid prolonged use (and abrupt withdrawal thereafter) |
| 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 | 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) |

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

Avoid prolonged use (and abrupt withdrawal thereafter)
### 4.1.2 Benzodiazepine

**Lorazepam**

| Condition | Dosage |
|-----------|--------|
| Status epilepticus | 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)

| Condition | Dosage |
|-----------|--------|
| Febrile convulsions | 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)

**CD 4.1 Premedication**

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.

By mouth

**Adult**

- 2–3 mg, to be taken the night before operation; 2–4 mg, to be taken 1–2 hours before operation.
4.3.1 Antidepressants

**Amitriptyline**

- **Antispasmodic**
  - **Indication:** For the relief of abdominal pain or discomfort caused by gas or spasm of the stomach or intestines.
  - **Dosage:**
    - **Adults:** Initially 25 mg (max. 75 mg) once daily, to be taken at bedtime.
    - **Elderly:** Initially 10 mg once daily, to be taken at bedtime.

**CD 4.1 Intravenous injection**

- **Amitriptyline**
  - **Indication:** For use in cases of poisoning caused by antidepressants.
  - **Dosage:**
    - **Adults:** Initially 25 mg by slow intravenous injection.
    - **Elderly:** Initially 10 mg by slow intravenous injection.

4.3.1 Antidepressants

**Oxazepam**

- **Antispasmodic**
  - **Indication:** For the relief of abdominal pain or spasm of the stomach or intestines.
  - **Dosage:**
    - **Adults:** Initially 20 mg 3 times a day, increased as necessary to 150 mg.
    - **Elderly:** Initially 10 mg 3 times a day, increased as necessary to 75 mg.

4.3.1 Antidepressants

**Lorazepam**

- **Antispasmodic**
  - **Indication:** For the relief of abdominal pain or spasm of the stomach or intestines.
  - **Dosage:**
    - **Adults:** Initially 4 mg for 1 dose, then 4 mg after 10 minutes if required for 1 dose, to be administered into a large vein.
    - **Elderly:** Initially 10–20 mg 3–4 times a day.

**4.1.2 Benzodiazepines**

**Lorazepam**

- **Antispasmodic**
  - **Indication:** For the relief of abdominal pain or spasm of the stomach or intestines.
  - **Dosage:**
    - **Adults:** Initially 20 mg 3 times a day, increased as necessary to 150 mg.
    - **Elderly:** Initially 10 mg 3 times a day, increased as necessary to 75 mg.

**Physiological benefits**

- **Contraindications:**
  - **Depression:** co-administration with other antidepressants.
  - **Oxazepam:** Patients with a history of epilepsy or who are taking other drugs known to interact with oxazepam.
  - **Lorazepam:** Patients with a history of addiction to alcohol or other drugs.

**4.1.2 Benzodiazepines**

**Oxazepam**

- **Antispasmodic**
  - **Indication:** For the relief of abdominal pain or spasm of the stomach or intestines.
  - **Dosage:**
    - **Adults:** Initially 20 mg 3 times a day, increased as necessary to 150 mg.
    - **Elderly:** Initially 10 mg 3 times a day, increased as necessary to 75 mg.

**Physiological benefits**

- **Contraindications:**
  - **Depression:** co-administration with other antidepressants.
  - **Oxazepam:** Patients with a history of epilepsy or who are taking other drugs known to interact with oxazepam.
  - **Lorazepam:** Patients with a history of addiction to alcohol or other drugs.

**4.1.2 Benzodiazepines**

**Lorazepam**

- **Antispasmodic**
  - **Indication:** For the relief of abdominal pain or spasm of the stomach or intestines.
  - **Dosage:**
    - **Adults:** Initially 20 mg 3 times a day, increased as necessary to 150 mg.
    - **Elderly:** Initially 10 mg 3 times a day, increased as necessary to 75 mg.

**Physiological benefits**

- **Contraindications:**
  - **Depression:** co-administration with other antidepressants.
  - **Oxazepam:** Patients with a history of epilepsy or who are taking other drugs known to interact with oxazepam.
  - **Lorazepam:** Patients with a history of addiction to alcohol or other drugs.

**4.1.2 Benzodiazepines**

**Oxazepam**

- **Antispasmodic**
  - **Indication:** For the relief of abdominal pain or spasm of the stomach or intestines.
  - **Dosage:**
    - **Adults:** Initially 20 mg 3 times a day, increased as necessary to 150 mg.
    - **Elderly:** Initially 10 mg 3 times a day, increased as necessary to 75 mg.

**Physiological benefits**

- **Contraindications:**
  - **Depression:** co-administration with other antidepressants.
  - **Oxazepam:** Patients with a history of epilepsy or who are taking other drugs known to interact with oxazepam.
  - **Lorazepam:** Patients with a history of addiction to alcohol or other drugs.

**4.1.2 Benzodiazepines**

**Lorazepam**

- **Antispasmodic**
  - **Indication:** For the relief of abdominal pain or spasm of the stomach or intestines.
  - **Dosage:**
    - **Adults:** Initially 20 mg 3 times a day, increased as necessary to 150 mg.
    - **Elderly:** Initially 10 mg 3 times a day, increased as necessary to 75 mg.

**Physiological benefits**

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  - **Depression:** co-administration with other antidepressants.
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4.3.1 Antidepressants

### Amitriptyline

| POM | Neuropathic pain | By mouth | Adult
|-----|-----------------|----------|----------|
|     | 30–75 mg once daily | Initially 30 mg, 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. |

**Perphenazine with Amitriptyline**

- **Migraine prophylaxis**
  - By mouth
  - Adult
  - Initially 10 mg once daily, increased if necessary to 50–75 mg once daily (max. per dose 150 mg), dose to be taken at night.

**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**

1.5.2.7 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.

### Notes

- **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.**

- **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.**

- **Followings, 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.**

- **Continuation of the treatment remains appropriate for the patient.**

### Recommendations

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

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**Antidepressants**

- **Neuropathic pain**
- **Migraine prophylaxis**
- **Depression with anxiety**

- **Elderly**
  - **By mouth**
  - **Adult**
  - **Initial 10 mg once daily, increased if necessary to 75 mg once daily, taken at bedtime.**
  - **200 mg daily, dose to be increased gradually.**

### NICE CG150

- **https://www.nice.org.uk/guidance/cg150/chapter/Recommendations**

### NICE CG173

- **https://www.nice.org.uk/guidance/cg173/chapter/1.3.22**

### NICE CG90

- **https://www.nice.org.uk/guidance/cg90**
4.3.1 Antidepressants

| Amoxapine | NOT LISTED IN BNF |
|-----------|--------------------|

### 4.3.1 Antidepressants

| Clomipramine | POM |
|--------------|-----|

#### 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 treatment 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.

1.5.2.8 The person with depression the need for continued antidepressant treatment beyond 6 months after remission.

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.

1.9.1.3 Advise 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

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.

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If possible tricyclic and related antidepressants should be withdrawn slowly.
### 4.3.1 Antidepressants

#### Clomipramine

**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.

#### Adjunctive treatment of cataplexy associated with narcolepsy

**Adult**
- Initially 10 mg daily; increased if necessary to 10–75 mg daily

**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 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.

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

**Doxepin**

POM (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).

**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.

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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 2 years 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.

1.9.1.3 Advise 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**

**Adult**
- Initially up to 75 mg daily, increased to 150–200 mg daily.

**Elderly**
- Initially 10 mg daily, increased to 30–50 mg daily.

**Patients** should be monitored 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.

**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.

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1.9.1.4 Advise people with depression who have benefited from taking an antidepressant to continue regular 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.

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### 4.3.1 Antidepressants

| Name          | Dose             | Depressive Illness | Adult | Elderly/Young Adults |
|---------------|------------------|--------------------|-------|----------------------|
| Lofepramine POM | 140–210 mg daily | 100 mg daily       |       | May respond to lower doses |
| Nortriptyline  |                  |                    |       |                      |

#### 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.

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maximum 150 mg per day.

Elderly
To be initiated at a low dose, then increased if necessary to 30–50 mg daily.

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) 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

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

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.

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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).

If possible tricyclic and related antidepressants should be withdrawn slowly.

Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment.

Patient 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.

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If possible tricyclic and related antidepressants should be withdrawn slowly.
4.3.1 Antidepressants

Mianserin

POM

Depression (particularly where agitation is required)

Adults 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

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If possible tricyclic and related antidepressants should be withdrawn slowly.

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

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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/umpc

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

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

1.9.1.4 Advise 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

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 symptoms 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 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.

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

1.9.1.4 Advise 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

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/umpc

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 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.

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

1.9.1.4 Advise 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

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 symptoms 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 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.

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

1.9.1.4 Advise 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

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 symptoms 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 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.

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

1.9.1.4 Advise 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.
4.3.1 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.

1.9.1.4 Advise 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

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 depression, taking into account age, comorbid conditions and other risk factors.

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

Isocarboxazid

Phenelzine

Not in BNF

Depressive Illness

Adult

Initially 15 mg 3 times a day, dose may be increased if necessary after 2 weeks if response not evident, increased dosage 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).

Elderly

5-10 mg daily

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

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.
| 4.3.2 Antidepressants | Tranylcypromine | Depressive Illness | Adult | Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment |
|----------------------|-----------------|-------------------|------|---------------------------------------------------------------------------------|
| Moclobemide | Tranylcypromine | Illness | 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 if necessary before 8 weeks of antidepressant treatment for this group. Patients should normally be seen after 1 week and then 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good.

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).

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

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).

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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).

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

If possible avoid abrupt withdrawal. MAOIs are associated with withdrawal symptoms on cessation of therapy. If possible MAOIs 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.

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).

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

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).

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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).

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

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).

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

If possible avoid abrupt withdrawal. MAOIs are associated with withdrawal symptoms on cessation of therapy. If possible MAOIs should be withdrawn slowly.
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.

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

1.9.1.4 Advise 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/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.

from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression.

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/
4.3.3 Antidepressants

Citalopram

Depressive illness

Tablets

Adults

20 mg once daily, maximum 40 mg per day.

Elderly

10–20 mg once daily, maximum 20 mg per day.

Oral drops

Adults

8–16 mg daily; maximum 16 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.

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).

1.4.25 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 1.4.5) should be offered.

NICE CG113

1.9.1.5 When deciding whether to continue antidepressants for at least 2 years if they are at risk of relapse, factors such as efficacy, benefit and risk should be considered. For more information, see NICE guidance on long-term antidepressant treatment for depression.

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

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

1.1.5 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

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
4.3.1 Antidepressants Escitalopram POM Depressive illness

By mouth
Adult
Initial 8 mg once daily, increased in steps of 8 mg if required, dose to be increased gradually; maximum 16 mg per day.

Elderly
Initial 5 mg once daily; maximum 10 mg per day.

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.

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).

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

Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment and then at longer intervals if response is good.

Follow the drug to determine the likelihood of relapse in the first year and whether maintenance treatment is needed.

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

Elderly
Initial 8 mg once daily, increased in steps of 8 mg if required, dose to be increased gradually; maximum 16 mg per day.

Elderly
Initial 5 mg once daily; maximum 10 mg per day.

If the drug is effective, advise the person to continue taking it for at least one year as the likelihood of relapse is high.

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

4.3.0 Antidepressants Escitalopram POM Generalised anxiety disorder

By mouth
Adult
Initial 10 mg once daily; increased if necessary up to 20 mg daily.

Elderly
Initial 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

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

4.3.1 Antidepressants Escitalopram POM Obsessive-compulsive disorder

By mouth
Adult
Initial 10 mg once daily; increased if necessary up to 20 mg daily.

Elderly
Initial 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

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
### Antidepressants

#### Escitalopram

**Panic disorder**

- **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.

- **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.
  - **Elderly**
    - Initially 20 mg daily, usual maximum 40 mg daily but dose up to 60 mg can be used.

- **Major depression**
  - By mouth
  - **Adult**
    - Initially 20 mg daily, maximum 60 mg daily.
    - Dose is increased after 3–4 weeks if necessary, and at appropriate intervals thereafter.
  - **Elderly**
    - Initially 20 mg daily, usual maximum 40 mg daily but dose up to 60 mg can be used.

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

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**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

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.

1.9.1.4 Advise 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.

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 40 mg daily but dose up to 60 mg can be used.

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.

Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment.

4.3.3 Antidepressants

Fluoxetine POM

Obsessive-compulsive disorder

Adult

20 mg daily, increased if necessary up to 60 mg daily

Elderly

20 mg, increased if necessary to 40 mg daily

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.

4.3.3 Antidepressants

Fluoxetine POM

Menopausal symptoms, particularly hot flushes, in women with breast cancer (except those taking tamoxifen)

20 mg daily

Patients who have benefited from taking an antidepressant should be encouraged to continue medication for at least 6 months after remission of an episode of depression.

4.3.3 Antidepressants

Fluvoxamine POM

Depressive illness

Maintenance 100 mg 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.

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.

1.9.1.4 Advise 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...
### 4.3.3 Antidepressants

| Drug          | Dosage | Indication                  | Duration |
|---------------|--------|-----------------------------|----------|
| **Fluvoxamine** | 100–300 mg daily | Obsessive-compulsive disorder | Maintenance beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors |
| **Paroxetine**  | 20 mg daily, maximum 50 mg per day | Major depression | At least 6 months to ensure 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. |

**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. Other risk factors include age, comorbid conditions and other risk factors.

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. 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.
### 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.

#### Post-traumatic stress disorder
- **Adult**
  - 20 mg daily, maximum 50 mg per day.
- **Elderly**
  - 20 mg daily; maximum 40 mg per day.

#### Generalised anxiety disorder
- **Adult**
  - 20 mg daily, maximum 50 mg per day.
- **Elderly**
  - 20 mg daily; maximum 40 mg per day.

#### 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.

#### 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.

#### Menopausal symptoms, particularly hot flushes, in women with breast cancer (except those taking tamoxifen)
- **Adult**
  - 10 mg once daily

#### Depressive illness
- **Maintenance 50 mg daily**

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

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

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

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

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.

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.

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.

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.

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.
3.3 Antidepressants Sertraline POM Social anxiety disorder
maximum 200 mg per day
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.

4.3.3 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
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.

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).

4.3.4 Antidepressants Agomelatine POM Major depression
Adult
25 mg daily, increased if necessary to 50 mg daily
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.

4.3.4 Antidepressants Agomelatine POM Major depression
Adult
25 mg daily, increased if necessary to 50 mg daily
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 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.

4.3.4 Antidepressants Duloxetine POM Major depression
Adult
60mg once daily
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.

19.1.1.1 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.

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

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

19.1.5 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.

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If the drug is effective, advise the person to continue taking it for at least a year as the likelihood of relapse is high.

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| 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

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

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

https://www.nice.org.uk/guidance/cg173/chapter/1-

Recommendations

| 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 |

Discontinue if inadequate 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

| 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. |

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.

1.9.1.4 Advise 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.

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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.

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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.

1.9.1.4 Advise 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

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4.3.4 Antidepressants Reboxetine POM Major depression Adult 4 mg twice daily for 4–4 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 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.

1.9.1.4 Advise 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

continuing antidepressants for at least 2 years if they are at risk of relapse.
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.

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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.

1.9.1.4 Advise 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

1.1.1 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.

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

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

1.1.5 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression.
Antidepressants Venlafaxine POM

**4.3.4 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.

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**4.3.4 Generalised anxiety disorder**
- Modified-release medicines
  - 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

**4.3.4 Social anxiety disorder**
- Modified-release medicines
  - 75 mg once daily, increased if necessary up to 225 mg once daily

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 Menopausal symptoms, particularly hot flushes,**
- Modified-release
  - 37.5 mg once daily for one week, then

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.

1.5.1.1 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.

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

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

1.5.1.5 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

1.5.1.6 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.

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

Vortioxetine POM

Major depression

Increased if necessary to 75 mg once daily.

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.

4.3.4 Antidepressants

Nefazodone Not in BNF

4.3.4 Antidepressants

Oxitriptan Not in BNF

4.7.2 Opioid pain medicines

Buprenorphine CD3

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 120 mg oral morphine equivalent/24 hours.

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.

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.

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.

1.9.1.4 Advise 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
| 4.7.2 Opioid pain medicines | **Buprenorphine** CD3 | **Premedication** | **By sublingual administration**<br>Adult 400 micrograms. By intramuscular injection<br>Adult 300 micrograms. Slow intravenous injection<br>Adult 300–450 micrograms. Sublingual tablets<br>Adult Usual dose 12–24 mg daily; maximum 32 mg per day. Oral lyophilisate<br>Adult Maximum 18 mg per day. | 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 | **Intra-operative analgesia** | **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 120 mg oral morphine equivalent/24 hours. | 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 | **Adjunct in the treatment of opioid dependence** | **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 time). Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120 mg oral morphine equivalent/24 hours. | 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. |

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.

Maximum 2 patches can be used at any one time.

When stable, review every 6 months.

4.7.2 Opioid pain medicines

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

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

Codeine

Tablet -CD5
Soln -CD2
Oral soln- CD5

Acute diarrhoea

Usual dose 15–60 mg 3–4 times a day

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.

4.7.2 Opioid pain medicines

Codeine

Tablet -CD5
Soln -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

Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
| 4.7.2 Opioid pain medicines | Codeine | Tablet, Soln, Inj, Oral soln - CD5, CD2 | Short-term treatment of acute moderate pain | 30–60 mg every 4 hours if required. Child dose only |
|------------------------------|---------|-------------------------------------------|---------------------------------------------|--------------------------------------------------|

| 4.7.2 Opioid pain medicines | Codeine | Tablet - CD5, Soln - CD2, CD5 | Dry or painful cough | By mouth using linctus |
|------------------------------|---------|-------------------------------|---------------------|----------------------|
| Adult                       | 15–30 mg 3–4 times a day. |                          |                     |                      |

| 4.7.2 Opioid pain medicines | Co-codamol | CD5 | Mild to moderate pain (using co-codamol 8/500 preparation(s) only) | 8/500–16/1000 mg every 4–6 hours as required; maximum 64/4000 mg per day. |
|------------------------------|-------------|-----|-------------------------------------------------------------------|---------------------------------------------------------------------|

| 4.7.2 Opioid pain medicines | Co-codamol | CD5 | Mild to moderate pain (using co-codamol 15/500 preparation(s) only) | 15/500–30/1000 mg every 4–6 hours as required; maximum 120/4000 mg per day. |
|------------------------------|-------------|-----|-------------------------------------------------------------------|---------------------------------------------------------------------|

| 4.7.2 Opioid pain medicines | Co-codamol | CD5 | Severe pain (using co-codamol 30/500 preparation(s) only) | 30/500–60/1000 mg every 4–6 hours as required; maximum 240/4000 mg per day. |
|------------------------------|-------------|-----|-------------------------------------------------------------------|---------------------------------------------------------------------|

| 4.7.2 Opioid pain medicines | Diamorphine | CD2 | Acute pain | 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. | Adult 1.25–2.5 mg every 4 hours if required. |
| 4.7.2 Opioid pain medicines | Diamorphine CD2 Chronic pain or 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. |
| 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. 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. |
| 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. 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. |
| 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. By mouth using immediate-release medicines Adult. 30 mg every 4–6 hours as required. By deep subcutaneous injection, or by intramuscular injection |
| 4.7.2 Opioid pain medicines | Dihydrocodeine MR tablet 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 |

**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 first 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

| Medicine          | Formulation                  | Severe Pain | By mouth | Adult | Up to 50 mg every 4–6 hours if required. 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. |
|-------------------|------------------------------|-------------|----------|-------|--------------------------------------------------------------------------------|-------|--------------------------|--------------------------------------------------------------------------------------------------|
| Dihydrocodeine    | MR tablet CD5                | Chronic    |          |       |                                                                                  |       |                          |                                                                                                  |
|                   | Tablet CD5                  |             |          |       |                                                                                  |       |                          |                                                                                                  |
|                   | Soln CD5                    |             |          |       |                                                                                  |       |                          |                                                                                                  |
|                   | Oral soln CD5               |             |          |       |                                                                                  |       |                          |                                                                                                  |
| CD2 Oral soln CD5 |                              |             |          |       |                                                                                  |       |                          |                                                                                                  |

### 4.7.2 Opioid pain medicines

| Medicine          | Formulation                  | Severe Pain | By mouth | 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. |
|-------------------|------------------------------|-------------|----------|-------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Dihydrocodeine    | For DF118 Forte®             |             |          |       |                                                                                  |                                                                                                  |
|                   | Soln inj CD5                |             |          |       |                                                                                  |                                                                                                  |
|                   | Oral soln CD5               |             |          |       |                                                                                  |                                                                                                  |

### 4.7.2 Opioid pain medicines

| Medicine          | Formulation                  | Severe Pain | By mouth | Adult | 10/500 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. |
|-------------------|------------------------------|-------------|----------|-------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Co-dydramol       | CD5                          |             |          |       |                                                                                  |                                                                                                  |
|                   |                              | Mild to moderate pain (using 10/500 preparations only) |          |       |                                                                                  |                                                                                                  |

### 4.7.2 Opioid pain medicines

| Medicine          | Formulation                  | Severe Pain | 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. |
|-------------------|------------------------------|-------------|----------|-------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Co-dydramol       | CD5                          |             |          |       |                                                                                  |                                                                                                  |
|                   |                              | Severe pain (using 20/500 preparations only) |          |       |                                                                                  |                                                                                                  |

### 4.7.2 Opioid pain medicines

| Medicine          | Formulation                  | Severe Pain | 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. |
|-------------------|------------------------------|-------------|----------|-------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Co-dydramol       | CD5                          |             |          |       |                                                                                  |                                                                                                  |
|                   |                              | Severe pain (using 30/500 preparations only) |          |       |                                                                                  |                                                                                                  |

### 4.7.2 Opioid pain medicines

| Medicine          | Formulation                  | 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. |
|-------------------|------------------------------|-------------|----------|-------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Dipipanone (with cyclizine) | CD2                      |             |          |       |                                                                                  |                                                                                                  |

### 4.7.2 Opioid pain medicines

| Medicine          | Formulation                  | Chronic intractable pain not currently treated with a strong opioid analgesic | 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 | Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms. |
|-------------------|------------------------------|--------------------------------------------------------------------------------|--------------|--------------------------------------------------------------------------------|----------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Fentanyl          | CD2                          |                                                                                  |              |                                                                                  |                                                                                                  |
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. By transdermal application Adult Initial dose based on previous 24-hour opioid requirement (consult product literature) benefits is 120mg oral morphine equivalent/24hours.

4.7.2 Opioid pain medicines

Fentanyl CD2

Chronic intractable pain currently treated with a strong opioid analgesic

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

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.

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

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 | 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/h, adjusted according to response, may require up to 180 micrograms/kg/h our 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.
| 4.7.2 Opioid pain medicines | Hydromorphone | CD2 | Severe pain in cancer |
|-----------------------------|---------------|-----|----------------------|
| 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.             |               |     |                      |

| 4.7.2 Opioid pain medicines | Meptazinol POM | Moderate to severe | By mouth |
|-----------------------------|----------------|-------------------|----------|
| Opioid trial                |               |                   |          |
| Avoid abrupt withdrawal     |               |                   |          |
| after long-term treatment;  |               |                   |          |
| they should be withdrawn    |               |                   |          |
| gradually to avoid          |               |                   |          |
| abstinence symptoms.        |               |                   |          |
| 4.7.2 Opioid pain medicines | Meptazinol POM Obstetric analgesia |
|----------------------------|----------------------------------|
| 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. |

| 4.7.2 Opioid pain medicines | Methadone CD2 Severe pain |
|----------------------------|--------------------------|
| 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 |

| 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. |

| 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. |

| 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) |

| 4.7.2 Opioid pain medicines | Methadone CD2 Obstetric analgesia |
|----------------------------|----------------------------------|
| 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. |

| Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms. |
| Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms. |
| Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms. |
| Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms. |
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| Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms. |
| Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms. |

| Opioid trial if possible, use immediate release morphine (tablets or liquid), prescribed for 1–2 weeks |

| 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. |
| Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms. |
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| Opioid trial if possible, use immediate release morphine (tablets or liquid), prescribed for 1–2 weeks |

| 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. |
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| Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms. |
| 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

Reduced to 1–2 mg twice daily, use twice daily frequency if prolonged use. Child dose only

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.

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.

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 12-hourly preparation) | 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. |
| Pain (with modified-release 24-hourly preparation) | 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. |
| Pain management in palliative care (starting dose for) | By mouth using modified-release preparations. Adult. 20-30 mg daily in divided doses, using immediate-release preparation 4-hourly or a 12-hourly preparation. |

**Opioid** states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/24hours.

**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 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 |
| 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. |
|避免突然撤药，长期治疗后应逐渐减量以免出现戒断症状。|

| 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. |
|避免突然撤药，长期治疗后应逐渐减量以免出现戒断症状。|

| 4.7.2 Opioid pain medicines | Morphine | CD 2 | Cough in terminal disease |
|-----------------------------|----------|------|--------------------------|
| By mouth                    | Adult    | 5 mg every 4 hours. |
| Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms. |
|避免突然撤药，长期治疗后应逐渐减量以免出现戒断症状。|

| 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. |
| Consult local protocol |
| Opioid trial |
| If possible, use immediate release morphine (tablets or liquid), prescribed for 1-2 weeks |
| Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms. |
|避免突然撤药，长期治疗后应逐渐减量以免出现戒断症状。|

| 4.7.2 Opioid pain medicines | Morphine | CD 2 | Patient controlled analgesia (PCA) |
|-----------------------------|----------|------|----------------------------------|
| Opioid Aware states that the dose of opioids above which harms |
| Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms. |
|避免突然撤药，长期治疗后应逐渐减量以免出现戒断症状。|
outweigh benefits is 120mg oral morphine equivalent/24 hours.

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.

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.
4.7.2 Opioid pain medicines

Morphine plus cyclizine

**For Cyclimorph-10®:**
Moderate to severe pain (short-term use only)

maximum 3 doses per day.

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

Postoperative pain

**For Cyclimorph-10®**
Moderate to severe pain (short-term use only)

maximum 3 doses per day.

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.

**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.

Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

**Oxycodone CD2**

**Postoperative pain**

**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.

Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

**Oxycodone CD2**

**Postoperative pain**

**By slow intravenous injection**

Adult
1–10 mg every 4 hours as required.

Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

**Oxycodone CD2**

**Postoperative pain**

**By intravenous infusion**

Adult
Initially 2 mg/hour, adjusted according to response.
| 4.7.2  | Opioid pain medicines | Oxycodone CD2 | Severe pain |
|--------|-----------------------|---------------|-------------|
|        |                      |               |             |

| 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. |

**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 120 mg oral morphine equivalents/24 hours.

**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 CD2 | Moderate to severe pain in palliative care |
|-----------------------------|--------------|------------------------------------------|

**Adult**

**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.
| 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. |
|-----------------------------|-------------------------------------------------|------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| 4.7.2 Opioid pain medicines | Oxycodone CD2 Severe pain (Oxela XL®) | By mouth Adult
Initial 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. |
| 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
Initial 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 be switched to Oxycodone with naloxone (on a mg for mg basis) and titrated to efficacy | Opioid Aware states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/24hours. |

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**Adult**

**Initially** 5 mg every 4 hours as required.

By subcutaneous infusion

**Adult**

Initially 7.5 mg/24 hours, adjusted according to response.

---

**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.

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**Opioid Aware** states that the dose of opioids above which harms outweigh benefits is 120mg oral morphine equivalent/24hours.
### 4.7.2 Opioid pain medicines

#### Oxycodone with naloxone

**Second-line treatment of symptomatic severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy**  

| Route                                      | Dosage                  |
|--------------------------------------------|-------------------------|
| 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 120 mg oral morphine equivalent/24 hours. |

*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.*

---

#### Papaveretum

**Postoperative analgesia**

| Route                                      | Dosage                  |
|--------------------------------------------|-------------------------|
| By subcutaneous injection, or by intramuscular injection Adult | 7.7–15.4 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.*

---

#### Papaveretum

**Severe chronic pain**

| Route                                      | Dosage                  |
|--------------------------------------------|-------------------------|
| By subcutaneous injection, or by intramuscular injection Adult | 7.7–15.4 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.*

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#### Papaveretum

**Premedication**

| Route                                      | Dosage                  |
|--------------------------------------------|-------------------------|
| 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.*
### 4.7.2 Opioid pain medicines

| Drug       | CD  | Pain Level          | Route of Administration                  | Dosage                                                                 |
|------------|-----|---------------------|------------------------------------------|------------------------------------------------------------------------|
| Pentazocine| CD3 | Moderate pain       | By mouth                                 | Usual dose 25–100 mg every 3–4 hours; maximum 600 mg per day           |
|            |     |                     |                                          | 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       |
|            |     |                    |                                          |                                                                        | Elderly Initially 25 mg, then 25–100 mg after 4 hours.               |
|            |     |                    |                                          |                                                                        | Elderly By slow intravenous injection                               |
|            |     |                    |                                          |                                                                        | Adult 25–50 mg, then 25–50 mg after 4 hours, for debilitated patients use dose described for elderly patients. |

Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

### Notes
- Elderly patients: Use dose described for elderly patients.
4.7.2 Opioid pain medicines

**Pethidine**

- **Obstetric analgesia**
  - Initially 25 mg, then 25–50 mg after 4 hours.
  - 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.

4.7.2 Opioid pain medicines

**Pethidine**

- **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.

4.7.2 Opioid pain medicines

**Pethidine**

- **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.

4.7.2 Opioid pain medicines

**Tapentadol**

- **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.

4.7.2 Opioid pain medicines

**Tapentadol**

- **Severe chronic pain**
  - By mouth, using modified-release

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**Opioid Aware**

- 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 | 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. |

| 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. |

| 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.

Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

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 120 mg oral morphine equivalent/24 hours. Doses of tapentadol above 300 mg/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.

- 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.

- Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

- Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

- Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

- Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
59

4.7.2 Opioid pain medicines

Tramadol

**CD3**

**Moderate to severe pain (with modified-release 24-hourly preparations)**

**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.

- 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.

- By mouth using modified-release tablets
  - 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.

Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.
Initially 150 mg once daily, increased if necessary up to 400 mg once daily.

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.

4.7.2 Opioid pain medicines

| Dextromoramide | Not in BNF |
|----------------|------------|

4.8.1 Gabapentinoids

| Gabapentin | POM |
|------------|-----|

4.8.1 Gabapentinoids

| Gabapentin | POM |
|------------|-----|

4.8.1 Gabapentinoids

| Gabapentin | POM |
|------------|-----|

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 |
|------------|-----|

4.8.1 Gabapentinoids

| Gabapentin | POM |
|------------|-----|

4.8.1 Gabapentinoids

| Gabapentin | POM |
|------------|-----|

Gradually to avoid abstinence symptoms.
| 4.8.1 Gabapentinoids | Pregabalin | POM | **Peripheral and central neuropathic pain** | 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 be increased at 7 day intervals. | N/A | 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 initial dose can be increased after 3–7 days, and then again after 7 days. | N/A | 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 |

| 4.8.1 Gabapentinoids | Pregabalin | POM | **Generalised anxiety disorder** | 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 can be increased at 7 day intervals. | N/A | 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 |
Drugs listed in Appendix A of the spec for this mapping exercise were checked against BNF 6B (sections 4.1, 4.3, 4.7 and 4.8).

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.

A small number of drugs listed in these sections of the BNF did 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

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.

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)  Adamipazine  Clomipramine  Dosulepin  Doxepin  Imipramine  Lofepramine  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-dydarialol**  Lormetazepam  Nitracepam  Temazepam |
### 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, Lorazepam, 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       | All years to Issue 9 of 12, September 2018          | None                       |
| (The Cochrane Library -Wiley)                |                                                      |                            |
| Epistemonikos                                 | All years to 24 September 2018                      | Systematic review studies  |
| Database of promoting health effectiveness    | All years to 19 September 2018                      | None                       |
| reviews (DoPHER)                              |                                                      |                            |
| HealthEvidence                                | All years to 19 September 2018                      | None                       |

#### Cochrane Library (Wiley) search terms

| #   | 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 utilizat* 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 lorazepam 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 fluoxetine or mirtazapine or nefazodone or oxtirptan or reboxetine or tryptophan or venlafaxine or vortioxetine):ti,ab
#64. (OR #10-#63)
### Epistemonikos search terms

|   | 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 “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 “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 “dosesulepin” OR “doxepin” OR “imipramine” OR “lofepramine” OR “mianserin” OR “nortriptlyline” OR “protriptlyline” 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”)) 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 “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 “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 “dosesulepin” OR “doxepin” OR “imipramine” OR “lofepramine” OR “mianserin” OR “nortriptlyline” OR “protriptlyline” 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 “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 “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 “dosesulepin” OR “doxepin” OR “imipramine” OR “lofepramine” OR “mianserin” OR “nortriptlyline” OR “protriptlyline” 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”) |
**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 "medicinal overuse" OR "deprescriptions" OR "abstinence" OR "abstain" OR "cessation" OR "taper" OR "withdrawal" OR "substitution" OR "dependency" OR "dependency" OR "abuse" OR "abstaining" OR "abuse" OR "chronic" OR "long term" OR "long-term" OR "short term" OR "short-term" OR "misuse" OR "overuse" OR "deprescribing"

2. Freetext (All but Authors): "overuse" near "use" near "prescription"

3. Freetext (All but Authors): "inappropriate" near "prescription"

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 "oxycodeone" OR "papaveretum" OR "pentazocine" OR "pethidine" OR "tapentadol" OR "tramadol" OR "heroin"

6. Freetext (All but Authors): "z drug" OR "z hypnotic" OR "non-benzodiazepine" OR "zaleplon" OR "zopiclone" OR "zolpidem"

7. Freetext (All but Authors): "generation" near "hypnotic"

8. Freetext (All but Authors): "benzodiazepine" OR "bd" OR "flurazepam" OR "lorazepam" OR "lorazepam" OR "nitrazepam" OR "temazepam" OR "diazepam" OR "chloralhydrate" OR "lorazepam" OR "oxazepam"

9. Freetext (All but Authors): "gabapentin" OR "pregabalin"

10. Freetext (All but Authors): "antidepressant" OR "anti depression" OR "thymoanaleptic" OR "thymoleptic" OR "MAOI" OR "monoamine oxidase inhibitor" OR "RIMA" OR "tricyclic" OR "SSRI" OR "SNRI" OR "SNORI"

11. Freetext (All but Authors): "amitriptyline" OR "amoxapine" OR "clomipramine" OR "dosulepin" OR "dopamine" OR "imipramine" OR "lortetan" OR "mianserin" OR "nortryptiline" OR "protriptiline" 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 "oxiristatin" 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 abstinence* or abstain* or cessat* or detox* or discontinuing* or reduce* or stop* or taper* or withdrawal* or substitution* or depend* or addiction* or abuse* or abusing or chronic or long* term or long-term 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 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 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 utilisat* 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 diamorphone* 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 dothiepine/ |
| 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 fluoxetine or mirtazapine or nefazodone or oxtirptan 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 utilizat* 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 lorazepam or nortriptyline or temazepam or diazepam or clordiazepoxide or lorazepam or oxazepam).ti,ab. |
| 49. | *pregabalin/ |
| 50. | (gabapentin* or pregabalin*).ti,ab. |
| 51. | *antidepressant agent/ |
| 52. | (antidepress* or anti depress* or thymoanalytic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit"* or RIMA* or tricyclic* or SSRI* or SNRI* or SNRI*).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 oxtiplatan or reboxetine or tricyclopam 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. (doubt* 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 metanalysize* 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 psycinfo 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 abstin* 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 utilisat* 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 clordiazepoxide 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: [Doxepine] 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 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 fluxetine or mirtazapine or nefazodone or oxtirptan or reboxetine or tryptophan or venlafaxine or vortioxetine):ti,ab |
| #64. | (OR #10-#63) |
| #65. | (OR #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* OR term OR short term OR misus* OR overus* OR deprescrib*) OR ti,ab(over* NEAR/3 (use* OR using OR utilisat* OR utilitizat*) 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(analg* 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("Meperidin") 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(z benzodiazepin* OR bdz OR flurazepam OR loprazolam OR lormetazepam OR nitrazepam OR temazepam OR diazepam OR chloridiazepoxide OR lorazepam OR ...
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)
|   | Description                                                                 |
|---|-----------------------------------------------------------------------------|
| 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 chlor Diazepoxide 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: [Tranylcyromine] 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: [Flupentixol] 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 llofepramine or maprotoline or mianserin or nortriptyline or protriptyline or trazodone or trimipramine or isocarboxazid or moclobemide or pheneilazine 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 oxtiriptan 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 "abstinence" OR "abstain" OR "cessation" OR "detox" OR "discontinuation" OR "reduce" OR "stop" OR "taper" OR "withdraw" OR "substitute" OR "depend" OR "addict" OR "abuse" OR "abusing" OR "chronic" OR "long term" OR "long term" OR "short term" OR "short term" OR "misuse" OR "overuse" OR "deprescribing"

2. Freetext (All but Authors): "over" near "use" near "prescribe"

3. Freetext (All but Authors): "inappropriate" near "prescribe"

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-benzodiazepine" OR "zaleplon" OR "zopiclone" OR "zolpidem"

7. Freetext (All but Authors): "generation" near "hypnotic"

8. Freetext (All but Authors): "benzodiazepine" OR "bdz" OR "flurazepam" OR "lormetazepam" OR "nitrazepam" OR "temazepam" OR "diazepam" OR "chlorzepoxide" OR "lorazepam" OR "oxazepam"

9. Freetext (All but Authors): "gabapentin" OR "pregabalin"

10. Freetext (All but Authors): "antidepressant" OR "anti depressant" OR "thymoanaleptic" OR "thymoleptic" OR "MAOI" OR "monoamine oxidase inhibitor" 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 "maprotoline" 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"
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 utilizat* OR utilisat*) NEAR/3 NEAR/3 (prescrip* 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("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("Benzodiazepeines") OR ti,ab(benzodiazepin* OR bzd OR flurazepam OR loprazolam OR lormetazepam OR nitrazepam OR temazepam OR diazepam OR chloridiazepoxide 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 thymoaanalytic* or thymoleptic* or MAOI* or monoamine oxidase inhibit* or RIMA* or tricyclic* or SSR1* or SNRI* or SNORI*) OR (MAINSUBJECT.EXACT.EXPLODE("Imipramine") OR MAINSUBJECT.EXACT.EXPLODE("Amitriptyline") OR MAINSUBJECT.EXACT.EXPLODE("Clomipramine") OR MAINSUBJECT.EXACT.EXPLODE("Moclubemide") 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 noritryptiline OR protriptyline OR trazodone OR trimipramine OR isocarboxazid OR moclobemide OR phenelzine OR tranylcyromine 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"))
### National Institute for Health Research Journals Library search terms

|   | 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

39,087 records identified through database searches

249 records identified through other sources

39,336 records screened

38,269 records excluded (113 requested but unobtainable)

1,067 text articles assessed for eligibility

77 articles included in review
30 on harms
28 on interventions
17 on risk factors
2 on patients' experience
(10 additionally identified from call-for-evidence)
0 on current practice
(3 identified from call-for-evidence, 1 from grey literature)

990 articles excluded from review
283 multiple illicit drugs, unanalyzable
213 study design not relevant
146 study questions not
100 study outcomes not relevant
66 published prior to 2008
54 population not relevant
51 excluded per question in evidence hierarchy
30 systematic review with different protocol
24 systematic review with insufficient quality/reporting
21 non-English language
2 non-UK (for patients' experience review)
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 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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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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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).

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Appendix web-material W4. Service models and evaluations

Four reports were identified:

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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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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**

| No of studies | Design            | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Tapentadol | Oxycodone | Relative (95% CI) | Absolute Effect | Quality | Importance |
|---------------|-------------------|--------------|---------------|--------------|-------------|----------------------|------------|------------|-------------------|----------------|---------|------------|
| **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) | 7 fewer per 1000 (from 6 fewer to 7 fewer) | ⬤⬤⬤⬤ 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) | ⬤⬤⬤⬤ 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)

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 | serious¹ | 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) | MODERATE |
| **Opioid vs control - no opioid withdrawal - COWS assessment at 4 days after last intake of medication** | | | | | | | | | | |
| 1 | randomised trials | serious¹ | 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) | CRITICAL |
| **Opioid vs control - no opioid withdrawal - COWS assessment 5+ days after last intake of medication** | | | | | | | | | | |
| 1 | randomised trials | serious¹ | 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) | MODERATE |
| **Opioid vs control - mild or moderate opioid withdrawal - COWS assessment 2-4 days after last intake of medication** | | | | | | | | | | |
| 1 | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | very serious² | none | 11/72 (15.3%) | 0% | RR 4.04 (0.55 to 29.59) | 150 more per 1000 (from 40 more to 270 more) | CRITICAL |
| **Opioid vs control - mild or moderate opioid withdrawal - COWS assessment at 4 days after last intake of medication** | | | | | | | | | | |
| 1 | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | very serious² | 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) | CRITICAL |
| **Opioid vs control - mild or moderate opioid withdrawal - COWS assessment 5+ days after last intake of medication** | | | | | | | | | | |
| 1 | randomised trials | serious¹ | very serious¹ | no serious indirectness | very serious² | 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) | 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, I²=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) | ☸️○○○ 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) | ☸️○○○ 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) | ☸️○○○ 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) | ☸️○○○ 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) | ☸️○○○ 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) | ☸️○○○ 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) | ☸️○○○ VERY LOW CRITICAL |

**Drug withdrawal syndrome**
**Table 4: Evidence profile: Z-drugs versus placebo**

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Z-drugs | Control | Relative (95% CI) | Absolute | Effect | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|---------|---------|-------------------|----------|--------|---------|------------|
| **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 serious¹ | 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) | @@@@ 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 serious¹ | none | 5/67 (7.5%) | 4% | RR 1.88 (0.56 to 6.27) | 35 more per 1000 (from 18 fewer to 211 more) | @@@@ 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 | serious¹ | 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) | @@@@ 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 serious¹ | none | 4/67 (6%) | 3.2% | RR 1.88 (0.49 to 7.28) | 28 more per 1000 (from 16 fewer to 201 more) | @@@@ 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 serious¹ | none | 5/67 (7.5%) | 4% | RR 1.88 (0.56 to 6.27) | 35 more per 1000 (from 18 fewer to 211 more) | @@@@ 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.

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.
| 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 |
| 1 randomised trials| very serious¹ | no serious inconsistency | no serious indirectness | no serious imprecision | none | 58 | 49 | - | MD 0.4 lower (3.09 lower to 2.29 higher) | LOW CRITICAL |
| 1 randomised trials| very serious¹ | no serious inconsistency | no serious indirectness | no serious imprecision | none | 54 | 44 | - | MD 0.5 higher (1.92 lower to 2.92 higher) | LOW CRITICAL |
| 1 randomised trials| very serious¹ | no serious consistency | no serious indirectness | no serious imprecision | none | 106 | 93 | - | MD 0.6 higher (1.08 lower to 2.28 higher) | LOW CRITICAL |
| 1 randomised trials| very serious¹ | no serious consistency | no serious indirectness | no serious imprecision | none | 109 | 99 | - | MD 1.3 lower (2.92 lower to 0.32 higher) | LOW CRITICAL |
| 1 randomised trials| very serious¹ | no serious consistency | no serious indirectness | no serious imprecision | 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) | VERY LOW CRITICAL |
| 1 randomised trials| very serious¹ | no serious consistency | no serious indirectness | no serious imprecision | none | 55/203 (27.1%) | 28% | RR 0.97 (0.66 to 1.42) | 8 fewer per 1000 (from 95 fewer to 118 more) | VERY LOW CRITICAL |
| Anxiety after period 1 |

¹ serious = serious or critical, ² serious = serious or critical
| Condition                  | Randomised Trials | Very Serious | No Serious Inconsistency | No Serious Indirectness | Very Serious | None | Odds Ratio | Confidence Interval | No. More/Fewer Per 1000 | No. More/Fewer From | CRITICAL |
|----------------------------|-------------------|-------------|--------------------------|-------------------------|--------------|------|------------|---------------------|-------------------------|----------------------|----------|
| Anxiety after period 2     | 1                 | very serious | no serious inconsistency | no serious indirectness | very serious | none | 3/110      | 2.7% to 4.12         | 11 fewer per 1000     | 34 fewer to 122 more | VERY LOW |
| Dizziness after period 1   | 1                 | very serious | no serious inconsistency | no serious indirectness | very serious | none | 11/203     | 5.4% to 1.63         | 26 fewer per 1000     | 58 fewer to 50 more   | CRITICAL |
| Headache after period 1    | 1                 | very serious | no serious inconsistency | no serious indirectness | very serious | none | 3/110      | 2.7% to 26.2         | 44 more per 1000      | 11 fewer to 479 more  | CRITICAL |
| Headache after period 2    | 1                 | very serious | no serious inconsistency | no serious indirectness | very serious | none | 8/203      | 3.9% to 9.11         | 19 more per 1000      | 11 fewer to 162 more  | CRITICAL |
| Insomnia after period 1    | 1                 | very serious | no serious inconsistency | no serious indirectness | serious      | none | 10/110     | 9.1% to 1.06         | 102 fewer per 1000    | 152 fewer to 12 more  | CRITICAL |
| Insomnia after period 2    | 1                 | very serious | no serious inconsistency | no serious indirectness | serious      | none | 21/203     | 10.3% to 4.14        | 43 more per 1000      | 17 fewer to 188 more  | CRITICAL |
| Nausea after period 1      | 1                 | very serious | no serious inconsistency | no serious indirectness | very serious | none | 7/110      | 6.4% to 7.69         | 25 more per 1000      | 25 fewer to 261 more  | CRITICAL |
Rebound anxiety after treatment period 1

| 1 | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | very serious² | 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) | ⚫⚫⚫⚫ VERY LOW | CRITICAL |

Rebound anxiety after treatment period 2

| 1 | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | serious² | none | 4/203 (2%) | 6% | RR 0.33 (0.09 to 1.14) | 40 fewer per 1000 (from 55 fewer to 8 more) | ⚫⚫⚫⚫ 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

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Antidepressants | Control | Relative (95% CI) | Absolute | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|----------------------|----------------|---------|------------------|----------|---------|------------|
| Rebound insomnia (after discontinuation) | 1 | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | very serious² | 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) | ⚫⚫⚫⚫ VERY LOW | CRITICAL |

Benzodiazepine Withdrawal symptom questionnaire criteria BWSQ

| 1 | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | very serious² | 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) | ⚫⚫⚫⚫ 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 serious² | 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) | ⚫⚫⚫⚫ LOW | CRITICAL |

Depression (after discontinuation; except one study time point not reported)

| 3 | randomised trials | serious¹ | serious³ | no serious indirectness | very serious² | 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) | ⚫⚫⚫⚫ VERY LOW | CRITICAL |
### Suicide ideation (after discontinuation in two studies, one during study and other time point not reported)

| Study | Randomised trials | Risk of bias | Inconsistency | Indirectness | Risk of bias | OR (95% CI) | RR (95% CI) | Additional Information |
|-------|-------------------|--------------|---------------|--------------|--------------|-------------|-------------|------------------------|
| 4     | 71498             | 0%           | 0             | 0            | 0            | 4.24 (0.82 to 21.90) | 0 more per 10000 (from 0 fewer to 10 more) | Very Low CRITICAL |
| 3     | 793               | 0%           | 0             | 0            | 0            | MD 0.56 higher (0.01 to 1.13 higher) | Very Low CRITICAL |
| 2     | 694               | 0%           | 0             | 0            | 0            | MD 0.48 higher (0.18 to 0.77 higher) | Moderate CRITICAL |
| 1     | 32                | 0%           | 0             | 0            | 0            | MD 6 lower (9.56 to 2.45 lower) | Low CRITICAL |

### Vertigo (after discontinuation)

| Study | Randomised trials | Risk of bias | Inconsistency | Indirectness | Risk of bias | OR (95% CI) | RR (95% CI) | Additional Information |
|-------|-------------------|--------------|---------------|--------------|--------------|-------------|-------------|------------------------|
| 1     | 12324             | 0%           | 0             | 0            | 0            | 4.63 (1.37 to 15.6) | 40 more per 1000 (from 10 more to 60 more) | Very Low CRITICAL |

### Change after discontinuation

| Study | Randomised trials | Risk of bias | Inconsistency | Indirectness | Risk of bias | OR (95% CI) | RR (95% CI) | Additional Information |
|-------|-------------------|--------------|---------------|--------------|--------------|-------------|-------------|------------------------|
| 1     | 14553             | 0%           | 0             | 0            | 0            | 1.27 (0.64 to 2.54) | 56 more per 1000 (from 75 fewer to 320 more) | Very Low CRITICAL |

### Discontinuation syndrome (after discontinuation)

| Study | Randomised trials | Risk of bias | Inconsistency | Indirectness | Risk of bias | OR (95% CI) | RR (95% CI) | Additional Information |
|-------|-------------------|--------------|---------------|--------------|--------------|-------------|-------------|------------------------|
| 1     | 953               | 0%           | 0             | 0            | 0            | 1.8 (0.65 to 5.02) | 75 more per 1000 (from 33 fewer to 378 more) | Low CRITICAL |

### Total taper/post study emergent AE

| Study | Randomised trials | Risk of bias | Inconsistency | Indirectness | Risk of bias | OR (95% CI) | RR (95% CI) | Additional Information |
|-------|-------------------|--------------|---------------|--------------|--------------|-------------|-------------|------------------------|
| 9     | 600/1728          | 0%           | 0             | 0            | 0            | 1.63 (1.44 to 1.84) | 129 more per 1000 (from 90 more to 172 more) | Very Low CRITICAL |

### Vomiting (after discontinuation)

| Study | Randomised trials | Risk of bias | Inconsistency | Indirectness | Risk of bias | OR (95% CI) | RR (95% CI) | Additional Information |
|-------|-------------------|--------------|---------------|--------------|--------------|-------------|-------------|------------------------|
| 1     | 1/149             | 0%           | 0             | 0            | 0            | 0.35 (0.04 to 3.34) | 12 fewer per 1000 (from 18 fewer to 44 more) | Very Low CRITICAL |
| Condition                        | Methodology | Risk of Bias | Consistency | Indirectness | Imprecision | Event Count | Event Rate | Relative Risk (95% CI) | Incidence (per 1000) (95% CI) | GRADE |
|---------------------------------|-------------|--------------|-------------|--------------|-------------|--------------|-------------|------------------------|--------------------------------|-------|
| Dizziness (after discontinuation) | 7            | very serious | 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) | CRITICAL |
| Nausea (after discontinuation)   | 6            | very serious | 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) | CRITICAL |
| Headache (after discontinuation) | 5            | very serious | no serious indirectness | serious | none | 83/1390 (6%) | 4.4% | RR 1.39 (0.96 to 2) | 17 more per 1000 (from 2 fewer to 44 more) | CRITICAL |
| Insomnia (after discontinuation) | 3            | very serious | no serious indirectness | very serious | 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) | CRITICAL |
| Diarrhoea (after discontinuation) | 1            | serious | no serious indirectness | very serious | 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) | CRITICAL |
| Serious adverse events during taper | 2            | serious | no serious indirectness | very serious | 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) | CRITICAL |
| Withdrawal syndrome (after discontinuation) | 1            | no serious risk of bias | 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) | CRITICAL |
| Upper respiratory tract infection (after discontinuation) | 1            | no serious risk of bias | no serious indirectness | very serious | 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) | 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, I²=65%, p=0.06, unexplained by subgroup analysis.
4 Downgraded by one increment because heterogeneity, I²=72%, p=0.01, unexplained by subgroup analysis.
5 Downgraded by one increment because heterogeneity, I²=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 |
| 1 | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | very serious² | 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) |

Suicide ideation - antidepressant v antidepressant (time point not reported)

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 |
| 1 | observational studies | very serious¹ | no serious inconsistency | very serious² | no serious imprecision | none | - | - | HR 1.53 (1.29 to 1.81) | - |

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.
| Substance                          | Study Design | Inconsistency | Outcome | Effect Size | 95% CI   | Confidence Level | Criticality       |
|-----------------------------------|--------------|---------------|---------|-------------|----------|-----------------|------------------|
| Alcohol abuse                     | observational| very serious 1 | no serious inconsistency | very serious 2 | serious 3 | none            | -                | HR 1.38 (0.9 to 2.12) | -  |
| Opioid abuse                      | observational| very serious 1 | no serious inconsistency | very serious 2 | serious 3 | none            | -                | HR 3.97 (0.87 to 18.12) | -  |
| Other substance abuse             | observational| very serious 1 | no serious inconsistency | very serious 2 | serious 3 | none            | -                | HR 1.81 (0.92 to 3.56)  | -  |
| Opioid overdose                   | observational| very serious 1 | no serious inconsistency | very serious 2 | no serial imprecision | none | -                | HR 5.12 (1.63 to 16.08)  | -  |
| Other substance overdose          | observational| very serious 1 | no serious inconsistency | very serious 2 | serious 3 | none            | -                | HR 1.82 (0.92 to 3.6)   | -  |
| Opioid dependence                 | observational| very serious 1 | no serious inconsistency | very serious 2 | no serial imprecision | none | -                | HR 2.85 (1.54 to 5.27)   | -  |
| Other substance dependence        | observational| very serious 1 | no serious inconsistency | very serious 2 | serious 3 | none            | -                | HR 1.73 (1.21 to 2.47)   | -  |
| Mortality                         |              |               |         |             |          |                 |                  |                        |     |
### 1.1.4 Short versus long term withdrawal

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

| 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 |        |              |               |              |             |                     |                   |                     | RR 1.01 (0.46 to 2.25) | 5 more per 1000 (from 249 fewer to 577 more) |
| 1             | randomised trials | very serious 1 | no serious inconsistency | no serious indirectness | very serious 2 | none | 7/15 (46.7%) | 46.2% |

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.

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

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Abrupt | Taper | Relative (95% CI) | Absolute |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|--------|-------|------------------|----------|
| DESS score    |        |              |               |              |             |                     |        |       | RR 0.98 (0.63 to 1.54) | 4 fewer per 1000 (from 80 fewer to 117 more) |
| 1             | randomised trials | very serious 1 | no serious inconsistency | no serious indirectness | very serious 2 | none | 31/146 (21.2%) | 21.6% |

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.
### Taper/post-therapy-emergent adverse events

| Event                     | Randomised Trials | Very Serious¹ | No Serious Inconsistency | No Serious Indirectness | Serious² | None | Total (Count) | RR (95% CI) | No. per 1000 (from 8 more to 280 more) | Risk of Bias |
|---------------------------|-------------------|----------------|--------------------------|--------------------------|----------|------|---------------|------------|---------------------------------------|--------------|
| **Headache**              |                   |                |                          |                          |          |      |               |            |                                       |              |
| 1                         | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | serious² | none | 75/146       | 38.9% (51.4%) | 124 more per 1000 (from 8 more to 280 more) | CRITICAL     |
| **Nausea**                |                   |                |                          |                          |          |      |               |            |                                       |              |
| 1                         | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | very serious² | none | 19/146       | 6.5% (13%)   | 66 more per 1000 (from 4 fewer to 214 more) | CRITICAL     |
| **Dizziness**             |                   |                |                          |                          |          |      |               |            |                                       |              |
| 1                         | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | very serious² | none | 14/146       | 5.8% (9.6%)   | 39 more per 1000 (from 16 fewer to 165 more) | CRITICAL     |
| **Suicide ideation**     |                   |                |                          |                          |          |      |               |            |                                       |              |
| 1                         | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | very serious² | none | 1/146        | 0.7% (0.68%) | 0 fewer per 1000 (from 7 fewer to 98 more) | CRITICAL     |
| **Suicide attempts**      |                   |                |                          |                          |          |      |               |            |                                       |              |
| 1                         | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | very serious² | none | 1/146        | 0% (0.68%)   | 10 fewer per 1000 (from 10 fewer to 30 more) | 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)

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Rapid withdrawal | Gradual withdrawal | Relative (95% CI) | Absolute | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|-----------------|-------------------|-----------------|----------|---------|------------|
| 1 observational studies | very serious | no serious inconsistency | serious | very serious | none | - | 0% | HR 1.5 (1.14 to 1.97) | - | ¤¡¡¡| VERY LOW |

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)

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Abrupt (alternate) | Relative (95% CI) | Absolute | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|-------------------|-------------------|----------|---------|------------|
| 1 randomised trials | serious | no serious inconsistency | no serious indirectness | serious | none | 59 | 59 | - | MD 1.44 higher (0.04 lower to 2.92 higher) | ¤¡¡¡| LOW | CRITICAL |

Any adverse events

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Abrupt (alternate) | Relative (95% CI) | Absolute | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|-------------------|-------------------|----------|---------|------------|
| 1 randomised trials | serious | no serious inconsistency | no serious indirectness | serious | none | 53/101 (52.5%) | 52% | RR 1.01 (0.78 to 1.31) | 5 more per 1000 (from 114 fewer to 161 more) | ¤¡¡¡| LOW | CRITICAL |

### Asthenia

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Abrupt (alternate) | Relative (95% CI) | Absolute | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|-------------------|-------------------|----------|---------|------------|
| 1 randomised trials | serious | no serious inconsistency | no serious indirectness | very serious | 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) | ¤¡¡¡| LOW | CRITICAL |

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

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Abrupt | Taper (50 mg then placebo) | Relative (95% CI) | Absolute | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|--------|-----------------------------|------------------|----------|----------|------------|
| 1             | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | very serious² | none | 3/101 (3%) | 6.9% | RR 0.43 (0.12 to 1.63) | 39 fewer per 1000 (from 61 fewer to 43 more) | ☒☒☒☒ VERY LOW | CRITICAL |

**Vasodilation**

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Abrupt | Taper (50 mg then placebo) | Relative (95% CI) | Absolute | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|--------|-----------------------------|------------------|----------|----------|------------|
| 1             | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | very serious² | 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) | ☒☒☒☒ 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)**

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Abrupt DESS after taper week 3 | Taper (50 mg then placebo) | Relative (95% CI) | Absolute | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|------------------------------|-----------------------------|------------------|----------|----------|------------|
| 1             | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | no serious imprecision | none | 47 | 59 | - | MD 0.08 lower (1.3 lower to 1.14 higher) | ☒☒☒☒ CRITICAL |

**Any adverse events**

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Abrupt Asthenia | Taper (50 mg then placebo) | Relative (95% CI) | Absolute | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|-----------------|-----------------------------|------------------|----------|----------|------------|
| 1             | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | very serious² | none | 43/87 (49.4%) | 52% | RR 0.95 (0.72 to 1.26) | 26 fewer per 1000 (from 146 fewer to 135 more) | ☒☒☒ CRITICAL |

**Diarrhoea**

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Abrupt Diarrhoea | Taper (50 mg then placebo) | Relative (95% CI) | Absolute | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|-----------------|-----------------------------|------------------|----------|----------|------------|
| 1             | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | very serious² | 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) | ☒☒ CRITICAL |

**Dizziness**

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Abrupt Dizziness | Taper (50 mg then placebo) | Relative (95% CI) | Absolute | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|-----------------|-----------------------------|------------------|----------|----------|------------|
| 1             | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | very serious² | 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) | ☒☒ CRITICAL |
| Condition   | Randomised Trials | Serious¹ | No Serious Inconsistency | No Serious Indirectness | Very Serious² | None | RR (CIs) | No. Fewer per 1000 (95% CIs) | Grade |
|-------------|-------------------|----------|--------------------------|-------------------------|---------------|------|---------|-----------------------------|-------|
| Emotional lability | 1                   | Serious¹ | No serious inconsistency | No serious indirectness | Very serious² | None | RR 0.98 (0.44 to 2.15) | 2 fewer per 1000 (from 66 fewer to 136 more) | VERY LOW |
| Headache    | 1                   | Serious¹ | No serious inconsistency | No serious indirectness | Very serious² | None | RR 0.78 (0.23 to 2.68) | 13 fewer per 1000 (from 45 fewer to 99 more) | CRITICAL |
| Hypertension| 1                   | Serious¹ | No serious inconsistency | No serious indirectness | Very serious² | None | RR 0.68 (0.28 to 1.66) | 38 fewer per 1000 (from 85 fewer to 78 more) | VERY LOW |
| Infection   | 1                   | Serious¹ | No serious inconsistency | No serious indirectness | Very serious² | None | RR 0.59 (0.15 to 2.28) | 24 fewer per 1000 (from 50 fewer to 76 more) | CRITICAL |
| Insomnia    | 1                   | Serious¹ | No serious inconsistency | No serious indirectness | Very serious² | None | RR 0.98 (0.31 to 3.09) | 1 fewer per 1000 (from 41 fewer to 123 more) | CRITICAL |
| Nausea      | 1                   | Serious¹ | No serious inconsistency | No serious indirectness | Very serious² | None | RR 0.91 (0.35 to 2.35) | 8 fewer per 1000 (from 57 fewer to 119 more) | CRITICAL |
| Sweating    | 1                   | Serious¹ | No serious inconsistency | No serious indirectness | Very serious² | None | RR 0.67 (0.2 to 2.21) | 23 fewer per 1000 (from 55 fewer to 83 more) | CRITICAL |
| Vasodilation| 1                   | Serious¹ | No serious inconsistency | No serious indirectness | Very serious² | None | RR 0.2 (0.02 to 1.59) | 47 fewer per 1000 (from 58 fewer to 35 more) | 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 |
|--------------------|----------------|--------|
| 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) | ★★★★★ 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) | ★★★★★ 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) \(^3\) | ★★★★★ 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) | ★★★★★ 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) | ★★★★★ 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) | ★★★★★ VERY LOW CRITICAL |
| Headache | | | | | | | | | | |

\(^1\) Serious bias of any kind.
\(^2\) Serious indirectness.
\(^3\) Indicates that the estimate is based on a single study.
| Phobia          | Randomised Trials | Serious¹ Inconsistency | Serious Indirectness | Very Serious² Indirectness | None | Risk | Effect Size | 95% CI | Absolute Effect | Risk Difference | Rating     |
|----------------|-------------------|------------------------|----------------------|-----------------------------|------|------|-------------|--------|-----------------|---------------|------------|
| Hypertension   | 1                 | Serioust¹              | No serious           | No serious indirectness    | None | 7/94 | RR 0.63    | 0.26 to 1.54 | 11.8%           | 44 fewer per 1000 (from 87 fewer to 64 more) | VERY LOW CRITICAL |
| Infection      | 1                 | Serious¹              | No serious           | No serious indirectness    | None | 0/94 | RR 0.36    | 0.07 to 1.75 | 5.9%            | 60 fewer per 1000 (from 110 fewer to 10 fewer)² | MODERATE |
| Insomnia       | 1                 | Serious¹              | No serious           | No serious indirectness    | None | 2/94 | RR 0.9     | 0.29 to 2.87 | 5.9%            | 38 fewer per 1000 (from 55 fewer to 44 more) | VERY LOW CRITICAL |
| Nausea         | 1                 | Serious¹              | No serious           | No serious indirectness    | None | 5/94 | RR 0.19    | 0.45 to 2.62 | 8.8%            | 6 more per 1000 (from 48 fewer to 110 more) | VERY LOW CRITICAL |
| Sweating       | 1                 | Serious¹              | No serious           | No serious indirectness    | None | 9/94 | RR 1.09    | 0.45 to 2.62 | 8 more per 1000 (from 48 fewer to 143 more) | VERY LOW CRITICAL |
| Vasodilation   | 1                 | Serious¹              | No serious           | No serious indirectness    | None | 5/94 | RR 0.31    | 0.07 to 1.46 | 6.9%            | 48 fewer per 1000 (from 64 fewer to 32 more) | 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)

| No of studies | Design     | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality   |
|---------------|------------|--------------|---------------|--------------|-------------|----------------------|------------------|-----------|
|               |            |              |               |              |             |                      |                  |           |
| **Long-term opioid use (12 months) – Age <24 years** | | | | | | | | |
| 1             | Observational studies | Very serious | No serious inconsistency | No serious indirectness | Serious | 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 | No serious inconsistency | No serious indirectness | Serious | 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 | No serious inconsistency | No serious indirectness | Serious | 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 | No serious inconsistency | No serious indirectness | Serious | 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) |
| lifetime dependence diagnosis | | | | | | | |
| 1 | Observational studies | Very serious¹ | 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 serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 2.7 (1.68 to 4.34) | LOW |

¹Downgraded 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 serious¹ | 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 serious¹ | 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

|   | Design          | Risk of bias   | Inconsistency          | Indirectness   | Imprecision    | Other considerations | Relative Effect (95% CI) | Quality |
|---|-----------------|----------------|------------------------|----------------|---------------|----------------------|--------------------------|---------|
| 1 | Observational studies | Very serious | 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

|   | Design          | Risk of bias   | Inconsistency          | Indirectness   | Imprecision    | Other considerations | Relative Effect (95% CI) | Quality |
|---|-----------------|----------------|------------------------|----------------|---------------|----------------------|--------------------------|---------|
| 1 | Observational studies | Very serious | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 2.45 (2.27 to 2.64) | LOW |

*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)

|   | Design          | Risk of bias   | Inconsistency          | Indirectness   | Imprecision    | Other considerations | Relative Effect (95% CI) | Quality |
|---|-----------------|----------------|------------------------|----------------|---------------|----------------------|--------------------------|---------|
|   |                 |                |                        |                |               |                      |                          |         |
| Long-term opioid use (12 months) - Long-term opioid use
| 1 | Observational studies | Very serious | No serious inconsistency | No serious indirectness | Serious | 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 | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.04 (0.99 to 1.09) | LOW |

*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.

*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 |
|--------------------|-----------------|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Relative (95% CI)** | **Quality** |
|-------------------|----------|-----------------|-------------------|------------------|-----------------|------------------------|---------------------|----------|
| Long-term opioid use (12 months) – Hispanic |
| 1 | Observational studies | Very serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | OR 0.73 (0.37 to 1.44) | VERY LOW |

¹Downgraded 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
²Downgraded 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 |
|--------------------|-----------------|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Relative (95% CI)** | **Quality** |
|-------------------|----------|-----------------|-------------------|------------------|-----------------|------------------------|---------------------|----------|
| Long-term opioid use (12 months) - < high school |
| 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | OR 0.69 (0.34 to 1.4) | VERY LOW |
| Long-term opioid use (12 months) - vocational/some college |
| 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | OR 0.9 (0.55 to 1.47) | VERY LOW |
| Long-term opioid use (12 months) - college graduate |
| 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | OR 0.58 (0.2 to 1.68) | VERY LOW |
### Opioid misuse (referent < high school) - Non-unhealthy drinkers

|   | Observational studies | Quality assessment | Adjusted effect | Quality  |
|---|-----------------------|--------------------|-----------------|---------|
| 1 |                       | Very serious¹      | No serious inconsistency | OR 0.53 (0.21 to 1.34) | VERY LOW |

¹Downgraded 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

### Opioid misuse (referent < high school) - Unhealthy drinkers

|   | Observational studies | Quality assessment | Adjusted effect | Quality  |
|---|-----------------------|--------------------|-----------------|---------|
| 1 |                       | Very serious¹      | No serious inconsistency | OR 1.39 (0.25 to 7.73) | VERY LOW |

¹Downgraded 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

²Downgraded 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)

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|-----------------|---------|
| Opioid misuse - Non-unhealthy drinkers | 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 0.39 (0.16 to 0.95) | LOW |

¹Downgraded 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

²Downgraded by 1 increment if the 95% CI crossed the null line

| Opioid misuse - Unhealthy drinkers | 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | OR 0.76 (0.12 to 4.81) | VERY LOW |

²Downgraded 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)

| Opioid misuse | 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 | Serious² | None | OR 1.5 (0.53 to 4.25) | VERY LOW |
| Opioid misuse - Unhealthy drinkers | 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | OR 1.84 (0.31 to 10.92) | VERY LOW |

¹Downgraded 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
²Downgraded 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)

| 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 serious¹ | 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 serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 6.25 (2.91 to 13.42) | LOW |

¹Downgraded 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 serious¹ | 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 serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 3.68 (3.34 to 4.05) | LOW |

¹Downgraded 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.75 (1.18 to 2.6) | LOW |

¹Downgraded 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 |
|----------------------|--------------------|----------------|---------|------------|
| **Opioid abuse**     |                    |                |         |            |
| No of studies        | 1                  | Design         | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) |
| Opioid abuse         | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | HR 3.97 (0.87 to 18.12) | VERY LOW |
| Opioid overdose      | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | HR 5.12 (1.63 to 16.08) | LOW |
| Opioid dependence    | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | HR 2.86 (1.54 to 5.31) | LOW |
| Alcohol abuse        | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | HR 1.38 (0.9 to 2.12) | VERY LOW |
| Other substance abuse| Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | HR 1.81 (0.92 to 3.56) | VERY LOW |
| Non-opioid overdose  | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | HR 1.82 (0.92 to 3.6) | VERY LOW |
| Other substance (non-opioid) dependence | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | HR 1.73 (1.21 to 2.47) | LOW |
| Depression           | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | HR 1.73 (1.21 to 2.47) | LOW |
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 27: Risk factor: History of opioid abuse (referent: no history) – Outcome: dependence diagnosis

| Risk factor | Quality assessment | Adjusted effect | Quality |
|-------------|--------------------|-----------------|---------|
| Life-time dependence diagnosis | | | |
| 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 |
| Current 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 |
| 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 |

¹Downgraded 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.

²Downgraded by 1 increment if the 95% CI crossed the null line.
**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 serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 12.14 (1.64 to 89.87) | LOW |

¹Downgraded 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 serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | OR 2.50 (0.98 to 6.38) | VERY LOW |

¹Downgraded 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.

²Downgraded 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 serious¹ | 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 serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.12 (0.5 to 2.51) | VERY LOW    |
| **Dependence - Early refill** |                     |                 |              |              |              |             |                    |                 |            |
|                          | 1                  | Observational studies | Very serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 0.78 (0.2 to 3.04) | VERY LOW    |

¹Downgraded 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

²Downgraded 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 | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.93 (1.51 to 2.47) | LOW |

1Downgraded 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 | No serious inconsistency | No serious indirectness | Serious | 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 | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.18 (0.84 to 1.66) | LOW |

1Downgraded 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
2Downgraded 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.65 (1.48 to 1.84) | LOW |

¹Downgraded 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 serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | Serious ² | None | OR 1.54 (0.94 to 2.52) | VERY LOW |

¹Downgraded 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

²Downgraded 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) | Quality |
|-------------------|---------|--------------|---------------|--------------|-------------|---------------------|-----------------|---------|
| Opioid misuse - Non-unhealthy drinkers |
| 1 |
| Observational studies |
| Very serious |
| 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 |

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) | Quality |
|-------------------|---------|--------------|---------------|--------------|-------------|---------------------|-----------------|---------|
| 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)

| No of studies | Design          | Risk of bias      | Inconsistency | Indirectness | Imprecision | Other considerations | Adjusted effect Relative (95% CI) | Quality |
|---------------|-----------------|-------------------|---------------|--------------|-------------|----------------------|----------------------------------|---------|
|               |                 |                   |               |              |             |                      |                                  |         |
|               |                 |                   |               |              |             |                      |                                  |         |
| 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 |

1Downgraded 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
2Downgraded 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)

| No of studies | Design          | Risk of bias      | Inconsistency | Indirectness | Imprecision | Other considerations | Adjusted effect Relative (95% CI) | Quality |
|---------------|-----------------|-------------------|---------------|--------------|-------------|----------------------|----------------------------------|---------|
|               |                 |                   |               |              |             |                      |                                  |         |
|               |                 |                   |               |              |             |                      |                                  |         |
| 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 |

1Downgraded 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
2Downgraded by 1 increment if the 95% CI crossed the null line

Long-term opioid use (12 months) - Low

1 | 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 | 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 |

1Downgraded 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
2Downgraded 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 |
|--------------------|-----------------|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
| life-time dependence diagnosis | | | | | | | OR 1.44 (1.09 to 1.9) | LOW |
| 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | | |
| Severity of lifetime dependence | | | | | | | OR 1.61 (1.19 to 2.18) | LOW |
| 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | | |

¹Downgraded 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 |
|--------------------|-----------------|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
| current dependence diagnosis | | | | | | | OR 1.29 (1.05 to 1.58) | LOW |
| 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | | |

¹Downgraded 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 |
|--------------------|-----------------|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
| current dependence diagnosis | | | | | | | OR 1.73 (1.21 to 2.47) | LOW |
| 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | | |
| Severity of lifetime dependence | | | | | | | OR 1.53 (1.08 to 2.17) | LOW |
| 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | | |

¹Downgraded 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 serious | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 3.1 (1.5 to 6.41) | LOW |

*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 phenecyclidine, 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 | No serious inconsistency | No serious indirectness | Serious | 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 | No serious inconsistency | No serious indirectness | Serious | None | OR 1.37 (0.67 to 2.8) | VERY LOW |

*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

*Downgraded by 1 increment if the 95% CI crossed the null line
| Quality assessment | Adjusted effect |
|--------------------|-----------------|
| No of studies      | Design          | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
| Early opioid refills - diagnosis without PTSD |
| 1 | Observational studies | Very serious¹ | 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 serious¹ | 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 serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 5.46 (4.91 to 6.07) | LOW |

¹Downgraded 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

| Quality assessment | Adjusted effect |
|--------------------|-----------------|
| No of studies      | Design          | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
| Early opioid refills - diagnosis without PTSD |
| 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 2.01 (1.87 to 2.16) | LOW |

¹Downgraded 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)

| No of studies | Design            | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Adjusted effect (95% CI) | Quality |
|---------------|-------------------|--------------|---------------|--------------|-------------|----------------------|--------------------------|---------|
|               |                   |              |               |              |             |                      |                          |         |
| Opioid misuse - Non-unhealthy drinkers |                   |              |               |              |             |                      |                          |         |
| 1             | Observational studies | Very serious | 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 | No serious inconsistency | No serious indirectness | No serious imprecision | None                  | OR 9.77 (1.7 to 56.15) | LOW     |

¹Downgraded 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
²Downgraded by 1 increment if the 95% CI crossed the null line

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

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

¹Downgraded 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
²Downgraded by 1 increment due to intervention indirectness as not all of the participants were receiving opioids (only 80%)
³Downgraded 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 | 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 | No serious inconsistency | No serious indirectness | Serious | 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

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 | No serious inconsistency | No serious indirectness | Serious | None | OR 0.98 (0.51 to 1.88) | VERY LOW |
| Long-term opioid use (12 months) – High | 1 | Observational studies | Very serious | 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 serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | OR 1.8 (0.76 to 4.26) | VERY LOW |
| Long-term opioid use (12 months) - 18-24 | 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 2.65 (1.2 to 5.85) | LOW |

¹Downgraded 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
²Downgraded 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 serious¹ | No serious inconsistency | Serious² | Serious³ | None | OR 1.64 (1.03 to 2.62) | VERY LOW |

¹Downgraded 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
²Downgraded by 1 increment because 20% of the sample were prescribed non-opioid analgesics
³Downgraded by 1 increment if the 95% CI crossed the null line
| Risk factor | 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 serious¹ | 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 serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.96 (1.83 to 2.1) | LOW |

¹Downgraded 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.
| No of studies | Design               | Risk of bias | Inconsistency     | Indirectness  | Imprecision | Other considerations | Relative (95% CI) | Quality   |
|---------------|----------------------|--------------|-------------------|---------------|-------------|----------------------|-------------------|-----------|
| Prescription overuse | 1 | Observational studies | Very serious¹ | No serious inconsistency | Serious indirectness² | No serious imprecision | None | OR 2.74 (1.14 to 6.63) | VERY LOW |
| Long-term opioid use (12 months) | 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | OR 0.95 (0.6 to 1.5) | VERY LOW |

¹Downgraded 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
²Downgraded by 1 increment because 20% of the sample were prescribed non-opioid analgesics
³Downgraded 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

| No of studies | Design     | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
|---------------|------------|--------------|---------------|--------------|-------------|----------------------|------------------|---------|
| Prescription overuse | Observational studies | Very serious¹ | No serious inconsistency | Serious² | Serious³ | None | OR 0.99 (0.91 to 1.07) | VERY LOW |

¹Downgraded 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
²Downgraded by 1 increment because 20% of the sample were prescribed non-opioid analgesics
³Downgraded 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

| No of studies | Design     | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
|---------------|------------|--------------|---------------|--------------|-------------|----------------------|------------------|---------|
| Long-term opioid use (12 months) | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 2.4 (1.5 to 3.84) | LOW |

¹Downgraded 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

| No of studies | Design                | Risk of bias       | Inconsistency | Indirectness | Imprecision | Other considerations | Adjusted effect              | Quality   |
|---------------|-----------------------|--------------------|---------------|--------------|-------------|----------------------|----------------------------|-----------|
|               |                       |                    |               |              |             |                      | Relative (95% CI)            |           |
| Benzodiazepine dependence – Black | Observational studies | Very serious¹      | No serious inconsistency | No serious indirectness | No serious imprecision | None | HR 0.18 (0.15 to 0.21) | LOW       |
| 1             |                       |                    |               |              |             |                      |                             |           |
| Benzodiazepine dependence – Latino | Observational studies | Very serious¹      | No serious inconsistency | No serious indirectness | No serious imprecision | None | HR 0.2 (0.17 to 0.23) | LOW       |
| 1             |                       |                    |               |              |             |                      |                             |           |
| Benzodiazepine dependence – Asian | Observational studies | Very serious¹      | No serious inconsistency | No serious indirectness | No serious imprecision | None | HR 0.43 (0.25 to 0.74) | LOW       |
| 1             |                       |                    |               |              |             |                      |                             |           |

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

| No of studies | Design                | Risk of bias       | Inconsistency | Indirectness | Imprecision | Other considerations | Adjusted effect              | Quality   |
|---------------|-----------------------|--------------------|---------------|--------------|-------------|----------------------|----------------------------|-----------|
|               |                       |                    |               |              |             |                      | Relative (95% CI)            |           |
| Chronic sedative use >275 days – Chinese | Observational studies | Very serious¹      | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 0.81 (0.76 to 0.86) | LOW       |
| 1             |                       |                    |               |              |             |                      |                             |           |
| Chronic sedative use >275 days - South Asian | Observational studies | Very serious¹      | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 0.69 (0.63 to 0.76) | LOW       |
| 1             |                       |                    |               |              |             |                      |                             |           |

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 serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | HR 1.33 (0.55 to 3.21) | VERY LOW |

¹Downgraded 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 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.41 (1.12-1.78) | LOW |

¹Downgraded 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

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Absolute effect | Quality |
|---------------|--------|--------------|---------------|--------------|-------------|----------------------|----------------|---------|
| Dependence (DSM-IV-TR) | | | | | | | | |
| 1 | Observational studies | Very serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | Only reported as non-significant – no data available² | NS | VERY LOW |

¹Downgraded 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
²Downgraded by 1 increment
NS = not significant
Table 63:  Risk factor: Age (referent: 18-24 years) – Outcome: Benzodiazepine dependence

| Quality assessment | Adjusted effect | Quality |
|--------------------|----------------|---------|
| **Benzodiazepine dependence - 25-34 years** | | |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | |
| 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious ² | None | HR 1.23 (0.35 to 4.31) | VERY LOW |

| **Benzodiazepine dependence - 35-44 years** | | |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | |
| 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious ² | None | HR 0.66 (0.33 to 1.31) | VERY LOW |

| **Benzodiazepine dependence - 45-54 years** | | |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | |
| 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious ² | None | HR 0.87 (0.37 to 2.06) | VERY LOW |

| **Benzodiazepine dependence - 55-64 years** | | |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | |
| 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious ² | None | HR 1.08 (0.37 to 3.11) | VERY LOW |

| **Benzodiazepine dependence - 65+ years** | | |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | |
| 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious ² | None | HR 1.47 (0.34 to 6.27) | VERY LOW |

¹Downgraded 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
²Downgraded by 1 increment if the 95% CI crossed the null line
Table 64: Risk factor: Age, years (referent: below 30) – Outcome: Long term use

| No of studies | Design       | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
|---------------|--------------|--------------|---------------|--------------|-------------|----------------------|-------------------|---------|
| Long term use |              |              |               |              |             |                      |                   |         |
|               |              |              |               |              |             |                      |                   |         |
|               |              |              |               |              |             |                      |                   |         |
| Long term use - 30-39 | |              |               |              |             |                      |                   |         |
| 1             | Observational studies | Very serious | No serious inconsistency | No serious indirectness | Serious | None | OR 1.24 (0.77 to 2) | VERY LOW |
| Long term use - 40-64 | |              |               |              |             |                      |                   |         |
| 1             | Observational studies | Very serious | 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 | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 6.36 (4.18 to 9.68) | LOW |

1Downgraded 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

2Downgraded 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

| No of studies | Design         | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
|---------------|----------------|--------------|---------------|--------------|-------------|----------------------|------------------|---------|
| Chronic sedative use >275 days - 55-59 | 1               | Observational studies | Very serious¹ | 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 serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.29 (1.24 to 1.34) | LOW |

¹Downgraded 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, \(\geq 75\) years (referent: 65-74) – Outcome: dependence/addiction

| No of studies | Design                        | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Adjusted effect       | Relative (95% CI) |
|---------------|-------------------------------|--------------|---------------|--------------|-------------|----------------------|-----------------------|---------------------|
| Dependence/Addiction - Dependence (DSM-IV-TR) | 1 | Observational studies | Very serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.7 (1.1 to 2.63) | LOW |

¹Downgraded 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
²Downgraded 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

| No of studies | Design                        | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Adjusted effect       | Quality |
|---------------|-------------------------------|--------------|---------------|--------------|-------------|----------------------|-----------------------|---------|
| Chronic sedative use >275 days - Single | 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.04 (1 to 1.08) | LOW |

¹Downgraded 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

| No of studies | Design            | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
|---------------|-------------------|--------------|---------------|--------------|-------------|----------------------|-------------------|---------|
| Chronic sedative use >275 days - Mixed urban / rural | 1 | Observational studies | Very serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.06 (1 to 1.12) | LOW |

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

| No of studies | Design            | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
|---------------|-------------------|--------------|---------------|--------------|-------------|----------------------|-------------------|---------|
| Chronic sedative use >275 days - Lowest | 1 | Observational studies | Very serious¹ | 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 serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.16 (1.11 to 1.21) | LOW |
### Table 70: Risk factor: Mental health diagnosis (vs no diagnosis) – Outcome long term use

| No of studies | Design     | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
|---------------|------------|--------------|---------------|--------------|-------------|----------------------|-------------------|---------|
| 1             | Observational studies | Very serious | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.08 (1.04 to 1.12) | LOW     |

*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

| No of studies | Design     | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
|---------------|------------|--------------|---------------|--------------|-------------|----------------------|-------------------|---------|
| Benzodiazepine dependence – Depression  
1             | Observational studies | Very serious | 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 | 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 | No serious inconsistency | No serious indirectness | Serious | None | HR 1.02 (0.69 to 1.51) | VERY LOW |
| Benzodiazepine dependence – PTSD  
1             | Observational studies | Very serious | No serious inconsistency | No serious indirectness | None | None | None | VERY LOW |
|   | Observational studies | Very serious | No serious inconsistency | No serious indirectness | Serious | None | HR 0.91 (0.65 to 1.27) | VERY LOW |
|---|-----------------------|--------------|--------------------------|------------------------|---------|------|-----------------------|----------|
| Benzodiazepine dependence - Sleeping disturbance | | |
| 1 | Observational studies | Very serious | 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

| Risk factor                           | Outcome                                      | 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) | Outcome: dependence or addiction             | 1                | Observational studies | Very serious¹ | 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 serious¹ | 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) | Outcome: dependence or addiction             | 1                | Observational studies | Very serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | Only reported as non-significant – no data available² | NS      | VERY LOW |

¹Downgraded 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

²Downgraded 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

| Risk factor                           | Outcome                                      | 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 | Outcome: Chronic sedative use >275 days      | 1                | Observational studies | Very serious¹ | 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

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Absolute effect | Quality |
|---------------|--------|--------------|---------------|--------------|-------------|----------------------|----------------|---------|
| 1             | Observational studies | Very serious¹ | 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

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Absolute effect | Quality |
|---------------|--------|--------------|---------------|--------------|-------------|----------------------|----------------|---------|
| 1             | Observational studies | Very serious¹ | 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

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Absolute effect | Quality |
|---------------|--------|--------------|---------------|--------------|-------------|----------------------|----------------|---------|
| 1             | Observational studies | Very serious¹ | 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

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Absolute effect | Quality |
|---------------|--------|--------------|---------------|--------------|-------------|----------------------|----------------|---------|
| 1             | Observational studies | Very serious¹ | 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

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Absolute effect | Quality |
|---------------|--------|--------------|---------------|--------------|-------------|----------------------|----------------|---------|
| 1             | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious | None | OR 1.1 (0.88 to 1.38) | VERY LOW |

¹Downgraded 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.

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

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Absolute effect | Quality |
|---------------|--------|--------------|---------------|--------------|-------------|----------------------|----------------|---------|
| Mild impairment vs intact - Dependence (DSM-IV-TR) |

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Absolute effect | Quality |
|---------------|--------|--------------|---------------|--------------|-------------|----------------------|----------------|---------|
| 1             | Observational studies | Very serious¹ | 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 |

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Absolute effect | Quality |
|---------------|--------|--------------|---------------|--------------|-------------|----------------------|----------------|---------|
| 1             | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | Only reported as non-significant – no data available⁸ | NS | VERY LOW |

¹Downgraded 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

⁸Downgraded 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

| No of studies | Design                  | Risk of bias   | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
|---------------|-------------------------|----------------|---------------|--------------|-------------|----------------------|-------------------|---------|
| Long term use - 2 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | OR 0.99 (0.7 to 1.4) | VERY LOW |
| 1             |                         |                |               |              |             |                      |                   |         |
| Long term use - 3 or more | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.56 (1.02 to 2.39) | LOW |
| 1             |                         |                |               |              |             |                      |                   |         |

¹Downgraded 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
²Downgraded 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

| No of studies | Design                  | Risk of bias   | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
|---------------|-------------------------|----------------|---------------|--------------|-------------|----------------------|-------------------|---------|
| Chronic sedative use >275 days - 1-2 ADGs | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.19 (1.16 to 1.22) | LOW |
| 1             |                         |                |               |              |             |                      |                   |         |
| Chronic sedative use >275 days - 3+ ADGs | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.34 (1.28 to 1.4) | LOW |
| 1             |                         |                |               |              |             |                      |                   |         |

¹Downgraded 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

| No of studies | Design            | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
|---------------|-------------------|--------------|---------------|--------------|-------------|----------------------|-------------------|---------|
| Chronic sedative use >275 days - 2-3 minor ADGs | 1 | Observational studies | Very serious¹ | 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 serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 1.08 (1.01 to 1.15) | LOW |

¹Downgraded 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

²Downgraded 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

| No of studies | Design            | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
|---------------|-------------------|--------------|---------------|--------------|-------------|----------------------|-------------------|---------|
| Long term use – 2 | 1 | Observational studies | Very serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 4.55 (2.85 to 7.26) | LOW |

¹Downgraded 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

| No of studies | Design            | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Adjusted effect (95% CI) | Quality |
|---------------|-------------------|--------------|---------------|--------------|-------------|----------------------|--------------------------|----------|
| Long term use - Short acting | 1 | Observational studies | Very serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 3.39 (1.69 to 6.8) | LOW |

¹Downgraded 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

| No of studies | Design            | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Adjusted effect (95% CI) | Quality |
|---------------|-------------------|--------------|---------------|--------------|-------------|----------------------|--------------------------|----------|
| Long term use – Hypnotics | 1 | Observational studies | Very serious¹ | 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 serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 2.03 (1.49 to 2.77) | LOW |

¹Downgraded 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

| Risk factor | Outcome | Quality assessment | Adjusted effect | Quality |
|-------------|---------|--------------------|-----------------|---------|
| Use of prescribed opioids (vs no opioids) | Long term use | No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) |
| | | 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | OR 0.87 (0.48 to 1.58) | VERY LOW |

¹Downgraded 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
²Downgraded 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

| Risk factor | Outcome | Quality assessment | Adjusted effect | Quality |
|-------------|---------|--------------------|-----------------|---------|
| Sedative use (referent: non-user) | Chronic sedative use >275 days - Short-term user | No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) |
| | | 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | OR 0.98 (0.94 to 1.02) | VERY LOW |
| Chronic sedative use >275 days - Moderate-term user | | No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) |
| | | 1 | Observational studies | Very serious¹ | 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 | | No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) |
| | | 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | OR 14.73 (1.24 to 174.99) | LOW |

¹Downgraded 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
²Downgraded by 1 increment if the 95% CI crossed the null line
Table 83: Risk factor: Substance use diagnosis (vs no diagnosis) – Outcome: Benzodiazepine dependence

| Risk factor                          | Outcome                     | Quality assessment | Adjusted effect      | Quality  |
|-------------------------------------|-----------------------------|--------------------|----------------------|----------|
| Substance use disorder              | Benzodiazepine dependence   | No of studies      | Design               | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Quality |
| Substance use diagnosis (vs no diagnosis) | Benzodiazepine dependence – Alcohol | 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | HR 0.77 (0.6 to 0.99) | LOW |
| Substance use disorder              | Benzodiazepine dependence – Marijuana | 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | HR 0.28 (0.2 to 0.38) | LOW |
| Substance use disorder              | Benzodiazepine dependence – Cocaine | 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | Serious² | None | HR 1.13 (0.79 to 1.61) | VERY LOW |
| Substance use disorder              | Benzodiazepine dependence – Opioid | 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | HR 3.9 (1.18 to 12.89) | LOW |
| Substance use disorder              | Benzodiazepine dependence – Tobacco | 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | HR 2.08 (1.18 to 3.67) | LOW |
| Substance use disorder              | Benzodiazepine dependence - Pain medications | 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | HR 0.71 (0.58 to 0.86) | LOW |
| Substance use disorder              | Benzodiazepine dependence - 2 or more substance use disorders | 1 | Observational studies | Very serious¹ | No serious inconsistency | No serious indirectness | No serious imprecision | None | HR 2.03 (1.04 to 3.95) | LOW |

¹Downgraded 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  
²Downgraded 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 |
|--------------------|-----------------|---------|
|                    | Relative (95% CI) |         |
| Long term use - Local community hospitals only | | |
| 1 | Observational studies | Very serious | 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 | 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 | 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 | 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 |
| 1 | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | very serious² | none | 23 | 25 | - | MD 0 higher (1.39 lower to 1.39 higher) | ☒☺☺☺ VERY LOW | CRITICAL |

Signs and symptoms/overall withdrawal syndrome (OOWS score) following induction of withdrawal (range of scores: 0-13; Better indicated by lower values)

| Quality of life - psychological health (POMS score) following induction of withdrawal (Better indicated by lower values) |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1 | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | serious² | none | 23 | 25 | - | MD 10 higher (7.04 lower to 27.04 higher) | ☒☺☺☺ 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)

| 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 serious¹ | no serious inconsistency | no serious indirectness | serious² | none | 23 | 25 | - | MD 2.6 lower (4.7 to 0.5 lower) | ☒☺☺☺ 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)

| 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 | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|------------------------------------------------|---------|-----------------|----------|---------|------------|
| Signs and symptoms/overall withdrawal syndrome (OOWS score) (range of scores: 0-13; Better indicated by lower values) |
| 1 | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | no serious imprecision | none | 33 | 33 | - | MD 0 higher (1.11 lower to 1.11 higher) | LOW | CRITICAL |
| Signs and symptoms/overall withdrawal syndrome (SOWS score) (range of scores: 0-64; Better indicated by lower values) |
| 1 | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | serious² | none | 33 | 33 | - | MD 0.3 higher (5.23 lower to 5.83 higher) | VERY LOW | CRITICAL |
| Quality of life - psychological health (POMS score) (Better indicated by lower values) |
| 1 | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | no serious imprecision | none | 33 | 33 | - | MD 1 higher (15.52 lower to 17.52 higher) | 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 |
|--------------------|----------------|--------|---------|-----------|
| Prescriber education/skills/knowledge/support (notification of overdose letter to GP) versus Usual care | 388 | 438 | MD 6 lower (8.54 to 3.46 lower) | LOW CRITICAL |

Reduction in prescribing (mean daily mg morphine equivalent) (follow-up 1-4 months; Better indicated by lower values)

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 |
|--------------------|----------------|--------|---------|-----------|
| Patient advice and support (Mindfulness based recovery enhancement) versus Patient advice and support (conventional support group) | 31 | 38 | MD 1.68 lower (2.5 to 0.86 lower) | VERY LOW CRITICAL |

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)

| 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) | 23 | 28 | MD 2.15 lower (3.44 to 0.86 lower) | 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 serious¹ | no serious inconsistency | serious² | serious³ | none | 31 | 38 | - | MD 1.72 lower (2.93 to 0.51 lower) | 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 serious¹ | no serious inconsistency | serious² | serious³ | none | 23 | 28 | - | MD 0.63 lower (2.31 lower to 1.05 higher) | 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 serious¹ | no serious inconsistency | serious² | serious³ | none | 31 | 38 | - | MD 4.24 lower (7.5 to 0.98 lower) | 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 serious¹ | no serious inconsistency | serious² | serious³ | none | 31 | 38 | - | MD 2.56 lower (5.79 lower to 0.67 higher) | 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 serious¹ | no serious inconsistency | serious² | serious³ | none | 31 | 38 | - | MD 0.81 higher (2.03 lower to 3.65 higher) | 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 serious¹ | no serious inconsistency | serious² | serious³ | none | 31 | 38 | - | MD 1.75 lower (3.82 lower to 0.32 higher) | 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 serious¹ | no serious inconsistency | serious² | serious³ | none | 31 | 38 | - | MD 1.76 lower (5.16 lower to 1.64 higher) | 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 serious¹ | no serious inconsistency | serious² | serious³ | none | 31 | 38 | MD 3.68 lower (6.13 to 1.23 lower) | ☒☒☒☒ 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 serious¹ | no serious inconsistency | serious² | serious³ | none | 31 | 38 | MD 2.78 lower (4.86 to 0.7 lower) | ☒☒☒ 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 serious¹ | no serious inconsistency | serious² | serious³ | none | 31 | 38 | MD 2.27 lower (4.61 lower to 0.07 higher) | ☒☒ CRITICAL |

| Rates of lapse/relapse (Current opioid misuse measure) post treatment | Better indicated by lower values |
|---|---|
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | serious³ | none | 31 | 38 | MD 4.41 lower (8.48 to 0.34 lower) | ☒☒ CRITICAL |

| Rates of lapse/relapse (Current opioid misuse measure) at 3 months follow up | Better indicated by lower values |
|---|---|
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | serious³ | none | 23 | 28 | MD 2.54 lower (6.71 lower to 1.63 higher) | ☒☒ 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 |
|--------------------|----------------|--------|---------|------------|
| Support for patients around medication management versus Usual care | 17 | 21 | - | MD 2.35 lower (23.13 lower to 18.43 higher) | VERY LOW CRITICAL |

#### 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)  
\(\star\star\star\)  
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)  
\(\star\star\star\)  
VERY LOW

#### 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)  
\(\star\star\star\)  
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)  
\(\star\star\star\)  
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 1.05 higher (16.84 lower to 18.94 higher)  
\(\star\star\star\)  
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)  
\(\star\star\star\)  
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 serious¹ | no serious inconsistency | serious² | very serious² | none | 17 | 21 | - | MD 1.54 lower (21.22 lower to 18.14 higher) | ⚫⚫⚫⚫ 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 serious¹ | no serious inconsistency | serious² | serious³ | none | 17 | 21 | - | MD 8.18 lower (26.89 lower to 10.53 higher) | ⚫⚫⚫⚫ 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 serious¹ | no serious inconsistency | serious² | very serious³ | none | 17 | 21 | - | MD 0.1 lower (19.21 lower to 19.01 higher) | ⚫⚫⚫⚫ 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 serious¹ | no serious inconsistency | serious² | very serious³ | none | 17 | 21 | - | MD 0.32 higher (16.77 lower to 17.41 higher) | ⚫⚫⚫⚫ VERY LOW | CRITICAL |

| Rates of lapse/relapse (drug misuse) (follow-up 6 months; assessed with: Drug misuse index) |
|---|
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | no serious imprecision | none | 17 | 21 | - | RR 0.36 (0.16 to 0.79) | 472 fewer per 1000 (from 155 fewer to 619 fewer) | ⚫⚫⚫⚫ 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 | serious¹ | no serious inconsistency | serious² | serious³ | none | 19 | 19 | - | MD 2.62 lower (4.9 to 0.34 lower) | ⚫⚫⚫⚫ 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 serious¹ | no serious inconsistency | serious² | serious³ | none | 19 | 19 | - | MD 3 lower (5.44 to 0.56 lower) | ⚫⚫⚫⚫ 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** |
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | serious³ | none | 12 | 18 | - | MD 74.2 lower (211.37 lower to 62.97 higher) | 🌟🌟🌟🌟 CRITICAL |
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | very serious³ | none | 11 | 18 | - | MD 0.4 higher (2.49 lower to 3.29 higher) | 🌟🌟🌟🌟 CRITICAL |
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | very serious³ | none | 11 | 18 | - | MD 23.6 lower (48.31 lower to 1.11 higher) | 🌟🌟🌟🌟 CRITICAL |
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | serious³ | none | 12 | 18 | - | MD 4.9 higher (2.98 lower to 12.78 higher) | 🌟🌟🌟🌟 CRITICAL |
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | serious³ | none | 12 | 18 | - | MD 5.3 higher (1.03 lower to 11.63 higher) | 🌟🌟🌟🌟 CRITICAL |

Reduction/cessation in prescribed drug use (daily opioid dose) (follow-up 4-6 weeks; Better indicated by lower values)

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)

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)

Signs and symptoms/overall withdrawal syndrome (continuous reaction time) (follow-up 4-6 weeks; Better indicated by lower values)

Signs and symptoms/overall withdrawal syndrome (finger tapping test) - Dominant hand (follow-up 4-6 weeks; Better indicated by higher values)

Signs and symptoms/overall withdrawal syndrome (finger tapping test) - Non-dominant hand (follow-up 4-6 weeks; Better indicated by higher values)
| Study | Randomised Trials | Very Serious\(^1\) | No Serious Inconsistency | Serious\(^2\) | Very Serious\(^3\) | None | 11 | 18 | Bias | Evidence | Effect Size | GRADE | Overall Impact |
|-------|-------------------|-------------------|------------------------|--------------|-------------------|------|----|----|------|----------|-------------|-------|----------------|
| 1     |                   |                   |                        |              |                   |      |    |    | MD 1 higher (0.99 lower to 2.99 higher) | 10000 VERY LOW | CRITICAL |
| 1     |                   |                   |                        |              |                   |      |    |    | MD 1.2 higher (1.19 lower to 3.59 higher) | 10000 VERY LOW | CRITICAL |
| 1     |                   |                   |                        |              |                   |      |    |    | MD 19.1 higher (13.36 lower to 51.56 higher) | 10000 VERY LOW | CRITICAL |
| 1     |                   |                   |                        |              |                   |      |    |    | MD 0.3 higher (0.63 lower to 1.23 higher) | 10000 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 | serious¹ | no serious inconsistency | no serious indirectness | serious² | none | - | 0% | OR 1.5 (1 to 2.25) | - | LOW | CRITICAL |
| Reduction/cessation in prescribed drug use (10% reduction in opioid dose among non-discontinued patients) (follow-up 12 months) | 1 | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | serious² | none | - | 0% | OR 1.6 (1.1 to 2.33) | - | 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)

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Effect | Control | Relative (95% CI) | Absolute | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|--------|---------|------------------|----------|---------|-------------|
| 1             | randomised trials | no serious risk of bias | no serious inconsistency | serious | no serious imprecision | none | - | MD 0 higher (1.13 lower to 1.13 higher) | MODERATE | CRITICAL |
| Reduction in prescribing (opioid prescriptions per patient) at 91-270 days post intervention (Better indicated by lower values) |
| 1             | randomised trials | very serious | no serious inconsistency | serious | serious | none | - | MD 0.1 lower (0.53 lower to 0.33 higher) | 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)

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Effect | Control | Relative (95% CI) | Absolute | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|--------|---------|------------------|----------|---------|-------------|
| Reduction in prescribing (opioid prescriptions per patient) at 91-270 days post intervention (Better indicated by lower values) |
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 education/skills/knowledge/support (GP notification + education) | Control | Relative (95% CI) | Absolute |
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | no serious imprecision | none | 399 | 391 | MD 11.1 lower (12.41 to 9.79 lower) | ††††† VERY CRITICAL |

Reduction in prescribing (chronic high-dose opioid use) at 91-270 days post intervention

| 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 notification + education) | Control | Relative (95% CI) | Absolute |
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | very serious³ | 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) | ††††† VERY CRITICAL |

Uptake of psychosocial interventions (visits to mental health specialists) at 91-270 days post intervention

| 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 notification + education) | Control | Relative (95% CI) | Absolute |
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | very serious³ | 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) | ††††† VERY CRITICAL |

Lapse/relapse (diagnosis of opioid abuse) at 91-270 days post intervention

| 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 notification + education) | Control | Relative (95% CI) | Absolute |
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | very serious³ | 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) | ††††† VERY CRITICAL |

Lapse/relapse (opioid associated ED visits) at 91-270 days post intervention

| 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 notification + education) | Control | Relative (95% CI) | Absolute |
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | serious³ | 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) | ††††† VERY 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
### Reduction in prescribing (opioid prescriptions per patient) at 91-270 days post intervention (Better indicated by lower values)

| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | no serious imprecision | none | 399 | 408 | MD 11.5 lower (12.85 to 10.15 lower) | □□□□ VERY LOW | CRITICAL |

### Reduction in prescribing (chronic high-dose opioid use) at 91-270 days post intervention

| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | very serious³ | 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) | □□□□ VERY LOW | CRITICAL |

### Uptake of psychosocial interventions (visits to mental health specialists) at 91-270 days post intervention

| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | very serious³ | 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) | □□□□ VERY LOW | CRITICAL |

### Lapse/relapse (diagnosis of opioid abuse) at 91-270 days post intervention

| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | serious³ | 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) | □□□□ VERY LOW | CRITICAL |

### Lapse/relapse (opioid associated ED visits) at 91-270 days post intervention

| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | serious³ | 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) | □□□□ 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 |
| 1                  | randomised trials | very serious¹ | no serious inconsistency | serious² | no serious imprecision | none | 399 | 821 | - | MD 11.6 lower (12.61 to 10.59 lower) | ⚠️⚠️⚠️⚠️ VERY LOW | CRITICAL |
| 1                  | randomised trials | very serious¹ | no serious inconsistency | serious² | very serious³ | 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) | ⚠️⚠️⚠️⚠️ VERY LOW | CRITICAL |
| 1                  | randomised trials | very serious¹ | no serious inconsistency | serious² | very serious³ | 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) | ⚠️⚠️⚠️⚠️ VERY LOW | CRITICAL |
| 1                  | randomised trials | very serious¹ | no serious inconsistency | serious² | very serious³ | 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) | ⚠️⚠️⚠️⚠️ VERY LOW | CRITICAL |
| 1                  | randomised trials | very serious¹ | no serious inconsistency | serious² | serious³ | 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) | ⚠️⚠️⚠️⚠️ 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 |
|--------------------|----------------|--------|---------|------------|
| Prescriber education/skills/knowledge/support (GP education) versus Prescriber education/skills/knowledge/support (GP notification + education) | | | | |
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Control** | **Relative (95% CI)** | **Absolute** | **Quality** | **Importance** |
| 1 | randomised trials | very serious | no serious inconsistency | serious² | no serious imprecision | none | 391 | 408 | - | MD 0.4 lower (2.1 lower to 1.3 higher) | VERY LOW | CRITICAL |
| **Reduction in prescribing (opioid prescriptions per patient) at 91-270 days post intervention (Better indicated by lower values)** | | | | | | | 6.9% | RR 0.71 (0.4 to 1.25) | 20 fewer per 1000 (from 41 fewer to 17 more) | VERY LOW | CRITICAL |
| 1 | randomised trials | very serious | no serious inconsistency | serious² | serious³ | none | 19/391 (4.9%) | 25/391 (6.4%) | 8.8% | RR 0.72 (0.44 to 1.18) | 25 fewer per 1000 (from 49 fewer to 16 more) | VERY LOW | CRITICAL |
| **Uptake of psychosocial interventions (visits to mental health specialists) at 91-270 days post intervention** | | | | | | | | | | | |
| 1 | randomised trials | very serious | no serious inconsistency | serious² | serious³ | none | 25/391 (6.4%) | 34/358 (9.5%) | 8.3% | RR 1.15 (0.72 to 1.84) | 12 more per 1000 (from 23 fewer to 70 more) | VERY LOW | CRITICAL |
| **Lapse/relapse (diagnosis of opioid abuse) at 91-270 days post intervention** | | | | | | | | | | | |
| 1 | randomised trials | very serious | no serious inconsistency | serious² | very serious³ | none | 34/358 (9.5%) | 100/391 (25.6%) | 30.6% | RR 0.83 (0.67 to 1.04) | 52 fewer per 1000 (from 101 fewer to 12 more) | VERY LOW | CRITICAL |
| **Lapse/relapse (opioid associated ED visits) at 91-270 days post intervention** | | | | | | | | | | | |
| 1 | randomised trials | very serious | no serious inconsistency | serious² | serious³ | none | 100/391 (25.6%) | | | | | | |
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)

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Indirectness | Other considerations | No of patients | Effect | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|--------------|---------------------|----------------|--------|---------|------------|
|               | randomised trials | very serious¹ | no serious inconsistency | serious² | no serious imprecision | none | 391 | 821 | MD 0.5 lower (1.94 lower to 0.94 higher) | ⚫⚫⚫⚫ VERY LOW CRITICAL |

Reduction in prescribing (opioid prescriptions per patient) at 91-270 days post intervention (Better indicated by lower values)

|               | randomised trials | very serious¹ | no serious inconsistency | serious² | serious³ | 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) | ⚫⚫⚫⚫ VERY LOW CRITICAL |

Reduction in prescribing (chronic high-dose opioid use) at 91-270 days post intervention

|               | randomised trials | very serious¹ | no serious inconsistency | serious² | serious³ | 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) | ⚫⚫⚫⚫ VERY LOW CRITICAL |

Uptake of psychosocial interventions (visits to mental health specialists) at 91-270 days post intervention

|               | randomised trials | very serious¹ | no serious inconsistency | serious² | serious³ | 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) | ⚫⚫⚫⚫ VERY LOW CRITICAL |

Lapse/relapse (diagnosis of opioid abuse) at 91-270 days post intervention

|               | randomised trials | very serious¹ | no serious inconsistency | serious² | serious³ | 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) | ⚫⚫⚫⚫ VERY LOW CRITICAL |

Lapse/relapse (opioid associated ED visits) at 91-270 days post intervention
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

| 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 | no serious inconsistency | serious | no serious imprecision | none | 408 | 821 | MD 0.1 lower (1.58 lower to 1.38 higher) | **VERY LOW** |
| **Reduction in prescribing (chronic high-dose opioid use)** at 91-270 days post intervention |
| 1             | randomised trials | very serious | no serious inconsistency | serious | very serious | 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) | **VERY LOW** |
| **Uptake of psychosocial interventions (visits to mental health specialists)** at 91-270 days post intervention |
| 1             | randomised trials | very serious | no serious inconsistency | serious | serious | 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) | **VERY LOW** |
| **Lapse/relapse (diagnosis of opioid abuse)** at 91-270 days post intervention |
| 1             | randomised trials | very serious | no serious inconsistency | serious | serious | 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) | **VERY LOW** |
Lapse/relapse (opioid associated ED visits) at 91-270 days post intervention

| No of patients | Effect | Quality | Importance |
|----------------|--------|---------|------------|
| 125/408 (30.6%) | RR 1.08 (0.9 to 1.3) | CRITICAL | VERY LOW |

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

| 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 | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|----------------------|-------------------------------------------------------------|---------|------------------|---------|---------|------------|
| Reduction/cessation in prescribed drug use (morphine equivalent dose) post intervention (Better indicated by lower values) |
| 1 | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | ² | none | 16 | 15 | MD 42.9 lower (92.42 lower to 6.62 higher) | 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 serious¹ | no serious inconsistency | no serious indirectness | ² | none | 16 | 16 | MD 26.71 lower (83.04 lower to 29.62 higher) | LOW | CRITICAL |
| Cessation of medication (complete discontinuation of opioids) post intervention |
| 1 | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | very serious² | 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) | VERY LOW | CRITICAL |
| Cessation of medication (complete discontinuation of opioids) at 3 month follow up |
| 1 | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | very serious² | none | 2/16 (12.5%) | 12.5% | RR 1 (0.16 to 6.25) | 0 fewer per 1000 (from 105 fewer to 656 more) | 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\(^2\) | none | 9/16 (56.3%) | 20% | RR 2.81 (0.94 to 8.45) | 362 more per 1000 (from 12 fewer to 1000 more) | ⬤⬤⬤⬤ 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\(^2\) | 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) | ⬤⬤⬤⬤ 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 | serious\(^2\) | none | 16 | 16 | - | MD 1.39 lower (2.78 lower to 0 higher) | ⬤⬤⬤⬤ 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 | serious\(^2\) | none | 16 | 16 | - | MD 1.21 lower (2.43 lower to 0.01 higher) | ⬤⬤⬤⬤ 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 | serious\(^2\) | none | 16 | 16 | - | MD 7.86 higher (1.22 to 14.5 higher) | ⬤⬤⬤⬤ 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 | serious\(^2\) | none | 16 | 16 | - | MD 7.26 higher (2.14 lower to 16.66 higher) | ⬤⬤⬤⬤ 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 | serious\(^2\) | none | 16 | 16 | - | MD 4.9 lower (8.4 to 1.4 lower) | ⬤⬤⬤⬤ 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 | serious\(^2\) | none | 16 | 16 | - | MD 0.16 higher (3.74 lower to 4.06 higher) | ⬤⬤⬤⬤ 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 | serious\(^2\) | none | 16 | 16 | - | MD 4.47 lower (10.13 lower to 1.19 higher) | ⬤⬤⬤⬤ 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 | no serious inconsistency | no serious indirectness | none | 16 | 16 | - | MD 1.62 higher (3.27 lower to 6.51 higher) | □□○○ 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 | no serious inconsistency | no serious indirectness | none | 16 | 16 | - | MD 2.21 lower (6.62 lower to 2.2 higher) | □□○○ 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 | no serious inconsistency | no serious indirectness | none | 16 | 16 | - | MD 1.89 lower (6.23 lower to 2.45 higher) | □□○○ 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 | no serious inconsistency | no serious indirectness | none | 16 | 16 | - | MD 2.73 lower (5.99 lower to 0.53 higher) | □□○○ 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 | no serious inconsistency | no serious indirectness | none | 16 | 16 | - | MD 2.39 lower (5.79 lower to 1.01 higher) | □□○○ 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 | no serious inconsistency | no serious indirectness | none | 16 | 16 | - | MD 3.13 lower (7.22 lower to 0.96 higher) | □□○○ 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 | no serious inconsistency | no serious indirectness | none | 16 | 16 | - | MD 1.91 lower (4.72 lower to 1.78 higher) | □□○○ 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 | no serious inconsistency | no serious indirectness | none | 16 | 16 | - | MD 1.47 lower (4.72 lower to 1.78 higher) | □□○○ 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 | no serious inconsistency | no serious indirectness | none | 16 | 16 | - | MD 0.43 lower (3.33 lower to 2.47 higher) | □□○○ LOW | CRITICAL |
|---|------------------|---------|-------------------------|------------------------|------|----|----|---|------------------------------------------|-----------|----------|

Signs and symptoms/overall withdrawal syndrome (opioid craving) post intervention (range of scores: 0-10; Better indicated by lower values)
| No of patients | 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 | Quality | Importance |
|----------------|--------|--------------|---------------|--------------|-------------|----------------------|-------------------------------------------------------------------------------------------------|---------|------------------|----------|---------|------------|
| No of studies  |        |              |               |              |             |                      |                                                                                                 |         |                  |          |         |            |
| 1              | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | none | 16 | 16 | - | MD 0.36 lower (2.42 lower to 1.7 higher) | ⬠⬠⬠◉  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)

| No of patients | 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 | Quality | Importance |
|----------------|--------|--------------|---------------|--------------|-------------|                      |                                                                                                 |         |                  |          |         |            |
| 1              | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | none | 16 | 16 | - | MD 0.46 lower (1.93 lower to 1.01 higher) | ⬠⬠⬠◉  LOW | CRITICAL |

Rates of lapse/relapse (Prescription opioid misuse index) post intervention (Better indicated by lower values)

| No of patients | 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 | Quality | Importance |
|----------------|--------|--------------|---------------|--------------|-------------|                      |                                                                                                 |         |                  |          |         |            |
| 1              | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | none | 16 | 16 | - | MD 0.08 higher (0.58 lower to 0.74 higher) | ⬠⬠⬠◉  LOW | CRITICAL |

Rates of lapse/relapse (Prescription opioid misuse index) at 3 month follow up (Better indicated by lower values)

| No of patients | 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 | Quality | Importance |
|----------------|--------|--------------|---------------|--------------|-------------|                      |                                                                                                 |         |                  |          |         |            |
| 1              | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | none | 16 | 16 | - | MD 0.06 higher (0.45 lower to 0.57 higher) | ⬠⬠⬠◉  LOW | CRITICAL |

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

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
### Reduction/cessation in prescribed drug use (number adding/increasing an antidepressant)

|   | randomised trials | very serious | no serious inconsistency | no serious indirectness | very serious | none | 8/26 (30.8%) | 18% | RR 1.71 (0.71 to 4.15) | 128 more per 1000 (from 52 fewer to 567 more) | ☐☐☐☐ | CRITICAL |
|---|------------------|--------------|--------------------------|-------------------------|-------------|------|--------------|----|----------------------|---------------------------------------------|--------|----------|

#### Quality of life - psychological (pain interference) (measured with: Brief pain inventory; range of scores: 0-10; Better indicated by lower values)

|   | randomised trials | very serious | no serious inconsistency | no serious indirectness | serious | none | 45 | 47 | - | MD 0.2 lower (1.22 lower to 0.82 higher) | ☐☐☐☐ | CRITICAL |

#### Quality of life - psychological (pain self-efficacy) (range of scores: 0-60; Better indicated by higher values)

|   | randomised trials | very serious | no serious inconsistency | no serious indirectness | serious | none | 45 | 47 | - | MD 6.1 higher (0.73 to 11.47 higher) | ☐☐☐☐ | CRITICAL |

#### Rates of lapse/relapse (Current opioid misuse measure) (Better indicated by lower values)

|   | randomised trials | very serious | no serious inconsistency | no serious indirectness | serious | none | 45 | 47 | - | MD 0.4 lower (3.12 lower to 2.32 higher) | ☐☐☐☐ | CRITICAL |

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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 |
|-------------------|-----------|-------------|---------------|--------------|-------------|---------------------|------------------------------------------|---------|----------------|---------|
| 1                 | randomised | serious | no serious inconsistency | serious | serious | none | 18 | 18 | - | MD 1.66 lower (3.01 to 0.31 lower) | ☐☐☐☐ | CRITICAL |

**Quality of life - psychological (sleep quality) (measured with: Northside Hospital Sleep Medicine Institute Test; range of scores: 0-8; Better indicated by lower values)**

|   | randomised trials | very serious | no serious inconsistency | no serious indirectness | none | 18 | - | MD 1.66 lower (3.01 to 0.31 lower) | ☐☐☐☐ | CRITICAL |

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### Cessation of medication (discontinuation of hypnotic drug)

| 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 | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|---------------------------------------------------------------------------------|---------|------------------|---------|---------|------------|
| 1             | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious¹ | none | 36/45 (80%) | 91.1% | RR 0.88 (0.74 to 1.04) | 109 fewer per 1000 (from 237 fewer to 36 more) | ✭✭✭✭ | MODERATE |

### Signs and symptoms/overall withdrawal syndrome (Geriatric Depression Scale) (range of scores: 1-30; Better indicated by lower values)

| 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 | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|---------------------------------------------------------------------------------|---------|------------------|---------|---------|------------|
| 1             | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | none | 18 | 18 | MD 1.45 lower (4.65 lower to 1.75 higher) | ✭✭✭✭ | VERY LOW | CRITICAL |

### Signs and symptoms/overall withdrawal syndrome (Goldberg Anxiety Scale) (range of scores: 0-9; Better indicated by lower values)

| 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 | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|---------------------------------------------------------------------------------|---------|------------------|---------|---------|------------|
| 1             | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | none | 18 | 18 | MD 1 lower (2.47 lower to 0.47 higher) | ✭✭✭✭ | 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 |
|--------------------|---------------|--------|---------|------------|
| Cessation of medication (total benzodiazepine withdrawal) post intervention | | | | |
| 1 randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious¹ | none | 36/45 (80%) | 91.1% | RR 0.88 (0.74 to 1.04) | 109 fewer per 1000 (from 237 fewer to 36 more) | ✭✭✭✭ | MODERATE |

| Cessation of medication (total benzodiazepine withdrawal) at 3 year follow up | | | | |
| 1 randomised trials | no serious | no serious inconsistency | no serious indirectness | very serious¹ | none | 12/42 (28.6%) | 34.2% | RR 0.84 (0.44 to 1.59) | 55 fewer per 1000 (from 192 more) | ✭✭✭ | LOW | CRITICAL |
| risk of bias | fewer to 202 more |
|-------------|------------------|

*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 |
| 1 | randomised trials | very serious | no serious inconsistency | serious | very serious | none | 15/18 (83.3%) | RR 0.98 (0.72 to 1.34) | 17 fewer per 1000 (from 237 fewer to 288 more) | 186 |
| Rates of lapse/relapse (Relapse to benzodiazepine use) at 11 month follow up | 1 | randomised trials | very serious | no serious inconsistency | serious | very serious | none | 1/10 (10%) | RR 1 (0.07 to 13.87) | 0 fewer per 1000 (from 93 fewer to 1000 more) | 186 |
| Signs and symptoms/overall withdrawal syndrome (number of withdrawal symptoms) post intervention (Better indicated by lower values) | 1 | randomised trials | very serious | no serious inconsistency | serious | very serious | none | 14 | MD 1.07 lower (4.38 lower to 2.24 higher) | 186 |
| 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 | no serious inconsistency | serious | very serious | none | 11 | MD 0.45 higher (3.25 lower to 4.15 higher) | 186 |
| Quality of life - psychological (Psychological Distress Inventory) post intervention (range of scores: 0-100; Better indicated by lower values) | 1 | randomised trials | very serious | no serious inconsistency | serious | very serious | none | 14 | MD 3.07 higher (5.07 lower to 11.21 higher) | 186 |
| 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 | no serious inconsistency | serious | very serious | none | 14 | MD 3.07 higher (5.07 lower to 11.21 higher) | 186 |
| 1 | randomised trials | very serious | no serious inconsistency | serious¹ | no serious inconsistency | serious² | very serious³ | none | 11 | 10 | - | MD 9.96 lower (20.85 lower to 0.93 higher) | 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 | no serious inconsistency | serious² | very serious³ | none | 11 | 10 | - | MD 0.05 higher (1.15 lower to 1.25 higher) | VERY LOW CRITICAL |

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

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality assessment | No of patients | Effect | Quality/Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|-------------------|---------------|--------|---------------------|

**Cessation of medication (follow-up 6 months)**

| 1 | randomised trials | very serious | no serious inconsistency | serious² | 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) | VERY LOW CRITICAL |

**Reduction/cessation in prescribed drug use (complete cessation plus benzodiazepine reduction) (follow-up 6 months)**

| 1 | randomised trials | very serious | no serious inconsistency | serious² | 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) | 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
| 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 | Quality | Importance |
|---------------|-----------------|--------------|---------------|--------------|-------------|----------------------|---------------------------------------------------------------------------------|---------|------------------|----------|---------|------------|
| Cessation of medication (follow-up 12 months) | 1 | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | serious² | none | - | 0% | OR 2.3 (1.21 to 4.37) | - | ☒=no 1 | 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

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| 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 | Quality | Importance |
|---------------|-----------------|--------------|---------------|--------------|-------------|----------------------|---------------------------------------------------------------------------------|---------|------------------|----------|---------|------------|
| Cessation of medication (follow-up 12 months) | 1 | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | serious² | none | - | 0% | OR 2.1 (1.11 to 3.97) | - | ☒=no 1 | 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
| 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 | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|----------------------|--------------------------------------------------------------------------------|---------|------------------|---------|---------|------------|
| Cessation of medication (complete benzodiazepine discontinuation) 0-3 months post discontinuation letter | 1 | randomised trials | very serious | no serious inconsistency | no serious imprecision | none | 998/11423 (8.7%) | | RR 1.06 (0.96 to 1.16) | 5 more per 1000 (from 3 fewer to 13 more) | || |
| Cessation of medication (complete benzodiazepine discontinuation) 4-6 months post discontinuation letter | 1 | randomised trials | very serious | no serious inconsistency | no serious imprecision | none | 1129/11423 (9.9%) | | RR 0.97 (0.89 to 1.06) | 3 fewer per 1000 (from 11 fewer to 6 more) | || |
| Reduction/cessation in prescribed drug use (at least 50% reduction in benzodiazepine use) 0-3 months post discontinuation letter | 1 | randomised trials | very serious | no serious inconsistency | no serious imprecision | none | 1793/11423 (15.7%) | | RR 1.06 (0.99 to 1.14) | 9 more per 1000 (from 1 fewer to 21 more) | || |
| Reduction/cessation in prescribed drug use (at least 50% reduction in benzodiazepine use) 4-6 months post discontinuation letter | 1 | randomised trials | very serious | no serious inconsistency | no serious imprecision | none | 1820/11423 (15.9%) | | RR 0.95 (0.89 to 1.02) | 8 fewer per 1000 (from 18 fewer to 3 more) | || |

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)

| 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 | serious¹ | no serious inconsistency | no serious indirectness | serious² | 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) | CRITICAL |
| **Cessation of medication (cessation of benzodiazepine use) at 36 month follow up** | 1 | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | serious² | 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) | CRITICAL |
| **Reduction/cessation of prescribed medication (initiation of antidepressants) at 12 months** | 1 | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | serious² | 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) | CRITICAL |
| **Signs and symptoms/overall withdrawal syndrome (attempted suicide by overdose) at 4 months** | 1 | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | very serious² | none | 0/191 (0%) | 0.6% | OR 0.12 (0 to 6) | 5 fewer per 1000 (from 6 fewer to 29 more) | CRITICAL |
| **Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Tremor** | 1 | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | serious² | none | 30/186 (16.1%) | 11.3% | RR 1.42 (0.83 to 2.46) | 47 more per 1000 (from 5 to 1000) | CRITICAL |
| Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Irritability |
|---|---|---|---|---|---|---|
| 1 | randomised trials | serious¹ no serious inconsistency | no serious indirectness | serious² 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) | @@@O LOW CRITICAL |

| Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Insomnia |
|---|---|---|---|---|---|---|
| 1 | randomised trials | serious¹ no serious inconsistency | no serious indirectness | serious² 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) | @@@O LOW CRITICAL |

| Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Anxiety |
|---|---|---|---|---|---|---|
| 1 | randomised trials | serious¹ no serious inconsistency | no serious indirectness | serious² 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) | @@@O LOW CRITICAL |

| Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Convulsions |
|---|---|---|---|---|---|---|
| 1 | randomised trials | serious¹ no serious inconsistency | no serious indirectness | very serious¹ 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) | @@@O VERY LOW CRITICAL |

| Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Tremor |
|---|---|---|---|---|---|---|
| 1 | randomised trials | serious¹ no serious inconsistency | no serious indirectness | very serious¹ 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) | @@@O VERY LOW CRITICAL |

| Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Irritability |
|---|---|---|---|---|---|---|
| 1 | randomised trials | serious¹ no serious inconsistency | no serious indirectness | very serious¹ 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) | @@@O VERY LOW CRITICAL |

| Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Insomnia |
|---|---|---|---|---|---|---|
| 1 | randomised trials | serious¹ no serious inconsistency | no serious indirectness | very serious¹ none | | | | |
| 1 | randomised trials | serious¹ no serious inconsistency no serious indirectness serious² 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) | □□□□ LOW CRITICAL |
|---|---|---|---|---|---|---|---|

**Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Anxiety**

| 1 | randomised trials | serious¹ no serious inconsistency no serious indirectness serious² 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) | □□□□ LOW CRITICAL |
|---|---|---|---|---|---|---|---|

**Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Convulsions**

| 1 | randomised trials | serious¹ no serious inconsistency no serious indirectness no serious imprecision none | 0/184 (0%) | 0% | not pooled not pooled | not pooled | □□□□ MODERATE CRITICAL |
|---|---|---|---|---|---|---|---|

**Rates of lapse/relapse (use of benzodiazepine at 36 months in those who stopped use at 12 months)**

| 1 | randomised trials | serious¹ no serious inconsistency no serious indirectness serious² 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) | □□□□ LOW CRITICAL |
|---|---|---|---|---|---|---|---|

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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

| 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          | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|----------------------|----------------------------------------------------------------------------------------|---------|------------------|------------------|---------|------------|
| Cessation of medication (cessation of benzodiazepine use) post intervention | 1      | randomised trials | serious¹ | 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) | MODERATE | CRITICAL |
| Cessation of medication (cessation of benzodiazepine use) at 36 month follow up | 1      | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | serious² | none | 79/191 (41.4%) | 26% RR 1.59 (1.17 to 2.15) 153 more per 1000 (from 44 more to 299 more) | LOW | CRITICAL |
| Reduction/cessation of prescribed medication (initiation of antidepressant medication) at 12 months | 1      | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | serious² | 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) | LOW | CRITICAL |
| Signs and symptoms/overall withdrawal syndrome (attempted suicide by overdose) at 4 months | 1      | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | no serious imprecision | none | 0/191 (0%) | 0% See comment - | LOW | CRITICAL |
| Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Tremor | 1      | randomised trials | serious¹ | 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) | MODERATE | CRITICAL |
| Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Irritability |
| 1 | randomised trials | serious | 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) | MODERATE CRITICAL |
|---|------------------|---------|--------------------------|------------------------|-----------------------|------|----------------|------|------------------|---------------------------------------------|------------------|
| 1 | randomised trials | serious | 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) | MODERATE CRITICAL |
| 1 | randomised trials | serious | 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) | MODERATE CRITICAL |
| 1 | randomised trials | serious | no serious inconsistency | no serious indirectness | very serious | 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) | VERY LOW CRITICAL |
| 1 | randomised trials | serious | no serious inconsistency | no serious indirectness | very serious | 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) | VERY LOW CRITICAL |
| 1 | randomised trials | serious | no serious inconsistency | no serious indirectness | very serious | none | 26/184 (14.1%) | 12.2% | RR 1.16 (0.67 to 2) | 20 more per 1000 (from 40 fewer to 122 more) | VERY LOW CRITICAL |
| 1 | randomised trials | serious | no serious inconsistency | no serious indirectness | serious | 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) | LOW CRITICAL |
### Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Anxiety

| No. | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No of patients | Relative (95% CI) | Absolute |
|-----|--------|--------------|---------------|--------------|-------------|---------------------|----------------|------------------|----------|
| 1   | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | serious² | none | 48/184 (26.1%) | RR 1.3 (0.88 to 1.91) | 60 more per 1000 (from 24 fewer to 183 more) |
|    |        |              |               |              |             |                    | 20.1%          |                  | LOW CRITICAL |

### Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Convulsions

| No. | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No of patients | Relative (95% CI) | Absolute |
|-----|--------|--------------|---------------|--------------|-------------|---------------------|----------------|------------------|----------|
| 1   | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | none | none | 0/184 (0%) | RR 0.83 (0.42 to 1.64) | 52 fewer per 1000 (from 179 fewer to 197 more) |
|    |        |              |               |              |             |                    | 0%             | not pooled        | not pooled | MODERATE CRITICAL |

### Rates of lapse/relapse (benzodiazepine use at 36 months in those who stopped use at 12 months)

| No. | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No of patients | Relative (95% CI) | Absolute |
|-----|--------|--------------|---------------|--------------|-------------|---------------------|----------------|------------------|----------|
| 1   | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | very serious² | none | 22/86 (25.6%) | RR 0.83 (0.42 to 1.64) | 52 fewer per 1000 (from 179 fewer to 197 more) |
|    |        |              |               |              |             |                    | 30.8%          |                  | 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

| No of patients | Effect | Quality | Importance |
|----------------|--------|---------|------------|
| Prescriber education/skills/knowledge/support (GP workshop + written instructions) versus Usual care | | | |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Control | Relative (95% CI) | Absolute |
|                |        |              |               |              |             |                    |         |                  |         |

Cessation of medication (cessation of benzodiazepine use) post intervention

| No. | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No of patients | Relative (95% CI) | Absolute |
|-----|--------|--------------|---------------|--------------|-------------|---------------------|----------------|------------------|----------|
| 1   | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | no serious imprecision | none | 72/168 (42.9%) | RR 2.97 (1.98 to 4.44) | 286 more per 1000 (from 142 more to 499 more) |
|    |        |              |               |              |             |                    | 14.5%          |                  | MODERATE CRITICAL |

Cessation of medication (cessation of benzodiazepine use) at 36 month follow up

| No. | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No of patients | Relative (95% CI) | Absolute |
|-----|--------|--------------|---------------|--------------|-------------|---------------------|----------------|------------------|----------|
| 1   | randomised trials | serious¹ | no serious inconsistency | no serious indirectness | serious² | none | 66/168 (39.3%) | RR 1.51 (1.1 to 2.07) | 133 more per 1000 (from 26 more) |
|    |        |              |               |              |             |                    | 25%            |                  | LOW CRITICAL |
### Reduction/cessation of prescribed medication (initiation of antidepressants) at 12 months

| Trials | Serious inconsistency | Serious indirectness | Serious imprecision | None | % | RR (95% CI) | Number of patients | % | CRITICAL |
|--------|-----------------------|----------------------|---------------------|------|---|-------------|-------------------|---|---------|
| 1      | 1/161 (12.4%)         |                      |                     |      |   | 0.91 (0.52 to 1.6) | 20/161 (12.4%)    |   | VERY LOW |

#### Signs and symptoms/overall withdrawal syndrome (attempted suicide by overdose) at 4 months

| Trials | Serious inconsistency | Serious indirectness | Serious imprecision | None | % | OR (95% CI) | Number of patients | % | CRITICAL |
|--------|-----------------------|----------------------|---------------------|------|---|-------------|-------------------|---|---------|
| 1      | 1/168 (0.6%)          |                      |                     |      |   | 7.61 (0.15 to 383.8) | 0% | -         | VERY LOW |

#### Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Tremor

| Trials | Serious inconsistency | Serious indirectness | Serious imprecision | None | % | RR (95% CI) | Number of patients | % | CRITICAL |
|--------|-----------------------|----------------------|---------------------|------|---|-------------|-------------------|---|---------|
| 1      | 18/159 (11.3%)        |                      |                     |      |   | 2.14 (0.99 to 4.62) | 5.3% | 60 more per 1000 (from 1 fewer to 192 more) | VERY LOW |

#### Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Irritability

| Trials | Serious inconsistency | Serious indirectness | Serious imprecision | None | % | RR (95% CI) | Number of patients | % | CRITICAL |
|--------|-----------------------|----------------------|---------------------|------|---|-------------|-------------------|---|---------|
| 1      | 42/159 (26.4%)        |                      |                     |      |   | 2.99 (1.73 to 5.18) | 8.8% | 175 more per 1000 (from 64 more to 368 more) | MODERATE |

#### Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Insomnia

| Trials | Serious inconsistency | Serious indirectness | Serious imprecision | None | % | RR (95% CI) | Number of patients | % | CRITICAL |
|--------|-----------------------|----------------------|---------------------|------|---|-------------|-------------------|---|---------|
| 1      | 83/159 (52.2%)        |                      |                     |      |   | 2.96 (2.07 to 4.23) | 17.7% | 347 more per 1000 (from 189 more to 572 more) | MODERATE |

#### Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Anxiety

| Trials | Serious inconsistency | Serious indirectness | Serious imprecision | None | % | RR (95% CI) | Number of patients | % | CRITICAL |
|--------|-----------------------|----------------------|---------------------|------|---|-------------|-------------------|---|---------|
| 1      | 64/159 (40.3%)        |                      |                     |      |   | 3.26 (2.09 to 5.07) | 12.4% | 280 more per 1000 (from 135 more to 505 more) | MODERATE |

#### Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 6 months - Convulsions

| Trials | Serious inconsistency | Serious indirectness | Serious imprecision | None | % | CRITICAL |
|--------|-----------------------|----------------------|---------------------|------|---|---------|
|        |                       |                      |                     |      |   |         |
| 1 | randomised trials | serious¹ no serious inconsistency | no serious indirectness | very serious² none | 1/159 (0.63%) | 0.6% | RR 1.07 (0.07 to 16.95) | 2 more per 1000 (from 6 fewer to 96 more) | ⚪️⚫️⚫️⚫️ VERY LOW | CRITICAL |
|---|-------------------|----------------------------------|------------------------|-------------------|----------------|------|-----------------------|------------------------------------------|-----------------|-----------|

**Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Tremor**

| 1 | randomised trials | serious¹ no serious inconsistency | no serious indirectness | very serious² 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) | ⚪️⚫️⚫️⚫️ VERY LOW | CRITICAL |
|---|-------------------|----------------------------------|------------------------|-------------------|----------------|------|-----------------------|------------------------------------------|-----------------|-----------|

**Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Irritability**

| 1 | randomised trials | serious¹ no serious inconsistency | no serious indirectness | very serious² 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) | ⚪️⚫️⚫️⚫️ VERY LOW | CRITICAL |
|---|-------------------|----------------------------------|------------------------|-------------------|----------------|------|-----------------------|------------------------------------------|-----------------|-----------|

**Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Insomnia**

| 1 | randomised trials | serious¹ no serious inconsistency | no serious indirectness | serious² 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) | ⚪️⚫️⚫️⚫️ LOW | CRITICAL |
|---|-------------------|----------------------------------|------------------------|---------------|----------------|------|-----------------------|------------------------------------------|-----------------|-----------|

**Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Anxiety**

| 1 | randomised trials | serious¹ no serious inconsistency | no serious indirectness | serious² none | 47/159 (29.6%) | 20.1% | RR 1.47 (1 to 2.17) | 94 more per 1000 (from 0 more to 235 more) | ⚪️⚫️⚫️⚫️ LOW | CRITICAL |
|---|-------------------|----------------------------------|------------------------|---------------|----------------|------|-----------------------|------------------------------------------|-----------------|-----------|

**Signs and symptoms/overall withdrawal syndrome (mild/moderate/severe withdrawal symptoms) at 12 months - Convulsions**

| 1 | randomised trials | serious¹ no serious inconsistency | no serious indirectness | no serious imprecision | 0/159 (0%) | 0% | not pooled | not pooled | ⚪️⚫️⚫️⚫️ MODERATE | CRITICAL |
|---|-------------------|----------------------------------|------------------------|----------------------|----------------|------|----------|----------|----------------|-----------|

**Rates of lapse/relapse (benzodiazepine use at 36 months in those who stopped use at 12 months)**

| 1 | randomised trials | serious¹ no serious inconsistency | no serious indirectness | very serious² 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) | ⚪️⚫️⚫️⚫️ 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 patients | 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 |
| No of studies | - | - | - | - | - | - | - | - | - | - |
| Cessation of medication (discontinuation of z-drugs) post treatment | 1 | randomised trials | very serious | no serious inconsistency | no serious indirectness | serious² | none | 17/24 (70.8%) | 84% | RR 0.84 (0.62 to 1.15) | 134 fewer per 1000 (from 319 fewer to 126 more) | ⚫⚫⚫⚫○○○○ VERY CRITICAL |
| Reduction in prescribed drug use (in those who did not discontinue) post treatment | 1 | randomised trials | very serious | no serious inconsistency | no serious indirectness | very serious² | none | 7/7 (100%) | 100% | RR 1 (0.71 to 1.41) | 0 fewer per 1000 (from 290 fewer to 410 more) | ⚫⚫⚫⚫○○○○ VERY 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 | no serious inconsistency | no serious indirectness | no serious imprecision | none | 24 | 25 | - | MD 16 lower (23.07 to 8.93 lower) | ⚫⚫⚫⚫○○○○ VERY 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 | no serious inconsistency | no serious indirectness | serious² | none | 24 | 25 | - | MD 0.6 lower (1.04 to 0.16 lower) | ⚫⚫⚫⚫○○○○ VERY 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 | no serious inconsistency | no serious indirectness | no serious imprecision | none | 25 | 25 | - | MD 6.89 higher (4.14 to 9.64 higher) | ⚫⚫⚫⚫○○○○ VERY 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 | no serious inconsistency | no serious indirectness | no serious imprecision | none | 25 | 25 | - | MD 6.89 higher (4.14 to 9.64 higher) | ⚫⚫⚫⚫○○○○ VERY CRITICAL |
| 1 | randomised trials | very serious¹ | no serious inconsistency | no serious indirectness | serious² | none | 25 | 25 | - | MD 0.55 lower (2.13 lower to 1.03 higher) | ⚠️⚠️⚠️⚠️ 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 serious¹ | no serious inconsistency | no serious indirectness | serious² | none | 25 | 25 | - | MD 0.35 lower (1.77 lower to 1.07 higher) | ⚠️⚠️⚠️⚠️ 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 serious¹ | no serious inconsistency | no serious indirectness | serious² | none | 25 | 25 | - | MD 1.1 lower (2.95 lower to 0.75 higher) | ⚠️⚠️⚠️⚠️ 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 serious¹ | no serious inconsistency | no serious indirectness | serious² | none | 22 | 23 | - | MD 3.53 higher (0.47 to 6.59 higher) | ⚠️⚠️⚠️⚠️ 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 serious¹ | no serious inconsistency | no serious indirectness | very serious² | none | 22 | 23 | - | MD 0.1 lower (1.82 lower to 1.62 higher) | ⚠️⚠️⚠️⚠️ 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 serious¹ | no serious inconsistency | no serious indirectness | serious² | none | 22 | 23 | - | MD 0.15 lower (1.55 lower to 1.25 higher) | ⚠️⚠️⚠️⚠️ 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 serious¹ | no serious inconsistency | no serious indirectness | very serious² | none | 22 | 23 | - | MD 0.21 lower (1.85 lower to 1.43 higher) | ⚠️⚠️⚠️⚠️ 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

| 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 |
|---------------|------------|--------------|----------------|---------------|-------------|---------------------|-----------------------------------------------------------------------------------|---------|-------------------|----------|
|               | Randomised trials | Very serious¹ | No serious inconsistency | Serious² | Very serious³ | None                | RR 0.75 (0.22 to 2.53) | 8%      | 20 fewer per 1000 (from 62 fewer to 122 more) | Very Low |

#### Cessation of medication (discontinuation of antidepressants) at 12 months

- **No of patients:** 4/67 (6%)
- **Relative (95% CI):** RR 0.75 (0.22 to 2.53)
- **Absolute:** 20 fewer per 1000 (from 62 fewer to 122 more)

#### Signs and symptoms/overall withdrawal syndrome (relapse of depression) at 12 months

- **No of patients:** 18/70 (25.7%)
- **Relative (95% CI):** RR 1.95 (0.97 to 3.94)
- **Absolute:** 125 more per 1000 (from 4 fewer to 388 more)

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

| Quality assessment | No of patients | Effect | Quality | Importance |
|--------------------|----------------|--------|---------|------------|
| **Alternatives to prescribing (CBT+therapeutic interactive voice response) versus Alternatives to prescribing (CBT only)** | | | | |
| **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** |
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | serious³ | none | 10/26 (38.5%) | 64% | RR 0.6 (0.34 to 1.06) | 256 fewer per 1000 (from 422 fewer to 38 more) | □□□□ VERY LOW CRITICAL |
| Reduction/cessation in prescribed drug use (number of patients taking prescribed drugs) post intervention - Opioids | | | | | | | | | | |
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | very serious³ | none | 9/26 (34.6%) | 40% | RR 0.87 (0.42 to 1.77) | 52 fewer per 1000 (from 232 fewer to 308 more) | □□□□ VERY LOW CRITICAL |
| Reduction/cessation in prescribed drug use (number of patients taking prescribed drugs) post intervention - Benzodiazepines | | | | | | | | | | |
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | serious³ | none | 20/26 (76.9%) | 84% | RR 0.92 (0.7 to 1.2) | 67 fewer per 1000 (from 252 fewer to 168 more) | □□□□ VERY LOW CRITICAL |
| Reduction/cessation in prescribed drug use (number of patients taking prescribed drugs) post intervention - Antidepressants | | | | | | | | | | |
| 1 | randomised trials | very serious¹ | no serious inconsistency | serious² | serious³ | none | 11/26 (42.3%) | 72% | RR 0.59 (0.35 to 0.98) | 295 fewer per 1000 (from 14 fewer to 468 fewer) | □□□□ 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 serious¹ | no serious inconsistency | serious² | serious³ | none | 9/26 (34.6%) | 36% | RR 0.96 (0.46 to 2.02) | 14 fewer per 1000 (from 194 fewer to 367 more) | □□□□ 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 serious¹ | no serious inconsistency | serious² | very serious³ | none | 9/26 (34.6%) | 36% | RR 0.96 (0.46 to 2.02) | 14 fewer per 1000 (from 194 fewer to 367 more) | □□□□ VERY LOW CRITICAL |
| Reduction/cessation in prescribed drug use (number of patients taking prescribed drugs) at 8 month follow up - Antidepressants | | | | | | | | | | |

¹ These studies have been excluded from the pooled analysis due to a lack of rigorous methodology.

² The majority of studies are of poor quality, but the evidence is insufficient to judge the quality of these analyses.

³ The studies are of very poor quality, and the evidence is insufficient to judge the quality of these analyses.
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) △△△△ VERY 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)

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality assessment | No of patients | Effect | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|-------------------|----------------|--------|----------|------------|
| *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 | Patient advice and support (intensive preventative programme) versus Usual care (no changes in drug use) | Control | Relative (95% CI) | Absolute | |
| 1              | randomised trials | very serious\(^1\) | no serious inconsistency | serious\(^2\) | 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) | △△△△ VERY 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) | △△△△ VERY 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) | △△△△ VERY 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) | △△△△ VERY CRITICAL |
| *Reduction/cessation of prescribed medication (irregular use) at 12 months* - Benzodiazepines
| No of patients | Effect | Quality | Importance |
|----------------|--------|---------|------------|
| MD 0.3 higher (0.49 lower to 1.09 higher) | 62 | - | MD 0.3 higher (0.49 lower to 1.09 higher) |
| RR 2.08 (0.81 to 5.38) | 93 more per 1000 (from 16 fewer to 377 more) | 8.6% | RR 2.08 (0.81 to 5.38) |

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 | Criteria | Rating | Overall assessment of confidence |
| **Design** | **Findings** | **Limitations** | **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 | |
| Study design and sample size | Quality assessment |
|-----------------------------|-------------------|
| **No of studies contributing to the finding** | **Criteria** | **Rating** | **Overall assessment of confidence** |
| **Study design** | **Findings** | **Limitations** | **Coherence** | **Relevance** | **Adequacy** | **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; 1 analysis 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 | Overall assessment of confidence |
|-----------------------------|--------------------|----------------------------------|
| **Patients experience side effects with prescribed benzodiazepines, z-drugs, opioids and antidepressants** | | |
| No of studies contributing to the finding | Design | Findings | Criteria | Rating |
| 3 | 2 reports; 1 HTA (qualitative and mixed methods) | Participants felt that there were diverse physical symptoms due to withdrawal. | Limitations | minor limitations |
| | | | Coherence | no concerns about coherence |
| | | | Relevance | no concerns about relevance |
| | | | Adequacy | no concerns about adequacy |
| | | LIMITATIONS | HIGH |
| | | | COHERENCE | |
| | | | RELEVANCE | |
| | | | 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 |
| | | | Coherence | no concerns about coherence |
| | | | Relevance | no concerns about relevance |
| | | | Adequacy | no concerns about adequacy |
| | | LIMITATIONS | HIGH |
| | | | COHERENCE | |
| | | | RELEVANCE | |
| | | | 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 |
| | | | Coherence | no concerns about coherence |
| | | | Relevance | no concerns about relevance |
| | | | Adequacy | no concerns about adequacy |
| | | LIMITATIONS | HIGH |
| | | | COHERENCE | |
| | | | RELEVANCE | |
| | | | 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**

| 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. |
Table S6: continued …/

| 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                  | 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 bedridden. 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. Sought 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. |
### Table S6. continued …/

| 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. |