# National Institute for Health and Care Excellence

Draft for Consultation

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

## [E] Evidence review: Risk factors for dependence

*NICE guideline <number>*

*Evidence reviews underpinning recommendations 1.2.2, 1.2.3, 1.2.6, 1.3. 5, 1.3.6 and the research recommendation in the NICE guideline*

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*These evidence reviews were developed by the National Guideline Centre*

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# 1. Risk factors for dependence

## 1.1. Review question

What are the risk factors (both patient and prescribing factors) for dependence on prescribed opioids, benzodiazepines, gabapentinoids or Z-drugs, or withdrawal symptoms associated with antidepressants?

### 1.1.1. Introduction

Dependence is a potentially harmful effect of prescribing some groups of medicines. In order to inform decisions and optimise prescribing safety, it is important for both prescriber and patient to understand if there are specific risk factors related either to the medicines used, patterns of prescribing or the individual that make dependence more likely to occur.

For some groups of medicines, notably benzodiazepines and opioids, some factors which influence risk of dependence are known. Less is known for other medicine classes in the review.

Prescribing without knowing the risks of dependence, may result in significant distress for the person, escalating doses and increasing the risk of severe or even fatal side effects. This review aims to identify risk factors for dependence, to support informed decision making and to identify where extra caution may be needed in prescribing.

### 1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

**Table 1: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adults (≥18 years) being prescribed medicines associated with dependence or withdrawal symptoms (opioids for chronic pain, benzodiazepines, gabapentinoids, Z-drugs, antidepressants). Ideally at the point of initial prescription for that medicine (i.e., not taking that medicine prior to entry to the study). Prescription medicines also be bought over the counter (e.g., codeine, co-codamol) also included.<br>**Stratification**<br>• Drug class<br>• Opioids<br>• Benzodiazepines,<br>• Gabapentinoids<br>• Z-drugs<br>• Antidepressants (further stratified by SSRIs, MAOIs, tricyclics, others). |
| **Prognostic variables under consideration** | The risk factors below are examples only and others identified will be included. Include any definition in the studies considered relevant to the factor of interest<br>• System level factors:<br>  ○ competency of prescriber,<br>  ○ training or supervision of prescribers.<br>• Prescribing factors:<br>  ○ duration of prescription,<br>  ○ initial dose,<br>  ○ use of different drugs within a class<br>  ○ different formulation and/or route of medication, for example: immediate release, slow release (including slow-release routes such as transdermal patches), |

| | |
|---|---|
| | ○ half-life comparisons (for benzodiazepines, long or short half-life)<br>• Socio-demographic factors of the patient<br>• Personal factors:<br>○ history of substance misuse<br>○ mental health diagnoses<br>○ co-prescription with other medications included in the review<br>○ pain intensity and level of distress at time of prescription.<br>• Others:<br>○ Patient-prescriber interaction. |
| **Confounding factors** | All risk factors will be considered as potential confounding factors. |
| **Outcomes** | Dependence on the prescribed medicine (dichotomous outcome, accept any definition as defined by the study (may also include measures suggesting dependence or addiction, examples to include early refill requests, loss of prescriptions, drug shopping behaviour, prescription misuse)). Withdrawal symptoms including rebound symptoms (dichotomous outcome, as defined by the study) |
| **Study design** | • Observational prospective cohort studies<br>• Observational retrospective cohort studies<br>• Only studies using multivariate analysis (adjusting for at least 3 confounders) will be included. Studies using univariate analysis or matched groups will be excluded (matching for confounders alone is not sufficient as there are multiple confounders). |

### 1.1.3. Methods and process

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

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

### 1.1.4. Prognostic evidence

#### 1.1.4.1. Included studies

Fourteen retrospective cohort studies were included in the review;[19, 52, 54, 60, 61, 68, 76, 113, 147, 152, 158, 169, 170, 180] these are summarised by drug class in Table 2 and Table 3 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 4 to Table 37).

Twelve of the studies were relevant to opioids and 2 were relevant to benzodiazepines. No relevant clinical studies looking at gabapentinoids, Z-drugs or antidepressants were identified. The majority of studies were conducted in the USA, 2 were conducted in France, 1 in Norway and 1 study was conducted in the UK.

This review aimed to assess the risk of prognostic factors for the outcome of dependence. The purpose of this was to make recommendations on the factors that might put someone at increased risk of dependence, to consider when making prescribing decisions, and are therefore predominantly at the point of initial prescription. It was important to ensure that the included population of the studies did not have the outcome at baseline. Therefore, studies were only included in populations not taking the medicine at the start of the study, and followed them up to see who developed problems with dependence. Studies in people already prescribed the medicine at the start of the study were excluded. Some studies were included where it was unclear if the population had taken the medicine in the past.

Both the scope of this guideline and the review protocol specify that the included population for opioids is only those prescribed for chronic pain; opioids prescribed for acute pain are excluded. Therefore, if a study gave a breakdown of what the opioids were prescribed for, and in more than 20% of the population the opioids were prescribed for people with acute pain, such as people undergoing surgery or dental procedures, then the study was excluded. If a breakdown was not provided by the study, and it was unclear, then the study was included but downgraded for population indirectness.

The studies included in this review examined risk factors including socio-demographic characteristics such as age, gender and family background, personal factors such as pain intensity, history of mood disorders, substance use disorders and opioid use disorders, mental health disorders, use of drugs other than the drug of interest, prescribing factors such as average daily dose, duration of action and days of opioid supply.

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

Outcomes reported by the studies included dependence, opioid shopping behaviour, opioid abuse, overlapping prescriptions, early opioid refills and a composite outcome (abuse, dependence or overdose). Maximum follow-up was 3.4 years for opioid and 5 years for benzodiazepine studies, but the majority of studies looked at 1-year incidence of the outcome examined from the first prescription. Pooling of results was not possible as studies were too heterogeneous. Studies used different definitions of outcomes, different cut-offs in the risk factor categories, the populations differed and/or analyses had adjusted for different confounders and/or reported different effect measures (e.g., ORs and HRs). For example, for the risk factor of opioid formulation: tapentadol immediate release (IR) versus oxycodone IR for the outcome of shopping behaviour was reported by 2 studies (Cepeda 2013 and Cepeda 2014) but results could not be pooled as the studies adjusted for different covariates. Also in that specific case, the 2 studies may have involved at least partially the same population as they used the same database but at a different time point, with some months overlapping and thus pooling could involve double counting of results from the same participants.

Effects measures (e.g., OR, RR, HR and RD or adjusted OR etc.) have been extracted as reported in the included studies. However, they were all a result of multivariate analyses adjusting for different confounders including demographic and clinical characteristics such as age, gender, smoking status, BMI, comorbidities, substance use disorder, co-prescribing of other drugs, specified in the summary of the prognostic evidence table footnotes.

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

#### 1.1.4.2. Excluded studies

See the excluded studies list in Appendix J.

### 1.1.5. Summary of studies included in the prognostic evidence

#### 1.1.5.1. Opioids

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

| Study | Population | Analysis | Prognostic variables | Confounders | Outcomes | Comments |
|---|---|---|---|---|---|---|
| **Opioids** | | | | | | |
| Bedson 2019[19] | New long-term opioid users with musculoskeletal conditions; starting on a new long-term opioid episode; with data from the Clinical Practice Research Datalink (CPRD)<br><br>N=98,140<br><br>Median age (IQR): 61 (47 to 73) years<br><br>UK | Prospective cohort study with Cox proportional hazards regression | Long-term opioid episode status: periods not on long term opioids (referent) versus periods on long-term opioids (defined as ≥3 or more opioid prescriptions within 90 days)<br>Average daily dose (ADD) (<20 mg morphine equivalent dose (MED); 20-50 mg MED; ≥50 mg MED) in those with a long-term episode | Age at baseline, gender, year of start of follow-up, ever smoking, ever alcohol drinking, overweight (BMI ≥25 kg/m2), geographical region, deprivation level, prior recorded depression, co-prescribing of NSAID and total number of co-morbid conditions | Incident addiction to opioids<br><br>From 90 days after the initial opioid prescription until the end of the study (Median follow-up 3.4 years). | |
| Cepeda 2013[54] | Opioid naïve people exposed to tapentadol IR or oxycodone IR from July 2009 to December 2010 (IMS LRx database) | Retrospective cohort study with conditional logistic regression models conducted using matched analysis (description of | Oxycodone (IR) versus Tapentadol (IR) | The tapentadol and oxycodone groups were matched for potentially confounding variables of time of opioid exposure, geographic area, specialty of the | • Shopping behaviour (>1 prescription by ≥2 different prescribers with ≥1 day of overlap and filled at ≥ 3 pharmacies) | Indirectness: Proportion of those treated with opioids for chronic pain was unclear. |

| Study | Population | Analysis | Prognostic variables | Confounders | Outcomes | Comments |
|---|---|---|---|---|---|---|
| | N=155,761<br><br>Mean age (SD): 51.11 (14.91)<br><br>USA | methods was assumed to include multivariate analysis) | | prescriber and age); gender, any exposure to benzodiazepines during the 3 months before the index date and type of payment at index date were also considered in the regression model. | • Heavy shopping behaviour (≥5 shopping episodes in 1 year)<br><br>At 1-year follow-up from the initial exposure | |
| Cepeda 2014[52] | Opioid-naïve patients initiating opioid use with tapentadol IR or oxycodone IR between January 2010 and July 2011 (IMS LRx & IMS DX databases)<br><br>N=277,401<br><br>Mean age (SD): 53.1 (17.1) years<br><br>USA | Retrospective cohort study with logistic regression | Tapentadol IR versus oxycodone IR, age (<18, 18-39 and 40-64 versus >64 (referent)), gender (referent: female), history of benzodiazepine use, type of payment, history of mood disorders, history of abuse of nonopioid drugs, painful condition (type) | Age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date<br><br>Index date: date of first opioid exposure | • Opioid shopping behaviour (overlapping opioid prescriptions from ≥2 prescribers filled at ≥ 3 pharmacies)<br>• Opioid abuse (ICD 9th revision diagnoses of abuse, addiction or dependence)<br><br>At 1-year follow-up from the initial exposure | Risk of bias: Median tapentadol equivalent dose was 300mg in the tapentadol group versus 200 mg in the oxycodone group i.e., 60 mg versus 40 mg in oxycodone equivalence respectively and not adjusted for in the analysis<br><br>Indirectness: Proportion of those treated with opioids for chronic pain was unclear. |
| Chenaf 2016a[60] | Chronic noncancer pain patients (CNCP) treated with codeine for at least six months. | Retrospective cohort study with Cox proportional hazards model | Age (≤40 versus >40), gender (referent: male), low-income status, history of opioid use disorder, history of substance use disorder, active chronic liver | Factors considered significant in univariate analysis (P<0.15) were entered to the multivariate analysis which was reported | (1year incidence of) Codeine shopping behaviour (≥1 day of overlapping prescriptions written by ≥2 different prescribers and | Some participants (but unclear how many) had been treated with opioids other than codeine before. Not downgraded for indirectness as those treated with codeine |

| Study | Population | Analysis | Prognostic variables | Confounders | Outcomes | Comments |
|---|---|---|---|---|---|---|
| | N=1958<br><br>Mean age (SD): 62.7 (16.1) years<br><br>France | | disease, mental health disorders, concurrent use of antidepressants, previous use of antipsychotics, previous use of hypnotic benzodiazepine, concurrent use of hypnotic benzodiazepine, previous use of anxiolytic benzodiazepine, concurrent use of anxiolytic benzodiazepine, previous use of strong opioids | to be done accordingly to clinically relevant variables such as age and gender. | filled in ≥3 different pharmacies) | before the study period were excluded.<br><br>Unclear which confounders were adjusted for in the analysis |
| Chenaf 2016b[61] | CNCP patients treated with tramadol<br><br>N=3505<br><br>Mean age (SD) 66.4 (14.7) years<br><br>France | Retrospective cohort study and cox proportional hazard model | Age: <40 versus ≥ 50 and 40-50 versus ≥ 50 (referent)<br>Gender (referent: male)<br>Low-income status<br>Prior use of strong opioids | It was not specified which confounders were adjusted in the multivariate analysis. | (1year incidence of) tramadol shopping behaviour (≥1 day of overlapping prescriptions written by ≥2 different prescribers and filled in ≥3 different pharmacies) | Some participants (but unclear how many) had been treated with opioids before. Not downgraded for indirectness as those treated with tramadol before the study period were excluded. |
| Chui 2018 [68] | Veterans aged ≥ 65 years with a new diagnosis of a musculoskeletal disorder (MSD) (who entered the VA | Retrospective cohort study and multivariable logistic regression analysis | Age (65-74 (referent) versus 75-84 versus 85+), race (white versus non-white), sex (referent: male), moderate-to- severe pain intensity (pain | Demographic and clinical characteristic: Age, sex and ethnicity (at index date), moderate-to-severe pain intensity (pain score from 4 to | Overlapping concurrent opioid prescriptions (prescription starting before the end-date of a prior prescription, | |

| Study | Population | Analysis | Prognostic variables | Confounders | Outcomes | Comments |
|---|---|---|---|---|---|---|
| | Musculoskeletal Disorders Cohort in 2008 and received an opioid prescription in 2010)<br><br>N=21,111<br><br>Mean age 75 years (SD: not reported)<br><br>USA | | scale 4-10), Charlson comorbidity index score (CCI) 2+ (score 0-1 referent), substance use disorder, PTSD, major depression, dual use of Veterans health administration and Medicare part D | 10 at the pain intensity numerical rating scale (NRS)) in 2008; co morbid diagnoses recorded at ≥2 outpatient visits or ≥1 inpatient stay up to 12 months before or 6 months after the MSD index date; overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and post-traumatic stress disorder (PTSD)<br>At index date (first MSD diagnosis) | inclusive of prescriptions outside the Veterans health administration)<br><br>In 1 year | |
| Hoffman 2017[113] | Patients with polyneuropathy<br><br>N= 2,892<br><br>Mean age (SD): 67.5 (16.5) years<br><br>USA | Retrospective cohort study and multivariable logistic regression | Long term opioid therapy ≥90 days versus shorter term opioid therapy <90 days (referent) | Charlson Comorbidity Index comorbidities, sex, and use of non-opioid analgesics, when applicable. | • Opioid dependence<br>• Opioid abuse<br><br>Determined by International Classification of Diseases, Ninth Revision, Clinical Modification, codes. | |
| Park 2016 [147] | Patients with one or more visits to a hospital-based primary care clinic | Retrospective cohort study with | Receipt of benzodiazepine prescription, compared to no receipt during the | Age, sex, race, medical insurance, medical comorbidities, pain, | Time to second early opioid refill (opioid prescription written 7-25 days | Indirectness: for each patient observations started at the first day of opioid prescription |

| Study | Population | Analysis | Prognostic variables | Confounders | Outcomes | Comments |
|---|---|---|---|---|---|---|
| | or one of two community health centres, receiving opioids for CNCP<br><br>N=847<br><br>Mean age (SD): 52.54 (11.03)<br><br>USA | Cox proportional hazards model | study period (12-months). | mental health and substance use disorders | after the previous prescription for the same drug) estimated as a function of time-varying benzodiazepine prescription. | during the defined 12-month study period; it cannot be determined whether and how many patients had ever been prescribed opioids before the study period; 63% had a drug use disorder diagnosis in their medical record that was reported to also include opioids along with cocaine, sedatives marijuana, polysubstance and other drug abuse or dependence; it was unclear if dependence was current or past so it is unclear if they were opioid naïve and if some could have dependence at baseline. |
| | Primary care patients with CNCP: random sample of VA Connecticut Healthcare system patients (n=50) and all patients enrolled in the Primary Care Centre (n=48). | Retrospective cohort study with multivariate logistic regression | Age (continuous); Number of medical diseases (mean, determined by the unweighted Charlson Index); Lifetime history of substance use disorder | Not reported | Prescription opioid abuse behaviour (defined by the presence of one or more of the following criteria: 1) one or more reports of lost or stolen opioid medication or prescriptions, 2) documented use of other sources e.g., other physician practices to obtain | Unclear if patients had already been on opioids before risk factor measurements were taken. |

| Study | Population | Analysis | Prognostic variables | Confounders | Outcomes | Comments |
|---|---|---|---|---|---|---|
| | N=98<br><br>Median age (range): VA sample 54 years (33 to 84);PCC sample 55 years (26 to 80)<br><br>USA | | | | opioid medication and 3) requests for 2 or more early refills) | |
| Seal 2012[158] | Iraq and Afghanistan veterans prescribed opioids within 1 year of receiving a pain-related diagnosis<br><br>N=15,676<br><br>Mean age (SD): not reported<br><br>USA | Retrospective cohort study and Poison regression with robust error variance | Mental health diagnosis versus no mental health diagnosis (referent): diagnosis without PTSD; PTSD with or without other mental health diagnosis | Sociodemographic factors (i.e., age, sex, race/ethnicity, marital status, VA facility type - medical centre versus community clinic) and military service characteristics (i.e., component, rank, service branch, and number of deployments) | • Early opioid refills (obtaining the same opioid prescription for more than 7 days before the end of the prior prescription)<br>• Concurrent opioids (>7 days overlap)<br><br>Within 1-year of receiving a pain-related diagnosis | Study also gives relative risks for the outcomes of highest quintile of average daily opioid use (≥33 mg/d), duration of opioid use ≥2 months and concurrent sedative hypnotics. |
| Udayachalerm 2021[170] | Opioid naïve (no prior opioid prescription in the past 12 months) and had at least 6 months data from index date from the Indiana Network for Patient Care | Retrospective cohort study and Cox proportional hazards with stepwise selection | Number days' supply (continuous), opioid dosage (continuous), concurrent short-acting (SA) and long-acting (LA) opioids within 30 days versus SA alone (referent), concurrent use of SA and LA opioids not within 30 | Age, sex and comorbidities | Composite outcome: any combination of opioid abuse, dependence or overdose<br><br>Within 6 months of index date (date of | Indirectness: Proportion of those treated with opioids for chronic pain was unclear.<br>Baseline: long term use 6.94% (long term use indicates patients who had a cumulative opioid days' supply of at least 90 days within 6 months |

| Study | Population | Analysis | Prognostic variables | Confounders | Outcomes | Comments |
|---|---|---|---|---|---|---|
| | which is a state-wide health information exchange.<br><br>N=341,722<br><br>Mean age (SD): 52.31 years (18.11)<br><br>USA | | days versus SA alone (referent), LA only versus SA alone (referent), concurrent use of benzodiazepines versus none - opioids only (referent), concurrent use of gabapentin/pregabalin versus opioids only (referent), concurrent use of benzodiazepines and gabapentin/pregabalin within 30 days versus opioids only (referent), concurrent use of benzodiazepines and gabapentin/pregabalin not within 30 days versus opioids only (referent) | | first opioid prescription) | after the index opioid prescription). |
| Zhang 2018[180] | Privately insured adults aged 18 to 64 years and<br>N= 63,419<br>Medicare advantage patients aged 65 or older filling an opioid prescription between July 1st 2011 and June 30th 2013<br><br>N=196,375 | Retrospective cohort study and linear probability models | Features of the first opioid prescription:<br>Duration of action of the first opioid prescription: long versus short acting status (referent)<br>Days of supply of the first opioid prescription: ≤ 3 days (referent) versus 4-7 days and > 7 days | Ordinal indicators of the quarters/3-month intervals following the first prescription (second, third, sixth, with the first quarter as the reference), calendar year indicators, patient demographics (age groups, sex); dichotomous indicators of back pain, neck pain, arthritis/joint pain and | High-risk opioid use:<br>• Overlapping opioid prescriptions for 7 days or more<br>• Three or more prescribers of opioids<br><br>In each of the six quarters (3-month intervals) following the first prescription) | Indirectness: Proportion of those treated with opioids for chronic pain was unclear.<br><br>Only results for adults aged 18 to 64 are given in the paper- thus, sample characteristic and other study data have only been extracted for this sample. |

| Study | Population | Analysis | Prognostic variables | Confounders | Outcomes | Comments |
|---|---|---|---|---|---|---|
| | Aged 18 to 64; mean age (SD) not reported<br><br>USA | | | other pain, an indicator of any mental health disorder, alcohol use disorder, any drug use disorder and tobacco use disorder, socio-demographic profiles at the patient's residential ZIP codes. | In the 18 months following the first prescription | Results for each category of risk factor were reported as a percentage point increase from the referent category; risk differences have been calculated and used as outcome measured in the summary of the prognostic evidence |

### 1.1.5.2. Benzodiazepines

**Table 3: Summary of studies included in the evidence review: benzodiazepines**

| Study | Population | Analysis | Prognostic variables | Confounders | Outcomes | Comments |
|---|---|---|---|---|---|---|
| **Benzodiazepines** | | | | | | |
| Cook 2018[76] | Benzodiazepine users<br><br>N=11,663<br><br>Mean age (SD) 49.8 (16.6) years<br><br>USA | Retrospective cohort study and multivariable Cox proportional hazards regression model | Race: Black, Latino, Asian versus White (referent); sex (female, referent); age: 25-34, 35-44, 45-54, 55-64, 65+ versus 18-24 (referent); substance use diagnosis (SUD): alcohol, marijuana, cocaine, opioid, tobacco, pain meds, 2+ SUD versus no diagnosis; mental health disorder diagnosis: depression, anxiety, bipolar, PTSD, sleeping disturbance versus no diagnosis (referent) | Substance use disorder diagnosis, mental health disorder diagnosis, age, sex, race; model also included interactions between age and sex. | Diagnosis of benzodiazepine dependence subsequent to receiving a prescription (defined as a diagnosis of dependence on a sedative, hypnotic or anxiolytic, ICD-9). | |

| Study | Population | Analysis | Prognostic variables | Confounders | Outcomes | Comments |
|---|---|---|---|---|---|---|
| Tvete 2016[169] | New benzodiazepine users with a first redemption for:<br>Diazepam (n=15,927)<br>mean age 46.5<br>or<br>Oxazepam (n=3,820)<br>mean age 47.29<br><br>Total N=19,747<br><br>Norway | Retrospective cohort study (observational prescription registry study) and Cox proportional hazard regression model | Sex: female versus male(referent); age (continuous); first benzodiazepine: oxazepam versus diazepam (referent); Previous medication: antidepressants and lithium, antipsychotics, opioids, anti-alcohol, and smoking cessation drugs, drugs and rheumatic diseases, drugs for Chronic obstructive pulmonary disease (COPD); education: high versus Low (referent); income: low (referent) versus average versus high; type of work: private versus public sector versus no registration (referent) | Socio-demographic status and previous drug use; unclear if the analysis adjusted for other covariates in addition to the aforementioned and those entered in the model as prognostic factors. | Time to reach consumption level 2: redemption of ≥1 defined daily doses on average per day over a 3-month period (from a starting point of <1 defined daily doses on average per day in the first 3 months). This outcome was defined as dose escalation which is considered a measure of drug misuse/ dependence by the primary study.<br><br>5-year follow-up from the first redemption (divided into 3-month periods for each individual) | |

See Appendix D for full evidence tables.

## 1.1.6. Summary of the prognostic evidence

### 1.1.6.1. Summary of the prognostic evidence for opioids

**Table 4: Clinical evidence summary: Age**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Age ≤40 versus age >40 for predicting codeine shopping behaviour (CNCP patients treated with codeine; mean (SD) age 62.7 (16.1) years) [a] | 1 | HR 7.29 (4.28 to 12.42) | No serious imprecision | MODERATE [b] |
| Age (continuous: increasing versus decreasing) for predicting prescription opioid abuse behaviour (CNCP patients aged 26 to 84 years) [c] | 1 | OR 0.94 (0.89 to 0.99) | No serious imprecision | LOW [d] |
| Age 75-84 versus 65-74 years for predicting overlapping concurrent opioid prescriptions (Veterans aged ≥ 65 years with a new MSD diagnosis) [e] | 1 | OR 0.81 (0.75 to 0.87) | No serious imprecision | HIGH |
| Age 85+ versus 65-74 years for predicting overlapping concurrent opioid prescriptions (Veterans aged ≥ 65 years with a new MSD diagnosis) [e] | 1 | OR 0.83 (0.74 to 0.92) | No serious imprecision | HIGH |
| Age <18 versus >64 for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [f] | 1 | OR 0.9 (0.5 to 1.8) | Serious imprecision [g] | VERY LOW [g, h] |
| Age <18 versus >64 for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [f] | 1 | OR 0.7 (0.3 to 1.4) | Serious imprecision [g] | VERY LOW [g, h] |
| Age 18-39 versus >64 for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [f] | 1 | OR 9.8 (7.9 to 12) | No serious imprecision | VERY LOWh |
| Age 18-39 versus >64 for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [f] | 1 | OR 13.9 (11.2 to 17.2) | No serious imprecision | VERY LOW [h] |
| Age 40-64 versus >64 for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [f] | 1 | OR 4.6 (3.8 to 5.6) | No serious imprecision | VERY LOW [h] |
| Age 40-64 versus >64 for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [f] | 1 | OR 6.7 (5.5 to 8.3) | No serious imprecision | VERY LOW [h] |
| Age <40 versus ≥ 50 for predicting tramadol shopping behaviour (CNCP patients treated with tramadol (mean age (SD) 66.4 (14.7) years)) [i] | 1 | HR 7.4 (2.8 to 19.7) | Serious imprecision [g] | VERY LOW [g, j] |

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| | | | | |
| Age 40-50 versus ≥ 50 and tramadol shopping behaviour (CNCP patients treated with tramadol (mean age (SD) 66.4 (14.7) years)) [i] | 1 | HR 2.8 (1 to 7.7) | No serious imprecision | LOW [j] |

*(a) Methods: multivariable analysis: cox proportional hazards developed according to clinically relevant variables such as age and gender*
*(b) Downgraded by 1 increment due to serious risk of bias*
*(c) Methods: Multivariate logistic regressions model; Covariates not specified*
*(d) Downgraded by 1 increment due to serious risk of bias and by 1 increment due to potential indirectness of the population which may not have been opioid naïve during baseline assessment*
*(e) Methods: multivariate logistic regression analysis adjusted for age, sex, ethnicity, pain intensity (NRS), co morbid diagnoses, overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and PTSD*
*(f) Methods: multivariate analysis: logistic regression adjusted for age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date*
*(g) Downgraded by 1 increment as the confidence interval crossed the null line or was judged to be very wide*
*(h) Downgraded by 2 increments due to very serious risk of bias, by 1 increment due to indirectness with the proportion of those taking opioids for chronic pain being unclear and by 1 more increment for participants in the <18 years age category*
*(i) Methods: multivariable analysis: cox proportional hazards model; Covariates not specified*
*(j) Downgraded by 2 increments due to very serious risk of bias*

**Table 5: Clinical evidence summary: Family Background**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Non-white race versus white for predicting overlapping concurrent opioid prescriptions<br>(Veterans aged ≥ 65 years with a new MSD diagnosis) [a] | 1 | OR 0.77 (0.71 to 0.84) | No serious imprecision | HIGH |

*(a) Methods: multivariate logistic regression analysis adjusted for age, sex, ethnicity, pain intensity (NRS), co morbid diagnoses, overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and PTSD*

**Table 6: Clinical evidence summary: Gender**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Female versus male for predicting codeine shopping behaviour (CNCP patients treated with codeine; mean (SD) age 62.7 (16.1) years) [a] | 1 | HR 0.92 (0.53 to 1.58) | Serious imprecision [b] | LOW [c] |
| Female versus male for predicting tramadol shopping behaviour (CNCP patients treated with tramadol (mean age (SD) 66.4 (14.7) years)) [d] | 1 | HR 1.6 (0.7 to 3.8) | Serious imprecision [b] | VERY LOW [e] |
| Female sex versus male sex for predicting overlapping concurrent opioid prescriptions (Veterans aged ≥ 65 years with a new MSD diagnosis) [f] | 1 | OR 0.97 (0.75 to 1.24) | Serious imprecision [b] | MODERATE [g] |
| Male versus female for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)) [h] | 1 | OR 1.6 (1.4 to 1.7) | No serious imprecision | VERY LOW [i] |
| Male versus female for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)) [h] | 1 | OR 1.5 (1.3 to 1.6) | No serious imprecision | VERY LOW [i] |

*(a) Methods: multivariable analysis: cox proportional hazards model developed according to clinically relevant variables such as age and gender*
*(b) Downgraded by 1 increment as the confidence interval crossed the null line*
*(c) Downgraded by 1 increment due to risk of bias and by 1 increment due to imprecision*
*(d) Methods: multivariable analysis: cox proportional hazards model; confounders not specified*
*(e) Downgraded by 2 increments due to very serious risk of bias*
*(f) Methods: multivariate logistic regression analysis adjusted for age, sex, ethnicity, pain intensity (NRS), co morbid diagnoses, overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and PTSD*
*(g) Downgraded by 1 increment due to imprecision*
*(h) Methods: multivariate analysis: logistic regression adjusted for age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date*
*(i) Downgraded by 2 increments due to very serious risk of bias and by 1 increment due to indirectness with the proportion of those taking opioids for chronic pain being unclear*

**Table 7: Clinical evidence summary: Low-income status**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Low-income status for predicting codeine shopping behaviour (CNCP patients treated with codeine; mean (SD) age 62.7 (16.1) years) [a] | 1 | HR 1.75 (0.96 to 3.21) | Serious imprecision [b] | LOW [C] |

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Low-income status for predicting tramadol shopping behaviour (CNCP patients treated with tramadol (mean age (SD) 66.4 (14.7) years)) [d] | 1 | HR 8.5 (3.6 to 20.5) | Serious imprecision [b] | VERY LOW [e] |

*(a) Methods: multivariable analysis: cox proportional hazards model developed according to clinically relevant variables such as age and gender*
*(b) Downgraded by 1 increment as the confidence interval crossed the null line or was judged to be very wide*
*(c) Downgraded by 1 increment due to risk of bias and by 1 increment due to imprecision*
*(d) Methods: multivariable analysis: cox proportional hazards model; confounders not specified*
*(e) Downgraded by 2 increments due to very serious risk of bias and by 1 increment due to serious imprecision*

**Table 8: Clinical evidence summary: Pain intensity**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Moderate-to-severe pain intensity (NRS score 4-10) for predicting overlapping concurrent opioid prescriptions (Veterans aged ≥ 65 years with a new MSD diagnosis) [a] | 1 | OR 1.40 (1.31 to 1.49) | No serious imprecision | HIGH |

*(a) Methods: multivariate logistic regression analysis adjusted for age, sex, ethnicity, pain intensity (NRS), co morbid diagnoses, overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and PTSD*

**Table 9: Clinical evidence summary: Clinical severity (Charlson comorbidity index (CCI))**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| CCI 2+ versus lower score for predicting overlapping concurrent opioid prescriptions (Veterans aged ≥ 65 years with a new MSD diagnosis) [a] | 1 | OR 0.96 (0.90 to 1.03) | Serious imprecision [b] | MODERATE [c] |
| Number of medical diseases (mean number of individual chronic medical diseases as per the unweighted Charlson Index) for predicting prescription opioid abuse behaviour (CNCP patients aged 26 to 84 years)[d] | 1 | OR 0.72 (0.45 to 1.1) | Serious imprecision [e] | VERY LOW [f] |

*(a) Methods: multivariate logistic regression analysis adjusted for age, sex, ethnicity, pain intensity (NRS), co morbid diagnoses, overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and PTSD*
*(b) Downgraded by 1 increment as the confidence interval crossed the null line*
*(c) Downgraded by 1 increment due to imprecision*

*(d) Methods: Multivariate logistic regressions model; Co variates not specified*
*(e) Downgraded by 1 increment as the confidence interval crossed the null line*
*(f) Downgraded by 1 increment due to risk of bias, by 1 increment due to potential indirectness of the population which may not have been opioid naïve during baseline assessment and by 1 increment due to imprecision*

**Table 10: Clinical evidence summary: History of opioid use disorder**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| History of opioid use disorder for predicting codeine shopping behaviour (CNCP patients treated with codeine; mean (SD) age 62.7 (16.1) years) [a] | 1 | HR 1.25 (0.19 to 8.40) | serious imprecision [b] | LOW [C] |

*(a) Methods: multivariable analysis: cox proportional hazards model developed according to clinically relevant variables such as age and gender*
*(b) Downgraded by 1 increment as the confidence interval crossed the null line*
*(c) Downgraded by 1 increment due to serious risk of bias and by 1 increment due to imprecision*

**Table 11: Clinical evidence summary: History of substance use disorder/abuse of non-opioids**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| History of substance use disorder for predicting codeine shopping behaviour (CNCP patients treated with codeine; mean (SD) age 62.7 (16.1) years) [a]<br><br>Nicotine & alcohol | 1 | HR 0.89 (0.21 to 3.83) | Serious imprecision [b] | LOW [c] |
| Lifetime history of substance use disorder for predicting prescription opioid abuse behaviour (CNCP patients aged 26 to 84 years) [d]<br><br>Alcohol & narcotics e.g., cocaine | 1 | OR 3.8 (1.4 to 10.8) | Serious imprecision [b] | VERY LOW [e] |
| Substance use disorder (at index date) for predicting overlapping concurrent opioid prescriptions (Veterans aged ≥ 65 years with a new MSD diagnosis) [f]<br><br>Illicit drugs & alcohol | 1 | OR 1.18 (1.05 to 1.33) | No serious imprecision | HIGH |
| History of abuse of non-opioid drugs (such as alcohol & tobacco) for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)) [g] | 1 | OR 1.5 (1.0 to 2.2) | No serious imprecision | VERY LOW [h] |

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| History of abuse of non-opioid drugs (such as alcohol & tobacco) for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)) [g] | 1 | OR 1.5 (1.1 to 2.1) | No serious imprecision | VERY LOW [h] |

*(a) Methods: multivariable analysis: cox proportional hazards developed according to clinically relevant variables such as age and gender*
*(b) Downgraded by 1 increment if the CI crossed the null line or was judged to be very wide*
*(c) Downgraded by 1 increment due to serious risk of bias and by 1 increment due to imprecision*
*(d) Methods: Multivariate logistic regressions model; Co variates not specified*
*(e) Downgraded by 2 increments due to risk of bias, by 1 increment due to potential indirectness of the population which may not have been opioid naïve during baseline assessment and by 1 increment due to imprecision*
*(f) Methods: multivariate logistic regression analysis adjusted for age, sex, ethnicity, pain intensity (NRS), co morbid diagnoses, overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and PTSD*
*(g) Methods: multivariate analysis: logistic regression adjusted for age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date*
*(h) Downgraded by 2 increments due to very serious risk of bias and by 1 increment due to indirectness with the proportion of those taking opioids for chronic pain being unclear*

**Table 12: Clinical evidence summary: Active chronic liver disease**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Active chronic liver disease for predicting codeine shopping behaviour (CNCP patients; mean (SD) age 62.7 (16.1) years) [a] | 1 | HR 2.09 (0.62 to 7.03) | Serious imprecision [b] | LOW [c] |

*(a) Methods: multivariable analysis: cox proportional hazards developed according to clinically relevant variables such as age and gender*
*(b) Downgraded by 1 increment as the confidence interval crossed the null line*
*(c) Downgraded by 1 increment due to risk of bias and by 1 increment due to imprecision*

**Table 13: Clinical evidence summary: Mental health disorders**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Mental health disorders for predicting codeine shopping behaviour (CNCP patients; mean (SD) age 62.7 (16.1) years) [a] | 1 | HR 2.25 (1.08 to 4.67) | No serious imprecision | MODERATE [b] |

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| PTSD with or without other mental health diagnosis versus no mental health diagnosis for predicting early opioid refills (Iraq and Afghanistan veterans prescribed opioids within 1 year of a pain-related diagnosis) [c] | 1 | RR 1.64 (1.53 to 1.75) | No serious imprecision | LOW [d] |
| Mental health diagnosis without PTSD versus no mental health diagnosis for predicting early opioid refills (Iraq and Afghanistan veterans prescribed opioids within 1 year of a pain-related diagnosis) [c] | 1 | RR 1.50 (1.39 to 1.62) | No serious imprecision | LOW [d] |
| PTSD with or without other mental health diagnosis versus no mental health diagnosis for predicting concurrent opioids (>7-day overlap) (Iraq and Afghanistan veterans prescribed opioids within 1 year of a pain-related diagnosis) [c] | 1 | RR 1.87 (1.70 to 2.06) | No serious imprecision | LOW [d] |
| Mental health diagnosis without PTSD versus no mental health diagnosis for predicting concurrent opioids (>7 d overlap) (Iraq and Afghanistan veterans prescribed opioids within 1 year of a pain-related diagnosis)[c] | 1 | RR 1.62 (1.44 to 1.81) | No serious imprecision | LOW [d] |
| PTSD for predicting overlapping concurrent opioid prescriptions (Veterans aged ≥ 65 years with a new MSD diagnosis) [e] | 1 | OR 0.94 (0.82 to 1.05) | Serious imprecision [f] | MODERATE [g] |
| Major depression for predicting overlapping concurrent opioid prescriptions (Veterans aged ≥ 65 years with a new MSD diagnosis) [e] | 1 | OR 1.32 (1.15 to 1.52) | No serious imprecision | HIGH |

*(a) Methods: multivariable analysis: cox proportional hazards developed according to clinically relevant variables such as age and gender*
*(b) Downgraded by 1 increment due to risk of bias*
*(c) Methods: Poison regression with robust error variance adjusted for sociodemographic factors (age, sex, race/ethnicity, marital status, VA facility type - medical centre versus community clinic) and military service characteristics (component, rank, service branch, and number of deployments)*
*(d) Downgraded by 2 increments due to very serious risk of bias*
*(e) Methods: multivariate logistic regression analysis adjusted for age, sex, ethnicity, pain intensity (NRS), co morbid diagnoses, overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and PTSD*
*(f) Downgraded by 1 increment as the confidence interval crossed the null line*
*(g) Downgraded by 1 increment due to imprecision*

**Table 14: Clinical evidence summary: History of mood disorders**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| History of mood disorders for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)) [a] | 1 | OR 1.4 (1.1 to 1.8) | No serious imprecision | VERY LOW [b] |

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| History of mood disorders for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)) [a] | 1 | OR 1.9 (1.5 to 2.3) | No serious imprecision | VERY LOW [b] |

*(a) Methods: multivariate analysis: logistic regression adjusted for Age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date*

*(b) Downgraded by 2 increments due to very serious risk of bias and by 1 increment due to indirectness with the proportion of those taking opioids for chronic pain being unclear*

**Table 15: Clinical evidence summary: Concurrent use of antidepressants**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Concurrent use of antidepressants for predicting codeine shopping behaviour (CNCP patients; mean (SD) age 62.7 (16.1) years) [a] | 1 | HR 0.93 (0.53 to 1.63) | Serious imprecision [b] | LOW [c] |

*(a) Methods: multivariable analysis: cox proportional hazards developed according to clinically relevant variables such as age and gender*

*(b) Downgraded by 1 increment as the confidence interval crossed the null line*

*(c) Downgraded by 1 increment due to risk of bias and by increment due to imprecision*

**Table 16: Clinical evidence summary: Previous use of antipsychotics**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Previous use of antipsychotics for predicting codeine shopping behaviour (CNCP patients; mean (SD) age 62.7 (16.1) years) [a] | 1 | HR 1.03 (0.42 to 2.53) | Serious imprecision [b] | LOW [c] |

*(a) Methods: multivariable analysis: cox proportional hazards developed according to clinically relevant variables such as age and gender*

*(b) Downgraded by 1 increment as the confidence interval crossed the null line*

*(c) Downgraded by 1 increment due to risk of bias and by increment due to imprecision*

**Table 17: Clinical evidence summary: History of benzodiazepine use**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Previous use of hypnotic benzodiazepines for predicting codeine shopping behaviour (CNCP patients; mean (SD) age 62.7 (16.1) years) [a] | 1 | HR 1.56 (0.70 to 3.49) | Serious imprecision [b] | LOW [c] |
| Previous use of anxiolytic benzodiazepines for predicting codeine shopping behaviour (CNCP patients; mean (SD) age 62.7 (16.1) years) [a] | 1 | HR 0.63 (0.32 to 1.26) | Serious imprecision [b] | LOW [c] |
| History of benzodiazepine use for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)) [d] | 1 | OR 1.6 (1.1 to 2.2) | No serious imprecision | VERY LOW [e] |
| History of benzodiazepine use for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)) [d] | 1 | OR 1.5 (1.3 to 1.5) | No serious imprecision | VERY LOW [e] |

*(a) Methods: multivariable analysis: cox proportional hazards developed according to clinically relevant variables such as age and gender*
*(b) Downgraded by 1 increment as the confidence interval crossed the null line*
*(c) Downgraded by 1 increment due to risk of bias and by 1 increment due to imprecision*
*(d) Methods: multivariate analysis: logistic regression adjusted for Age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date*
*(e) Downgraded by 2 increments due to very serious risk of bias and by 1 increment due to indirectness with the proportion of those taking opioids for chronic pain being unclear*

**Table 18: Clinical evidence summary: Concurrent use of benzodiazepine/ concurrent use of gabapentin/pregabalin**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Concurrent use of hypnotic benzodiazepine for predicting codeine shopping behaviour (CNCP patients; mean (SD) age 62.7 (16.1) years) [a] | 1 | HR 0.89 (0.43 to 1.83) | Serious imprecision [b] | LOW [b, c] |
| Concurrent use of anxiolytic benzodiazepine for predicting codeine shopping behaviour (CNCP patients; mean (SD) age 62.7 (16.1) years) [a] | 1 | HR 3.12 (1.55 to 6.26) | No serious imprecision | MODERATE [c] |
| Receipt of benzodiazepine prescription for predicting second early opioid refill (CNCP patients; mean age (SD) 52.54 (11.03)) [d] | 1 | HR 1.54 (1.09 to 2.18) | No serious imprecision | MODERATE [e] |

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Concurrent use of benzodiazepine compared to opioid alone for predicting composite outcome – any combination of opioid abuse, dependence or overdose (opioid naïve patients aged 18 and over)[f] | 1 | HR 1.38 (1.17 to 1.61) | No serious imprecision | LOW[g] |
| Concurrent use of gabapentin/pregabalin compared to opioid alone for predicting composite outcome – any combination of opioid abuse, dependence or overdose (opioid naïve patients aged 18 and over) [f] | 1 | HR 1.54 (1.29 to 1.84) | No serious imprecision | LOW[g] |
| Concurrent use of benzodiazepine and gabapentin/pregabalin within 30 days compared to opioid alone for predicting composite outcome – any combination of opioid abuse, dependence or overdose (opioid naïve patients aged 18 and over) [f] | 1 | HR 1.68 (1.38 to 2.04) | No serious imprecision | LOW[g] |
| Concurrent use of benzodiazepine and gabapentin/pregabalin not within 30 days compared to opioid alone for predicting composite outcome – any combination of opioid abuse, dependence or overdose (opioid naïve patients aged 18 and over) [f] | 1 | HR 1.66 (1.24 to 2.22) | No serious imprecision | LOW[g] |

*(a) Methods: multivariable analysis: cox proportional hazards developed according to clinically relevant variables such as age and gender*
*(b) Downgraded by increment as the confidence interval crossed the null line*
*(c) Downgraded by 1 increment due to serious risk of bias*
*(d) Methods: cox proportional hazards model analysis, including key covariates used in analysis to assess if receipt of benzodiazepine prescription is an independent risk factor. Key covariates included: sex, age, race, medical insurance, medical comorbidities, pain, mental health and substance use disorders*
*(e) Downgraded by 1 increment due to potential indirectness of part of the population who may not have been opioid naïve or could have drug use disorder/ dependence that could include opioids at baseline*
*(f) Methods: multivariable analysis: Cox proportional hazards with stepwise selection adjusted for age, sex and comorbidities*
*(g) Downgraded by 1 increment due to serious risk of bias and 1 increment due to indirectness*

**Table 19: Clinical evidence summary: Previous use of strong opioids**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Previous use of strong opioids for predicting codeine shopping behaviour (CNCP patients; mean (SD) age 62.7 (16.1) years) [a] | 1 | HR 2.94 (1.24 to 6.98) | No serious imprecision | MODERATE [b] |
| Prior use of strong opioids for predicting tramadol shopping behaviour (CNCP patients treated with tramadol (mean age (SD) 66.4 (14.7) years)) [c] | 1 | HR 5.7 (1.9 to 17.0) | Serious imprecision [d] | VERY LOW [e] |

*(a) Methods: multivariable analysis: cox proportional hazards developed according to clinically relevant variables such as age and gender*
*(b) Downgraded by 1 increment due to risk of bias*
*(c) Methods: multivariable analysis: cox proportional hazards model; confounders not specified*

*(d) Downgraded by 1 increment as the confidence interval was judged to be very wide*
*(e) Downgraded by 2 increments due to serious risk of bias and by 1 increment due to imprecision*

**Table 20: Clinical evidence summary: Long-term opioid therapy**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Periods on long-term opioids* versus not being in an episode of long-term prescribing for predicting incident addiction to opioids (new long-term opioid users; median age (IQR) 61 (47 to 73) years) [a]<br><br>**3 or more prescriptions within 90 days* | 1 | HR 2.83 (2.13 to 3.76) | No serious imprecision | HIGH |
| Long term opioid therapy (≥90 days) versus shorter term opioid therapy (<90 days) for predicting opioid dependence (patients with polyneuropathy (mean age (SD): 67.5 (16.5) years) [b] | 1 | HR 2.85 (1.54 to 5.31) | No serious imprecision | LOW [c] |
| Long term opioid therapy (≥90 days) versus shorter term opioid therapy (<90 days) for predicting opioid abuse (patients with polyneuropathy (mean age (SD): 67.5 (16.5) years) [b] | 1 | HR 3.97 (0.87-28.9) | Very serious imprecision [d] | VERY LOW [c, d] |

*(a) Methods: multivariable analysis: Cox proportional hazards regression adjusted for age at baseline, gender, year of start of follow-up, ever smoking, ever alcohol drinking, overweight (BMI ≥25 kg/m2), geographical region, deprivation level, prior recorded depression, co-prescribing of NSAID and total number of co-morbid conditions.*
*(b) Methods: Multivariate logistic regression adjusted for Charlson Comorbidity Index comorbidities, sex, and use of non-opioid analgesics*
*(c) Downgraded by 2 increments due to very serious risk of bias*
*(d) Downgraded by 2 increments as the confidence interval crossed the null line and was judged to be very wide*

**Table 21: Clinical evidence summary: Opioid dosage**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Long-term episode at an average daily dose (ADD) <20 mg morphine equivalent dose (MED) versus not being in an episode of long-term prescribing for predicting incident addiction to opioids (new long-term opioid users; median age (IQR) 61 (47 to 73) years) [a] | 1 | HR 1.06 (0.71 to 1.60) | Serious imprecision [b] | LOW [c] |
| Long-term episode at an ADD ≥20 and <50 mg MED versus not being in an episode of long-term prescribing for predicting incident addiction to opioids (new long-term opioid users; median age (IQR) 61 (47 to 73) years) [a] | 1 | HR 3.59 (2.55 to 5.06) | No serious imprecision | MODERATE [d] |

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| | | | | |
| Long-term episode at an ADD ≥ 50 mg MED versus not being in an episode of long-term prescribing for predicting incident addiction to opioids (new long-term opioid users; median age (IQR) 61 (47 to 73) years) [a] | 1 | HR 9.33 (6.55 to 13.29) | No serious imprecision | MODERATE [d] |
| Opioid dosage, morphine milligram equivalents (MME)/d (continuous) for predicting composite outcome – any combination of opioid abuse, dependence or overdose (opioid naïve patients aged 18 years and over)[e] | 1 | HR 1.003 (1.001 – 1.006) | No serious imprecision | LOW[f] |

*(a) Methods: multivariable analysis: Cox proportional hazards regression adjusted for age at baseline, gender, year of start of follow-up, ever smoking, ever alcohol drinking, overweight (BMI ≥25 kg/m2), geographical region, deprivation level, prior recorded depression, co-prescribing of NSAID and total number of co-morbid conditions.*
*(b) Downgraded by 1 increment as the CI crossed the null line*
*(c) Downgraded by 1 increment due to serious risk of bias and by 1 increment due to imprecision*
*(d) Downgraded by 1 increment due to serious risk of bias*
*(e) Methods: multivariable analysis: Cox proportional hazards with stepwise selection adjusted for age, sex and comorbidities*
*(f) Downgraded by 1 increment due to serious risk of bias and by 1 increment due to indirectness*

**Table 22: Clinical evidence summary: Opioid formulation (Oxycodone IR & tapentadol IR)**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Tapentadol IR versus oxycodone IR for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)) [a] | 1 | OR 0.45 (0.36 to 0.55) | No serious imprecision | LOW [b] |
| Tapentadol IR versus oxycodone IR for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)) [a] | 1 | OR 0.44 (0.37 to 0.54) | No serious imprecision | LOW [b] |
| Oxycodone IR versus tapentadol IR for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 51.11 (14.91) years)) [c] | 1 | OR 3.5 (2.8 to 4.4) | No serious imprecision | MODERATE [d] |
| Oxycodone IR versus tapentadol IR for predicting heavy shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 51.11 (14.91) years)) [c] | 1 | OR 6.9 (2.5 to 19.3) | Serious imprecision [e] | VERY LOW [d,e,f] |

*(a) Methods: multivariate analysis: logistic regression adjusted for age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date*
*(b) Downgraded by 1 increment due to risk of bias and by 1 increment due to potential indirectness with the proportion of participants taking opioids for chronic pain being unclear*

*(c) Methods: multivariate analysis: conditional logistic regression conducted using matched analysis (description of methods assumed to include multivariate analysis), taking into account matching variables of time of opioid exposure, geographic area, specialty of the prescriber and age and adjusting for gender, benzodiazepine use and type of payment at the first opioid exposure.*

*(d) Downgraded by 1 increment due to potential indirectness with the proportion of participants taking opioids for chronic pain being unclear*

*(e) Downgraded by 1 increment as the confidence interval was judged to be very wide*

*(f) Downgraded by 1 increment due to risk of bias*

**Table 23: Clinical evidence summary: Duration of action in the first prescription**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Long versus short acting opioids in the first prescription for predicting overlapping opioid prescriptions across the six following 3-month quarters (privately insured patients aged 18-64 years) [a] | 1 | Risk difference 14.70 (12.7 to 16.7) [b] | No serious imprecision | VERY LOW [c] |
| Long versus short acting opioids in the first prescription for predicting having 3 or more opioid prescribers across the following six 3-month quarters (privately insured patients aged 18-64 years) [a] | 1 | Risk difference 1.8 (0.9 to 2.7) [b] | Serious imprecision [d] | VERY LOW [c,d] |
| Long-acting versus short-acting for predicting composite outcome – any combination of opioid abuse, dependence or overdose (opioid naïve patients aged 18 or over)[e] | 1 | HR 2.17 (0.81 to 5.86) | Serious imprecision [d] | VERY LOW[f] |
| Concurrent use of short-acting and long-acting opioids within 30 days versus short-acting alone for predicting composite outcome – any combination of opioid abuse, dependence or overdose (opioid naïve patients aged 18 or over) [e] | 1 | HR 2.12 (1.78 to 2.54) | No serious imprecision | LOW[g] |
| Concurrent use of short-acting and long-acting opioids not within 30 days versus short-acting alone for predicting composite outcome – any combination of opioid abuse, dependence or overdose (opioid naïve patients aged 18 or over) [e] | 1 | HR 1.99 (1.24 to 3.18) | No serious imprecision | LOW[g] |

(a) *Methods: multivariate analysis: linear probability model adjusting for ordinal indicators of the quarters/3-month intervals following the first prescription (second, third, sixth, with the first quarter as the reference), calendar year indicators, patient demographics (age groups, sex); dichotomous indicators of back pain, neck pain, arthritis/joint pain and other pain, an indicator of any mental health disorder, alcohol use disorder, any drug use disorder and tobacco use disorder, socio-demographic profiles at the patient's residential ZIP codes*

*(b) Risk differences have been calculated from percentage point increase results reported in the paper using the CIs; the null line for a risk difference is 0*

*(c) Downgraded by 2 increments due to very serious risk of bias and 1 increment due to indirectness*

*(d) Downgraded by 1 increment due to serious imprecision*

*(e) Methods: Methods: multivariate analysis: cox proportional hazards with stepwise selection adjusted for age, sex and comorbidities*

*(f) Downgraded by 1 increment due to serious risk of bias, 1 increment due to indirectness and 1 increment due to imprecision*

*(g) Downgraded by 1 increment due to serious risk of bias and 1 increment due to indirectness*

**Table 24: Clinical evidence summary: Days of opioid supply in the first prescription**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Number of days' supply for predicting composite outcome (any combination of opioid abuse, dependence or overdose) (opioid naïve patients aged 18 years and over)[a] | 1 | HR 1.025 (1.019 to 1.032) | No serious imprecision | LOW[b] |
| >7 days versus ≤ 3 days for predicting overlapping opioid prescriptions across the six following 3-month quarters (privately insured patients aged 18-64 years) [c] | 1 | Risk difference 6.65 (6.3 to 7) [d] | No serious imprecision | VERY LOW [e] |
| >7 days versus 4-7 days for predicting overlapping opioid prescriptions across the six following 3-month quarters (privately insured patients aged 18-64 years) [c] | 1 | Risk difference 5.65 (5.3 to 6) [d] | No serious imprecision | VERY LOW [e] |

(a) *Methods: multivariate analysis: cox proportional hazards with stepwise selection adjusted for age, sex and comorbidities*
(b) *Downgraded by 1 increment due to serious risk of bias and 1 increment due to indirectness*
(c) *multivariate analysis: linear probability model adjusting for ordinal indicators of the quarters/3-month intervals following the first prescription (second, third, sixth, with the first quarter as the reference), calendar year indicators, patient demographics (age groups, sex); dichotomous indicators of back pain, neck pain, arthritis/joint pain and other pain, an indicator of any mental health disorder, alcohol use disorder, any drug use disorder and tobacco use disorder, socio-demographic profiles at the patient's residential ZIP codes*
*(d) Risk differences have been calculated from percentage point increase results reported in the paper using the CIs*
*(e) Downgraded by 2 increments due to very serious risk of bias and 1 increment due to indirectness*

**Table 25: Clinical evidence summary: Dual use of Veterans health administration (VHA) pharmacy and Medicare part D**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Dual use of VHA pharmacy and Medicare part D versus no dual use for predicting overlapping concurrent opioid prescriptions (Veterans aged ≥ 65 years with a new MSD diagnosis) [a] | 1 | OR 5.28 (4.60 to 6.05) | No serious imprecision | MODERATE [b] |

*(a) Methods: multivariate logistic regression analysis adjusted for age, sex, ethnicity, pain intensity (NRS), co morbid diagnoses, overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and PTSD*
*(b) Downgraded by 1 increment due to. indirectness as the risk factor may be of limited relevance to the NHS setting.*

**Table 26: Clinical evidence summary: Type of payment**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Medicaid versus cash for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)) [a] | 1 | OR 0.3 (0.3 to 0.4) | No serious imprecision | VERY LOW [b] |
| Medicaid versus cash for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)) [a] | 1 | OR 1.1 (0.9 to 1.2) | Serious imprecision [c] | VERY LOW [b,c] |
| Medicare versus cash for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)) [a] | 1 | OR 0.4 (0.3 to 0.4) | No serious imprecision | VERY LOW [b] |
| Medicare versus cash for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)) [a] | 1 | OR 0.7 (0.6 to 0.8) | No serious imprecision | VERY LOW [b] |
| Commercial insurance versus cash for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)) [a] | 1 | OR 0.2 (CI 0.2 to 0.2) | No serious imprecision | VERY LOW [b] |
| Commercial insurance versus cash for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)) [a] | 1 | OR 0.3 (CI 0.3 to 0.4) | No serious imprecision | VERY LOW [b] |

*(a) Methods: multivariate analysis: logistic regression adjusted for Age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date*

*(b) Downgraded by 2 increments due to very serious risk of bias and by 2 increments due to indirectness with the proportion of those taking opioids for chronic pain being unclear and the risk factor being of limited relevance to the NHS setting*

*(c) Downgraded by 1 increment as the confidence interval crossed the null line*

**Table 27: Clinical evidence summary: Painful condition (present versus absent)**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Arthritis for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 0.8 (0.7 to 0.1) | No serious imprecision | VERY LOW [b] |
| Arthritis for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 1 (0.8 to 1.1) | Serious imprecision [c] | VERY LOW [b, c] |
| Back pain for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 2.0 (1.7 to 2.3) | No serious imprecision | VERY LOW [b] |

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Back pain for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 1.7 (1.5 to 2) | No serious imprecision | VERY LOW [b] |
| Fractures for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 1.1 (0.75 to 1.7) | Serious imprecision [c] | VERY LOW [b, c] |
| Fractures for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 1.2 (0.8 to 1.6) | Serious imprecision [c] | VERY LOW [b, c] |
| Headache for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 0.8 (0.6 to 1.2) | Serious imprecision [c] | VERY LOW [b, c] |
| Headache for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 1.2 (0.9 to 1.5) | No serious imprecision | VERY LOW [b] |
| Malignancy for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 0.7 (0.5 to 0.9) | No serious imprecision | VERY LOW [b] |
| Malignancy for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 0.4 (0.3 to 0.5) | No serious imprecision | VERY LOW [b] |
| Musculoskeletal pain for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 0.9 (0.7 to 1.1) | No serious imprecision | VERY LOW [b] |
| Musculoskeletal pain for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 1.1 (0.9 to 1.3) | Serious imprecision [c] | VERY LOW [b, c] |
| Neuropathic pain for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 1.2 (0.8 to 1.8) | Serious imprecision [c] | VERY LOW [b, c] |
| Neuropathic pain for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 1.1 (0.7 to 1.6) | Serious imprecision [c] | VERY LOW [b, c] |
| Other pains for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 1.2 (0.6 to 2.3) | Serious imprecision [c] | VERY LOW [b, c] |
| Other pains for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 1.7 (1.0 to 2.8) | No serious imprecision | VERY LOW [b] |
| Reproductive pain for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 0.7 (0.3 to 1.8) | Serious imprecision [c] | VERY LOW [b, c] |
| Reproductive pain for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 0.8 (0.4 to 1.7) | Serious imprecision [c] | VERY LOW [b, c] |

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Visceral pain for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 1.0 (0.8 to 1.2) | Serious imprecision [c] | VERY LOW [b, c] |
| Visceral pain for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 1.1 (0.9 to 1.3) | Serious imprecision [c] | VERY LOW [b, c] |
| Wound injury for predicting shopping behaviour (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 1.0 (0.5 to 1.8) | Serious imprecision [c] | VERY LOW [b, c] |
| Wound injury for predicting opioid abuse (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years) [a] | 1 | OR 0.7 (0.4 to 1.4) | Serious imprecision [c] | VERY LOW [b, c] |

*(a) Methods: multivariate analysis: logistic regression adjusted for Age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date*

*(b) Downgraded by 1 increment due to indirectness with the proportion of those taking opioids for chronic pain being unclear and by 2 increments due to very serious risk of bias*

*(c) Downgraded by 1 increment as the confidence interval crossed the null line*

### 1.1.6.2. Summary of the prognostic evidence for benzodiazepines

**Table 28: Clinical evidence summary: Age**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Age (continuous) for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (new benzodiazepine users with a first redemption for diazepam or oxazepam) [a] | 1 | HR 0.98 (0.98 to 0.99) | No serious imprecision | LOW [b] |
| 25-34 versus 18-24 years for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [c] | 1 | HR 1.23 (0.35 to 4.31) | Serious imprecision [d] | VERY LOW [e] |
| 35-44 versus 18-24 years for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [c] | 1 | HR 0.66 (0.33 to 1.31) | Serious imprecision [d] | VERY LOW [e] |
| 45-54 versus 18-24 years for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [c] | 1 | HR 0.87 (0.37 to 2.06) | Serious imprecision [d] | VERY LOW [e] |
| 55-64 versus 18-24 years and benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [c] | 1 | HR 1.08 (0.37 to 3.11) | Serious imprecision [d] | VERY LOW [e] |

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| 65+ versus 18-24 years for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [c] | 1 | HR 1.47 (0.34 to 6.27) | Serious imprecision [d] | VERY LOW [e] |

*(a) Methods: Cox proportional hazard regression model adjusted for socio-demographic status and previous drug use; unclear if the analysis adjusted for other covariates in addition to the aforementioned and those entered in the model as prognostic factors.*
*(b) Downgraded by 1 increment due to serious risk of bias and by 1 increment due to indirectness of the outcome*
*(c) Methods: Cox proportional hazard regression model adjusted for substance use disorder diagnosis (alcohol, marijuana, cocaine, opioid, tobacco, pain medication), mental health disorder diagnosis, age, sex, race; model also included interactions between age and sex.*
*(d) Downgraded by 1 increment as the confidence interval crossed the null line*
*(e) Downgraded by 2 increments due to serious risk of bias and by 1 increment due to imprecision*

**Table 29: Clinical evidence summary: Gender**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Female versus male for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (new benzodiazepine users with a first redemption for diazepam or oxazepam) [a] | 1 | HR 0.57 (0.50 to 0.65) | No serious imprecision | LOW [b] |
| Male versus female for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [c] | 1 | HR 1.33 (0.55 to 3.21) | Serious imprecision [d] | VERY LOW [e] |

*(a) Methods: Cox proportional hazard regression model adjusted for socio-demographic status and previous drug use; unclear if the analysis adjusted for other covariates in addition to the aforementioned and those entered in the model as prognostic factors.*
*(b) Downgraded by 1 increment due to serious risk of bias and by 1 increment due to outcome indirectness*
*(c) Methods: Cox proportional hazard regression model adjusted for substance use disorder diagnosis (alcohol, marijuana, cocaine, opioid, tobacco, pain medication), mental health disorder diagnosis, age, sex, race; model also included interactions between age and sex.*
*(d) Downgraded by 1 increment as the confidence interval crossed the null line*
*(e) Downgraded by 2 increments due to serious risk of bias and by 1 increment due to imprecision*

**Table 30: Clinical evidence summary: Family Background**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Black versus white for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [a] | 1 | HR 0.18 (0.15 to 0.21) | No serious imprecision | LOW [b] |

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Latino versus white for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [a] | 1 | HR 0.2 (0.17 to 0.23) | No serious imprecision | LOW [b] |
| Asian versus white for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [a] | 1 | HR 0.43 (0.25 to 0.74) | No serious imprecision | LOW [b] |

*(a) Methods: Cox proportional hazard regression model adjusted for substance use disorder diagnosis (alcohol, marijuana, cocaine, opioid, tobacco, pain medication), mental health disorder diagnosis, age, sex, race; model also included interactions between age and sex.*

*(b) Downgraded by 2 increments due to very serious risk of bias*

**Table 31: Clinical evidence summary: First benzodiazepine dispensation**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Oxazepam versus diazepam for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (new benzodiazepine users with a first redemption for diazepam or oxazepam) [a] | 1 | HR 1.33 (1.17 to 1.51) | No serious imprecision | LOW [b] |

*(a) Methods: Cox proportional hazard regression model adjusted for socio-demographic status and previous drug use; unclear if the analysis adjusted for other covariates in addition to the aforementioned and those entered in the model as prognostic factors.*

*(b) Downgraded by 1 increment due to serious risk of bias and by 1 increment due to outcome indirectness*

**Table 32: Clinical evidence summary: Previous medication**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Antidepressants and lithium for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (new benzodiazepine users with a first redemption for diazepam or oxazepam) [a] | 1 | HR 1.69 (1.49 to 1.91) | No serious imprecision | LOW [b] |
| Antipsychotics for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (new benzodiazepine users with a first redemption for diazepam or oxazepam) [a] | 1 | HR 1.75 (1.49 to 2.07) | No serious imprecision | LOW [b] |
| Opioids, anti-alcohol and smoking cessation drugs for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month | 1 | HR 3.04 (2.28 to 4.05) | No serious imprecision | LOW [b] |

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| period) (new benzodiazepine users with a first redemption for diazepam or oxazepam) [a] | | | | |
| Drugs for rheumatic disease for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (new benzodiazepine users with a first redemption for diazepam or oxazepam) [a] | 1 | HR 1.22 (0.97 to 1.53) | Serious imprecision [c] | VERY LOW [b,c] |
| Drugs for COPD for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (new benzodiazepine users with a first redemption for diazepam or oxazepam) [a] | 1 | HR 1.29 (1.09 to 1.52) | No serious imprecision | LOW [b] |

*(a) Methods: Cox proportional hazard regression model adjusted for socio-demographic status and previous drug use; unclear if the analysis adjusted for other covariates in addition to the aforementioned and those entered in the model as prognostic factors.*
*(b) Downgraded by 1 increment due to serious risk of bias and by 1 increment due to outcome indirectness*
*(c) Downgraded by 1 increment as the confidence interval crossed the null line*

**Table 33: Clinical evidence summary: Education**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| High versus low for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (new benzodiazepine users with a first redemption for diazepam or oxazepam) [a] | 1 | HR 0.65 (0.57 to 0.73) | No serious imprecision | LOW [b] |

*(a) Methods: Cox proportional hazard regression model adjusted for socio-demographic status and previous drug use; unclear if the analysis adjusted for other covariates in addition to the aforementioned and those entered in the model as prognostic factors.*
*(b) Downgraded by 1 increment due to serious risk of bias and by 1 increment due to outcome indirectness*

**Table 34: Clinical evidence summary: Income**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Average versus low for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (new benzodiazepine users with a first redemption for diazepam or oxazepam) [a] | 1 | HR 0.72 (0.62 to 0.84) | No serious imprecision | LOW [b] |
| High versus low for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (new benzodiazepine users with a first redemption for diazepam or oxazepam) [a] | 1 | HR 0.57 (0.45 to 0.71) | No serious imprecision | LOW [b] |

*(a) Methods: Cox proportional hazard regression model adjusted for socio-demographic status and previous drug use; unclear if the analysis adjusted for other covariates in addition to the aforementioned and those entered in the model as prognostic factors.*
*(b) Downgraded by 1 increment due to serious risk of bias and by 1 increment due to outcome indirectness*

**Table 35: Clinical evidence summary: Type of work**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Private sector versus no registration for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (new benzodiazepine users with a first redemption for diazepam or oxazepam) [a] | 1 | HR 0.62 (0.52 to 0.74) | No serious imprecision | LOW [b] |
| Public sector versus no registration for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (new benzodiazepine users with a first redemption for diazepam or oxazepam) [a] | 1 | HR 0.61 (0.52 to 0.73) | No serious imprecision | LOW [b] |

*(a) Methods: Cox proportional hazard regression model adjusted for socio-demographic status and previous drug use; unclear if the analysis adjusted for other covariates in addition to the aforementioned and those entered in the model as prognostic factors.*
*(b) Downgraded by 1 increment due to serious risk of bias and by 1 increment due to outcome indirectness*

**Table 36: Clinical evidence summary: Substance use diagnosis**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Alcohol versus no diagnosis for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [a] | 1 | HR 0.77 (0.6 to 0.99) | No serious imprecision | LOW [b] |
| Marijuana versus no diagnosis for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [a] | 1 | HR 0.28 (0.2 to 0.38) | No serious imprecision | LOW [b] |
| Cocaine versus no diagnosis for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [a] | 1 | HR 1.13 (0.79 to 1.61) | Serious imprecision [c] | VERY LOW [b, c] |
| Opioid versus no diagnosis for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [a] | 1 | HR 3.9 (1.18 to 12.89) | Serious imprecision [c] | VERY LOW [b, c] |
| Tobacco versus no diagnosis for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [a] | 1 | HR 2.08 (1.18 to 3.67) | No serious imprecision | LOW [b] |
| Pain medication versus no diagnosis for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [a] | 1 | HR 0.71 (0.58 to 0.86) | No serious imprecision | LOW [b] |

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Two or more substance use disorders versus no diagnosis for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [a] | 1 | HR 2.03 (1.04 to 3.95) | No serious imprecision | LOW [b] |

*(a) Methods: Cox proportional hazard regression model adjusted for substance use disorder diagnosis (alcohol, marijuana, cocaine, opioid, tobacco, pain medication), mental health disorder diagnosis, age, sex, race; model also included interactions between age and sex.*
*(b) Downgraded by 2 increments due to very serious risk of bias*
*(c) Downgraded by 1 increment as the confidence interval crossed the null line or was judged to be very wide*

**Table 37: Clinical evidence summary: Mental health disorder diagnosis**

| Risk factor and outcome (population) | Number of studies | Effect (95% CI) | Imprecision | GRADE Quality |
|---|---|---|---|---|
| Depression versus no diagnosis for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [a] | 1 | HR 1.43 (0.99 to 2.08) | No serious imprecision | LOW [b] |
| Anxiety versus no diagnosis for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [a] | 1 | HR 1.6 (1.02 to 2.51) | No serious imprecision | LOW [b] |
| Bipolar versus no diagnosis for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [a] | 1 | HR 1.02 (0.69 to 1.51) | Serious imprecision [c] | VERY LOW [b, c] |
| PTSD versus no diagnosis for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [a] | 1 | HR 0.91 (0.65 to 1.27) | Serious imprecision [c] | VERY LOW [b, c] |
| Sleeping disturbance versus no diagnosis for predicting benzodiazepine dependence (benzodiazepine users, mean age (SD) 49.8 (16.6) years) [a] | 1 | HR 0.69 (0.53 to 0.89) | No serious imprecision | LOW [b] |

*(a) Methods: Cox proportional hazard regression model adjusted for substance use disorder diagnosis (alcohol, marijuana, cocaine, opioid, tobacco, pain medication), mental health disorder diagnosis, age, sex, race; model also included interactions between age and sex.*
*(b) Downgraded by 2 increments due to very serious risk of bias*
*(c) Downgraded by 1 increment as the confidence interval crossed the null line*

See Appendix F for full GRADE tables.

## 1.1.7. Economic evidence

### 1.1.7.1. Included studies

No health economic studies were included.

### 1.1.7.2. Excluded studies

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

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

## 1.1.8. Summary of included economic evidence

None.

## 1.1.9. Economic model

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

## 1.1.10. Evidence statements

### 1.1.10.1. Economic

- No relevant economic evaluations were identified.

## 1.1.11. The committee's discussion and interpretation of the evidence

### 1.1.11.1. The outcomes that matter most

This review aimed to examine risk factors (both patient and prescribing factors) associated with dependence on prescribed opioids, benzodiazepines, gabapentinoids or Z-drugs, or withdrawal symptoms associated with antidepressants.

The primary (critical) outcomes for this review were dependence on the prescribed medicine and withdrawal symptoms (including rebound symptoms). The committee acknowledged at the protocol development stage that evidence was likely to be limited. They agreed to consider any outcome definition given by the studies and to also include surrogate measures suggesting dependence such as early refills, drug shopping behaviour and prescription misuse. Long-term or chronic use was agreed not to be used as a proxy for dependence as long-term use does not always indicate dependence and people might be on safe doses and deriving benefit or for some drug classes such as antidepressants, long-term use may be recommended. There were no further core outcome measures considered relevant for this topic.

Evidence was identified for outcomes including dependence (ICD 9$^{th}$ version diagnoses of abuse, addiction or dependence), opioid shopping behaviour (overlapping prescriptions from ≥ 2 prescribers filled at ≥ 3 pharmacies), opioid abuse, overlapping prescriptions (>7 days), early drug refills, daily average intake of ≥ 1 defined daily dose (i.e., dose escalation) for the drug classes of opioids and benzodiazepines.

No evidence was identified for the risk of withdrawal symptoms, or for the other drug classes; antidepressants, gabapentinoids and Z-drugs.

### 1.1.11.2. The quality of the evidence

Evidence from 14 retrospective cohort studies was identified for opioids (n=12) and benzodiazepines (n=2). No evidence was identified for gabapentinoids, Z-drugs or antidepressants.

For opioids, there was evidence for the following factors; age, family background, gender, low-income status, pain intensity, clinical severity, history of opioid use disorder, history of substance use disorder/abuse of non-opioid drugs, active chronic liver disease, mental health disorders, history of mood disorders, concurrent use of antidepressants, previous use of antipsychotics, history of benzodiazepine use, concurrent use of benzodiazepines, concurrent use of gabapentinoids, concurrent use of benzodiazepines and gabapentinoids, previous use of strong opioids, long-term opioid therapy, opioid dosage, opioid formulation, duration of action in the first prescription, days of opioid supply in the first prescription, dual use of Veterans' health administration pharmacy and Medicare part D (Medicare is an insurance plan for people over 65), type of payment and type of painful condition.

For benzodiazepines, there was evidence for the following factors: age, gender, family background, first benzodiazepine dispensation, previous medication, education, income, type of work, substance use diagnosis and mental health disorder diagnosis.

Across both drug classes, a range of different confounders were adjusted in the multivariate analyses, including age, gender, ethnicity, smoking, status, BMI, different comorbidities, pain intensity, clinical severity, substance use disorder, co-prescribing of other drugs, type of payment used, with some studies adjusting for some confounders but not others.

There was substantial variation in the populations for opioids, with studies including; new long-term opioid users with musculoskeletal conditions, new opioid users exposed to tapentadol or oxycodone (whose chronic pain condition was unclear), people with chronic non-cancer pain treated with codeine or tramadol, veterans (aged 65 years or older) with a musculoskeletal disorder diagnosis, Iraq and Afghanistan veterans with a pain-related diagnosis, people with polyneuropathy and people with private healthcare insurance. The committee considered that the heterogeneity of the study populations resembled that seen in clinical practice and therefore, did not consider this a limitation.

Pooling of results was not possible as studies used different definitions for the factors studied (e.g., compared different age groups or types of mental health disorder), different effect measures (e.g., RR, HR, OR), adjusted for different confounders, and looked at different outcomes and/or populations. Therefore, although for different risk factors there may be evidence from more than one study, evidence for each risk factor for predicting different outcomes was based on single studies.

#### Opioids

The majority of the evidence for opioids was of low or very low quality. The main reasons for downgrading were due to risk of bias, indirectness, and occasionally for imprecision in the effect estimate. Although the results presented were based on single studies, the committee noted that the majority of the study sample sizes were large (N > 1000). However, there were a few studies where the number of people who had a prognostic factor at baseline or the outcome of interest was small enough to potentially impact the rigour of the analysis and this was taken into account and reflected the risk of bias assessment rating given to the studies. Other reasons for downgrading due to risk of bias included missing information in order to determine

the confounding factors or the outcome for some participants and whether there was appropriate accounting for confounding (for example, although all studies accounted for at least 3 confounders within the analysis, as per the protocol, some studies did not account for opioid dose within the analysis, which the committee considered might have an influence on the outcome). For some studies, the population was downgraded for indirectness due to either the proportion of the population being treated for chronic pain being unclear, or due to it being unclear whether all participants were opioid naïve at baseline. In one study, the risk factor was downgraded for indirectness due to concerns over the relevance of the risk factor to the NHS setting.

There were some exceptions when evidence was not downgraded for any of the above reasons and was therefore graded as high-quality evidence. These included 2 factors for age (75-84 years versus 65-74 years, and 85 years and over versus 65-74 years), family background (people of non-white family background versus white family background), pain intensity (moderate to severe pain), substance use disorder, and major depression, all for predicting overlapping concurrent opioid prescriptions, and periods on long-term opioids for predicting incident addiction to opioids. It was noted that although this evidence was of high quality, most of it came from a study conducted in the US, as did most of the other evidence for opioids. The committee highlighted that due to legislation and differences in the access to pain medication, some evidence from a US setting may have limited relevance to the UK setting. For example, in the US, opioid shopping behaviour is more problematic due to the nature of the healthcare system, and it may be unlikely for outcomes such as shopping behaviour and early opioid refills to be seen in the UK.

**Benzodiazepines**

The quality of the evidence relevant to benzodiazepines ranged from very low to low and was most typically downgraded due to risk of bias, imprecision and concerns over the indirectness of the outcome of dose escalation (a daily average intake of at least 1 defined daily dose over a 3-month period, from a starting point of a daily average intake of less than 1 defined daily doses in the first 3 months), to which the majority of the evidence related. This dose escalation outcome was considered by the study authors to reflect a measure of drug misuse/dependence; however, the committee did not agree that this was always directly related to dependence and agreed to downgrade to account for the indirectness. Reasons for downgrading due to risk of bias included whether there was appropriate accounting for confounding (including the fact that some studies did not account for opioid dose within the analysis, which the committee considered might have an influence on the outcome) and whether a valid and reliable measure of the risk factor was used.

#### 1.1.11.3. Risk factors

Evidence examining different factors for predicting outcomes meeting the review protocol was reviewed and discussed by the guideline committee. This is outlined by drug class below. The committee noted that the outcomes for which there was evidence may be more closely related to problematic drug use or misuse behaviours, rather than dependence. Although problematic drug use or misuse behaviours are likely to be due to an underlying dependence, the committee noted that people may still be dependent on medicines but not show the problematic drug use or misuse behaviours examined in the studies. As a result, the committee noted that the population of interest may not be fully captured by the evidence. They also noted that the literature only provides evidence of an association. Although studies adjusted for possible confounding factors, other factors not adjusted for in the analysis, such as

medicine dose, may also influence the relationship between prognostic factors and outcomes. Therefore, the confounders adjusted for need to be considered when interpreting the results. For these reasons, the committee agreed that evidence should be interpreted with caution.

**Opioids**

Evidence from 4 out of 5 studies looking at age, showed that younger age groups (≤40 versus >40 year; 65-74 versus 75-84 and 85 and over; 18-39 and 40-54 versus aged over 64; less than 40 and 40-50 versus 50 or older) were associated with an increased risk for 5 different outcomes (codeine shopping; overlapping prescriptions; shopping behaviour; opioid abuse; tramadol shopping). In 2 studies examining multiple age groups in particular, the elevated risk as indicated by the effect size appeared to decrease with increasing age. This inverse relationship was not evidenced for people aged under 18 years. However, the committee noted that although the study was included as <20% of the population were aged under 18 years, findings for this particular age group were outside the scope of the guideline and did not influence decision making. The committee noted that the findings relating to age were in line with their experience and discussed that this may be due to a greater likelihood for a specific pathology to underlie opioid prescribing in older groups which may make them less likely to misuse opioids, whereas a lack of a specific pathology which is more likely to be seen in younger groups and may increase the likelihood of misuse and/or dependence.

Evidence from 1 study showed there was a lower risk of overlapping concurrent opioid prescriptions for non-white people, compared to white study participants. The committee noted that the study examining family background was conducted in the US where racial and ethnic minority groups may face challenges in accessing healthcare, while people with white ethnicity are more likely to have health insurance allowing them to visit more prescribers, and therefore family background was not necessarily a risk factor, but it may be a proxy for other risk factors (for example deprivation, or in the case of the US setting, having health insurance). They agreed this finding may be less applicable to the UK setting and the NHS healthcare system.

Evidence from 2 studies, showed that male gender was a risk factor for shopping behaviour and opioid abuse while evidence from 1 study showed that female gender was a risk factor for tramadol shopping behaviour. The committee noted the findings were conflicting and a further 2 studies examining codeine shopping behaviour and overlapping concurrent opioid prescriptions did not demonstrate any association with gender and increased risk. The evidence indicating an association was of very low quality, and it was agreed there was no consistent evidence to inform a recommendation.

Evidence from 2 studies showed that low-income status was associated with a greater risk of codeine and tramadol shopping behaviour. The committee agreed that these findings were not surprising and highlighted that deprivation, which may be represented in studies by low-income status or a minority ethnic background (which may be a proxy for deprivation in some settings) can have a profound impact on people and may enhance the desire for medicines. Based on their clinical experience, the committee noted that factors such as cardiac disease and obesity that also relate to deprivation have been associated with a greater risk of problematic drug use, however no evidence was identified for these factors in this review. The committee agreed that low-income status was related to many other factors that impacted health and wellbeing and that it was not possible to identify which particular factors were most related to increased risk of problems associated with dependence. They agreed not to include this factor in a recommendation for that reason.

Evidence from 1 study showed greater pain intensity scores (moderate-to-severe-pain; NRS score 4-10) to be associated with a greater risk of overlapping concurrent opioid prescriptions compared to people with lower pain intensity. The committee noted the subjectivity of pain intensity and agreed the perception of greater pain may lead to an increased likelihood of people seeking more opioid prescriptions. As this result was from a single study, the committee did not consider it strong enough to inform a recommendation.

Contrarily, the number of medical diseases as a continuous outcome was associated with lower risk of prescription opioid abuse behaviour in 1 study (although this evidence was rated as very low quality) and higher clinical severity score (CCI 2+) was not associated with an increased or decreased risk of overlapping concurrent opioid prescriptions versus a lower score. The committee noted this finding was imprecise with the confidence interval crossing the null line complicating conclusions about where the true effect lies. The committee did however consider this may also relate to a point raised below, that the risk of problems associated with dependence was lower when a specific pathology underlies a pain medication prescription.

History of opioid use disorder was associated with a greater risk of codeine shopping behaviour in 1 study. Evidence quality was low and there was imprecision in the effect estimate, but the committee raised this was in line with their experience. History of substance use disorder (with studies defining this as including alcohol, tobacco, narcotics or illicit drugs) was also associated with greater risk of 4 different outcomes suggesting problematic drug use (prescription opioid abuse behaviour; concurrent opioid prescriptions; shopping behaviour; opioid abuse) in 3 out of 4 studies examining it. The committee raised that people with a history of substance misuse may require higher opioid doses in order to manage their pain and in line with their experience, higher doses can increase the likelihood of dependence. They thought the evidence suggesting history of substance use to be a risk factor for dependence to be quite strong, supported by 3 separate studies, and took this into account alongside the evidence of people with a history of opioid use disorder being at greater risk. A recommendation was made to highlight this as a risk factor for developing problems associated with dependence.

Evidence from 1 study suggested active chronic liver disease as a risk factor for codeine shopping behaviour. The committee noted there was imprecision in the effect estimate and that it was difficult to draw a conclusion based on limited evidence from a single study. They noted that the study examining chronic liver disease also looked at history of substance use disorder that included alcohol as a risk factor for codeine shopping behaviour. Thus, the committee noted that chronic liver disease may be linked to alcohol abuse and that it could be that past alcohol abuse underlies the association of chronic liver disease and codeine shopping behaviour. Within this line of thought the committee thought that the association of chronic liver disease and codeine shopping behaviour could be due to an underlying association between history of alcohol use disorder and problematic opioid use and may thus provide indirect evidence for history of substance use disorder as a risk factor for dependence.

Evidence from 3 studies suggested different mental health disorders including major depression and PTSD co-existing with or without other mental health diagnoses, were associated with greater risk of 4 different outcomes (codeine shopping behaviour; overlapping concurrent opioids prescriptions; early opioid refills; concurrent opioids). One study showed a greater risk of shopping behaviour and opioid abuse in people with a history of mood disorder. The committee noted findings were in line with their clinical experience and agreed that similarly to deprivation (potentially caused by low income or being part of a racial minority group),

morbidities including mental health disorders, can have a profound impact on peoples' lives which may have an impact on the desire for medicines. The committee emphasised that in many cases people from groups appearing to have a higher risk of dependence such as people with mental health disorders, may be likely to benefit from medication and that prescribing decisions should be made by the careful consideration of the needs of the individual. A recommendation was made to highlight that a comorbid mental health diagnosis may lead to a higher risk of developing problems associated with dependence.

Evidence from 2 studies showed history of benzodiazepine use to be associated with a greater risk of codeine shopping behaviour, opioid shopping behaviour and opioid abuse. The association appeared to be applicable to hypnotic benzodiazepines but not anxiolytic benzodiazepines, for which there was a decreased risk for the outcome of codeine shopping behaviour in 1 study.

Evidence for concurrent use of benzodiazepines was available from 3 studies. Two of these looked at concurrent use of any benzodiazepine and the outcomes of second early opioid refill and a composite outcome of any combination of opioid abuse, dependence or overdose, both of which showed a greater risk with concurrent use of benzodiazepines. The remaining study looked at concurrent use of anxiolytic and hypnotic benzodiazepines separately, with anxiolytic benzodiazepines, but not hypnotic benzodiazepines, appearing to predict a greater risk of codeine shopping behaviour. Overall, 3 out of the 4 prognostic factor and outcome combinations showed a greater risk with concurrent benzodiazepine use (and 2 of these were of moderate quality), and the committee agreed this was in line with their clinical experience that concurrent use of opioids and benzodiazepines can increase the risks of problems associated with dependence such as opioid misuse or overdose. One of the studies also assessed the risk with the concurrent use of pregabalin or gabapentin, and again, a greater risk was observed. This was also the case for concurrent use of both gabapentinoids and benzodiazepines (either within 30 days or not within 30 days), which increased the risk of any combination of opioid abuse, dependence or overdose. However, the evidence for concurrent use of gabapentinoids in people prescribed opioids was of low quality. A further study reported no association between concurrent use of antidepressants and previous use of antipsychotics and codeine shopping behaviour. Again, this was low quality evidence and the committee agreed it was at odds with evidence demonstrating an association with concurrent use of benzodiazepines and risk of various problems including problems associated with dependence and overdose. The committee agreed this larger body of evidence, of better quality, showing an association was in alignment with their experience. Therefore, a recommendation was made to highlight that taking an opioid together with a benzodiazepine may lead to a higher risk of developing problems associated with dependence.

Evidence from 2 studies suggested that previous use of strong opioids is predictive of a greater risk of codeine and tramadol shopping behaviour. The committee mentioned that similarly to history of substance misuse, people with past use of strong opioids may require higher doses in order to manage their pain and this may result in greater likelihood of dependence. They agreed that a separate recommendation wasn't required however as they agreed it was related to other factors already highlighted in the recommendation.

Evidence from 2 studies showed that long-term opioid therapy (periods on long-term opioids (3 or more prescriptions in 90 days) versus not being in an episode of long-term prescribing, or opioid therapy for ≥90 days versus <90 days) predicted a greater risk of incident addiction to opioids, opioid dependence, and opioid abuse. There was imprecision in the effect estimate for opioid abuse, but the committee thought

evidence of an association was sufficiently strong and in line with their clinical experience. They agreed that long-term opioid use can lead to dependence irrespectively of other risk factors and that people can become dependent simply by taking medicines as prescribed over a long period of time. The committee agreed that it is important for this risk to be considered by prescribers and people taking these medicines, but that long-term prescribing may be appropriate in some cases, where the benefits of taking the medicine outweigh the potential risks associated with problematic use or dependence. Based on their clinical experience suggesting that the duration of prescribing is likely to increase the risk of dependence or the difficulty to withdraw the prescribed drug, the committee agreed that medicines should not be prescribed for longer than required. They agreed that the trade-off between the risks associated with problematic use or dependence and the clinical benefit the person derives from the medication should determine prescribing decisions and it may be clinically appropriate for medicines to continue being prescribed for as long as they continue to be helpful. This was reflected in recommendations discussed in other evidence reviews included within this guideline.

Evidence from 1 study showed higher average daily opioid doses (ADD) in people who had an episode of long-term prescribing to be associated with a greater risk of incident addiction to opioids, when compared to not being on an episode of long-term prescribing. A long-term episode at an ADD of less than 20 mg morphine equivalent dose (MED) was not associated with an increased risk of incident addiction to opioids, versus not being on an episode of long-term prescribing. However, an episode of long-term prescribing with an ADD between 20 and 50 mg MED, or an ADD of 50 mg or greater MED, predicted a greater risk, compared with not having an episode of long-term prescribing. The committee noted that the evidence showed a dose-response association, with the risk of incident addiction increasing progressively with each dose increase. The committee agreed this was an important finding and it was in line with their clinical experience. Another study also showed an increase in risk with opioid dosage on the outcome of any combination of opioid abuse, dependence or overdose. However, this was reported as the continuous variable of morphine milligram equivalents per day (MME/d), and the committee noted it was difficult to draw firm conclusions from the incremental risk increase with each MME/d. Based on the evidence and the consensus of the committee, a recommendation was made that the risk of developing problems associated with dependence can be reduced by starting the medicine at a lower dose.

There was evidence from 2 studies looking at different opioid formulations. Oxycodone IR was associated with a greater risk of shopping behaviour and heavy shopping behaviour compared to tapentadol IR as shown in moderate and very low-quality evidence, with the latter outcome also downgraded due to imprecision in the effect estimate. Similarly, tapentadol IR was associated with a reduced risk of shopping behaviour and opioid abuse compared to oxycodone. Evidence from the 2 studies was in agreement, suggesting oxycodone may increase risk of problematic drug use compared to tapentadol. However, the committee noted there were baseline differences in opioid dose between the 2 different opioid formulation groups in 1 study, with average dose in the oxycodone group being higher at baseline. Furthermore, information on dose was not available for the other contributing study. The committee agreed that differences in dose could be an important confounding factor in the examination of different opioid formulations and this impacted their ability to draw conclusions regarding opioid formulations as a risk factor for dependence.

Evidence from 2 studies showed there was a greater risk with long-acting opioids (compared to short acting opioids) for the following outcomes: having overlapping prescriptions, having 3 or more prescribers, and having any combination of opioid abuse, dependence or overdose. The committee raised this was in line with their

experience and that standard release formulations are often preferred, are less frequently associated with problems and more appropriate for dose reduction purposes. They agreed that prescribers should be aware that shorter acting preparations may reduce the risk of problematic behaviour related to opioid use, and that modified release preparations should be avoided. This would also include avoiding concurrent standard- and modified-release opioids, for which there was also evidence. This evidence was from 1 study, showing that concurrent use of short- and long-acting opioids (either within 30 days or not within 30 days), versus short-acting opioids alone, increased the risk of having any combination of opioid abuse, dependence or overdose. Modified release opioids may include slow-release morphine, slow-release oxycodone or transdermal preparations (such as fentanyl or buprenorphine patches). However, the committee specified that the appropriateness of the drug formulation is context-specific and different settings may require different prescribing decisions; for example, long-acting formulations can be more appropriate than short-acting formulations if one is treated for substance misuse or in secure environments where there are different considerations around prescribing. The committee emphasised that the prescribing framework differs in prison settings, for example, medicines may only be dispensed once a day, and medicines associated with dependence may not be held in possession.. They were aware of the NICE guideline NG57, on the Physical Health of People in Prison and highlighted this in the recommendations. They specified that considerations around practicalities of administration as well as risks for the individual and for the wider population are particularly important in those settings. In line with their clinical experience, the committee also noted that different formulations may be appropriate for different drug classes and short-acting formulations are associated with a reduced likelihood of problematic use of opioids in particular, but are not necessarily appropriate across drug classes.

For the factor of number of days of opioid supply in the first prescription, evidence was available from 2 studies. Evidence from 1 study showed that more than 7 days of opioid supply during the first prescription was associated with a greater risk of overlapping opioid prescriptions compared to fewer days of opioid supply (either 4-7 days or ≤ 3 days). The other study also showed an increase in risk with the number of days' supply on the outcome of any combination of opioid abuse, dependence or overdose. However, this was reported as the continuous variable of the increase in risk with each additional day supply, and the committee noted it was difficult to draw firm conclusions from this. The committee raised that a longer supply may predict the likelihood of remaining on the drug long-term and that the days of supply can influence the number of prescriptions which may in turn increase the risk for dependence or problematic use. They agreed to highlight in the recommendations that the prescription duration should reflect the management plan agreed with the person.

Dual use of the Veterans health administration and Medicare part D was associated with a greater risk of overlapping concurrent opioid prescriptions compared to single use in 1 study conducted in the USA. Cash payments for opioids were also associated with a greater risk of shopping behaviour and opioid abuse compared to payment through Medicaid, Medicare and commercial insurance in 1 study. The committee noted that these prognostic factors referred to types of health insurance and federal state programs available in the USA and were not relevant to the NHS setting and therefore did not base a recommendation on this evidence.

Evidence from 1 study examined the presence of different painful conditions (versus the absence of that painful condition) for predicting shopping behaviour and opioid abuse. Back pain and 'other pains' the nature of which was not specified were associated with a greater risk of both outcomes. Contrarily, arthritis and headache were associated with a reduced risk of shopping behaviour (there was no difference in

opioid abuse), malignancy and reproductive pain were associated with a reduced risk of both shopping behaviour and opioid abuse and wound injury was associated with a reduced risk of opioid abuse (but not shopping behaviour). Visceral pain, neuropathic pain, musculoskeletal pain and fractures were not associated with an increased risk of either outcome. The committee agreed that evidence suggesting back pain and 'other' types of pain, were risk factors for problematic drug use, were not surprising, as according to their experience, non-specific causes of pain may increase the risk of problematic use. This was confirmed by evidence of a reduced risk in cases where there was specific cause of pain such as arthritis, reproductive pain or malignancy. A recommendation was made to take into account that someone with a lack of clear, defined diagnosis to support the prescription may have a higher risk of developing problems associated with dependence

**Benzodiazepines**

The committee noted that the majority of the evidence for benzodiazepines reported dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period from a starting point of <1 defined daily doses on average per day in the first 3 months). This was considered to be a measure indicating misuse or dependence by the study authors, however the committee had concerns over the extent to which the outcome can be interpreted to indicate misuse or dependence. This was taken into account in the quality assessment of the evidence which was downgraded for outcome indirectness. The committee agreed that inferences about factors predicting daily average intake of ≥ 1 defined daily dose as predicting misuse or dependence should be made with caution.

Evidence from 2 studies showed conflicting findings for age as factor for predicting benzodiazepine dependence. When compared to younger age (18-24 years), age 35-54 had a lower risk of benzodiazepine dependence, age 45-54 had a slightly lower risk compared to 18-24 whereas older age (65 and over) had an increased risk for the same outcome. Age 25-34 and 55-64 were not predictive of benzodiazepine dependence. Age as continuous outcomes was not associated with daily average intake of ≥ 1 defined daily dose. The committee noted that as well as results being conflicting, there was imprecision across the effect estimates showing an association and so conclusions could not be drawn from the current evidence base.

Evidence from 1 study suggested female gender decreases the risk of daily average intake of ≥ 1 defined daily dose. Similarly, evidence from another study suggested there was a greater likelihood for benzodiazepine dependence in males, although there was imprecision in the effect. The committee raised that due to social stereotypes, males may be less likely to accept social support and instead turn to medicines. They emphasised however, that the underlying mechanism for such a relationship is unclear and agreed this was insufficient evidence to inform a recommendation.

Evidence from 1 study suggested non-white family background (Black, Latino and Asian) was associated with a lower risk of benzodiazepine dependence, when compared to white family background. There was a strong relationship across groups with Black family background associated with the lowest risk. These findings were in line with those seen for non-white family bakground in the opioid drug class, and the committee agreed they may be due to challenges non-white ethnic groups may face in accessing healthcare and as a consequence medication in the US and were less related to family background as a risk factor per se.

Evidence from 1 study showed first benzodiazepine dispensation of oxazepam (versus diazepam) was associated with a slightly increased risk of daily average

intake of ≥ 1 defined daily dose. Evidence quality was low, and the committee noted the effect size was small and that other factors such as dose rather than dispensation are likely to be more important for problematic drug use.

High level of education predicted a lower risk of daily average intake of ≥ 1 defined daily dose compared to low level of education in 1 study. Similarly, average compared to low income was associated with a reduced risk for the same outcome, and risk decreased even further for a high income compared to a low income. The same relationship was observed for the type of work with people working in the private or the public sector having lower risk of daily average intake of ≥ 1 defined daily dose compared to those who had no registration on their type of work. The committee thought that low education and type of work may reflect social deprivation and a wider underlying social or personal distress and similarly to income level, as also evidenced in the opioid drug class, can increase the desire for medicines to cope with life adversity. It was raised that social deprivation can impact both one's clinical presentation in that their experience of pain may differ, as well as access to non-medical sources of support such as from the family, the community or to non-pharmacological approaches such as talking therapy.

Evidence from 1 study showed different types of previous medication were risk factors for predicting daily average intake of ≥ 1 defined daily dose. There was a greater risk with antidepressants and lithium, antipsychotics, opioids, anti-alcohol or smoking cessation drugs and drugs for COPD, with opioids, anti-alcohol or smoking cessation drugs being the strongest predictor. Drugs for rhematic diseases did not strongly predict a risk for daily average intake of ≥ 1 defined daily dose and there was imprecision in the effect estimate. Past use of these medications could indicate the presence of comorbidities such as depression. These comorbidities could have a profound effect on peoples' lives and enhance the desire for medicines. The committee raised that the evidence was in line with findings on opioids about history of substance misuse and past use of strong opioids for predicting problematic drug use or misuse. They therefore agreed that this strengthened their consensus view that this factor was relevant across drug classes.

Evidence from 1 study showed substance use diagnosis of alcohol, marijuana or pain medication were associated with a reduced risk of benzodiazepine dependence. The committee noted this was likely to be due to people deriving the benefit they would derive from medication from those substances with benzodiazepines becoming less desired. Use of cocaine did not strongly predict benzodiazepine dependence. Contrarily, substance use diagnosis of opioids, tobacco or having 2 or more substance use diagnoses were associated with a greater risk for the same outcome, although there was imprecision around the effect estimate for opioids. This was in line with evidence relevant to history of substance misuse in opioids, and the committee noted that people with past or current substance use may require higher drug doses to get the same effect and which can increase the likelihood of dependence. The committee thought the evidence suggesting substance use diagnosis to be a risk factor for benzodiazepine dependence added to similar evidence on substance use seen in opioids and increased their confidence that this is an important factor to be considered during prescribing.

Mental health diagnoses of depression and anxiety were associated with a greater risk of benzodiazepine dependence compared to no such diagnoses in 1 study. Bipolar and PTSD diagnoses did not predict benzodiazepine dependence, although there was imprecision around both the effect estimates. Sleep disturbance on the other hand was associated with a reduced risk of benzodiazepine dependence. The committee noted that evidence on depression and anxiety were in line with evidence on mental health disorders relevant to the opioid drug class and emphasised that the

profound impact that mental health diagnoses can have on people's lives may enhance their desire for medicines increasing the risk of dependence. They agreed this strengthened the rationale for including this in a recommendation for all of the relevant drug classes. However, the committee thought findings on sleep disturbance were counter-intuitive and agreed people with sleep disturbance could be taking a different drug to deal with their sleep problems and may be less likely to develop dependence on benzodiazepines.

#### 1.1.11.4. Cost effectiveness and resource use

There was no cost-effectiveness evidence for this question.

The clinical review found that a number of individual factors increase the risk of misuse, long-term dependency and shopping behaviour. It is likely that the recommendations will raise awareness on the individual risk factors potentially reducing the number of people having long-term dependence. This should, in turn, reduce the demand on services leading to savings for the NHS.

In addition, the clinical review found that a number of prescribing factors were associated with a lower risk of developing long-term dependency and misuse. The recommendation should help prescribers to adopt the most appropriate prescribing strategy to reduce problems associated with dependence and drug-related problematic behaviour, leading to NHS savings and improvement in people's quality of life.

#### 1.1.11.5. Other factors the committee took into account

The committee highlighted the importance of being cautious when making recommendations about risk factors associated with dependence and although they agreed the aforementioned factors were important to highlight, they stressed that the recommendations should not prevent access to medicines for people having one or more of the risk factors but for whom the medication is indicated.

The committee discussed that according to what they see in clinical practice, there is often great pressure on health-care professionals, exerted from patient distress and/or expectations of patients or other medical professionals, to prescribe medicines associated with dependence or withdrawal symptoms although, depending on individual circumstances including one's existing prescriptions, it may not always be the best decision for the patient, resulting in dependence, problematic drug use or side-effects which could be avoided. The committee agreed that it may be more appropriate to delay the decision to prescribe at the first consultation to allow time to consider all factors and enable consultation with a health care team and for patients to consider all treatment options through the provision of relevant information.

The committee raised that making prescribing decisions in consultation with other health care professionals, could provide a way to prevent prescribing that may not be the best option for an individual at a given time. The collaboration of different health care professionals could prevent professionals from prescribing medicines in patients already on other prescriptions and increase the likelihood that prescribing decisions that are in the best interest of the patient are made.

The committee noted that there are various factors that may influence dependence, that not all are captured by the evidence. They agreed that social distress and access to alternative sources of support may be risk factors for problems associated with dependence on prescribed medicines, but there was no evidence to reflect that. They agreed to make recommendations for further research in this area. It was also noted

that factors related to the healthcare system could also have an impact, but no evidence was identified on this aspect. Further research was therefore proposed in this area to identify whether system-level factors, such as the training received by prescribers, leads to an increased risk of dependence on prescribed medicines.

### 1.1.12. Recommendations supported by this evidence review

This evidence review supports recommendations 1.2.2, 1.2.3, 1.2.6, 1.3.5,1.3.6 and the research recommendation on individual circumstances and the risk of dependence; system-level factors and the risk of dependence. Other evidence supporting these recommendations can be found in the evidence reviews on B Prescribing Strategies.

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# Appendices

## Appendix A Review protocols

### A.1 Review protocol for Risk factors for dependence

| Field | Content |
|---|---|
| PROSPERO registration number | CRD42020188126 |
| Review title | Risk factors (both patient and prescribing factors) for dependence on prescribed opioids, benzodiazepines, gabapentinoids or Z-drugs, or withdrawal symptoms associated with antidepressants. |
| Review question | What are the risk factors (both patient and prescribing factors) for dependence on prescribed opioids, benzodiazepines, gabapentinoids or Z-drugs, or withdrawal symptoms associated with antidepressants? |
| Objective | Prognostic review: to identify key risk factors associated with dependence on prescribed opioids, benzodiazepines, gabapentinoids or Z-drugs or withdrawal symptoms associated with antidepressants. To include both factors relating to the individual and prescribing factors. |
| Searches | The following databases (from inception) will be searched:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR)<br>• Embase<br>• MEDLINE<br>• Epistemonikos<br>• Health and Evidence<br>• HTA<br>**Searches will be restricted by:**<br>• English language studies<br>• Human studies<br>• Letters and comments are excluded |

| Field | Content |
|---|---|
| | **Other searches:**<br>• Inclusion lists of relevant systematic reviews will be checked by the reviewer<br>The searches may be re-run 6 weeks before the final committee meeting, and further studies retrieved for inclusion if relevant.<br>For full search strategies see Appendix B |
| Condition or domain being studied | Dependence on prescribed opioids, benzodiazepines, gabapentinoids or Z-drugs and withdrawal symptoms associated with antidepressants |
| Population | Inclusion: adults (≥18 years) being prescribed medicines associated with dependence or withdrawal symptoms (opioids for chronic pain, benzodiazepines, gabapentinoids, Z-drugs or antidepressants). This should ideally be the point of initial prescription for that medicine (i.e., not taking that medicine prior to entry to the study).<br>NB. for this question, include prescription medicines which can also be bought over the counter (e.g., codeine, co-codamol).<br>**Stratification**<br>• Drug class<br>• Opioids<br>• Benzodiazepines,<br>• Gabapentinoids<br>• Z-drugs<br>• Antidepressants (further stratified by SSRIs, MAOIs, tricyclics, others).<br>Rationale: risk factors associated with dependence or for experiencing withdrawal symptoms are expected to differ between the different drug classes, and within class for antidepressants.<br>**Exclusions:**<br>Children and young people (<18 years)<br>People taking opioids prescribed for end-of-life care, acute pain, cancer pain<br>Use of gabapentinoids when prescribed for epilepsy<br>People taking any of the above drugs that have not been prescribed for their own use (with the exception of prescription medicines which can also be bought over the counter (these will be included in this question)). |

| Field | Content |
|---|---|
| | **Decision rules for inclusion of primary studies**<br>If the study includes people <18 years old, the study will only be included if at least 80% of people were ≥18 years old.<br>If the study includes a mix of the different drug classes (e.g., people being prescribed Z-drugs and people being prescribed benzodiazepines), the following hierarchy will be followed:<br>• The study will be included if results are reported separately, and it is possible to separate into the relevant drug class stratum.<br>• Only if there is no available evidence for a particular drug class in the review, will studies be included with mixed populations.<br>The population should not be taking the prescribed medicine prior to entry to the study, however we will accept studies where this is unclear, as this may not always be defined in the study. |
| Risk factors | The risk factors below are examples only and others identified will be included.<br>Include any definition in the studies considered relevant to the factor of interest<br>• System level factors:<br>- competency of prescriber,<br>- training or supervision of prescribers.<br>• Prescribing factors:<br>- duration of prescription,<br>- initial dose,<br>- use of different drugs within a class<br>- different formulation and/or route of medication: for example, immediate release, slow release (including slow-release routes such as transdermal patches),<br>- half-life comparisons (for benzodiazepines, long or short half-life)<br>• Socio-demographic factors of the patient<br>• Personal factors:<br>- history of substance misuse, |

| Field | Content |
|---|---|
| | - mental health diagnoses,<br>- co-prescription with other medications included in the review,<br>- pain intensity and level of distress at time of prescription.<br>• Others:<br>- Patient-prescriber interaction. |
| Confounding factors | All risk factors will be considered as potential confounding factors. |
| Types of study to be included | Observational prospective cohort studies<br>Observational retrospective cohort studies<br>*Only studies using multivariate analysis (adjusting for at least 3 confounders) will be included. Studies using univariate analysis or matched groups will be excluded (matching for confounders alone is not sufficient as there are multiple confounders).*<br>**Exclusions**<br>Case-control studies<br>Cross-sectional studies. |
| Other exclusion criteria | Studies assessing the risk factors for dependence on medicines that have not been prescribed/illicitly obtained.<br>Non-NHS prescribed medicines (for the full list of medicines to be included in the guideline see Appendix L)<br>Medicines prescribed for end-of-life care, cancer pain or acute pain.<br>Use of gabapentinoids when prescribed for epilepsy.<br>Antipsychotic and stimulant medicines.<br>Medicines to treat drug misuse disorders (e.g., methadone and buprenorphine when prescribed for withdrawal from illicit drugs).<br>Non-English language studies.<br>Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available. |
| Context | This will cover any setting in which one of the above-mentioned medicines are being prescribed. As this is an overarching guideline covering many different conditions, it needs to cover all settings. |
| Primary outcomes (critical outcomes) | Dependence on the prescribed medicine (dichotomous outcome, accept any definition as defined by the study (may also include measures suggesting dependence or addiction, examples to include early refill requests, loss of prescriptions, drug shopping behaviour, prescription misuse)). Withdrawal symptoms including rebound symptoms (dichotomous outcome, as defined by the study) |

| Field | Content |
|---|---|
| Secondary outcomes (important outcomes) | Not applicable |
| Data extraction (selection and coding) | EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.<br>A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). |
| Risk of bias (quality) assessment | Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.<br>For risk factor studies, risk of bias assessment of individual studies will be undertaken according to the Quality in Prognosis Studies (QUIPS) checklist.<br>10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:<br>• papers were included/excluded appropriately<br>• a sample of the data extractions<br>• correct methods are used to synthesise data<br>• a sample of the risk of bias assessments<br>Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. |
| Strategy for data synthesis | Drugs will be pooled within classes stated in the population and antidepressants pooled by sub-class of type of antidepressant.<br>ORs, RRs, or HRs, with their 95% CIs, for the effect of the risk factors will be extracted from the studies. Studies sufficiently similar in terms of population, risk factor, outcome and effect measure (OR, RR, HR) will be pooled for analysis (i.e., for age as a risk factor, if the studies use the same age categories and referent group, and define/measure dependence in the same way). Studies will only be pooled if they also take into account similar confounding factors in the multivariate analysis. If studies do not report very similar populations, risk factors and outcome, they will not be pooled or meta-analysed and results presented separately in tables. |

| Field | Content | |
|---|---|---|
| | Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5).<br><br>Where pooled, heterogeneity between the studies in effect measures will be assessed using the $I^2$ statistic and visually inspected. An $I^2$ value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random effects.<br><br>Imprecision will be assessed according to the position of the 95% CIs in relation to the null line. If the 95% CI do not cross the null line, then no serious imprecision will be recorded. If the 95% CI cross the null line, then serious imprecision will be recorded.<br><br>The quality of the evidence will be assessed using a modified GRADE approach. Quality rating will start at High for prospective studies, and each major limitation will bring the rating down by 1 increment to a minimum grade of Very Low. | |
| Analysis of sub-groups | **Subgroups that will be investigated if heterogeneity is present:**<br><br>• Gabapentin and pregabalin will be pooled in the analysis as 'gabapentinoids' unless heterogeneity is observed. | |
| Type and method of review | ☐ | Intervention |
| | ☐ | Diagnostic |
| | ☒ | Prognostic |
| | ☐ | Qualitative |
| | ☐ | Epidemiologic |
| | ☐ | Service Delivery |
| | ☐ | Other (please specify) |

| Field | Content |
|---|---|
| Language | English |
| Country | England |
| Review team members | From the National Guideline Centre:<br>Serena Carville, Guideline lead<br>Emily Terrazas-Cruz, Senior systematic reviewer<br>Melina Vasileiou, Senior systematic reviewer<br>Alfredo Mariani, Health economist<br>Elizabeth Pearton, Information specialist<br>Tamara Diaz, Project Manager |
| Funding sources/sponsor | This systematic review is being completed by the National Guideline Centre which receives funding from NICE. |
| Conflicts of interest | All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. |
| Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10141 |
| Other registration details | n/a |
| Reference/URL for published protocol | https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020188126 |

| Field | Content |
|---|---|
| Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>• notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. |
| Details of existing review of same topic by same authors | None |
| Additional information | None |
| Details of final publication | www.nice.org.uk |

1

# Appendix B Literature search strategies

This literature search strategy was used for the following review:

- Risk factors (both patient and prescribing factors) for dependence on prescribed opioids, benzodiazepines, gabapentinoids or Z-drugs, or withdrawal symptoms associated with antidepressants.

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[143] For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

## B.1 Clinical search literature search strategy

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

**Table 38: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline (OVID) | 1946 - 15 June 2021 | Randomised controlled trials<br>Systematic review studies<br>Observational studies<br>Qualitative studies<br><br>Exclusions (animal studies, letters, comments) |
| Embase (OVID) | 1974 - 15 June 2021 | Randomised controlled trials<br>Systematic review studies<br>Observational studies<br>Qualitative studies<br><br>Exclusions (animal studies, letters, comments) |
| The Cochrane Library (Wiley) | Cochrane Reviews to 2021 Issue 6 of 12<br>CENTRAL to 2021 Issue 6 of 12 | None |
| Epistemonikos (The Epistemonikos Foundation) | Inception - 15 June 2021 | English |
| Health and Evidence | Inception - 15 June 2021 | None |
| CINAHL, Current Nursing and Allied Health Literature (EBSCO) | Inception - 15 June 2021 | Qualitative studies |
| PsycINFO (ProQuest) | Inception - 15 June 2021 | Qualitative studies |
| ASSIA, Applied Social Sciences Index and Abstracts (ProQuest) | Inception - 15 June 2021 | Qualitative studies |

**Medline (Ovid) search terms**

| | |
|---|---|
| 1. | *substance-related disorders/ or *narcotic-related disorders/ |
| 2. | *Substance Withdrawal Syndrome/ |
| 3. | exp Inappropriate Prescribing/ |
| 4. | *Medical Overuse/ |
| 5. | exp Prescription Drug Misuse/ |
| 6. | exp Deprescriptions/ |
| 7. | Medication Therapy Management/ |
| 8. | ((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) adj2 (drug* or medicine* or medicat* or medical* or pharm*)).ti,ab. |
| 9. | ((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw*) adj3 (prescription* or prescrib*)).ti,ab. |
| 10. | (addict* adj3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)).ti,ab. |
| 11. | (deprescription* or de-prescription* or deprescrib* or de-prescrib*).ti,ab. |
| 12. | ((therap* or treat*) adj2 (manag* or substit*)).ti,ab. |
| 13. | ((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) adj2 symptom*).ti,ab. |
| 14. | ((drug* or medic*) adj2 (prescription* or prescrib*)).ti,ab. |
| 15. | or/1-14 |
| 16. | ((withdraw* or prescription* or prescrib*) adj2 opi*).ti,ab. |
| 17. | Opiate Substitution Treatment/ or *Opioid-related disorders/ |
| 18. | or/16-17 |
| 19. | letter/ |
| 20. | editorial/ |
| 21. | news/ |
| 22. | exp historical article/ |
| 23. | Anecdotes as Topic/ |
| 24. | comment/ |
| 25. | case report/ |
| 26. | (letter or comment*).ti. |
| 27. | or/19-26 |
| 28. | randomized controlled trial/ or random*.ti,ab. |
| 29. | 27 not 28 |
| 30. | animals/ not humans/ |
| 31. | exp Animals, Laboratory/ |
| 32. | exp Animal Experimentation/ |
| 33. | exp Models, Animal/ |
| 34. | exp Rodentia/ |
| 35. | (rat or rats or mouse or mice or rodent*).ti. |
| 36. | or/29-35 |
| 37. | (exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/) |

| | |
|---|---|
| 38. | 15 not (36 or 37) |
| 39. | limit 38 to English language |
| 40. | 18 not (36 or 37) |
| 41. | limit 40 to English language |
| 42. | exp Narcotics/ |
| 43. | ((analgesic* adj3 narcotic) or (opioid* or opiate*)).ti,ab. |
| 44. | (alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*).ti,ab. |
| 45. | (z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon).ti,ab. |
| 46. | Zolpidem/ or Eszopiclone/ |
| 47. | (generation adj3 hypnotic*).ti,ab. |
| 48. | exp Benzodiazepines/ |
| 49. | (benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam).ti,ab. |
| 50. | exp Antidepressive Agents/ |
| 51. | (antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*).ti,ab. |
| 52. | exp Flupenthixol/ |
| 53. | (Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine).ti,ab. |
| 54. | (5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine).ti,ab. |
| 55. | (Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine).ti,ab. |
| 56. | gabapentin/ or pregabalin/ |
| 57. | (gabapentin* or pregabalin*).ti,ab. |
| 58. | or/42-57 |
| 59. | 39 and 58 |
| 60. | 41 or 59 |
| 61. | randomized controlled trial.pt. |
| 62. | controlled clinical trial.pt. |
| 63. | randomi#ed.ab. |
| 64. | placebo.ab. |

| | |
|---|---|
| 65. | randomly.ab. |
| 66. | clinical trials as topic.sh. |
| 67. | trial.ti. |
| 68. | or/61-67 |
| 69. | Meta-Analysis/ |
| 70. | Meta-Analysis as Topic/ |
| 71. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 72. | ((systematic* or evidence*) adj2 (review* or overview*)).ti,ab. |
| 73. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 74. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 75. | (search* adj4 literature).ab. |
| 76. | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 77. | cochrane.jw. |
| 78. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |
| 79. | or/69-78 |
| 80. | Epidemiologic studies/ |
| 81. | Observational study/ |
| 82. | exp Cohort studies/ |
| 83. | (cohort adj (study or studies or analys* or data)).ti,ab. |
| 84. | ((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab. |
| 85. | ((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 86. | Controlled Before-After Studies/ |
| 87. | Historically Controlled Study/ |
| 88. | Interrupted Time Series Analysis/ |
| 89. | (before adj2 after adj2 (study or studies or data)).ti,ab. |
| 90. | exp case control study/ |
| 91. | case control*.ti,ab. |
| 92. | Cross-sectional studies/ |
| 93. | (cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 94. | or/80-93 |
| 95. | Qualitative research/ or Narration/ or exp Interviews as Topic/ or exp Questionnaires/ or Health care surveys/ |
| 96. | (qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab. |
| 97. | (metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab. |
| 98. | or/95-97 |
| 99. | 60 and (68 or 79 or 94 or 98) |

**Embase (Ovid) search terms**

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

| | |
|---|---|
| 39. | limit 38 to English language |
| 40. | *narcotic agent/ |
| 41. | *alphaprodine/ or *buprenorphine/ or *codeine/ or *dextromoramide/ or *dextropropoxyphene/ or *diamorphine/ or *dihydrocodeine/ or *dihydromorphine/ or *dipipanone/ or *ethylmorphine/ or *hydrocodone/ or *hydromorphone/ or *levorphanol/ or *methadone/ or *morphine/ or *oxycodone/ or *pethidine/ or *tapentadol/ or *tilidine/ |
| 42. | *alfentanil/ or *butorphanol/ or *cocodamol/ or *fentanyl/ or *meptazinol/ or *oxymorphone/ or *opiate/ or *pentazocine/ or *phenazocine/ or *remifentanil/ or *sufentanil/ or *tramadol/ or *trimeperidine/ |
| 43. | ((analgesic* adj3 narcotic) or (opioid* or opiate*)).ti,ab. |
| 44. | (alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*).ti,ab. |
| 45. | (z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon).ti,ab. |
| 46. | *zolpidem/ or *zopiclone/ or *eszopiclone/ or *zaleplon/ |
| 47. | (generation adj3 hypnotic*).ti,ab. |
| 48. | *benzodiazepine derivative/ or *alprazolam/ or *benzodiazepine/ or *chlordiazepoxide/ or *clobazam/ or *clonazepam/ or *diazepam/ or *flurazepam/ or *loprazolam/ or *lorazepam/ or *lormetazepam/ or *midazolam/ or *nitrazepam/ or *olanzapine/ or *oxazepam/ or *temazepam/ |
| 49. | (benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam).ti,ab. |
| 50. | exp *antidepressant agent/ |
| 51. | (antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*).ti,ab. |
| 52. | *flupentixol/ |
| 53. | (Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine).ti,ab. |
| 54. | (5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine).ti,ab. |
| 55. | (Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine).ti,ab. |
| 56. | *pregabalin/ or *gabapentin/ |
| 57. | (gabapentin* or pregabalin*).ti,ab. |
| 58. | or/40-57 |
| 59. | 37 and 58 |

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|---|---|
| 60. | 39 or 59 |
| 61. | random*.ti,ab. |
| 62. | factorial*.ti,ab. |
| 63. | (crossover* or cross over*).ti,ab. |
| 64. | ((doubl* or singl*) adj blind*).ti,ab. |
| 65. | (assign* or allocat* or volunteer* or placebo*).ti,ab. |
| 66. | crossover procedure/ |
| 67. | single blind procedure/ |
| 68. | randomized controlled trial/ |
| 69. | double blind procedure/ |
| 70. | or/61-69 |
| 71. | systematic review/ |
| 72. | Meta-Analysis/ |
| 73. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 74. | ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. |
| 75. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 76. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 77. | (search* adj4 literature).ab. |
| 78. | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 79. | cochrane.jw. |
| 80. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |
| 81. | or/71-80 |
| 82. | Clinical study/ |
| 83. | Observational study/ |
| 84. | family study/ |
| 85. | longitudinal study/ |
| 86. | retrospective study/ |
| 87. | prospective study/ |
| 88. | cohort analysis/ |
| 89. | follow-up/ |
| 90. | cohort*.ti,ab. |
| 91. | 89 and 90 |
| 92. | (cohort adj (study or studies or analys* or data)).ti,ab. |
| 93. | ((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab. |
| 94. | ((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 95. | (before adj2 after adj2 (study or studies or data)).ti,ab. |
| 96. | exp case control study/ |
| 97. | case control*.ti,ab. |
| 98. | cross-sectional study/ |
| 99. | (cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab. |

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|---|---|
| 100. | or/82-88,91-99 |
| 101. | health survey/ or exp questionnaire/ or exp interview/ or qualitative research/ or narrative/ |
| 102. | (qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab. |
| 103. | (metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab. |
| 104. | or/101-103 |
| 105. | 60 and (70 or 81 or 100 or 104) |

1 **Cochrane Library (Wiley) search terms**

| | |
|---|---|
| #1. | MeSH descriptor: [Substance-Related Disorders] this term only |
| #2. | MeSH descriptor: [Narcotic-Related Disorders] this term only |
| #3. | MeSH descriptor: [Substance Withdrawal Syndrome] this term only |
| #4. | MeSH descriptor: [Inappropriate Prescribing] explode all trees |
| #5. | MeSH descriptor: [Medical Overuse] this term only |
| #6. | MeSH descriptor: [Deprescriptions] 1 tree(s) exploded |
| #7. | MeSH descriptor: [Prescription Drug Misuse] explode all trees |
| #8. | MeSH descriptor: [Medication Therapy Management] this term only |
| #9. | ((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) NEAR/2 (drug* or medicine* or medicat* or medical* or pharm*)):ti,ab |
| #10. | ((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw*) NEAR/3 (prescription* or prescrib*)):ti,ab |
| #11. | (addict* NEAR/3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)):ti,ab |
| #12. | (deprescription* or de-prescription* or deprescrib* or de-prescrib*):ti,ab |
| #13. | ((therap* or treat*) NEAR/2 (manag* or substit*)):ti,ab |
| #14. | ((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) NEAR/2 symptom*):ti,ab |
| #15. | ((drug* or medic*) NEAR/2 (prescription* or prescrib*)):ti,ab |
| #16. | (OR #1-#15) |
| #17. | ((withdraw* or prescription* or prescrib*) near/2 (opioid* or opiate*)):ti,ab |
| #18. | MeSH descriptor: [Opiate Substitution Treatment] this term only |
| #19. | MeSH descriptor: [Opioid-Related Disorders] this term only |
| #20. | MeSH descriptor: [Narcotics] explode all trees |
| #21. | (OR #17-#20) |
| #22. | ((analgesic* NEAR/3 narcotic NEAR/3 agent*) or (opioid* or opiate*)):ti,ab |
| #23. | (alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*):ti,ab |

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|---|---|
| #24. | (z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon):ti,ab |
| #25. | MeSH descriptor: [Zolpidem] this term only |
| #26. | MeSH descriptor: [Eszopiclone] this term only |
| #27. | (generation NEAR/3 hypnotic*):ti,ab |
| #28. | MeSH descriptor: [Benzodiazepines] explode all trees |
| #29. | (benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam):ti,ab |
| #30. | MeSH descriptor: [Antidepressive Agents] explode all trees |
| #31. | (antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*):ti,ab |
| #32. | MeSH descriptor: [Flupenthixol] explode all trees |
| #33. | (Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine):ti,ab |
| #34. | (5 Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine):ti,ab |
| #35. | (Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine):ti,ab |
| #36. | MeSH descriptor: [Gabapentin] this term only |
| #37. | MeSH descriptor: [Pregabalin] this term only |
| #38. | (gabapentin* or pregabalin*):ti,ab |
| #39. | (OR #22-#38) |
| #40. | #16 AND #39 |
| #41. | #21 or #40 |

1 **Epistemonikos search terms**

| | |
|---|---|
| 1. | (advanced_title_en:((advanced_title_en:(("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses)) OR advanced_abstract_en:(("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses)))) OR advanced_abstract_en:((advanced_title_en:(("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses)) OR advanced_abstract_en:(("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses))))) AND (advanced_title_en:((opioid* OR opiate* OR narcotic* OR alfentanil* OR alphaprodine* OR buprenorphine* OR butorphanol* OR codeine* OR co-codamol* OR dextromoramide* OR dextropropoxyphene* OR diamorphine* OR dihydrocodeine* OR |

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

1 **Health and evidence**

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| 1. | [(("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses) OR abstract:("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR |

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

1 **CINAHL (EBSCO) search terms**

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| S1. | (MH "Substance Use Disorders") OR (MH "Substance Withdrawal Syndrome") OR (MH "Inappropriate Prescribing") OR (MH "Drugs, Prescription") |
| S2. | TI ((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) n2 (drug* or medicine* or medicat* or medical* or pharm*)) |
| S3. | AB ((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) n2 (drug* or medicine* or medicat* or medical* or pharm*)) |
| S4. | TI ((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or innapropriate) n3 (prescription* or prescrib*)) |
| S5. | AB ((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or innapropriate) n3 (prescription* or prescrib*)) |
| S6. | TI (addict* n3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)) |
| S7. | AB (addict* n3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)) |
| S8. | TI (deprescription* or de-prescription* or deprescrib* or de-prescrib*) |
| S9. | AB (deprescription* or de-prescription* or deprescrib* or de-prescrib*) |
| S10. | TI ((therap* or treat*) n2 (manag* or substit*)) |
| S11. | AB ((therap* or treat*) n2 (manag* or substit*)) |

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| S12. | TI ((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) n2 symptom*) |
| S13. | AB ((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) n2 symptom*) |
| S14. | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 |
| S15. | PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website |
| S16. | S14 NOT S15 |
| S17. | (MH "Narcotics+") OR (MH "Antianxiety Agents, Benzodiazepine+") OR (MH "Antidepressive Agents+") OR (MH "Antidepressive Agents, Second Generation+") OR (MH "Antidepressive Agents, Tricyclic+") OR (MH "Zolpidem") OR (MH "Eszopiclone") OR (MH "Analgesics, Opioid+") |
| S18. | TI ((analgesic* n3 narcotic n3 agent*) or (opioid* or opiate*)) |
| S19. | AB ((analgesic* n3 narcotic n3 agent*) or (opioid* or opiate*)) |
| S20. | TI (alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*) |
| S21. | AB (alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*) |
| S22. | TI (z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon) |
| S23. | AB (z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon) |
| S24. | TI (generation n3 hypnotic*) |
| S25. | AB (generation n3 hypnotic*) |
| S26. | TI (benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam) |
| S27. | AB (benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam) |
| S28. | TI (antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*) |

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| S29. | AB (antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*) |
| S30. | TI (Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine) |
| S31. | AB (Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine) |
| S32. | TI (5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine) |
| S33. | AB (5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine) |
| S34. | TI (Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine) |
| S35. | AB (Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine) |
| S36. | (MH "Gabapentin") OR (MH "Pregabalin") |
| S37. | TI (gabapentin* or pregabalin*) |
| S38. | AB (gabapentin* or pregabalin*) |
| S39. | S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 |
| S40. | S16 AND S39 |
| S41. | TI ((withdraw* or prescription* or prescrib*) n2 opi*) OR AB ((withdraw* or prescription* or prescrib*) n2 opi*) |
| S42. | S40 OR S41 |
| S43. | (MH "Qualitative Studies+") |
| S44. | (MH "Qualitative Validity+") |
| S45. | (MH "Interviews+") OR (MH "Focus Groups") OR (MH "Surveys") OR (MH "Questionnaires+") |
| S46. | (qualitative or interview* or focus group* or theme* or questionnaire* or survey*) |
| S47. | (metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*) |
| S48. | S42 OR S43 OR S44 OR S45 OR S46 |
| S49. | S42 and S48 |

**PsycINFO (ProQuest) search terms**

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| 1. | "Substance Use Disorder"/ or "Substance Related and Addictive Disorders"/ or Prescription Drug Misuse/ or Drug Withdrawal/ |
| 2. | ((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) adj2 (drug* or medicine* or medicat* or medical* or pharm*)).ti,ab. |
| 3. | ((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or innapropriate) adj3 (prescription* or prescrib*)).ti,ab. |
| 4. | (addict* adj3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)).ti,ab. |
| 5. | (deprescription* or de-prescription* or deprescrib* or de-prescrib*).ti,ab. |
| 6. | ((therap* or treat*) adj2 (manag* or substit*)).ti,ab. |
| 7. | ((drug* or medic*) adj2 (prescription* or prescrib*)).ti,ab. |
| 8. | ((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) adj2 symptom*).ti,ab. |
| 9. | or/1-8 |
| 10. | ((withdraw* or prescription* or prescrib*) adj2 opi*).ti,ab. |
| 11. | "opioid use disorder"/ |
| 12. | 10 or 11 |
| 13. | exp narcotic drugs/ |
| 14. | ((analgesic* adj3 narcotic) or (opioid* or opiate*)).ti,ab. |
| 15. | (alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*).ti,ab. |
| 16. | (z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon).ti,ab. |
| 17. | (generation adj3 hypnotic*).ti,ab. |
| 18. | exp Benzodiazepines/ |
| 19. | (benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam).ti,ab. |
| 20. | exp antidepressant drugs/ |
| 21. | (antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit* or SNRI*" or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*).ti,ab. |
| 22. | (Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine).ti,ab. |

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| 23. | (5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine).ti,ab. |
| 24. | (Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine).ti,ab. |
| 25. | Gabapentin/ or pregabalin/ |
| 26. | (gabapentin* or pregabalin*).ti,ab. |
| 27. | or/13-26 |
| 28. | 9 and 27 |
| 29. | 12 or 28 |
| 30. | exp Qualitative Methods/ or Narratives/ or exp Questionnaires/ or exp Interviews/ or exp Health Care Services/ |
| 31. | (qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab. |
| 32. | (metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical-sampl* or purposive-sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab. |
| 33. | or/30-32 |
| 34. | 29 and 33 |
| 35. | limit 34 to English language |

1 **ASSIA (ProQuest) search terms**

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| 1. | ((TI,AB:withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* N/2 symptom*) AND (MAINSUBJECT.EXACT("Gabapentin") OR MAINSUBJECT.EXACT.EXPLODE("Narcotics") OR MAINSUBJECT.EXACT.EXPLODE("Benzodiazepines") OR MAINSUBJECT.EXACT.EXPLODE("Antidepressant drugs") OR MAINSUBJECT.EXACT("Zolpidem") OR ti,ab(opioid* OR opiate*) OR ti,ab(alfentanil* OR alphaprodine* OR buprenorphine* OR butorphanol* OR codeine* OR co-codamol* OR dextromoramide* OR dextropropoxyphene* OR diamorphine* OR dihydrocodeine* OR dihydromorphine* OR dipipanone* OR ethylmorphine* OR fentanyl* OR heroin* OR hydrocodone* OR hydromorphone* OR levorphanol* OR meperidine* OR meptazinol* OR methadone* OR morphine* OR oxycodone* OR oxymorphone* OR papaveretum* OR pentazocine* OR pethidine* OR phenazocine* OR promedol* OR remifentanil* OR sufentanil* OR tapentadol* OR tilidine* OR tramadol*) OR ti,ab(z drug* OR z hypnotic* OR non-benzodiazepin* OR nonbenzodiazepin* OR imidazopyridines OR cyclopyrrolones OR pyrazolopyrimidines OR zolpidem OR zopiclone OR eszopiclone OR zaleplon) OR ti,ab(generation NEAR/3 hypnotic*) OR ti,ab(benzodiazepin* OR bzd OR Alprazolam OR Chlordiazepoxide OR Clobazam OR Clonazepam OR Diazepam OR Flurazepam OR Loprazolam OR Lorazepam OR Lormetazepam OR Midazolam OR Nitrazepam OR Olanzapine OR Oxazepam OR Temazepam)) AND (MAINSUBJECT.EXACT.EXPLODE("Interviews") OR MAINSUBJECT.EXACT.EXPLODE("Qualitative research") OR MAINSUBJECT.EXACT.EXPLODE("Questionnaires") OR MAINSUBJECT.EXACT.EXPLODE("Narratives") OR ti,ab(qualitative or interview* or focus group* or theme* or questionnaire* or survey*) or ti,ab(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* near/3 analys*) or theoretical-sampl* or purposive-sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*))) NOT ((((MAINSUBJECT.EXACT("Substance dependency") OR MAINSUBJECT.EXACT("Substance abuse disorders") OR |

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| | MAINSUBJECT.EXACT("Overprescribing") OR MAINSUBJECT.EXACT("Withdrawal symptoms") OR MAINSUBJECT.EXACT("Withdrawal")) OR ti,ab(over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or addict* or depend*) OR ti,ab(prescription* OR prescrib*) OR ti,ab(deprescription* OR de-prescription* OR deprescrib* OR de-prescrib*)) AND (MAINSUBJECT.EXACT("Gabapentin") OR MAINSUBJECT.EXACT.EXPLODE("Narcotics") OR MAINSUBJECT.EXACT.EXPLODE("Benzodiazepines") OR MAINSUBJECT.EXACT.EXPLODE("Antidepressant drugs") OR MAINSUBJECT.EXACT("Zolpidem") OR ti,ab(opioid* OR opiate*) OR ti,ab(alfentanil* OR alphaprodine* OR buprenorphine* OR butorphanol* OR codeine* OR co-codamol* OR dextromoramide* OR dextropropoxyphene* OR diamorphine* OR dihydrocodeine* OR dihydromorphine* OR dipipanone* OR ethylmorphine* OR fentanyl* OR heroin* OR hydrocodone* OR hydromorphone* OR levorphanol* OR meperidine* OR meptazinol* OR methadone* OR morphine* OR oxycodone* OR oxymorphone* OR papaveretum* OR pentazocine* OR pethidine* OR phenazocine* OR promedol* OR remifentanil* OR sufentanil* OR tapentadol* OR tilidine* OR tramadol*) OR ti,ab(z drug* OR z hypnotic* OR non-benzodiazepin* OR nonbenzodiazepin* OR imidazopyridines OR cyclopyrrolones OR pyrazolopyrimidines OR zolpidem OR zopiclone OR eszopiclone OR zaleplon) OR ti,ab(generation NEAR/3 hypnotic*) OR ti,ab(benzodiazepin* OR bzd OR Alprazolam OR Chlordiazepoxide OR Clobazam OR Clonazepam OR Diazepam OR Flurazepam OR Loprazolam OR Lorazepam OR Lormetazepam OR Midazolam OR Nitrazepam OR Olanzapine OR Oxazepam OR Temazepam))) AND (MAINSUBJECT.EXACT.EXPLODE("Interviews") OR MAINSUBJECT.EXACT.EXPLODE("Qualitative research") OR MAINSUBJECT.EXACT.EXPLODE("Questionnaires") OR MAINSUBJECT.EXACT.EXPLODE("Narratives") OR ti,ab(qualitative or interview* or focus group* or theme* or questionnaire* or survey*) or ti,ab(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* near/3 analys*) or theoretical-sampl* or purposive-sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*))) |

## B.2 Health Economics literature search strategy

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

**Table 39: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline | Health Economics<br>1 January 2014 – 17 June 2021 | Health economics studies<br>Quality of life studies<br>Modelling studies<br><br>Exclusions (animal studies, letters, comments) |
| | Quality of Life<br>1946 – 17 June 2021 | |
| | Modelling<br>1946 – 17 June 2021 | |

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

1 **Medline (Ovid) search terms**

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

| | |
|---|---|
| 24. | comment/ |
| 25. | case report/ |
| 26. | (letter or comment*).ti. |
| 27. | or/19-26 |
| 28. | randomized controlled trial/ or random*.ti,ab. |
| 29. | 27 not 28 |
| 30. | animals/ not humans/ |
| 31. | exp Animals, Laboratory/ |
| 32. | exp Animal Experimentation/ |
| 33. | exp Models, Animal/ |
| 34. | exp Rodentia/ |
| 35. | (rat or rats or mouse or mice or rodent*).ti. |
| 36. | or/29-35 |
| 37. | (exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/) |
| 38. | 15 not (36 or 37) |
| 39. | limit 38 to English language |
| 40. | 18 not (36 or 37) |
| 41. | limit 40 to English language |
| 42. | exp Narcotics/ |
| 43. | ((analgesic* adj3 narcotic) or (opioid* or opiate*)).ti,ab. |
| 44. | (alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*).ti,ab. |
| 45. | (z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon).ti,ab. |
| 46. | Zolpidem/ or Eszopiclone/ |
| 47. | (generation adj3 hypnotic*).ti,ab. |
| 48. | exp Benzodiazepines/ |
| 49. | (benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam).ti,ab. |
| 50. | exp Antidepressive Agents/ |
| 51. | (antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*).ti,ab. |
| 52. | exp Flupenthixol/ |
| 53. | (Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or |

| | |
|---|---|
| | Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine).ti,ab. |
| 54. | (5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine).ti,ab. |
| 55. | (Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine).ti,ab. |
| 56. | gabapentin/ or pregabalin/ |
| 57. | (gabapentin* or pregabalin*).ti,ab. |
| 58. | or/42-57 |
| 59. | 39 and 58 |
| 60. | 41 or 59 |
| 61. | quality-adjusted life years/ |
| 62. | sickness impact profile/ |
| 63. | (quality adj2 (wellbeing or well being)).ti,ab. |
| 64. | sickness impact profile.ti,ab. |
| 65. | disability adjusted life.ti,ab. |
| 66. | (qal* or qtime* or qwb* or daly*).ti,ab. |
| 67. | (euroqol* or eq5d* or eq 5*).ti,ab. |
| 68. | (qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab. |
| 69. | (health utility* or utility score* or disutilit* or utility value*).ti,ab. |
| 70. | (hui or hui1 or hui2 or hui3).ti,ab. |
| 71. | (health* year* equivalent* or hye or hyes).ti,ab. |
| 72. | discrete choice*.ti,ab. |
| 73. | rosser.ti,ab. |
| 74. | (willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab. |
| 75. | (sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab. |
| 76. | (sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab. |
| 77. | (sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab. |
| 78. | (sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab. |
| 79. | (sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab. |
| 80. | or/61-79 |
| 81. | exp models, economic/ |
| 82. | *Models, Theoretical/ |
| 83. | *Models, Organizational/ |
| 84. | markov chains/ |
| 85. | monte carlo method/ |
| 86. | exp Decision Theory/ |
| 87. | (markov* or monte carlo).ti,ab. |
| 88. | econom* model*.ti,ab. |
| 89. | (decision* adj2 (tree* or analy* or model*)).ti,ab. |
| 90. | or/81-89 |
| 91. | economics/ |
| 92. | value of life/ |

| | |
|---|---|
| 93. | exp "costs and cost analysis"/ |
| 94. | exp Economics, Hospital/ |
| 95. | exp Economics, medical/ |
| 96. | Economics, nursing/ |
| 97. | economics, pharmaceutical/ |
| 98. | exp "Fees and Charges"/ |
| 99. | exp budgets/ |
| 100. | budget*.ti,ab. |
| 101. | cost*.ti. |
| 102. | (economic* or pharmaco?economic*).ti. |
| 103. | (price* or pricing*).ti,ab. |
| 104. | (cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. |
| 105. | (financ* or fee or fees).ti,ab. |
| 106. | (value adj2 (money or monetary)).ti,ab. |
| 107. | or/91-106 |
| 108. | 60 and (80 or 90 or 107) |

1 **Embase (Ovid) search terms**

| | |
|---|---|
| 1. | *drug dependence/ |
| 2. | *withdrawal syndrome/ |
| 3. | exp inappropriate prescribing/ |
| 4. | deprescription/ |
| 5. | exp prescription drug misuse/ |
| 6. | medication therapy management/ |
| 7. | ((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) adj2 (drug* or medicine* or medicat* or medical* or pharm*)).ti,ab. |
| 8. | ((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw*) adj3 (prescription* or prescrib*)).ti,ab. |
| 9. | (addict* adj3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)).ti,ab. |
| 10. | (deprescription* or de-prescription* or deprescrib* or de-prescrib*).ti,ab. |
| 11. | ((therap* or treat*) adj2 (manag* or substit*)).ti,ab. |
| 12. | ((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) adj2 symptom*).ti,ab. |
| 13. | ((drug* or medic*) adj2 (prescription* or prescrib*)).ti,ab. |
| 14. | or/1-13 |
| 15. | ((withdraw* or prescription* or prescrib*) adj2 (opioid* or opiate*)).ti,ab. |
| 16. | *benzodiazepine dependence/ |
| 17. | Opiate Substitution Treatment/ |
| 18. | or/15-17 |
| 19. | letter.pt. or letter/ |
| 20. | note.pt. |
| 21. | editorial.pt. |

| | |
|---|---|
| 22. | case report/ or case study/ |
| 23. | (letter or comment*).ti. |
| 24. | or/19-23 |
| 25. | randomized controlled trial/ or random*.ti,ab. |
| 26. | 24 not 25 |
| 27. | animal/ not human/ |
| 28. | nonhuman/ |
| 29. | exp Animal Experiment/ |
| 30. | exp Experimental Animal/ |
| 31. | animal model/ |
| 32. | exp Rodent/ |
| 33. | (rat or rats or mouse or mice or rodent*).ti. |
| 34. | or/26-33 |
| 35. | (exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/) |
| 36. | 14 not (34 or 35) |
| 37. | limit 36 to English language |
| 38. | 18 not (34 or 35) |
| 39. | limit 38 to English language |
| 40. | *narcotic agent/ |
| 41. | *alphaprodine/ or *buprenorphine/ or *codeine/ or *dextromoramide/ or *dextropropoxyphene/ or *diamorphine/ or *dihydrocodeine/ or *dihydromorphine/ or *dipipanone/ or *ethylmorphine/ or *hydrocodone/ or *hydromorphone/ or *levorphanol/ or *methadone/ or *morphine/ or *oxycodone/ or *pethidine/ or *tapentadol/ or *tilidine/ |
| 42. | *alfentanil/ or *butorphanol/ or *cocodamol/ or *fentanyl/ or *meptazinol/ or *oxymorphone/ or *opiate/ or *pentazocine/ or *phenazocine/ or *remifentanil/ or *sufentanil/ or *tramadol/ or *trimeperidine/ |
| 43. | ((analgesic* adj3 narcotic) or (opioid* or opiate*)).ti,ab. |
| 44. | (alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*).ti,ab. |
| 45. | (z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon).ti,ab. |
| 46. | *zolpidem/ or *zopiclone/ or *eszopiclone/ or *zaleplon/ |
| 47. | (generation adj3 hypnotic*).ti,ab. |
| 48. | *benzodiazepine derivative/ or *alprazolam/ or *benzodiazepine/ or *chlordiazepoxide/ or *clobazam/ or *clonazepam/ or *diazepam/ or *flurazepam/ or *loprazolam/ or *lorazepam/ or *lormetazepam/ or *midazolam/ or *nitrazepam/ or *olanzapine/ or *oxazepam/ or *temazepam/ |
| 49. | (benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam).ti,ab. |
| 50. | exp *antidepressant agent/ |
| 51. | (antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or |

| | |
|---|---|
| | NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*).ti,ab. |
| 52. | *flupentixol/ |
| 53. | (Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine).ti,ab. |
| 54. | (5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine).ti,ab. |
| 55. | (Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine).ti,ab. |
| 56. | *pregabalin/ or *gabapentin/ |
| 57. | (gabapentin* or pregabalin*).ti,ab. |
| 58. | or/40-57 |
| 59. | 37 and 58 |
| 60. | 39 or 59 |
| 61. | quality-adjusted life years/ |
| 62. | "quality of life index"/ |
| 63. | short form 12/ or short form 20/ or short form 36/ or short form 8/ |
| 64. | sickness impact profile/ |
| 65. | (quality adj2 (wellbeing or well being)).ti,ab. |
| 66. | sickness impact profile.ti,ab. |
| 67. | disability adjusted life.ti,ab. |
| 68. | (qal* or qtime* or qwb* or daly*).ti,ab. |
| 69. | (euroqol* or eq5d* or eq 5*).ti,ab. |
| 70. | (qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab. |
| 71. | (health utility* or utility score* or disutilit* or utility value*).ti,ab. |
| 72. | (hui or hui1 or hui2 or hui3).ti,ab. |
| 73. | (health* year* equivalent* or hye or hyes).ti,ab. |
| 74. | discrete choice*.ti,ab. |
| 75. | rosser.ti,ab. |
| 76. | (willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab. |
| 77. | (sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab. |
| 78. | (sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab. |
| 79. | (sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab. |
| 80. | (sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab. |
| 81. | (sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab. |
| 82. | or/61-81 |
| 83. | statistical model/ |
| 84. | exp economic aspect/ |
| 85. | 83 and 84 |
| 86. | *theoretical model/ |

| | |
|---|---|
| 87. | *nonbiological model/ |
| 88. | stochastic model/ |
| 89. | decision theory/ |
| 90. | decision tree/ |
| 91. | monte carlo method/ |
| 92. | (markov* or monte carlo).ti,ab. |
| 93. | econom* model*.ti,ab. |
| 94. | (decision* adj2 (tree* or analy* or model*)).ti,ab. |
| 95. | or/85-94 |
| 96. | health economics/ |
| 97. | exp economic evaluation/ |
| 98. | exp health care cost/ |
| 99. | exp fee/ |
| 100. | budget/ |
| 101. | funding/ |
| 102. | budget*.ti,ab. |
| 103. | cost*.ti. |
| 104. | (economic* or pharmaco?economic*).ti. |
| 105. | (price* or pricing*).ti,ab. |
| 106. | (cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. |
| 107. | (financ* or fee or fees).ti,ab. |
| 108. | (value adj2 (money or monetary)).ti,ab. |
| 109. | or/96-108 |
| 110. | 60 and (82 or 95 or 109) |

1 **NHS EED and HTA (CRD) search terms**

| | |
|---|---|
| #1. | (MeSH DESCRIPTOR Substance-Related Disorders) |
| #2. | (MeSH DESCRIPTOR Substance Withdrawal Syndrome) |
| #3. | (MeSH DESCRIPTOR Inappropriate Prescribing EXPLODE ALL TREES) |
| #4. | (MeSH DESCRIPTOR Medical Overuse) |
| #5. | (MeSH DESCRIPTOR Deprescriptions EXPLODE ALL TREES) |
| #6. | (MeSH DESCRIPTOR Prescription Drug Misuse EXPLODE ALL TREES) |
| #7. | (MeSH DESCRIPTOR Medication Therapy Management) |
| #8. | (((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) adj2 (drug* or medicine* or medicat* or medical* or pharm*))) |
| #9. | (((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw*) adj3 (prescription* or prescrib*))) |
| #10. | ((addict* adj3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*))) |
| #11. | ((deprescription* or de-prescription* or deprescrib* or de-prescrib*)) |
| #12. | (((therap* or treat*) adj2 (manag* or substit*))) |
| #13. | (((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) adj2 symptom*)) |
| #14. | MeSH DESCRIPTOR Narcotic-Related Disorders |

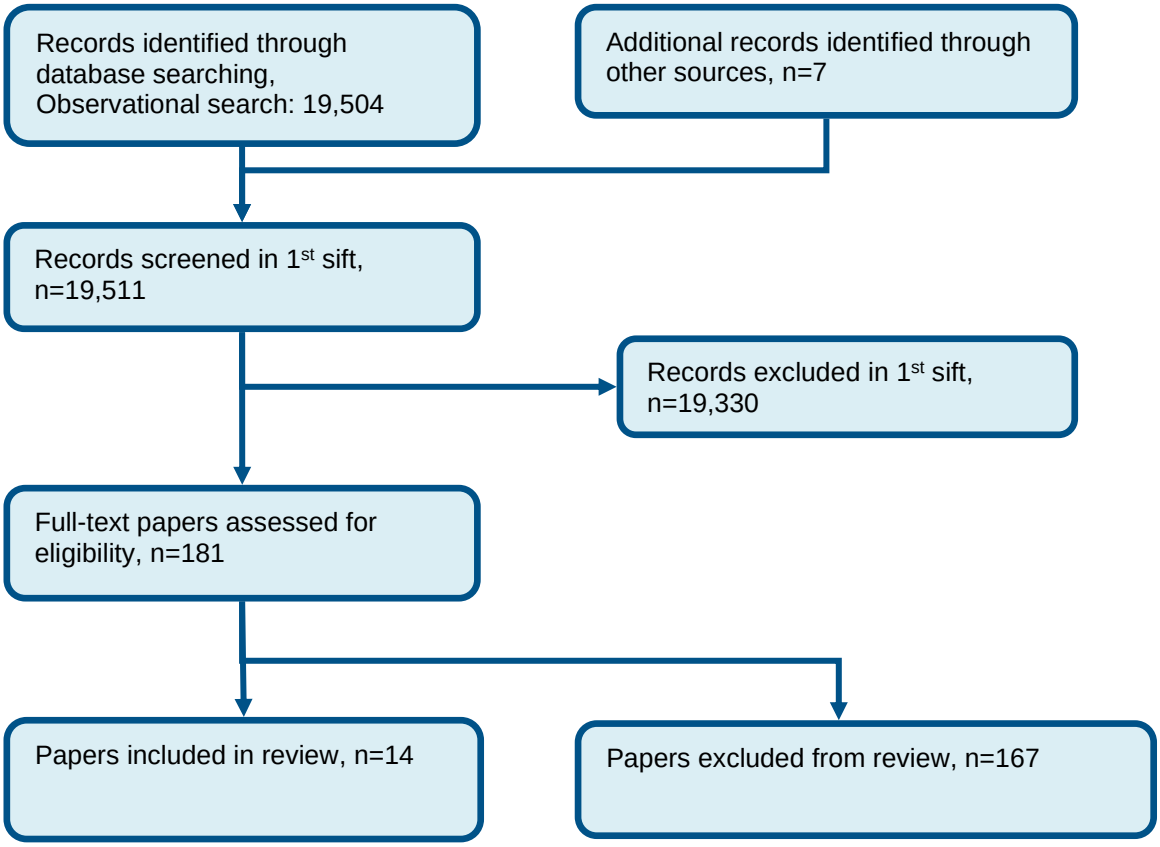
| | |
|---|---|
| #15. | (((drug* or medic*) adj2 (prescription* or prescrib*))) |
| #16. | (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15) |
| #17. | (MeSH DESCRIPTOR narcotics EXPLODE ALL TREES) |
| #18. | (((analgesic* adj3 narcotic adj3 agent*) or (opioid* or opiate*))) |
| #19. | ((alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*)) |
| #20. | ((z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon)) |
| #21. | (MeSH DESCRIPTOR Eszopiclone) |
| #22. | ((generation adj3 hypnotic*)) |
| #23. | (MeSH DESCRIPTOR Benzodiazepines EXPLODE ALL TREES) |
| #24. | ((benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam)) |
| #25. | (MeSH DESCRIPTOR Antidepressive Agents EXPLODE ALL TREES) |
| #26. | ((antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or NDRI* or SSRI* or SNRI* or SNORI* SARI* or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*)) |
| #27. | (("monoamine oxidase inhibit*")) |
| #28. | ((Norepinephrine adj2 dopamine)) |
| #29. | (("Selective serotonin reuptake inhibit*")) |
| #30. | ((Serotonin adj2 norepinephrine)) |
| #31. | ((Serotonin antagonist)) |
| #32. | (("Reversible Monoamine Oxidase Inhibit*")) |
| #33. | (MeSH DESCRIPTOR Flupenthixol EXPLODE ALL TREES) |
| #34. | ((Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine)) |
| #35. | ((5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine)) |
| #36. | ((Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine)) |
| #37. | (MeSH DESCRIPTOR pregabalin) |
| #38. | ((gabapentin* or pregabalin*)) |
| #39. | (#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38) |
| #40. | #16 AND #39 |
| #41. | (((withdraw* or prescription* or prescrib*) adj2 (opioid* or opiate*))) |

| | |
|---|---|
| #42. | MeSH DESCRIPTOR Opiate Substitution Treatment |
| #43. | MeSH DESCRIPTOR Opioid-Related Disorders |
| #44. | #41 OR #42 OR #43 |
| #45. | #40 OR #44 |

1
2

# Appendix C Prognostic evidence study selection

**Figure 1: Flow chart of clinical study selection for the review of risk factors for dependence**



# Appendix D Prognostic evidence

| Reference | Bedson 2019[19] |
|---|---|
| Study type and analysis | Prospective cohort analysed using Cox proportional hazards regression |
| Number of participants and characteristics | N=98,140<br>N=106,818 long-term opioid episodes were identified<br>Average daily dose (ADD) of prescribed opioids during the long-term episodes in percentiles (%):<br>5% 3.1mg<br>25% 7.1mg<br>50% 12.3 mg<br>75% 20.3 mg<br>95% 42.8%<br>Incident addiction to opioids:<br>N=90 for periods not on long term opioids<br>N=142 for periods on long term opioids<br>N=35 for Average daily dose (ADD) <20 mg morphine equivalent dose (MED) while on a long-term episode of opioid prescribing<br>N=56 for ADD ≥20 and <50 mg MED while on a long-term episode of opioid prescribing<br>N=51 for ADD ≥50 mg MED while on a long-term episode of opioid prescribing<br>Inclusion and exclusion criteria:<br>Patients aged 18 and over starting a new long-term opioid episode (defined as ≥3 or more opioid prescriptions within 90 days) at the time of a recorded noninflammatory, potentially painful musculoskeletal condition between 2002 and 2012. Patients were included if a visit for a musculoskeletal condition occurred within a period starting 14 days before the initial opioid |

| Reference | Bedson 2019[19] |
|---|---|
| | prescription and up to 90 days following it. Each participant was also required to have at least 12 months of records in the CPRD database before the initial opioid prescription and have no record of cancer diagnosis prior to the initial opioid prescription and up to 6 months after the initial prescription.<br><br>For the outcome of incident addiction to opioids, patients with a previous event in their records were excluded from the analysis.<br><br>The start of an episode of opioid prescribing defined as the date an opioid prescription was issued for a patient who had not received an opioid prescription within the previous 6 months. An episode ended if a period of 6 months elapsed without an opioid prescription. The end date of a long-term opioid episode was defined as the date 28 days following the issue of the last opioid prescription.<br><br>The population was sourced from the CPRD database with information from UK general practices. Data associated with n=350 practices across England were included as practices were required to have linked Office for National Statistics (ONS, for mortality information), Hospital Episode statistics (HES) and Index of Multiple Deprivation (IMD, neighbourhood deprivation) data.<br><br>Baseline details:<br><br>Median age (IQR): 61 (47 to 73) years; 41% male.<br><br>Median length (IQR) of long-term opioid episodes was 237 (103 to 658) days; median average daily dose of opioid prescribed to patients was 12.3 mg MED (IQR 7.1, 20.3 mg MED)<br><br>Smoking status: 12.9% non-smoker, 38.4% ever smoker, 12.5% unknown<br><br>Alcohol drinking: 12.9% non-drinker, 74% ever drinker, 13.1 % unknown<br><br>BMI: 27.3% <25 kg/$m^2$, 61.2% ≥25 km/$m^2$, 11.6% unknown<br><br>Neighbourhood deprivation level: 18.2% 1(least), 21.8% 2, 19.4% 3, 20% 4, 20% 5 (most), 0.6% unknown<br><br>Co-prescribing NSAID only: basic oral NSAID only 39.4%, none 53.7%<br><br>Comorbidity (total number of prescriptions), medial (IQR): 9 (6 to 14) |
| Prognostic variables | Long-term opioid episode status: periods not on long-term opioids (referent) vs periods on long-term opioids |

| Reference | Bedson 2019[19] |
|---|---|
| | Average daily dose (ADD) during a long-term opioid episode (grouped into three categories: <20 mg MED; ≥20 and <50 mg MED; ≥50 mg MED) |
| Confounders OR Stratification strategy | Age at baseline, gender, year of start of follow-up, ever smoking, ever alcohol drinking, overweight (BMI ≥25 kg/$m^2$), geographical region, deprivation level, prior recorded depression, co-prescribing of NSAID and total number of co-morbid conditions were included as baseline covariates in the final model.<br>The analysis was further stratified by gender.<br>Sensitivity analysis excluded patients with missing data on covariates. |
| Outcomes and effect sizes | Incident addiction to opioids<br>Adjusted HR 2.83 (95% 2.13 to 3.76) for periods on long-term opioids (i.e., during episodes of long-term opioid prescribing) vs periods not on long term opioids<br>Adjusted HR 1.06 (0.71 to 1.60) for ADD <20 mg MED during periods on long-term opioids<br>Adjusted HR 3.59 (2.55 to 5.06) for ADD ≥20 and <50 mg MED during periods on long-term opioids<br>Adjusted HR 9.33 (6.55 to 13.29) for ADD ≥50 mg MED |
| Funding | Not stated; authors state the study was based in part on data from the Clinical Practice Research Datalink database under licence from the UK Medicines and Healthcare products Regulatory Agency, but the interpretation and conclusions contained in the report are those of the authors alone. |
| Comments | Low risk of bias for periods on long-term opioids as per the QUIPS checklist<br>High risk of bias for ADD during periods on long-term opioids outcomes as per the QUIPS checklist |

| Reference | Cepeda 2013[54] |
|---|---|
| Study type and analysis | Retrospective cohort study with conditional logistic regression models conducted using matched analysis (description of methods assumed to include multivariate analysis) |
| Number of participants and characteristics | N=155,761 opioid naïve people<br>N=42,940 exposed to tapentadol IR |

| Reference | Cepeda 2013[54] |
|---|---|
| | N= 112,821 exposed to oxycodone IR<br>N=88 of tapentadol group exhibited shopping behaviour<br>N=967 of oxycodone group exhibited shopping behaviour<br>N= 4 of tapentadol group exhibited heavy shopping behaviour<br>N=80 of oxycodone group exhibited heavy shopping behaviour<br>Inclusion criteria:<br>People exposed to tapentadol IR or oxycodone IR from July 2009 to December 2010 who had not received an opioid of any type in the 3 months before the index date (date of the first prescription of tapentadol IR or oxycodone IR after June 30, 2009)<br>Exclusion criteria:<br>People who filled a prescription for an opioid other than tapentadol IR or oxycodone IR on the index date or in the next three days.<br>Data source:<br>The study used the IMS LRx longitudinal database that cover 65% of all retail dispensing in the US and includes all types of pharmacies and prescriptions filled for patients with any insurance type or those who pay cash.<br>Because fewer were exposed to tapentadol IR than oxycodone IR, each tapentadol IR-exposed subject was matched to up to 4 randomly selected oxycodone IR-exposed subjects by: calendar quarter and year of initial exposure (index date); first three digits of the zip code of the pharmacy dispensing the opioid at the index date; age ±5 years; and specialty of prescriber (e.g. primary care for specialties such as family practice, orthopaedic or general surgery, pain medicine, dentistry, emergency medicine addiction medicine and other for cardiology, nephrology, plastic surgery etc.) Matching variables were selected because they are potential confounders or sources of bias in observational studies. To ascertain the duration of follow-up in the database, prescriptions for any medication during the year of follow-up were searched.<br>A total of 42,940 eligible subjects exposed to tapentadol were matched to 112,821 eligible subjects exposed to oxycodone; 13,937 eligible subjects exposed to tapentadol could not be matched to any eligible subjects exposed to oxycodone.<br>Baseline details:<br>Mean age (SD): 51.11 (14.91)<br>Oxycodone IR: 48.3% male; 17.1% history of BZD use; prescriber specialty:0.06% dentistry, 2.2% emergency medicine, 15.6% surgery, 5.7% pain medicine, 39.7% primary care medicine, 36.8% other |

| Reference | Cepeda 2013[54] |
|---|---|
| | Tapentadol IR: 37.3% male; 12% history of BZD use; prescriber specialty 0.1% dentistry, 2.2% emergency medicine, 19.1% surgery, 7.8% pain medicine, 35% primary care medicine, 35.7% other<br>Indirectness: Proportion of those treated with opioids for chronic pain was unclear. |
| Prognostic variable | Exposure to Oxycodone IR vs Tapentadol IR (referent) |
| Confounders | The tapentadol and oxycodone groups were matched for potentially confounding variables of time of opioid exposure, geographic area, specialty of the prescriber and age; gender, any exposure to benzodiazepines during the 3 months before the index date and type of payment at index date were also considered in the regression model. |
| Outcomes and effect sizes | Shopping behaviour (>1 prescription by ≥2 different prescribers with≥1 day of overlap and filled at ≥3 pharmacies):<br>Matched and Adjusted OR 3.5 (95% CI 2.8 to 4.4) for oxycodone IR vs tapentadol IR<br>Heavy shopping behaviour (≥5 shopping episodes in 1 year):<br>Matched and Adjusted OR 6.9 (95% CI 2.5 to 19.3) for oxycodone IR vs tapentadol IR |
| Funding | Janssen Research & Development, LLC (formerly Johnson & Johnson Pharmaceutical Research & Development, LLC) provided funding for the study including collection and analysis of the data. |
| Comments | Low risk of bias for the outcome of shopping behaviour as per the QUIPS checklist<br>High risk of bias for the outcome of heavy shopping behaviour as per the QUIPS checklist |

| Reference | Cepeda 2014[52] |
|---|---|
| Study type and analysis | Retrospective cohort study with logistic regression analysis |
| Number of participants and characteristics | N=277,401 opioid-naïve patients<br>N=39,524 initiating opioid use with tapentadol IR<br>N= 237,877 initiating opioid use with oxycodone IR<br>N=1,656 (0.6%) developed shopping behaviour<br>N=2,086 (0.75%) developed opioid abuse<br>Gender: 60.3% female<br>Type of payment: 5.3% cash, 8.8% Medicaid, 18.6% Medicare, 67.3% commercial insurance |

| Reference | Cepeda 2014[52] |
|---|---|
| | Benzodiazepine use: 1.6%<br><br>Abuse of nonopioid drugs: 0.7%<br><br>Mood disorders: 2.6%<br><br>Painful conditions: 8.4% arthritis,6.7% back pain, 1.5% fractures,1.9% headache, 7.9% malignancy, 6.7% musculoskeletal pain, 1.2% neuropathic pain,0.7% other pain, 0.4% reproductive pain, 5.3 % visceral pain, 0.5% wound injury<br><br>Inclusion criteria:<br><br>Opioid naïve patients defined as patients without any opioid prescription in the 90 days before the first exposure to tapentadol IR or oxycodone IR which occurred between January 2010 and July 2011. The date of this exposure is each patient's index date (and each patient was followed for 1 year from the index date)<br><br>Exclusion criteria:<br><br>Patients with a history of opioid abuse/dependence 12 months before or at the index date and patients who filled a prescription for an opioid other than the index opioid within 3 days after the index date; patients with no claims related to diagnoses from 12 months before the index date to 12 months after the index date.<br><br>Characteristics & data source:<br><br>Opioid naïve patients from 2 linked dispensing and diagnosis databases (the IMS LRx database: prescription database that covers 65% of all retail dispensing in the US and includes all types of pharmacies and the IMS DX database: a physician claims database capturing claims from approximately 505,000 American Medical Association office-based practitioners in the US)<br><br>Selection:<br><br>To identify each patient uniquely so the databases could be linked, a probabilistic match was performed using a proprietary algorithm based on encrypted nonidentifiable data elements, including sex, date of birth, last name, first name, address, city state, zip code and payer identification.<br><br>Baseline details:<br><br>Mean age (SD): 53.1 (17.1) years; 60.3% female; benzodiazepine use 1.6%; abuse of non-opioid drugs 0.7%; mood disorders 2.6%<br><br>Tapentadol: 69.6% female; painful conditions included: 10.4% arthritis, 10.2% back pain, 1.1% fractures, 2.7% headache, 7.9% malignancy, 9.1% musculoskeletal pain, 1.9% neuropathic pain, 0.9% other pain, 0.6% reproductive pain 5.5% visceral pain, 0.4% wound injury |

| Reference | Cepeda 2014[52] |
|---|---|
| | Oxycodone: 58.7% female; painful conditions included: 8.1% arthritis, 6.2% back pain, 1.6% fractures, 1.8% headache, 7.9% malignancy, 6.3% musculoskeletal pain,1.1% neuropathic pain; 0.7% other pain, 0.3% reproductive pain, 5.3% visceral pain, 0.4% wound injury<br>Median number of days (25th to 75th percentile) from the index date to developing shopping behaviour was 163 (78 to 261) days; median number of days to developing abuse was 142 (45 to 249) days<br>Indirectness: Proportion of those treated with opioids for chronic pain was unclear. |
| Prognostic variables | Tapentadol immediate release vs oxycodone immediate release (follow-up: 1 year after initial exposure)<br>Age: <18, 18-39 and 40-64 vs >64 (referent)<br>Gender: male vs female(referent)<br>History of benzodiazepine use<br>Type of payment: Medicaid, Medicare, commercial insurance vs cash (referent)<br>History of mood disorders<br>History of abuse of nonopioid drugs (e.g., alcohol and tobacco)<br>Painful condition (type) |
| Confounders | Age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date |
| Outcomes and effect sizes | (Opioid) shopping behaviour (Opioid dispensing within ≥1 day of overlap written by ≥ different prescribers and filled in ≥3 pharmacies):<br>Adjusted OR 0.45 (95% CI 0.36 to 0.55) for tapentadol IR vs oxycodone IR<br>OR 0.9 (95% CI 0.5 to 1.8) for age <18 vs >64<br>OR 9.8 (95% CI 7.9 to 12) for age 18-39 vs >64<br>OR 4.6 (95% CI 3.8 to 5.6) for age 40-64 vs >64<br>OR 1.6 (95% CI 1.4 to 1.7) for male vs female<br>OR 1.6 (95% CI 1.1 to 2.2) for history of benzodiazepine use<br>OR 0.3 (95% CI 0.3 to 0.4) for Medicaid vs cash payment |

| Reference | Cepeda 2014[52] |
|---|---|
| | OR 0.4 (95% CI 0.3 to 0.4) for Medicare vs cash payment |
| | OR 0.2 (95% CI 0.2 to 0.2) for commercial insurance vs cash payment |
| | OR 1.4 (95% CI 1.1 to 1.8) for history of mood disorder |
| | OR 1.5 (95% CI 1.0 to 2.2) for history of abuse of non-opioid drugs |
| | OR 0.8 (95% CI 0.7 to 1.0) for arthritis |
| | OR 2.0 (95% CI 1.7 to 2.3) for back pain |
| | OR 1.1 (95% CI 0.75 to 1.7) for fractures |
| | OR 0.8 (95% CI 0.6 to 1.2) for headache |
| | OR 0.7 (95% CI 0.5 to 0.9) for malignancy |
| | OR 0.9 (95% CI 0.7 to 1.1) for musculoskeletal pain |
| | OR 1.2 (95% CI 0.8 to 1.8) for neuropathic pain |
| | OR 1.2 (95% CI 0.6 to 2.3) for other pains |
| | OR 0.7 (95% CI 0.3 to 1.8) for reproductive pain |
| | OR 1.0 (95 % CI 0.8 to 1.2) for visceral pain |
| | OR 1.0 (95% CI 0.5 to 1.8) for wound injury |
| | Opioid abuse (or addiction or dependence based on ICD-9 codes): |
| | Adjusted OR 0.44 (95% CI 0.37 to 0.54) for tapentadol IR vs oxycodone IR |
| | OR 0.7 (95% CI 0.3 to 1.4) for age <18 vs >64 |
| | OR 13.9 (95% CI 11.2 to 17.2) for age 18-39 vs >64 |
| | OR 6.7 (95% CI 5.5 to 8.3) for age 40-64 vs >64 |
| | OR 1.5 (95% CI 1.3 to 1.6) for male vs female |
| | OR 1.4 (95% CI 1.0 to 1.9) for history of benzodiazepine use |
| | OR 1.1 (95% CI 0.9 to 1.2) for Medicaid vs cash payment |
| | OR 0.7 (95% CI 0.6 to 0.8) for Medicare vs cash payment |

| Reference | Cepeda 2014[52] |
|---|---|
| | OR 0.3 (95% CI 0.3 to 0.4) for commercial insurance vs cash payment<br>OR 1.9 (95% CI 1.5 to 2.3) for history of mood disorder<br>OR 1.5 (95% CI 1.1 to 2.1) for history of abuse of non-opioid drugs<br>OR 1.0 (95% CI 0.8 to 1.1) for arthritis<br>OR 1.7 (95% CI 1.5 to 2.0) for back pain<br>OR 1.2 (95% CI 0.8 to 1.6) for fractures<br>OR 1.2 (95% CI 0.9 to 1.5) for headache<br>OR 0.4 (95% CI 0.3 to 0.5) for malignancy<br>OR 1.1 (95% CI 0.9 to 1.3) for musculoskeletal pain<br>OR 1.1 (95% CI 0.7 to 1.6) for neuropathic pain<br>OR 1.7 (95% CI 1.0 to 2.8) for other pains<br>OR 0.8 (95% CI 0.4 to 1.7) for reproductive pain<br>OR 1.1 (95 % CI 0.9 to 1.3) for visceral pain<br>OR 0.7 (95% CI 0.4 to 1.4) for wound injury |
| Funding | Not stated; two authors were employees of Janssen, Research & Development, an affiliate of Janssen Pharmaceuticals Inc., which markets several analgesic drug products including tapentadol, three authors were employees of IMS, which is the owner of the databases used in this study. |
| Comments | High risk of bias for tapentadol IR vs oxycodone IR for both opioid shopping behaviour and opioid abuse outcomes as per the QUIPS checklist<br>Very high risk of bias for all other risk factors for both opioid shopping behaviour and opioid abuse outcomes as per the QUIPS checklist |

| Reference | Chenaf 2016 a[60] |
|---|---|
| Study type and analysis | Retrospective cohort study with Cox proportional hazards model |

| Reference | Chenaf 2016 a[60] |
|---|---|
| Number of participants and characteristics | N=1958 Chronic noncancer pain patients (CNCP) treated with codeine in the period from 2004 to 2014 with data from a French health insurance database<br>N= 65 developed at least 1 episode of shopping behaviour: 1-year incidence rate of codeine shopping behaviour was 4.03% (95% CI 3.07 to 5.28). The first shopping episode occurred in a median time of 190 (IQR=112-351) days; n=18 developed only 1 episode of shopping behaviour, n=24 had 2 to 10 episodes and n=23 had >10 episodes.<br>Of those:<br>N=37 (56.9%) were female<br>N=16 (24.6%) had low-income status<br>N=3 (4.6%) had history of opioid use disorder<br>N=5 (7.7%) had history of substance use disorder<br>N=17 (26.2%) presented with a mental health disorder<br>Inclusion criteria:<br>All patients aged 18 years and older treated with codeine for at least 6 consecutive months (180 days) between January 1 2004 and September 30 2013. The index date was the date of the first dispensation of this continuous sequence of at least 180 days of treatment. A continuous sequence was defined as an interval between 2 consecutive dispensations inferior to 35 days (on the basis that prescription drugs in France are dispensed for a maximum of 4 weeks and accordingly drugs prescribed for 3 months will be dispensed 3 times. To detect prescription interruption, 1 week was added to the maximum duration of prescription. The 6 months of continuous treatment period was used to identify chronic use of codeine in the absence of a specific code identifying chronic pain status as for research purposes pain lasting longer than 6 months is recommended to be defines as chronic pain.<br>Exclusion criteria:<br>Patients occasionally treated with codeine in the 6 months before the index date were excluded in order to select incident codeine users. Patients with a cancer condition were excluded (according to the presence of cancer related ICD-10 code among the previously collected LTD) to ensure non-malignant origin of pain.<br>Selection:<br>A representative 1/97th random sample of the population covered by the French national health insurance system (the Echallon Generaliste des Beneficiers (EGB)), containing administrative, medical and pharmacy data.<br>N=167,630 patients with at least 1 dispensation of codeine form January 1, 2004 to September 30, 2013<br>N=2,806 chronic pain patients treated with codeine for at least 6 months |

| Reference | Chenaf 2016 a[60] |
|---|---|
| | N=2,305 chronic pain patients with at least 6 months of data available before the index date and with a possible follow-up of 12 months after the index date were selected.<br>N=1,958 excluding those with a cancer diagnosis (n=347)<br><br>In 2014 the EGB database was comprised of almost 700,000 beneficiaries with more than 10 years of follow-up.<br>Patients were followed until September 2014 allowing at least 12 months of follow-up for all included patients.<br>Baseline details:<br>Age mean (SD): 62.7 (16.1) years; 63.2% women; n=168 (8.6%) low-income status; n=197 (10.1%) had mental health disorders.<br>n=43 (2.1%) had a history of substance use disorder; n=11 (0.6%) had a history of opioid use disorder |
| Prognostic variables | Age: ≤40 vs >40 (referent)<br>Gender: female vs male<br>Low-income status (yes vs no)<br>History of opioid use disorder (yes vs no)<br>History of substance use disorder (yes vs no)<br>Active chronic liver disease (yes vs no)<br>Mental health disorders (yes vs no)<br>Antidepressants (concurrent use) (yes vs no)<br>Antipsychotics (previous use) (yes vs no)<br>Hypnotic BZD (previous use) (yes vs no)<br>Hypnotic BZD (concurrent use) (yes vs no)<br>Anxiolytic BZD (previous use) (yes vs no)<br>Anxiolytic BZD (concurrent use) (yes vs no)<br>Strong opioids (previous use) (yes vs no) |
| Confounders | Factors considered significant in univariate analysis (P<0.15) were entered to the multivariate analysis which was reported to be done accordingly to clinically relevant variables such as age and gender. |

| Reference | Chenaf 2016 a[60] |
|---|---|
| Outcomes and effect sizes | One-year incidence of codeine shopping behaviour (≥1 day of overlapping prescriptions written by ≥2 different prescribers and filled in ≥3 different pharmacies)<br>**HR 7.29 (95% CI 4.28 to 12.42) for younger age (≤40)**<br>HR 0.92 (95% CI 0.53 to 1.58) for gender (female vs male)<br>HR 1.75 (95% CI 0.96 to 3.21) for low-income status<br>HR 1.25 (95% 0.19 to 8.40) for history of opioid use disorders<br>HR 0.89 (95% 0.21 to 3.83) for history of substance use disorder<br>HR 2.09 (95% CI 0.62 to 7.03) for active chronic liver disease<br>**HR 2.25 (95% CI 1.08 to 4.67) for mental health disorders**<br>HR 0.93 (95% CI 0.53 to 1.63) for concurrent use of antidepressants<br>HR 1.03 (95% CI 0.42 to 2.53) for previous use of antipsychotics<br>HR 1.56 (95% CI 0.70 to 3.49) for previous use of hypnotic BZD<br>HR 0.89 (95% CI 0.43 to 1.83) for concurrent use of hypnotic BZD<br>HR 0.63 (95% CI 0.32 to 1.26) for previous use of anxiolytic BZD<br>**HR 3.12 (95% CI 1.55 to 6.26) for concurrent use of anxiolytic benzodiazepines**<br>**HR 2.94 (95% CI 1.24 to 6.98) for previous use of strong opioids** |
| Funding | The French National Agency for Medicines and Health Products Safety |
| Comments | High risk of bias for all prognostic factors as per the QUIPS checklist |

| Reference | Chenaf 2016 b[61] |
|---|---|
| Study type and analysis | Retrospective cohort study and cox proportional hazard model |
| Number of participants and characteristics | N=3505 CNCP patients treated with tramadol<br>N=26 became tramadol shoppers |

| Reference | Chenaf 2016 b[61] |
|---|---|
| | N=19 (73%) of those were female vs n=2315 (66.5%) of non-shoppers<br>N=9 (35%) had low-income status vs 133 (3.8%) of non-shoppers<br>None of the opioid shoppers had previous opioid use disorder vs 14 (0.4%) of non-shoppers<br>Tramadol shoppers had a mean (SD) age of 47.6 (13.5) years vs non-shoppers had a mean (SD) age of 66.5 (14.6)<br>Inclusion criteria:<br>All patients aged 18 years and older treated by tramadol for at least six consecutive months (180 days) between January 1 January 2005 and 31 December 2012. The index date was the first dispensation of this continuous sequence of at least 180 days of treatment. A continuous sequence was defined as an interval between two consecutive dispensations inferior to 35 days.<br>Exclusion criteria:<br>Non-chronic pain patients, patients with a cancer condition, patients with less than 6 months available prior to index date or with less than 12 months of possible follow-up after the index date were excluded. Patients occasionally treated by tramadol in the 6 months before the index date were excluded to select incident tramadol users.<br>Data source:<br>Anonymous data came from a French health insurance claims database: Echantillon Generaliste des Beneficiaires (EGB), a representative 1/97th random sample of the population covered by the French national health insurance system. In 2014 the EGB database was comprised of almost 700,000 beneficiaries with more than 10 years of follow-up.<br>People treated with tramadol in the period from 2005 to 2013 were selected.<br>Characteristics:<br>Mean age (S): 66.4 (14.7) years; 66.4% female; 4.1% were low-income status<br>Median tramadol treatment duration was 260 (IQR 211 to 356) days; median daily dose of tramadol from index date to first shopping episode was 442 mg; median time from index date to first shopping episode of doctor shopping was 165 (IQR 78 to 238) days; Number of shopping episodes ranged from 1 to 64 during the study follow-up.<br>Strong opioids used included morphine, fentanyl and oxycodone. |
| Prognostic variables | Age <40 vs ≥ 50 (referent)<br>Age 40-50 vs ≥ 50 (referent)<br>Gender: female vs male (referent) |

| Reference | Chenaf 2016 b[61] |
|---|---|
| | Low-income status (yes vs no)<br>Prior use of strong opioids (yes vs no) |
| Confounders | It was not specified which confounders were adjusted in the multivariate analysis. |
| Outcomes and effect sizes | Shopping behaviour:<br>HR 7.4 (95% CI 2.8 to 19.7) for age <40 vs ≥ 50<br>HR 2.8 (95% CI 1 to 7.7) for age 40-50 vs ≥ 50<br>HR 1.6 (95% CI 0.7 to 3.8) for female gender vs male<br>HR 8.5 (95% CI 3.6 to 20.5) for low-income status<br>HR 5.7 (95% CI 1.9 to 17.0) for prior use of strong opioids vs no prior use |
| Funding | The French National Agency for Medicines and Health Products Safety |
| Comments | Very high risk of bias for all risk factors as per the QUIPS checklist |

| Reference | Chui 2018[68] |
|---|---|
| Study type and analysis | Retrospective cohort study with multivariable logistic regression analysis |
| Number of participants and characteristics | N=21,111<br>Veterans aged ≥ 65 years with musculoskeletal disorder (MSD), enrolled in Medicare.<br>Prescription drug benefit utilisation: N=14,085 Veteran's health administration (VHA) only; 5,596 CMS only; N=1,430 both<br>Proportion of patients with overlapping concurrent opioid prescriptions: 38% of VHA only, 24% of CMS only and 75% of both VHA and CMS utilisation<br>N=11,254 65-74 years old<br>N=7,597 75-84 years old<br>N= 2,260 85+ years old<br>N=20,755 Male (98.3%)<br>83.6% White |

| Reference | Chui 2018[68] |
|---|---|
| | 42% moderate-to-severe pain intensity (pain scale 4-10)<br>N= 1,538 (7.3%) substance use (illicit drugs & alcohol)<br>N=1,172 (5.6%) major depression<br>N= 1,514 (7.2%) PTSD<br>N= 8,205 (38.9%) Charlson Comorbidity Score (CCI) 2+<br>Data source:<br>Data from the VA Musculoskeletal Disorders Cohort were linked with claims data from the Centres for Medicare and Medicaid Services (CMS) from VA Information Resource Centre (VIRec) using patient scrambled SSN (VIReC 2016). The VA Musculoskeletal Disorders Cohort is a comprehensive registry for all Veterans with MSD diagnoses who received care in a VHA inpatient and/or outpatient medical facility between 2000 and 2013,<br>To be eligible for the VA Musculoskeletal Disorders Cohort, a veteran had to have one of 1,685 distinct International Classification of Diseases, 9th revision, Clinical Modification (ICD-9CM) diagnoses representing a musculoskeletal disorder recorded at ≥ 2 outpatient visits occurring within 18 months of one another or at ≥1 inpatient stay.<br>Additional demographic and clinical information was extracted from VHA electronic clinical and administrative data sources in the Corporate Data Warehouse (CDW) for all eligible Veterans both prior to and following the date of their first MSD diagnosis (index date) to enable the analysis of longitudinal outcomes.<br>Inclusion criteria:<br>Veterans that entered the MSD cohort in 2008 and received an opioid prescription in 2010.<br>Exclusion criteria:<br>Veterans under 65 years of age, not eligible for Medicare part D, without an opioid prescription in 2010 and those who died during the study period.<br>Characteristics:<br>Mean age: 75; 83.6% white; 98.3% male; 58% reported no or mild pain intensity on the NRS at MSD index date (2008); BMI mean (SD): 29.18 (5.8)<br>Median IQR number of prescriptions: 2 (1-6) in VHA only, 2 (1-5) in CMS only, 9 (4-15) in those who used both VHA and CMS<br>MSD diagnoses: non-traumatic joint, back pain, osteoarthritis, fracture, gout, neck pain, fibromyalgia, temporomandibular joint pain |

| Reference | Chui 2018[68] |
|---|---|
| | Opioid medications included: codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, morphine, oxycodone, oxymorphone, pentazocine, propoxyphene, tapentadol and tramadol. |
| Prognostic variables | Age: 65-74 years (referent) vs 75-84 years vs 85+ years old<br>Non-white race vs white race (referent)<br>Female sex vs male sex (referent)<br>Moderate to severe pain intensity (pain scale 4-10)<br>Charlson comorbidity index (CCI) 2+ vs CCI score 0-1 (referent)<br>Substance use disorder (alcohol and illicit drug use disorders)<br>PTSD<br>Major depression<br>Dual Use of VHA and Medicare part D (Veterans were identified as VHA only if they did not have any Medicare opioid prescription in 2010, Medicare only if all of their opioid prescriptions were from Medicare providers or dual use if they received opioid prescriptions from both VHA and Medicare in 2010) |
| Confounders | Demographic and clinical characteristics: Age, sex and ethnicity (at index date), moderate-to-severe pain intensity (pain score from 4 to 10 at the pain intensity numerical rating scale (NRS)) in 2008; co morbid diagnoses recorded ≥2 outpatient visits or ≥1 inpatient stay up to 12 months before or 6 months after the MSD index date; overall clinical severity (Charlson comorbidity index-CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and post-traumatic stress disorder (PTSD)<br>At index date. |
| Outcomes and effect sizes | Overlapping concurrent opioid prescriptions (prescription starting before the end-date of a prior prescription, inclusive of prescriptions outside the VHA):<br>OR 0.81 (95% CI 0.75 to 0.87) for age 75-84 years old vs 65-74 years<br>OR 0.83 (95% CI 0.74 to 0.92) for age 85+ years old vs 65-74 years<br>OR 0.77 (95% CI 0.71 to 0.84) for non-white vs white race<br>OR 0.97 (95% 0.75 to 1.24) for female sex vs male sex<br>OR 1.40 (95% 1.31 to 1.49) for moderate-to-severe pain intensity (NRS score 4-10)<br>OR 0.96 (95% 0.90 to 1.03) for overall clinical severity: CCI 2+ versus CCI score 0-1 |

| Reference | Chui 2018[68] |
|---|---|
| | OR 1.18 (95% 1.05 to 1.33) for substance use disorder<br>OR 0.94 (95% 0.82 to 1.05) for PTSD<br>OR 1.32 (95% CI 1.15 to 1.52) for major depression<br>OR 5.28 (95% CI 4.60 to 6.05) for dual use of VHA and Medicare part D<br>Median (IQR) number of prescriptions: 9 (4-15) in those with dual use vs 2 (1-6) in VHA only and 2 (1-5) in Medicare only. |
| Funding | The Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, and Health Services Research and Development, and Office of Academic Affairs HSR&D Fellowship |
| Comments | Low risk of bias for all other risk factors as per the QUIPS checklist |

| Reference | Cook 2018[76] |
|---|---|
| Study type and analysis | Retrospective cohort with multivariable Cox proportional hazards regression model |
| Number of participants and characteristics | N=11,663 Benzodiazepine users<br>White: n= 7179; Black: n= 1265; Latino: n= 2854; Asian: n= 365 Sex: 65% female<br>Substance use disorder diagnosis:<br>Alcohol: 17%; Marijuana: 2%; Cocaine: 11%; Opioid: 32%; Tobacco: 25%; pain medication: 44%<br>Mental health disorder diagnosis:<br>Depression: 31%; Anxiety: 45%; Bipolar: 8%; Psychosis: 3%; PTSD: 11%; Sleeping disturbance: 12%<br>BZD dependence diagnosis: 2.2%<br>Data source:<br>Electronic health records from an urban healthcare system in New England, serving predominantly low SES, publicly insured and racial/ethnic/linguistic minority populations. The healthcare system has a network of three hospitals and fifteen community-based clinics that provide primary care, inpatient and outpatient specialty mental health care and intensive outpatient substance use treatment. The data included medication events in the 32 months between January 2013 and September 2015. Diagnoses were identified from outpatient and inpatient primary care and specialty treatment.<br>Inclusion criteria: |

| Reference | Cook 2018[76] |
|---|---|
| | Age 18 years or over with at least 3 visits to primary care during the 32-month period with 1 or more benzodiazepine prescription<br>Exclusion criteria:<br>Received a diagnosis of benzodiazepine use disorder before the first recorded benzodiazepine prescription<br>Additional characteristics:<br>Mean (SD) age: 49.8 (16.6); mean (SD) number of BZD prescriptions: 4.6 (7.1) |
| Prognostic variables | Race (referent = white)<br>Sex (referent = female)<br>Age (referent = 18-24)<br>Substance use diagnosis (vs no diagnosis)<br>Mental health disorder diagnosis (vs no diagnosis) |
| Confounders | Regression model adjusted for: substance use disorder diagnosis (alcohol, marijuana, cocaine, opioid, tobacco, pain medication), mental health disorder diagnosis, age, sex, race; model also included interactions between age and sex. |
| Outcomes and effect sizes | Diagnosis of benzodiazepine dependence subsequent to receiving a prescription, defined as a diagnosis of dependence on a sedative, hypnotic or anxiolytic (ICD-9).<br>For the main evidence review sections confidence intervals have been calculated using the standard errors (SEs) reported in the paper<br>Race (referent = white)<br>- Black: HR 0.18 (SE 0.08)<br>- Latino: HR 0.20 (SE 0.08)<br>- Asian: HR 0.43 (SE 0.28)<br>Sex (referent = female)<br>- HR: 1.33 (SE 0.45)<br>Age (referent = 18-24)<br>- 25-34: HR 1.23 (SE 0.64)<br>- 35-44: HR 0.66 (SE 0.35) |

| Reference | Cook 2018[76] |
|---|---|
| | - 45-54: HR 0.87 (SE 0.44)<br>- 55-64: HR 1.08 (SE 0.54)<br>- 65+: HR 1.47 (SE 0.74)<br>Substance use diagnosis (vs no diagnosis)<br>- Alcohol: HR 0.77 (SE 0.13)<br>- Marijuana: HR 0.28 (SE 0.16)<br>- Cocaine: HR 1.13 (SE 0.18)<br>- Opioid: HR 3.90 (SE 0.61)<br>- Tobacco: HR 2.08 (SE 0.29)<br>- Pain meds: HR 0.71 (SE 0.10)<br>- 2+ SUD: HR 2.03 (SE 0.34)<br>Mental health disorder diagnosis (vs no diagnosis)<br>- Depression: HR 1.43 (SE 0.19)<br>- Anxiety: HR 1.60 (SE 0.23)<br>- Bipolar: HR 1.02 (SE 0.20)<br>- PTSD: HR 0.91 (SE 0.17)<br>- Sleeping disturbance: HR 0.69 (SE 0.13) |
| Funding | The National Institute of Drug Abuse (country: USA) |
| Comments | High risk of bias across risk factors as per the QUIPS checklist. |

| Reference | Hoffman, 2017[113] |
|---|---|
| Study type and analysis | Retrospective cohort; multivariable logistic regression. |
| Number of participants | Total cohort =1993 |

| Reference | Hoffman, 2017[113] |
|---|---|
| and characteristics | Duration of opioid use <90 days, n=1452<br>Duration of opioid use ≥90 days, n=541<br>Inclusion criteria:<br>People with polyneuropathy receiving 90 or more consecutive days of opioid therapy<br>Exclusion criteria:<br>Not reported<br>Characteristics & data source:<br>People who resided in Olmsted County, Minnesota from January 1 2006 to December 31 2010, identified by the Rochester Epidemiology Project database |

| Baseline characteristics | Duration of opioid use <90 days<br>N=1452 | Duration of opioid use ≥90 days<br>N=541 |
|---|---|---|
| Duration of consecutive opioids, median (IQR), d | 17 (8-34) | 228 (133-392) |
| Female sex, No. (%) | 674 (46.4) | 308 (56.9) |
| Nonopioid analgesic prescriptions, No. (%) | 456 (31.4) | 335 (61.9) |
| α2Δ antagonist | 161 (11.1) | 129 (23.8) |
| Serotonin norepinephrine reuptake inhibitor Tricyclic antidepressant | 218 (15.0) | 162 (29.9) |
| Topical analgesics | 156 (10.7) | 148 (27.4) |
| Any nonopioid analgesic | 670 (46.1) | 430 (79.5) |
| Lower limb complications, No. (%) | | |
| Ulcers | 300 (20.7) | 151 (27.9) |
| Amputations | 73 (5.0) | 29 (5.4) |
| Neuroma, bunion, and toe deformity | 46 (3.2) | 19 (3.5) |

| | |
|---|---|
| **Reference** | **Hoffman, 2017[113]** |
| | Ankle fusions: 10 (0.7); 5 (0.9) |
| Prognostic variables | Long term opioid therapy ≥90 days vs shorter term opioid therapy <90 days (referent) |
| Confounders | Multivariate models were used to adjust ORs and HRs for the potentially confounding effects of Charlson Comorbidity Index comorbidities, sex and use of non-opioid analgesics, when applicable. |
| Outcomes and effect sizes | Hazard ratio for outcomes of opioid dependence, opioid abuse (determined by International Classification of Diseases, Ninth Revision, Clinical Modification, codes) from 2006 to 2014. 'Given that HRs were used for the analysis, only incident diagnoses occurring after the initial opioid prescription were counted'.<br>Opioid dependence:<br>Adjusted HR: 2.85 (95% CI 1.54 to 5.47) for long term opioid therapy ≥90 vs <90 days<br>Opioid abuse:<br>Adjusted HR: 3.97 (95% CI 0.87 to 28.9) for long term opioid therapy ≥90 vs <90 days |
| Funding | The Mayo Foundation for Medical Education and Research, Mayo Clinic Centre for Individualised Medicine, the National Institutes of Health (NIH)- Funded Rochester Epidemiology Project |
| Comments | High risk of bias for all outcomes as per the QUIPS checklist. |

| | |
|---|---|
| **Reference** | **Park 2016[147]** |
| Study type and analysis | Retrospective cohort study analysed using a Cox proportional hazards model. |
| Number of participants and characteristics | N=847<br>Patients receiving ≥ one benzodiazepine prescription n=196 (23%)<br>Patients who had ≥ two early opioid refills n=183 (22%)<br>Inclusion criteria:<br>Patients aged 18 to 89 years who met the following criteria during the study period from September 1, 2011 – August 31, 2012: 1)<br>≥ one visit to a hospital-based primary care clinic or one of two community health centres, 2) received chronic opioid therapy for chronic non-cancer pain, previously defined as receiving ≥ 3 opioid prescriptions at least 21 days apart within a 6-month period, and 3) completed at least one urine drug test. |

| Reference | Park 2016[147] |
|---|---|
| | Selection:<br>1,285 patients received chronic opioid therapy in the 3 primary care clinics during the study period.<br>325 (25%%) did not receive a drug test during the study period and thus were excluded.<br>847 remaining patients constituted the final sample size.<br>The study utilized de-identified data abstracted from the electronic medical record (EMR) and housed at the Boston Medical Center Clinical Data Warehouse.<br>Baseline details:<br>Age, mean (SD): 51 (11) for Benzodiazepine prescription, 53 (11) for no Benzodiazepine prescription during the study period<br>Female, % (n): 58 (114) for Benzodiazepine prescription, 38 (250) for no Benzodiazepine prescription during the study period<br>Race white, % (n): 50 (98) for Benzodiazepine prescription, 32 (207) for no Benzodiazepine prescription during the study period<br>Charlson Comorbidity Index ≥ 1, % (n): 73 (143) for Benzodiazepine prescription, 69 (447) for no Benzodiazepine prescription during the study period<br>Any depressive disorder, % (n): 73 (144) for Benzodiazepine prescription, 47 (307) for no Benzodiazepine prescription during the study period<br>Any anxiety disorder, % (n): 61 (120) for Benzodiazepine prescription, 30 (197) for no Benzodiazepine prescription during the study period<br>Any drug use disorder, % (n): 67 (131) for Benzodiazepine prescription, 62 (406) for no Benzodiazepine prescription during the study period; that included opioids, cocaine, sedatives, marijuana, polysubstance and other drug abuse or dependence<br>Overall, 63% had a drug use disorder diagnosis in their medical record (reported to also include opioids along with cocaine, sedatives marijuana, polysubstance and other drug abuse or dependence)<br>The most common pain diagnosis was musculoskeletal (82%); Patients who received benzodiazepines were more likely to be female, white and have a diagnosis of depressive, anxiety or other psychiatric disorder. |
| Prognostic variable | Receipt of benzodiazepine prescription prescribed by a primary care clinician. This was treated as a time-varying variable, indicating that benzodiazepine prescription status was allowed to vary over time.<br>Benzodiazepines included: alprazolam, bromazepam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, and triazolam. |

| Reference | Park 2016[147] |
|---|---|
| Confounders | Potential confounders included age, sex, race, and Medicaid insurance. Medical comorbidities were assessed using the Charlson Comorbidity Index24 and pain, and mental health and substance use disorders were also assessed. Diagnoses were obtained using ICD-9 (International Classification of Diseases, ninth edition) codes from the EMR problem list or through billing codes and included any anxiety disorder, any depressive disorder, any other psychiatric disorder (bipolar and psychotic disorders), any drug use disorder (opioids, cocaine, sedatives, marijuana, polysubstance and other drug abuse and dependence), and any alcohol use disorder (alcohol abuse and dependence).<br>All of the above were adjusted for in the analysis. |
| Outcomes and effect sizes | Time to second early opioid refill prescription. Early opioid refill was defined as an opioid prescription written 7-25 days after the previous prescription for the same drug.<br>Cox proportional hazards model was used to calculate the hazard of time to second early opioid refill for those in receipt of benzodiazepine prescription compared to no receipt.<br>Adjusted HR 1.54 (95% CI 1.09 to 2.18) for receipt of benzodiazepine prescription compared to non-receipt of benzodiazepine prescription |
| Funding | The National Institute on Drug Abuse (country: USA) |
| Comments | Low risk of bias as per the QUIPS checklist |

| Reference | Reid 2002[152] |
|---|---|
| Study type and analysis | Retrospective cohort study and multivariate logistic regression analysis |
| Number of participants<br>and characteristics | N=98<br>Patients with prescription opioid abusive behaviours: n=27 (27.55%)<br>Patients with lifetime history of substance use disorder: n= 41 (41.84%)<br>Inclusion criteria:<br>Individuals at either of two primary care practices (one at the VA Connecticut Healthcare System (VACHS) and the Primary Care Centre (PCC) located at Yale-New Haven Hospital) who received 6 or more months of opioid prescriptions during a 1-year period (April 1, 1997 through March 31, 1998) for noncancer pain and were not on methadone maintenance.<br>Selection: |

| Reference | Reid 2002[152] |
|---|---|
| | Populations were drawn from the aforementioned two primary care practices, selecting a random sample of VA patients and all PCC patients as follows.<br><br>Potentially eligible PCC patients were identified by reviewing duplicate copies of all scheduled prescriptions written from April 1, 1997 through March 31,1998.<br><br>N=54 PCC patients who received 6 or more months of opioid prescriptions over the 12-month period were identified.<br><br>N=6 PCC patients were excluded due to opioid use for cancer-related pain<br><br>N=48 PCC patients remained as the final PCC sample<br><br>Potentially eligible VA patients were identified through searching the VA pharmacy computer records.<br><br>N=392 VA patients who received 6 or more months of opioid prescriptions over the 12-month period were identified.<br><br>N=60 potentially eligible VA patients were randomly sampled in order to obtain a final similar number of 50 participants (representing the expected total number of eligible PCC patients)<br><br>N=9 VA patients were ineligible due to the use of an opioid medication for cancer-related pain and n=1 was on methadone maintenance.<br><br>N=50 VA patients remained as the final VA sample.<br><br>Baseline details:<br><br>VA population median age (range): 54 (33 to 84); 92% male; 88% white; type of chronic pain: 44% low back pain; median (range) duration of pain: 10 (3 to 50) years; psychiatric comorbidity: 44% depression, 20% anxiety; lifetime history of substance use disorder: alcohol abuse/dependence: 46%, narcotic abuse/dependence 18%; medical diseases mean (SD): 2 (1.5)<br><br>PCC population median age (range): 55 (26 to 80); 33% male; 52% white; type of chronic pain: 25% low back pain; median (range) duration of pain: 13 (1 to 49) years; psychiatric comorbidity: 54% depression, 21% anxiety; lifetime history of substance use disorder: alcohol abuse/dependence: 31%, narcotic abuse/dependence 38%; medical diseases mean (SD): 2 (1.6)<br><br>A lifetime history of substance use disorder was recorded for 23 VA and 18 PCC patients, among whom evidence in support of a current (i.e., occurring while on opioids) substance disorder was found in 9 VA and 5 PCC patient records<br><br>Most frequently prescribed types of opioids: oxydocodone/acetaminophen (short-acting opioid) and extended-release morphine sulfate (long-acting opioid)<br><br>Of the total sample N=98, most patients (n=88) were prescribed daily doses, while n=10 received as-needed doses of opioids (e.g., for chronic headache). |

| **Reference** | **Reid 2002[152]** |
|---|---|
| Prognostic variables | Age<br>Number of medical diseases (mean number of individual chronic medical diseases determined by the unweighted Charlson Index)<br>Lifetime history of substance use disorder (demonstrated by 1 or more of the following: 1) admission for detoxification e.g., alcohol, cocaine or referral for detoxification that was declined by the patient, 2) testing positive for other substances e.g., elevated blood alcohol level or urine screen positive for cocaine and 3) recorded episodes of alcohol abuse or dependence.) |
| Confounders | The confounders are not specified in the study |
| Outcomes and effect sizes | Prescription opioid abuse behaviour (included reports of lost or stolen opioid medication or prescriptions, documentation that patients were using multiple sources to obtain opioid medication or requests for 2 or more early refills). Median time to onset of prescription opioid abuse behaviours was 24 months (range 3 to 72 months)<br>Adjusted OR 0.94 (95% CI 0.89 to 0.99) for age<br>Adjusted OR 0.72 (95% CI 0.45 to 1.1) for number of medical diseases<br>Adjusted OR 3.8 (95% CI 1.4 to 10.8) for lifetime history of substance use disorder |
| Funding | Advanced Career Development Award from the Department of Veteran Affairs Health Services Research Division, Robert Wood Johnson Foundation Generalist Physician Faculty Scholar Award, Paul Beeson Physician Faculty Scholar in Aging Research Award (country: USA) |
| Comments | High risk of bias for age as per the QUIPS checklist<br>Very high risk of bias for history of substance use disorder as per the QUIPS checklist<br>High risk of bias for number of medical diseases as per the QUIPS checklist |

| **Reference** | **Seal 2012[158]** |
|---|---|
| Study type and analysis | Retrospective cohort and Poison regression with robust error variance. |
| Number of participants and characteristics | Total sample N= 15,676<br>N= 7983 had PTSD<br>N= 3205 had other metal health diagnoses but not PTSD<br>N=4488 without a mental health diagnosis |

| Reference | Seal 2012[158] |
|---|---|
| | N= 4595 had an early opioid refill<br>Inclusion: veterans who entered VA health care from October 1, 2005, through December 31, 2008. Iraq and Afghanistan veterans who received a<br>new non−cancer-pain diagnosis within 1 year of VA entry. Veterans were required to have at least 1 opioid prescription for a minimum of 20<br>consecutive days in the first year of pain diagnosis.<br>Exclusion: not reported<br>Characteristics & data source: participants were identified from the national VA's OEF/OIF roster, an accruing national database of veterans who have separated from military service and have enrolled in Veterans Affairs health care. The roster data were linked to 2 other VA administrative<br>databases: the VA National Patient Care Database to obtain information on VA clinical visits and associated clinical diagnoses and the VA decision<br>support system to obtain detailed VA pharmacy records.<br>Baseline characteristics reported for wider population of veterans with an index pain diagnosis, not reported for those with an index pain<br>diagnosis and who had received prescription opioids for 20 or more consecutive days |
| Prognostic variables | No mental health diagnosis (referent) vs mental health diagnosis:<br>-PTSD diagnosis with and without other mental health diagnoses (depressive, anxiety, alcohol use, drug use disorders and traumatic brain injury) ---Other mental health diagnoses excluding PTSD |
| Confounders | Confounding variables included sociodemographic (i.e., age, sex, race/ethnicity, marital status, VA facility type - medical centre vs community<br>clinic) and military service characteristics (i.e., component, rank, service branch, and number of deployments) |
| Outcomes and effect sizes | Early opioid refills (obtaining the same opioid prescription for more than 7 days before the end of the prior prescription), used as a proxy for high-risk opioid behaviour in the study, determined by reviewer to be a surrogate measure of opioid misuse/dependence (as also used by other studies)<br>Adjusted RR 1.50 (95% CI 1.39-1.62) for mental health diagnosis without PTSD<br>Adjusted RR 1.64 (95% CI 1.53-1.75) for PTSD with or without other mental health diagnosis vs no mental health diagnosis |

| **Reference** | **Seal 2012[158]** |
|---|---|
| | Concurrent opioids (>7 days overlap):<br>Adjusted RR 1.62 (95% CI 1.44 to 1.81) for mental health diagnosis without PTSD<br>Adjusted RR 1.87 (95% CI 1.70 to 2.06) for PTSD with or without other mental health diagnosis vs no mental health diagnosis<br>*Note: study also gives relative risks for the outcomes of highest quintile of average daily opioid use (≥33 mg/d) , duration of opioid use ≥2 months and concurrent sedative hypnotics.* |
| Funding | The Department of Veterans Affairs (VA) Health Services Research and Development (HSRD) Research Enhancement Award Program at the San Francisco VA Medical Centre, VA HSRD Career Development Awards and the National Institutes of Health, National Heart, Lung and Blood Institute (country: USA) |
| Comments | Very high risk of bias across risk factors and outcomes as per the QUIPS checklist |

| **Reference** | **Tvete 2016[169]** |
|---|---|
| Study type and analysis | Retrospective cohort (observational prescription registry) study with cox proportional hazard regression model analysis |
| Number of participants and characteristics | N= 19,747 new BZD users with a first redemption for diazepam or oxazepam<br>N=15,927 (80.7%) started on diazepam<br>Of these: n=5998 (37.7%) were male; previous medication: 19.2% antidepressants and lithium, 5.3% antipsychotics, 0.6% opioids, anti-alcohol and smoking cessation drugs, 21.8% drugs for cardiac disease, 6.3% drugs for rheumatic diseases, 10.3% drugs for COPD<br>N=19,946 (68.7%) had high education<br>N=5943 (37.3%) had low income; n=6663 (41.8%) had average income; n=3321 (20.9%) had high income<br>N=5309 (33.3%) worked in the private sector; n=5902 (37.1%) worked in the public sector; n=4715 (29.6%) bot registered<br>N=3820 (19.3%) started on oxazepam<br>Of these: n=1629 (42.6%) were male; previous medication: 26.8% antidepressants and lithium, 9.1% antipsychotics, 1.7% opioids, anti-alcohol and smoking cessation drugs, 22.8% drugs for cardiac disease, 5.2% drugs for rheumatic diseases, 10.8% drugs for COPD<br>N=2509 (65.7%) had high education |

| Reference | Tvete 2016[169] |
|---|---|
| | N=1657 (43.4%) had low income; n=1443 (37.8%) had average income; n=720 (18.8%) had high income<br>N=1080 (28.3%) worked in the private sector; n=1330 (34.8%) worked in the public sector; n=1410 (36.9%) bot registered<br>Data source:<br>Data on prescription fulfilments were extracted from the Norwegian Prescription Registry (NorPD) linked with socio-economic data from Statistics Norway (SSB)<br>Inclusion and exclusion criteria:<br>Norwegian inhabitants aged 30-60 years who had a first redemption for diazepam or oxazepam during 2006, without redemptions for alprazolam, nitrazepam, flunitrazepam, hydroxyzine or buspirone from January 2004 to December 2005; the first redemption being between 10 and 30 defined daily doses and average defined daily dose per day redeemed in the first three months <1. Individuals who died during the observation period and individuals whose education level was registered is SSB were excluded.<br>Baseline details:<br>Diazepam group: mean age: 46.75 years<br>Oxazepam group: mean age :47.29 years |
| Prognostic variables | Sex: female vs male (referent)<br>Age (continuous)<br>First BZD: oxazepam vs diazepam (referent)<br>Previous medication: antidepressants and lithium, antipsychotics, opioids, anti-alcohol, and smoking cessation drugs, drugs and rheumatic diseases, drugs for Chronic obstructive pulmonary disease (COPD)<br>Education: high (upper secondary school or higher) vs Low (until lower secondary school) (referent)<br>Income: low (referent; equivalent of14500 GBP) vs average (equivalent of 22000GBP) vs high (equivalent of 29000 GBP or higher)<br>Type of work: private sector, public sector vs no registration (referent: e.g., unemployment, working from home, being ill and/or disabled) |
| Confounders | Socio-demographic status and previous drug use; unclear if the analysis adjusted for other covariates in addition to the aforementioned and those entered in the model as prognostic factors |

| Reference | Tvete 2016[169] |
|---|---|
| Outcomes and effect sizes | Time to reach consumption level 2: redemption of ≥1 defined daily doses on average per day over a 3-month period (from a starting point of <1 defined daily doses on average per day in the first 3 months). This outcome was defined as dose escalation which is considered a measure of drug misuse/ dependence by the primary study.<br>HR 0.571 (95% CI 0.505 to 0.645) for male vs female<br>HR 0.984 (95% CI 0.977 to 0.99) for age (continuous)<br>HR 1.328 (95% CI 1.167 to 1.512) for first BZD prescription: oxazepam vs diazepam<br>HR 1.687 (95% CI 1.491 to 1.91) for previous medication: antidepressants and lithium<br>HR 1.753 (95% CI 1.488 to 2.066) for previous medication: antipsychotics<br>HR 3.042 (95% CI 2.285 to 4.049) for previous medication: opioids, anti-alcohol and smoking cessation drugs<br>HR 1.216 (95% CI 0.968 to 1.529) for previous medication: drugs for rhematic diseases<br>HR 1.288 (95% CI 1.089 to 1.523) for previous medication: drugs for COPD<br>HR 0.647 (95% 0.574 to 0.73) for education high vs low<br>HR 0.719 (95% CI 0.615 to 0.841) for average income vs low<br>HR 0.569 (95% CI 0.453 to 0.714) for high income vs low<br>HR 0.622 (95% CI 0.520 to 0.743) for type of work: private sector vs no registration<br>HR 0.613 (95% CI 0.518 to 0.725) for type of work: public sector vs no registration |
| Funding | The Norwegian Research council (project number 190420/V50) |
| Comments | High risk of bias for all risk factors as per the QUIPS checklist |

| Reference | Udayachalerm 2021[170] |
|---|---|
| Study type and analysis | Retrospective cohort study, Cox proportional hazards with stepwise selection |
| Number of participants and characteristics | Total N=341, 722<br>N= 274,272 opioids only<br>N= 67,450 benzodiazepine cohort (opioids and benzodiazepines) |

| Reference | Udayachalerm 2021[170] |
|---|---|
| | Baseline characteristics (N=341, 722):<br>Mean age (SD): 52.31 years (18.11); Female: 58.5%<br>White: n=226,728, Black: n=30,578, Hispanic/Latino: n=1543, Asian: n=907, Native Hawaiian and other pacific Islanders: n=887, American Indian and Alaska Native: n=245, Others: n=11,530<br>Charlson Comorbidity index score: Score 0= 178,025 and score 1-10=93,815<br>Mental health conditions: 73,515<br>Patients receiving medication for OUD: n=2270<br>Short-acting opioids only: n=334,243, long-acting only: n=348; short-acting and long-acting within 30 days: n=6301, short-acting and long-acting not within 30d: n=830<br>Concurrent medications with opioids: None (opioid only): n=275, 355, Benzodiazepine: n=34,829, Gabapentin/pregabalin: n=21,714, benzodiazepine and gabapentin/pregabalin within 30 days: n=7561; benzodiazepine and gabapentin/pregabalin not within 30 days: n=2263<br>Data source:<br>The study used medical, pharmacy, and encounter data contained within the Indiana Network for Patient Care (INPC) from 1 January 2012 to 31 December 2017. INPC, managed by Regenstrief Institute, is a state-wide health Information exchange that captures and stores clinical data for most of Indiana's health systems, hospital, clinics, and providers, with data for more than 18 million patients. Most clinical data are from electronic health record entries. Pharmacy prescription data are contributed from Surescripts, a health information network that connects more than 95% of US pharmacies.<br>Inclusion criteria:<br>At least 18 years old, opioid naïve (no prior opioid prescription in the past 12 months) and had an opioid index date (first date of opioid prescription) within the study period. Had at least 6 months of available data from index date.<br>Exclusion criteria:<br>Diagnoses of cancer, dementia, or chronic liver disease and those who used medication for OUD at baseline.<br>Indirectness: Proportion of those treated with opioids for chronic pain was unclear.<br>Baseline: long term use 6.94% (long term use indicates patients who had a cumulative opioid days' supply of at least 90 days within 6 months after the index opioid prescription). |
| Prognostic variable | Number days' supply (continuous) |

| Reference | Udayachalerm 2021[170] |
|---|---|
| | Opioid dosage, MME/d (continuous) (opioid dosage in milligrams was converted to morphine milligram equivalents (MME) by multiplying the dose in milligrams (average of all opioid medications prescribed for the person before the outcome occurred) with the conversion factor. Further converted to MME/d using formula (opioid dose in milligrams x MME conversion factor x dispensed amount)/ (number of days' supply)<br>**Concurrent short-acting (SA)/long-acting (LA) opioids:**<br>Concurrent use of SA and LA opioids within 30 days vs SA alone (referent)<br>Concurrent use of SA and LA opioids not within 30 days vs SA alone (referent)<br>Long acting only vs SA alone (referent)<br>**Concurrent medications with opioids:**<br>Concurrent use of benzodiazepines vs none – opioids only (referent)<br>Concurrent use of gabapentin/pregabalin vs opioids only (referent)<br>Concurrent use of benzodiazepines and gabapentin/ pregabalin within 30 days vs opioids only (referent)<br>Concurrent use of benzodiazepines and gabapentin/ pregabalin not within 30 days vs opioids only (referent) |
| Confounders | Analyses adjusted for age, sex and comorbidities. |
| Outcomes and effect sizes | Composite outcome (any combination of opioid abuse, dependence, or overdose): created using ICD-9 and ICD-10 codes and defined as having a diagnosis of any combination of opioid abuse, dependence, or overdose within the study period (n=208,959), Incidence was 1.90 per 1000 person-years for the full patient cohort<br>*Note: the primary study also reports results for this outcome for other prognostic factors such as age and gender in table 3. However, the methods suggests that only those variables listed as 'independent variables' in the methods section are adjusted for age, sex and comorbidities. It is not clear whether the other HRs in table 3 are adjusted for age, sex, race and comorbidities, and therefore, only those variables listed as 'independent variables' in the methods have been extracted.*<br>Composite outcome (any combination of opioid abuse, dependence, or overdose):<br>Adjusted HR: 1.025 (95% CI 1.019-1.032) for number of days' supply<br>Adjusted HR: 1.003 (95% CI 1.001-1.006) for opioid dosage (MME/d)<br>Adjusted HR: 2.12 (1.78-2.54) for concurrent use of SA and LA opioids within 30 days vs SA alone<br>Adjusted HR: 1.99 (1.24-3.18) for concurrent use of SA and LA opioids not within 30 days vs SA alone<br>Adjusted HR: 2.17 (0.81-5.86) for LA alone vs SA alone |

| **Reference** | **Udayachalerm 2021[170]** |
|---|---|
| | Adjusted HR: 1.38 (1.17-1.61) for concurrent use of benzodiazepines vs opioid alone<br>Adjusted HR: 1.54 (1.29-1.84) for concurrent use of gabapentin/pregabalin vs opioid alone<br>Adjusted HR: 1.68 (1.38-2.04) for concurrent use of benzodiazepines and gabapentin/ pregabalin within 30 days vs opioid alone<br>Adjusted HR: 1.66 (1.24-2.22) for concurrent use of benzodiazepines and gabapentin/ pregabalin not within 30 days vs opioid alone<br>*Note: study also gives results for the outcomes of abuse and dependence separately. However, it is unclear from the methods in the primary study whether these HRs were adjusted for confounders, therefore the results for the composite outcome only were used.* |
| Funding | Regenstrief Foundation Grant |
| Comments | High risk of bias for all risk factors and outcomes as per the QUIPS checklist |

| **Reference** | **Zhang 2018[180]** |
|---|---|
| Study type and analysis | Retrospective cohort study and linear probability models |
| Number of participants and characteristics | N= 196,375 privately insured adults aged 18 to 64 years<br>N= 63,419 Medicare advantage patients aged 65 or older<br>Only results for the privately insured patients aged 18 to 64 years are presented in the paper, hence only characteristics relevant to them have been extracted.<br>Features of the first opioid prescription:<br>Short vs long-acting opioids: 99.1% were prescribed a short-acting opioid during their first prescription<br>Daily average MMEs: 32.2% <30, 41.2% 30-50, 26.7% ≥ 50<br>Days of opioid supply: 40.2% ≤3 days, 41.6% 4-7 days, 18.3% > 7 days' supply<br>Data source:<br>The study used data from the 2011-2014 Health Care Cost Institute (HCCI) insurance claims database, including claims from private insurance plans and Medicare Advantage plans. Privately insured adults aged 18-64 and Medicate Advantage patients aged 65 or older who did not have recent use of prescription opioids (period of 6-months without any opioid prescription) and filled an opioid prescription between July 1st 2011 and June 30th 2013. |

| Reference | Zhang 2018[180] |
|---|---|
| | Inclusion criteria:<br>At least 6 months of continuous enrolment in a private healthcare plan or a MA plan contributing data to HCCI prior to the months of their first opioid prescription (the index month) and continuously enrolled for at least 18 months after the index month<br>Exclusion criteria:<br>A cancer diagnosis in the 6 months prior to the index month<br>Characteristics:<br>Age: 35.5% aged 18-34; 23.4% aged 35-44; 24.3% aged 45-54 and 16.9% aged 55-64; 55.3% female; 11.5% back pain, 5.3% neck pain, 23% arthritis, 12.8% other pain; 12.6% had a mental health disorder; 0.6% had an alcohol use disorder; 0.5% had a drug use disorder; 2.2% had a tobacco use disorder<br>Of the 340,629 patient-quarters with at least 1 day of opioid use, 4% had overlapping opioid prescriptions, 6.7% had overlapping opioid-benzodiazepine prescriptions, 2.5% had three or more prescribers and 4.2% had 120 or more daily average MMEs.<br>Indirectness: Proportion of those treated with opioids for chronic pain was unclear. |
| Prognostic variable | Duration of action of the first opioid prescription: long vs short acting status (referent)<br>Dosage of the first opioid prescription: daily average (morphine milligram equivalents) MMEs: <30 (referent) vs ≥30 but <50 or ≥50<br>Days of supply of the first opioid prescription: ≤ 3days (referent) vs 4-7 days and > 7 days |
| Confounders | Analyses controlled for ordinal indicators of the quarters (second, third, sixth, with the first quarter as the reference), calendar year indicators, patient demographics (age groups, sex); dichotomous indicators of back pain, neck pain, arthritis/joint pain and other pain, an indicator of any mental health disorder, alcohol use disorder, any drug use disorder and tobacco use disorder, socio-demographic profiles at the patient's residential ZIP codes. |
| Outcomes and effect sizes | Results were reported as percentage point increase compared to the reference category. Risk differences have been calculated using the confidence intervals. These are similar to the percentage point increases reported which had however been rounded to the nearest whole number. Thus, the confidence intervals, which were exact were used to get the risk difference as a more approximate measure.<br>**High-risk opioid use:**<br>Overlapping opioid prescriptions for 7 days or more (across the six 3-month quarters following the first prescription):<br>Risk difference 14.70 (95% CI 12.7 to 16.7) for long vs short acting opioids in the first prescription<br>Risk difference 6.65 (95% CI 6.3 to 7) for >7 days vs ≤3 days opioid supply in the first prescription |

| **Reference** | **Zhang 2018[180]** |
|---|---|
| | Risk difference 5.65 (95% CI 5.3 to 6) for >7 days vs 4-7 days opioid supply in the first prescription<br>Three or more prescribers of opioids (across the six 3-month quarters following the first prescription):<br>Risk difference 1.8 (95% CI 0.9 to 2.7) for long vs short acting opioids in the first prescription |
| Funding | Centre for Health Economics of Treatment Interventions for Substance Use Disorder, HCV and HIV (CHERISH), the National Institute on Drug Abuse Centre of Excellence (country: USA), the National Institute of Mental Health, the National Institute on Aging, the New York State Health foundation, the Agency for Healthcare Research and Quality and the Weill Cornell Medical College Department of Healthcare Policy and Research. |
| Comments | Very high risk of bias for all risk factors and outcomes as per the QUIPS checklist |

# Appendix E Forest plots

## E.1 Opioids

### E.1.1 Age

**Figure 2: Age ≤40 (compared to >40) for predicting codeine shopping behaviour**

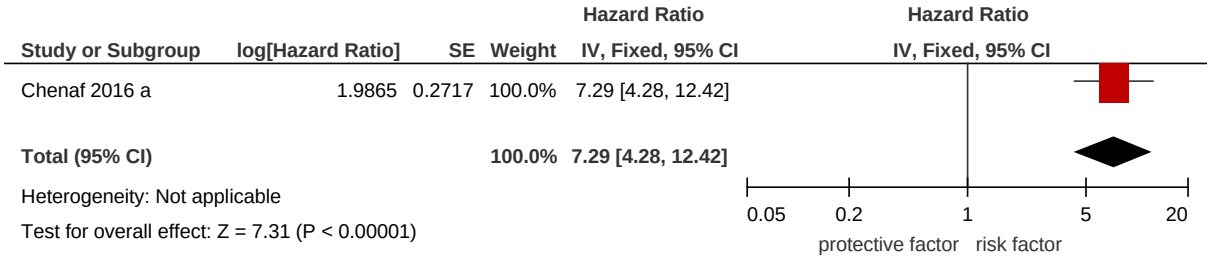



**Figure 3: Age continuous: increasing (compared to decreasing) for predicting prescription opioid abuse**

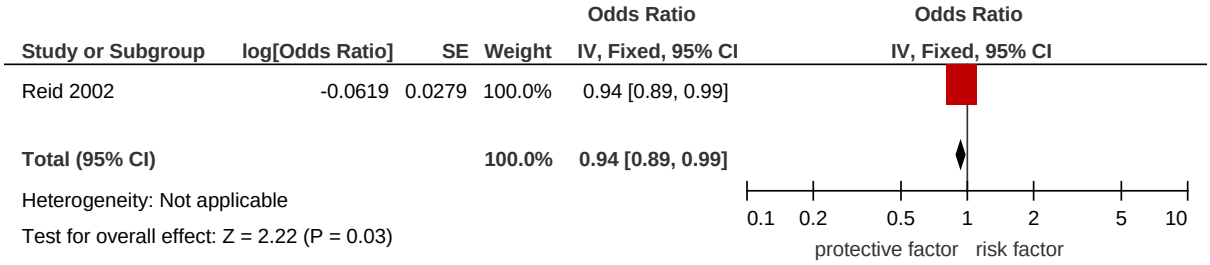
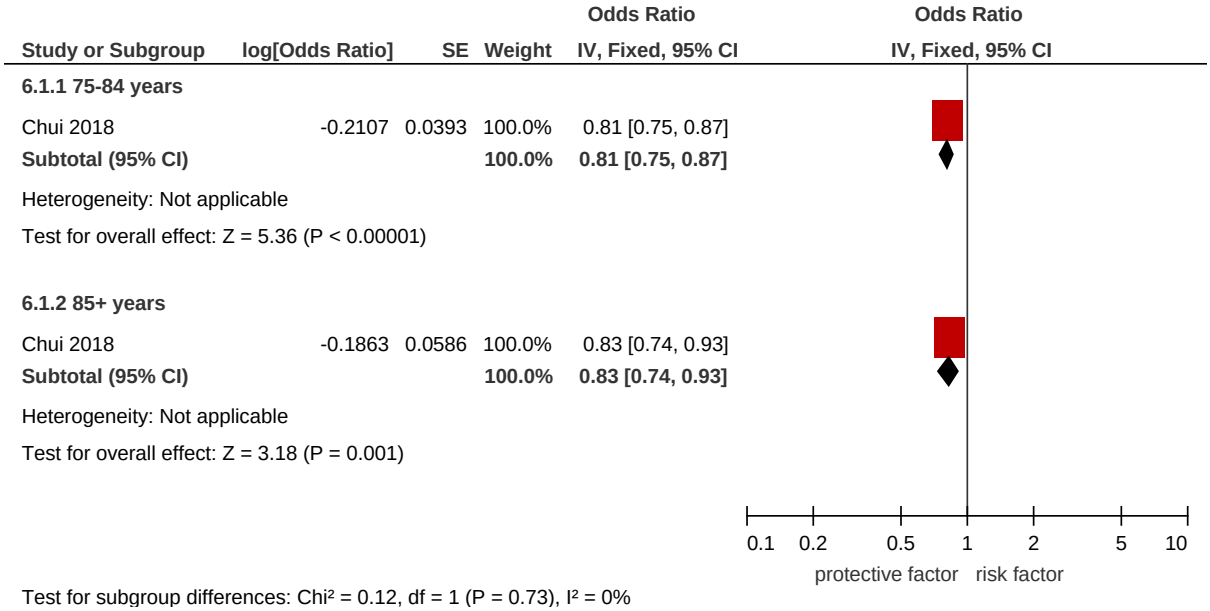
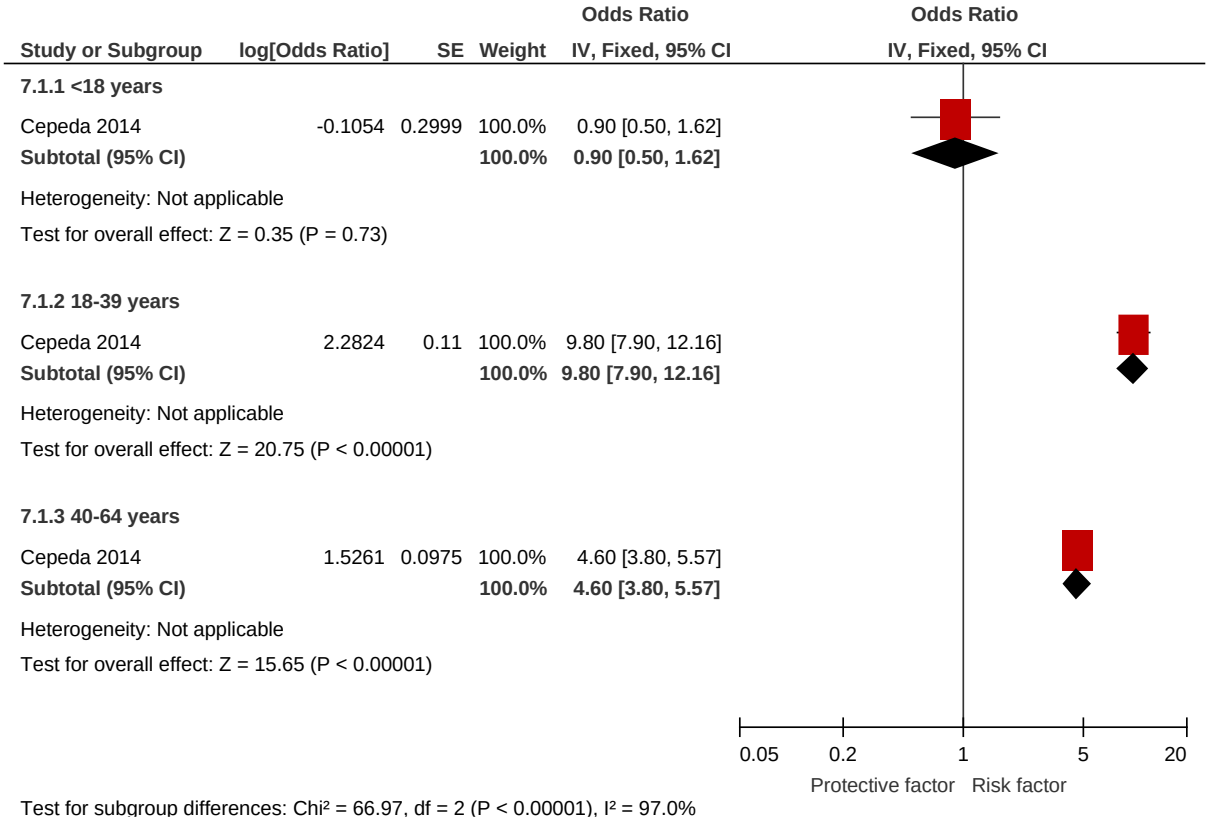



**Figure 4: Age (compared to 65-74 years) for predicting overlapping concurrent opioid prescription**



1

**Figure 5: Age (compared to >64 years) for predicting shopping behaviour**




2

**Figure 6: Age (compared to >64 years) for predicting opioid abuse**

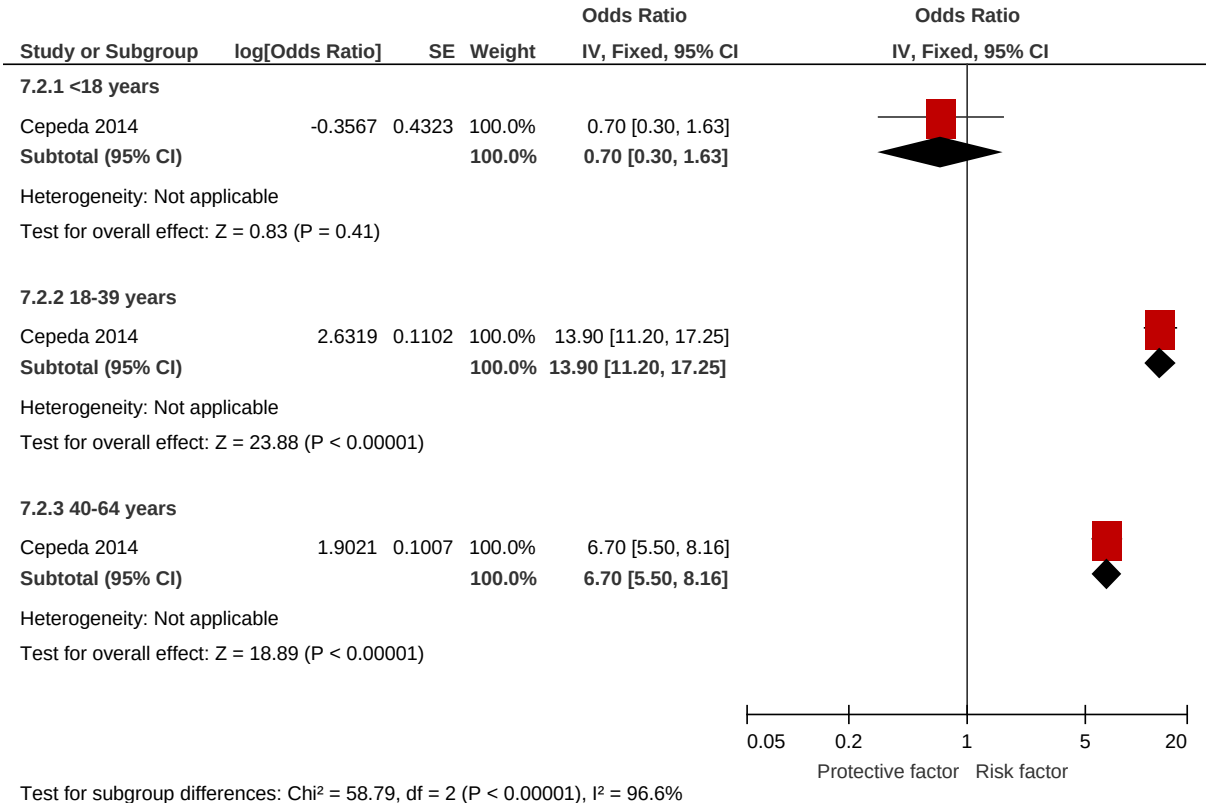
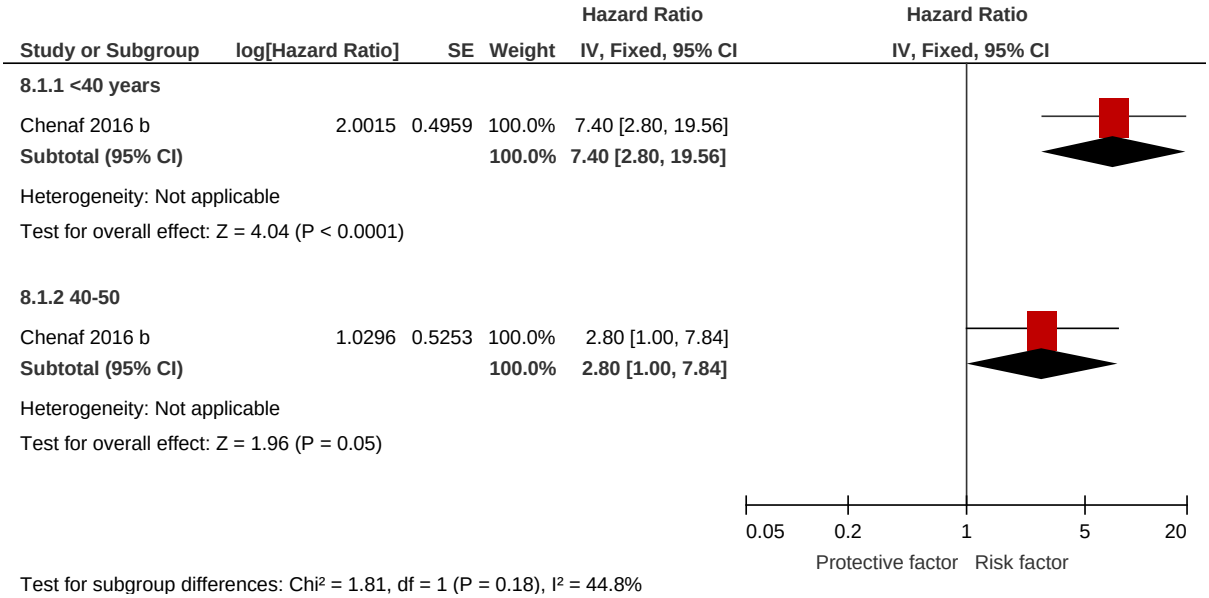
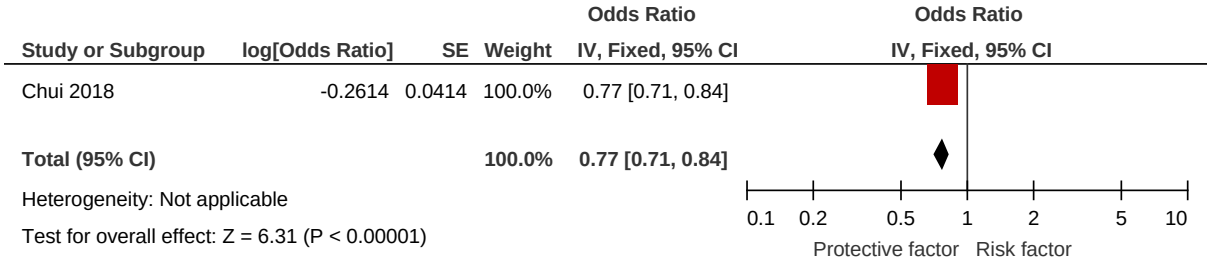



**Figure 7: Age (compared to ≥50 years) for predicting tramadol shopping behaviour**




## E.1.2 Family background

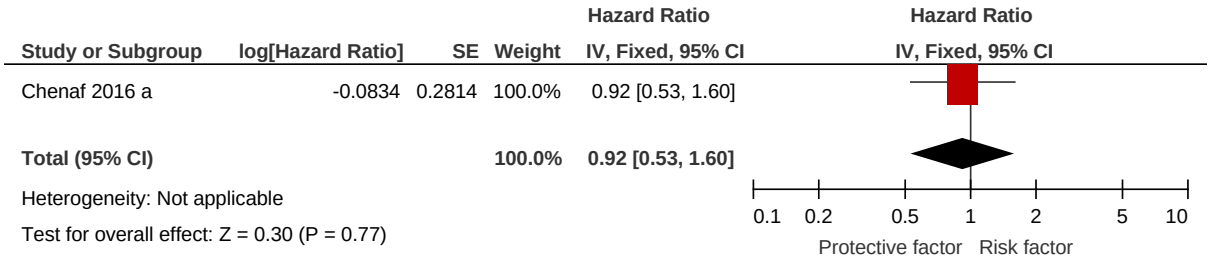
**Figure 8: Family background: white (compared to non-white) for predicting overlapping concurrent opioid prescriptions**




## 1 E.1.3 Gender

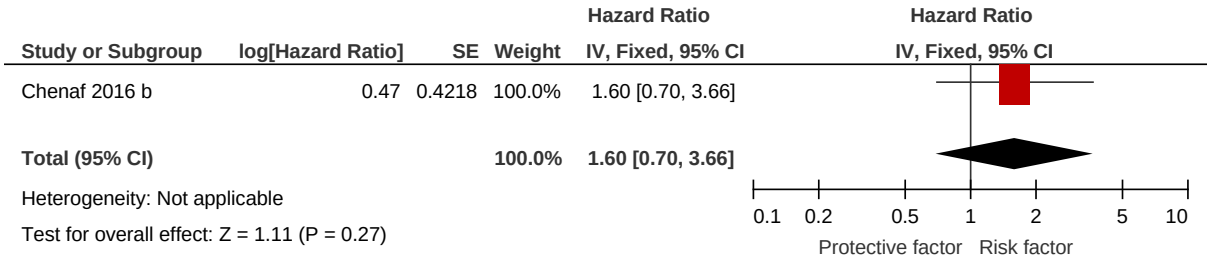
2

**Figure 9: Gender: female (compared to male) for predicting codeine shopping behaviour**



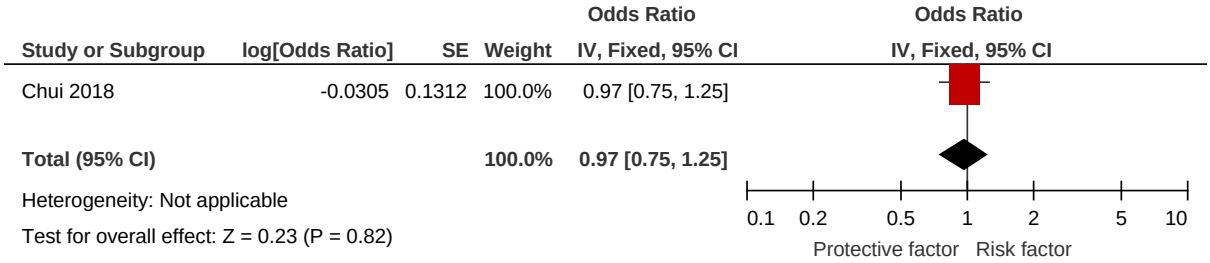

3

**Figure 10: Gender: female (compared to male) for predicting tramadol shopping behaviour**



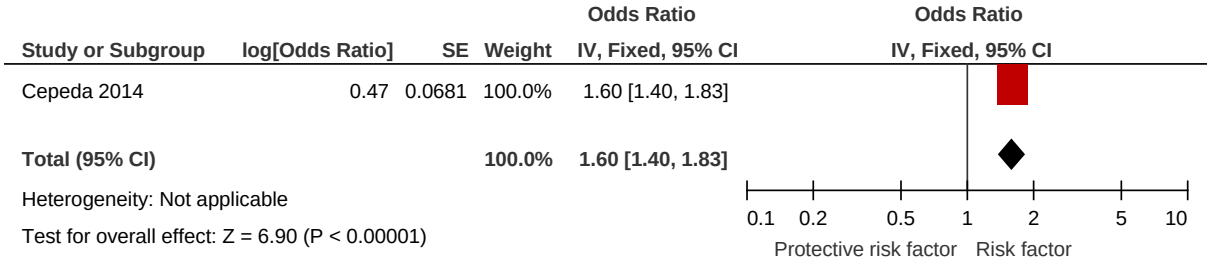

4

**Figure 11: Gender: female (compared to male) for predicting overlapping concurrent opioid prescription**



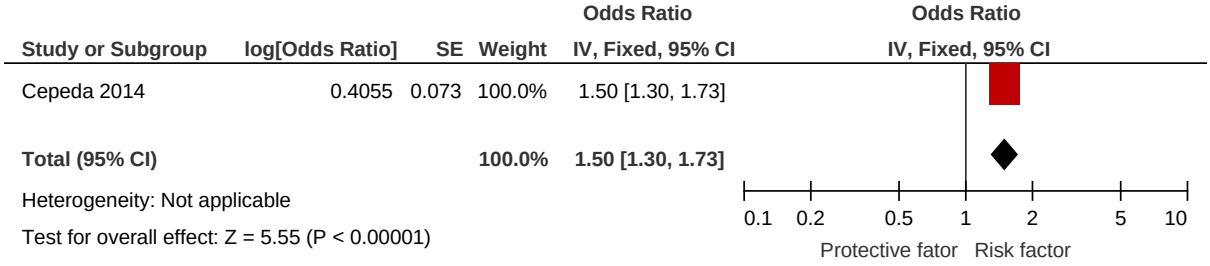
1

**Figure 12: Gender: male (compared to female) for predicting shopping behaviour**




2

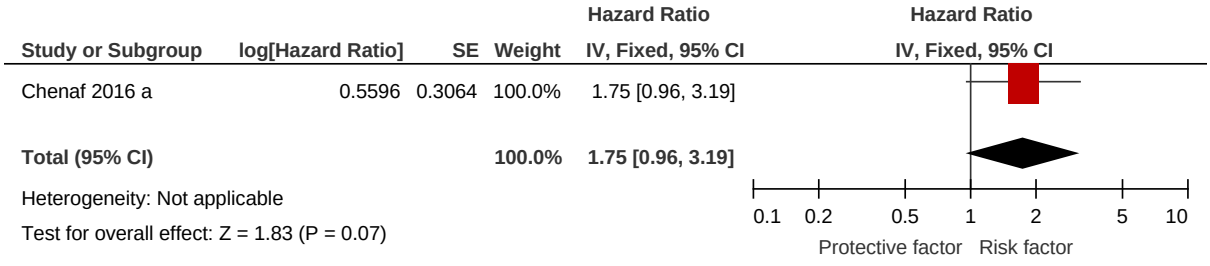
**Figure 13: Gender: male (compared to female) for predicting opioid abuse**




3

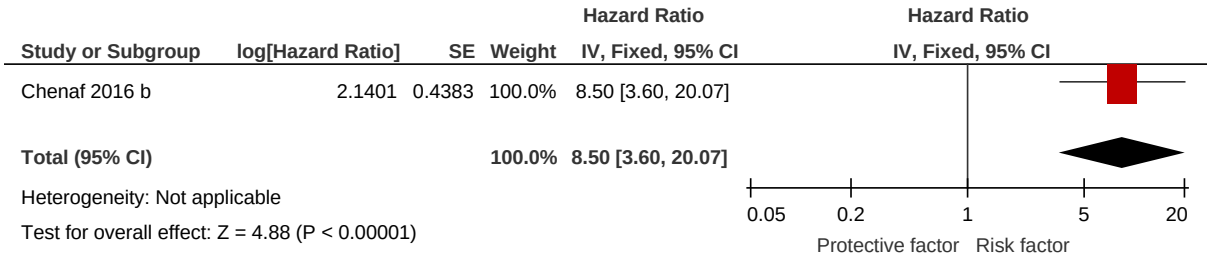
## 4 E.1.4 Low-income status

**Figure 14: Low income status (compared to no low-income status) for predicting codeine shopping behaviour**



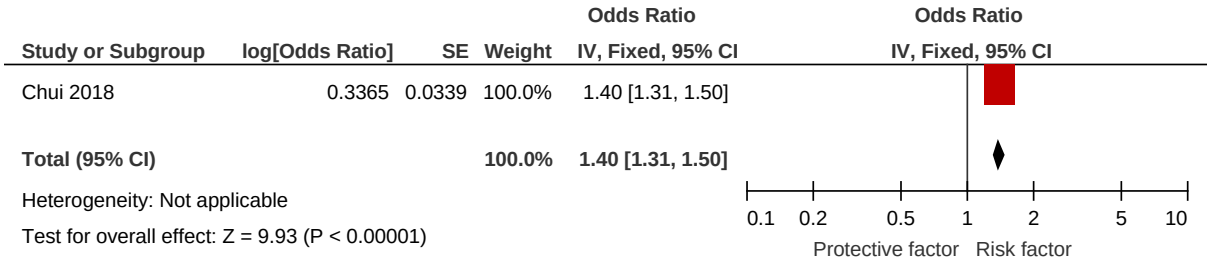

5

**Figure 15: Low-income status (compared to no low-income status) for predicting tramadol shopping behaviour**



## E.1.5 Pain intensity

**Figure 16: Moderate-to-severe pain intensity: NRS score 4-10 (compared to lower score) for predicting overlapping concurrent opioid prescriptions**




## E.1.6 Clinical severity

**Figure 17: Clinical severity: Charlson comorbidity index +2 (compared to lower score) for predicting overlapping concurrent opioid prescriptions**

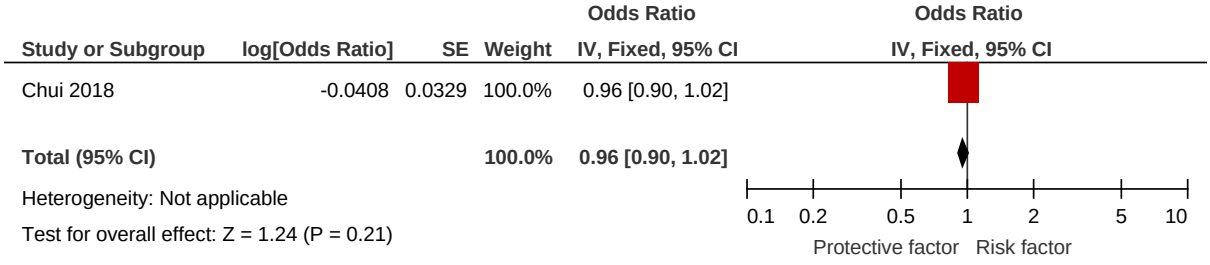
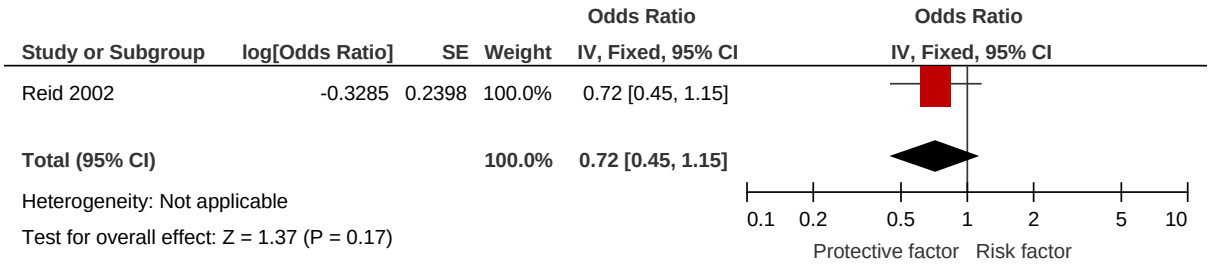
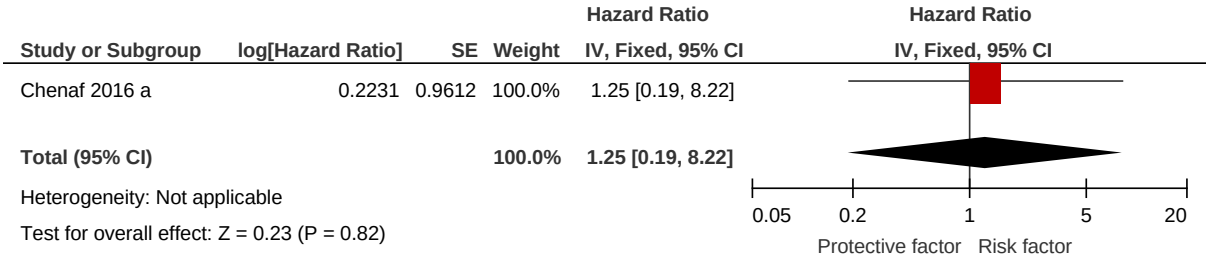



**Figure 18: Number of medical diseases (mean, determined by the unweighted Charlson Index) for predicting prescription opioid abuse**




## E.1.7 History of opioid use disorder

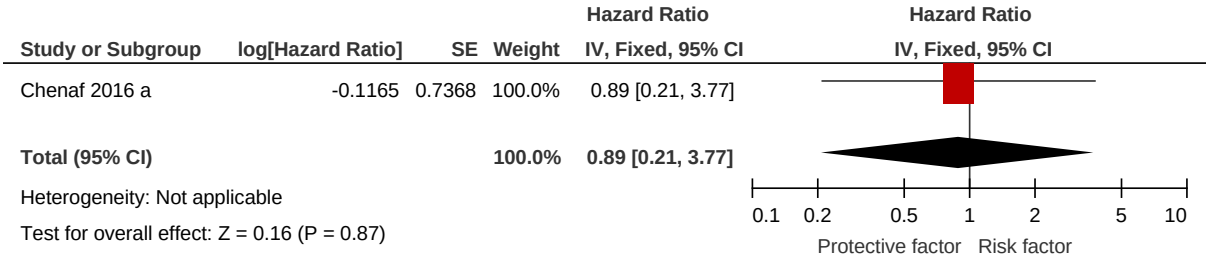
**Figure 19: History of opioid use disorder (compared to no history of disorder) for predicting codeine shopping behaviour**




## 1 E.1.8 History of substance use disorder/abuse of non-opioid drugs

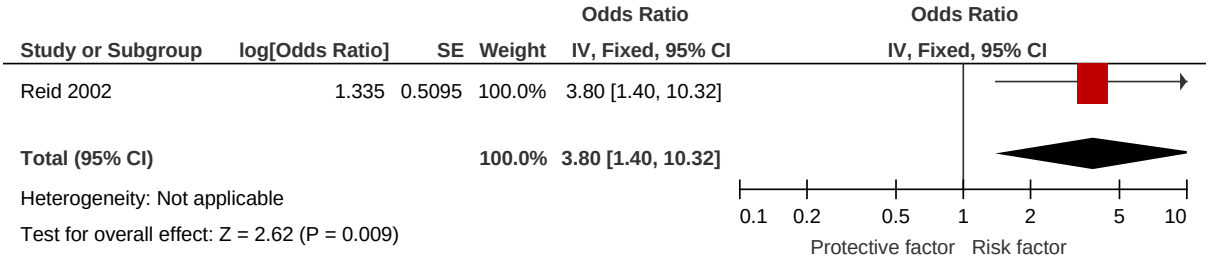
2

**Figure 20: History of substance use disorder for non-opioids (compared to history of disorder) for predicting codeine shopping behaviour**



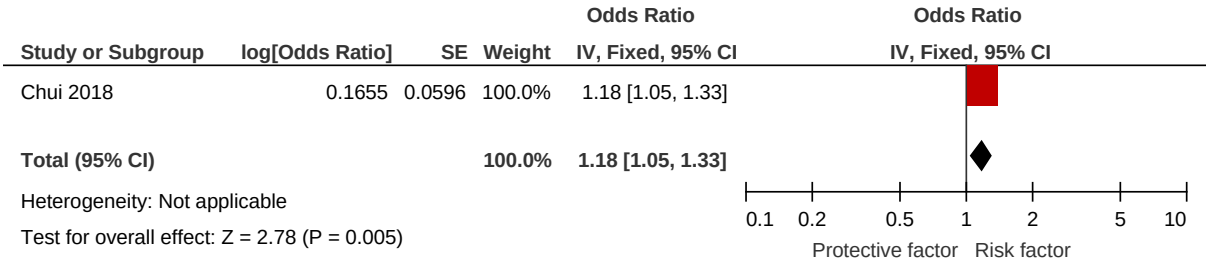

3

**Figure 21: Lifetime history of substance use disorder (compared to no history of disorder) for predicting prescription opioid abuse behaviour**



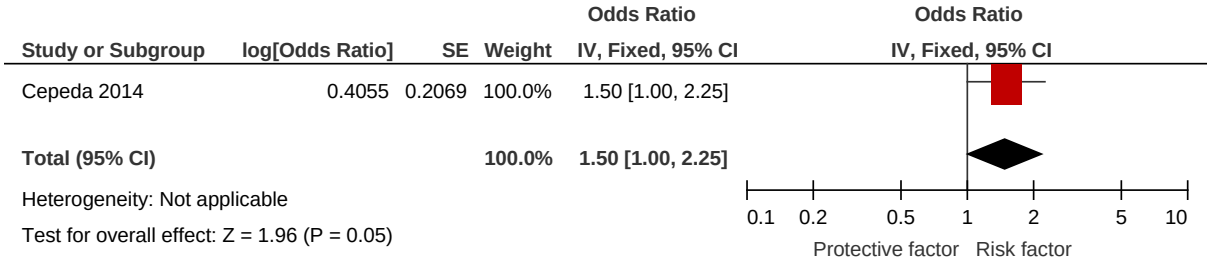

4

**Figure 22: Substance use disorder (at index date; compared to no substance use disorder) for predicting overlapping concurrent opioid prescriptions**



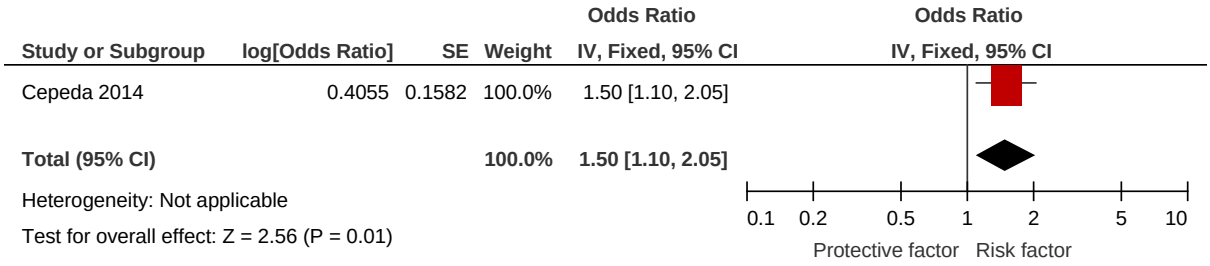
1

**Figure 23: History of abuse of non-opioid drugs (compared to no history of abuse) for predicting shopping behaviour**




2

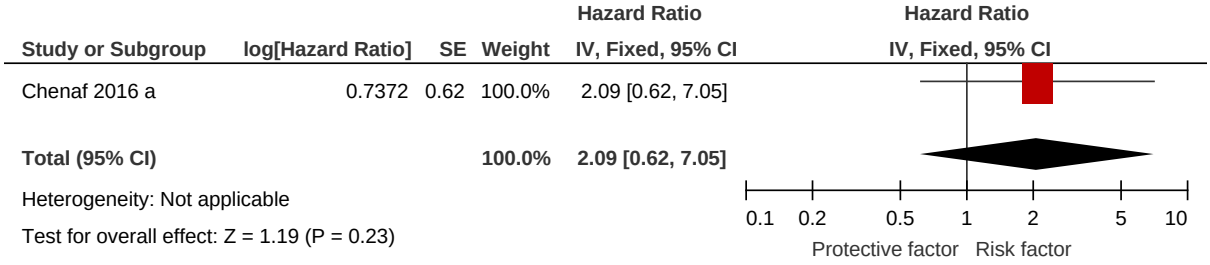
**Figure 24: History of abuse of non-opioid drugs (compared to no history of abuse) for predicting opioid abuse**




3 ## E.1.9 Active chronic liver disease

4

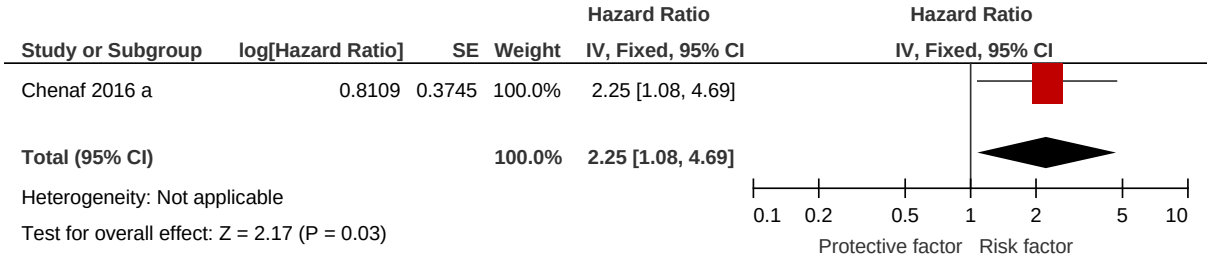
**Figure 25: Active chronic liver disease (compared to no liver disease) for predicting codeine shopping behaviour**




5 ## E.1.10 Mental health disorders

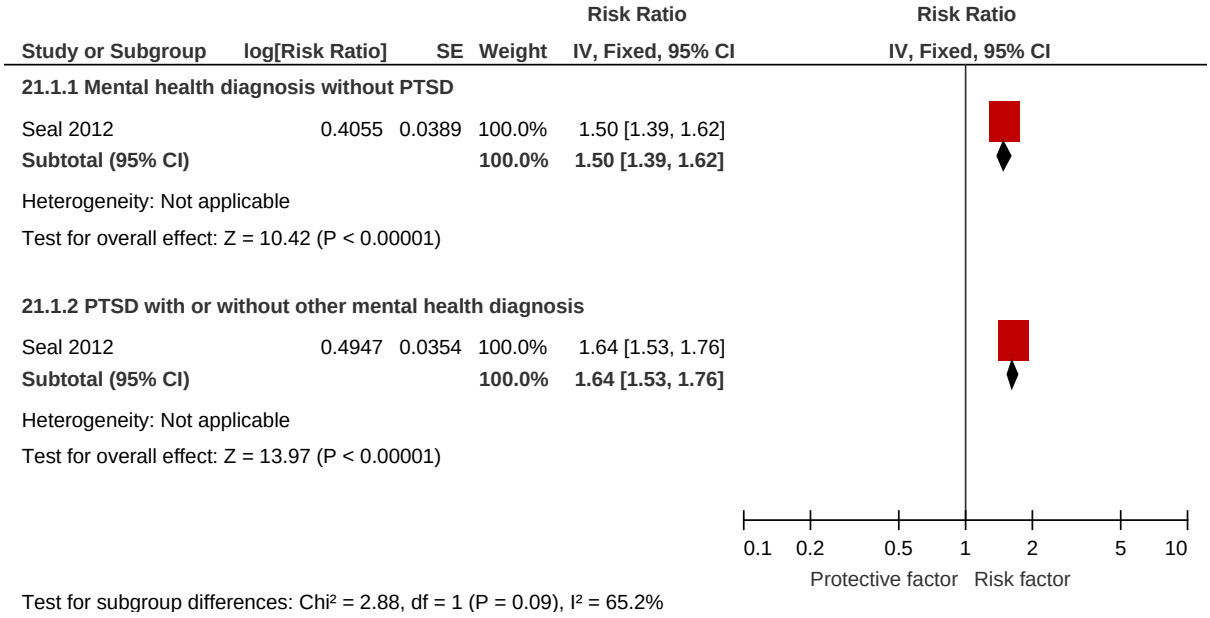
6

**Figure 26: Mental health disorders (compared to no diagnosis) for predicting codeine shopping behaviour**



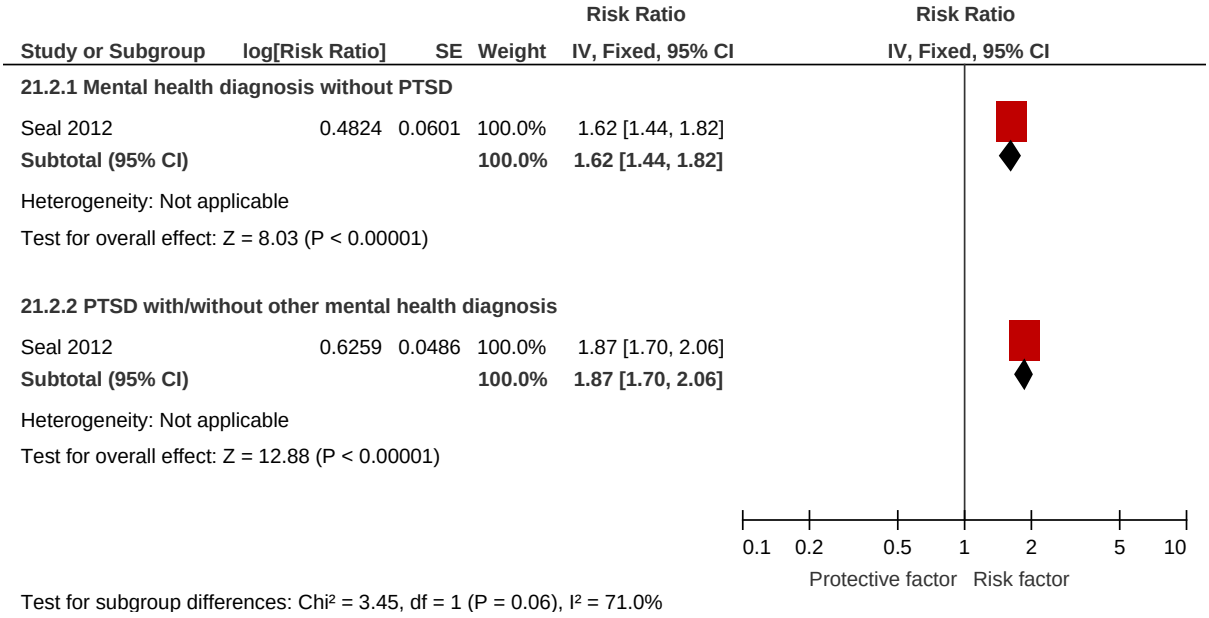

1

**Figure 27: Mental health diagnosis with or without PTSD (compared to no mental health diagnosis) for predicting early opioid refill**



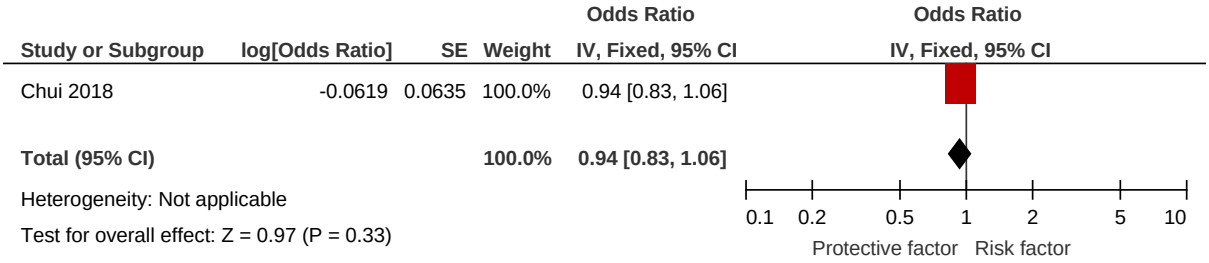

2

**Figure 28: Mental health diagnosis with or without PTSD (compared to no mental health diagnosis) for predicting concurrent opioids**



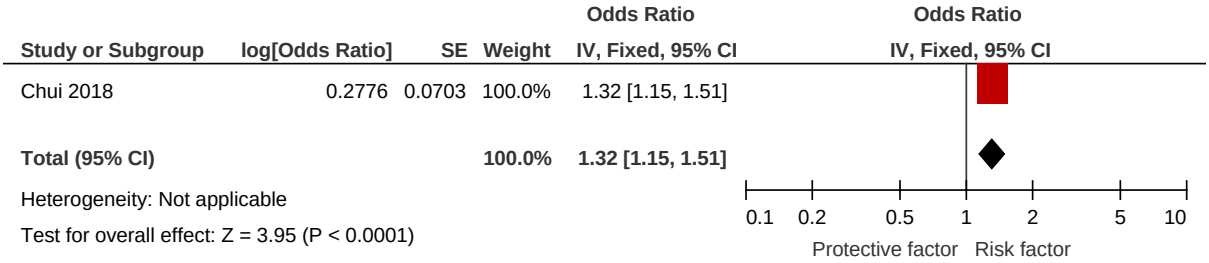

1

**Figure 29: PTSD (compared to no PTSD) for predicting overlapping concurrent opioid prescription**




2

**Figure 30: Major depression (compared to no major depression) for predicting overlapping concurrent opioid prescriptions**



## E.1.11 History of mood disorders

**Figure 31: History of mood disorders (compared to no history of mood disorders) for predicting shopping behaviour**

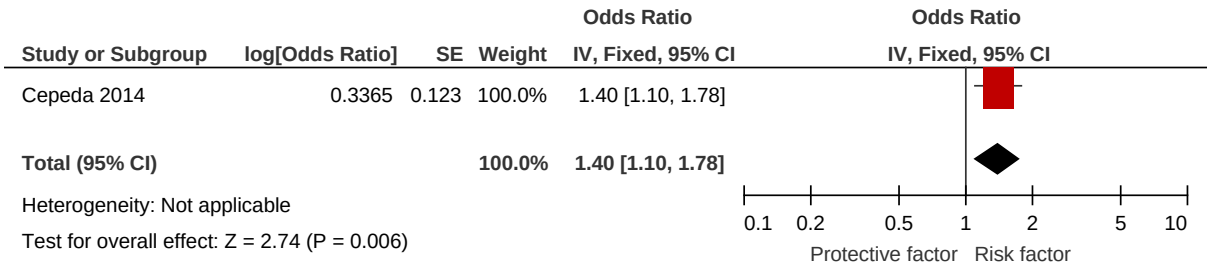
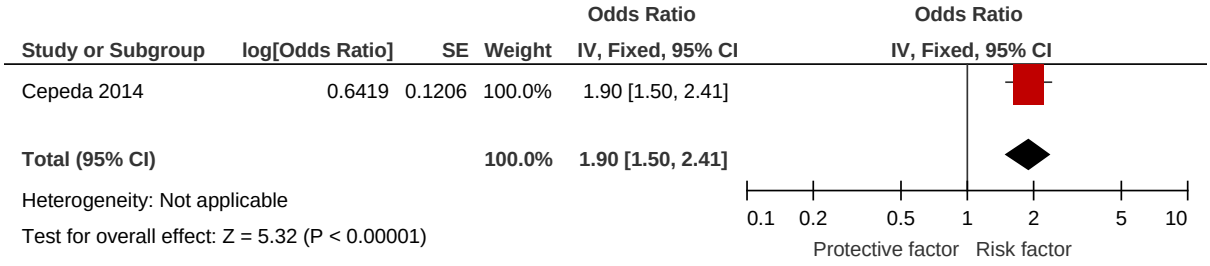
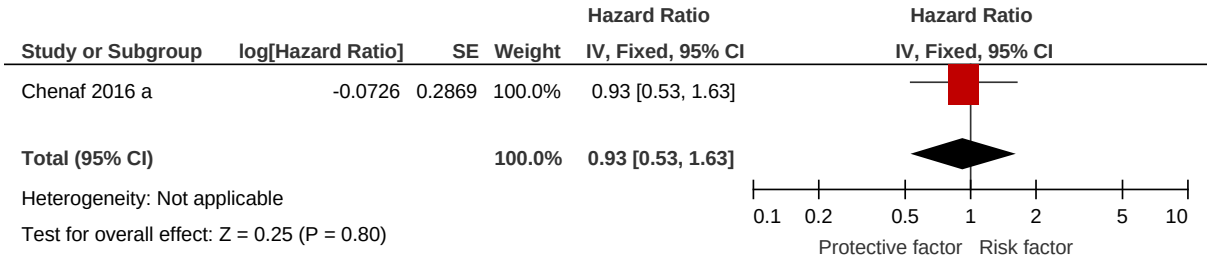



**Figure 32: History of mood disorders (compared to no history of mood disorders) for predicting opioid abuse**



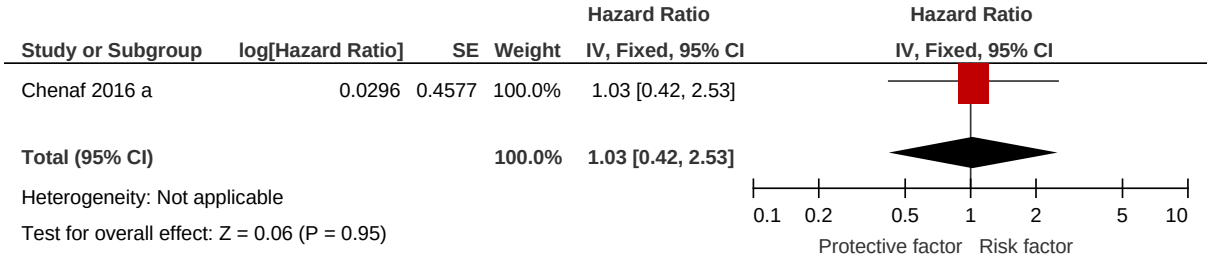

## E.1.12 Concurrent use of antidepressants

**Figure 33: Concurrent use of antidepressants (compared to no concurrent use) for predicting codeine shopping behaviour**



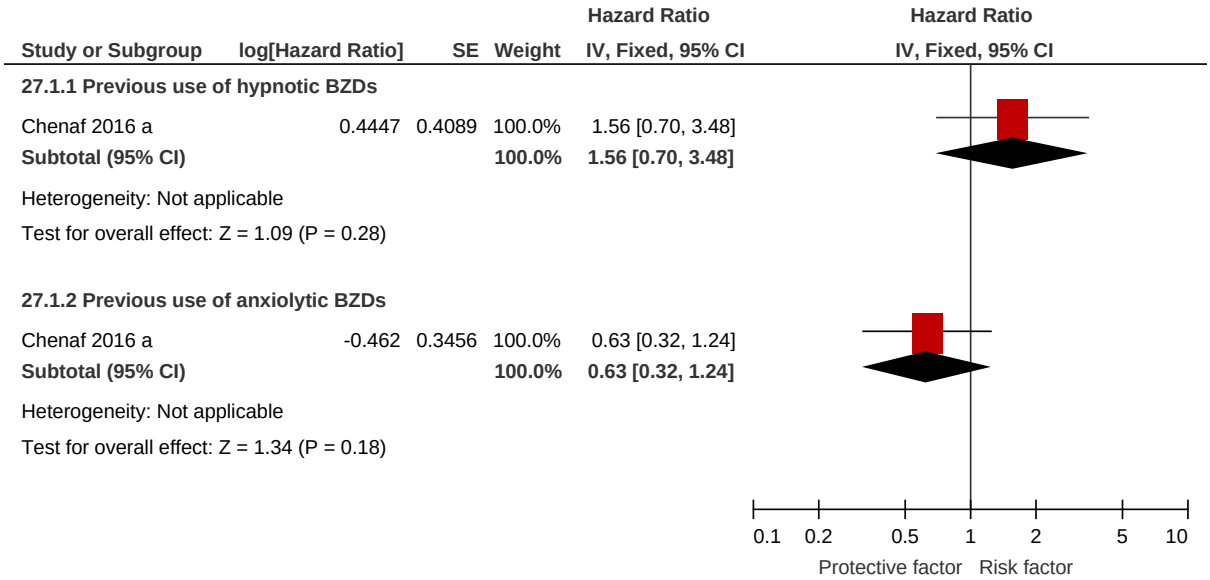

## E.1.13 Previous use of antipsychotics

**Figure 34: Previous use of antipsychotics (compared to no previous use) for predicting codeine shopping behaviour**




## 1 E.1.14 History of benzodiazepine use

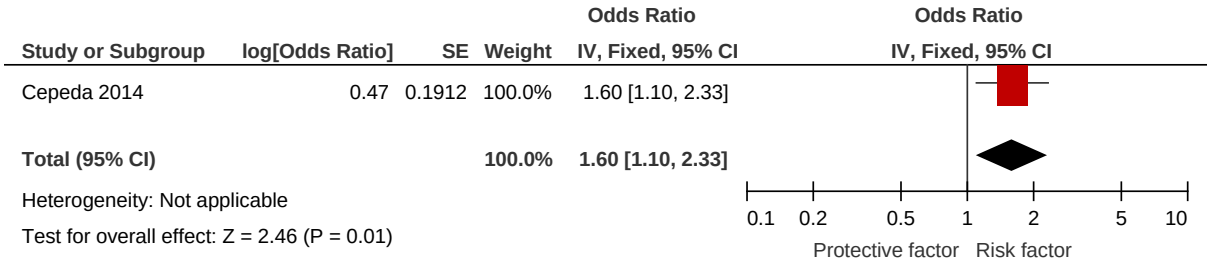
**Figure 35: Previous use of benzodiazepine (compared to no previous use) for predicting codeine shopping behaviour**




Test for subgroup differences: Chi² = 2.87, df = 1 (P = 0.09), I² = 65.1%

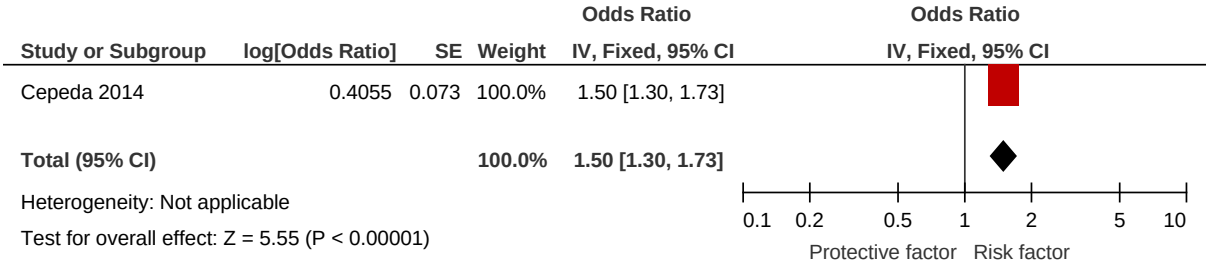
2

**Figure 36: History of benzodiazepine use (compared to no history of use) for predicting shopping behaviour**




3

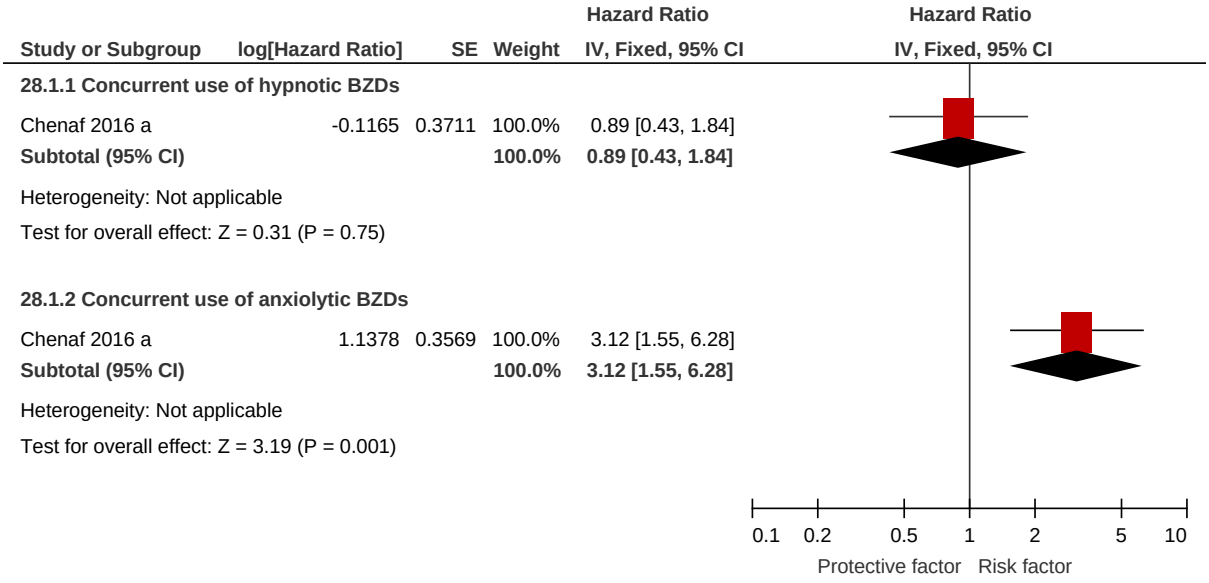
**Figure 37: History of benzodiazepine use (compared to now history of use) for predicting opioid abuse**




## 1 E.1.15 Concurrent use of benzodiazepines/ concurrent use of gabapentin/pregabalin

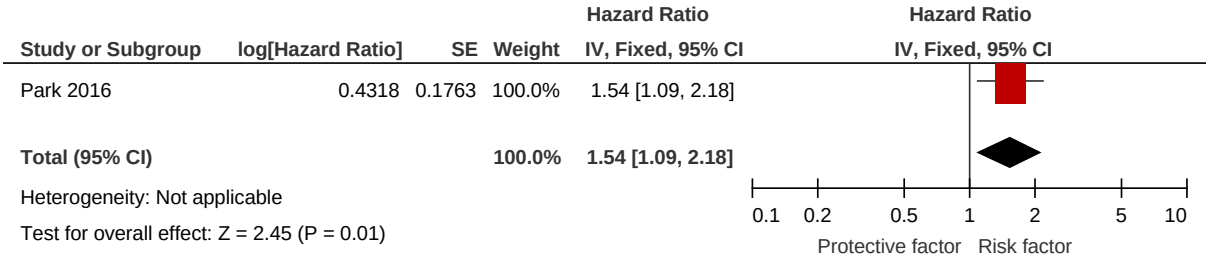
2

**Figure 38: Concurrent use of benzodiazepine (compared to no concurrent use) for predicting codeine shopping behaviour**




3

**Figure 39: Receipt of benzodiazepine prescription (compared to no receipt) for predicting second early opioid refill**




4

**Figure 40: Concurrent use of benzodiazepines (compared to opioid alone) for predicting composite outcome – any combination of opioid abuse, dependence or overdose**

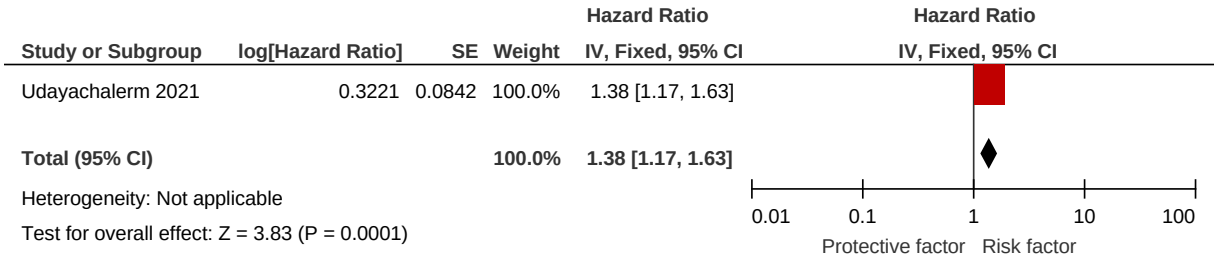



**Figure 41: Concurrent use of gabapentin/pregabalin (compared to opioid alone) for predicting composite outcome – any combination of opioid abuse, dependence or overdose**

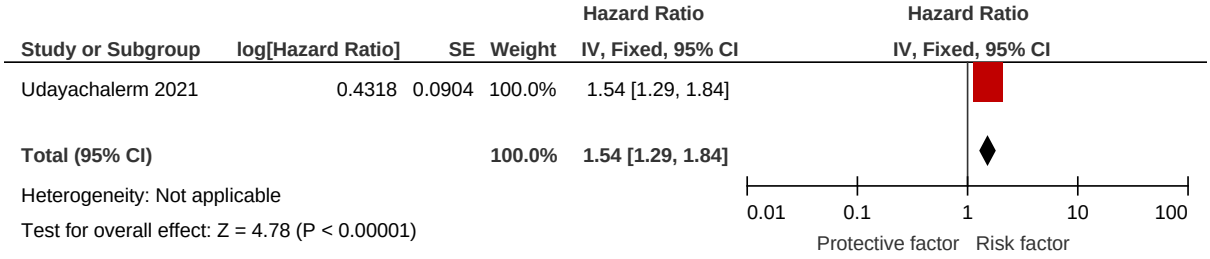



**Figure 42: Concurrent use of benzodiazepines and gabapentin/pregabalin within 30 days (compared to opioid alone) for predicting composite outcome – any combination of opioid abuse, dependence or overdose**

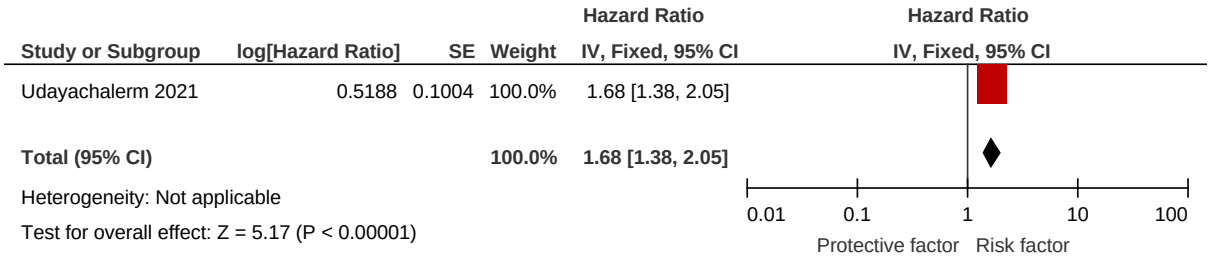
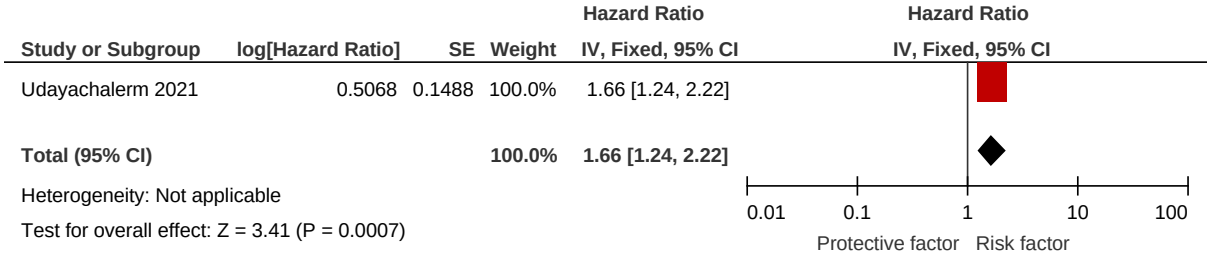


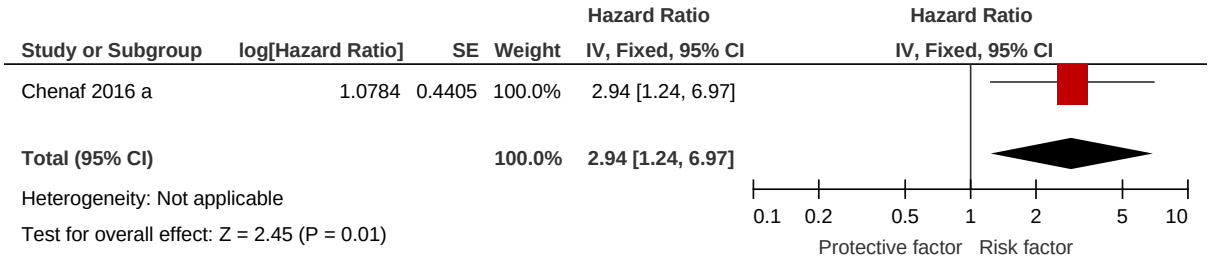
**Figure 43: Concurrent use of benzodiazepines and gabapentin/pregabalin not within 30 days (compared to opioid alone) for predicting composite outcome – any combination of opioid abuse, dependence or overdose**




1

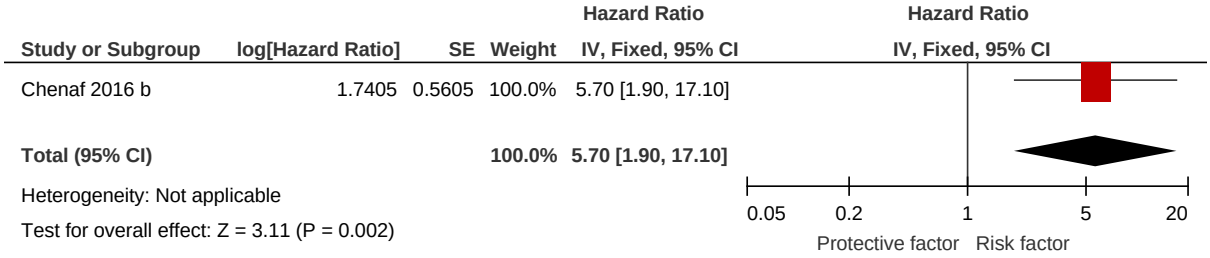
## 2 E.1.16 Previous use of strong opioids

**Figure 44: Previous use of strong opioids (compared to no previous use) for predicting codeine shopping behaviour**




3

**Figure 45: Prior use of strong opioids (compared to no previous use) and tramadol shopping behaviour**



## E.1.17 Long-term opioid therapy

**Figure 46: Periods on long term opioids (compared to not being on a long-term opioid episode) for predicting incident addiction to opioids**

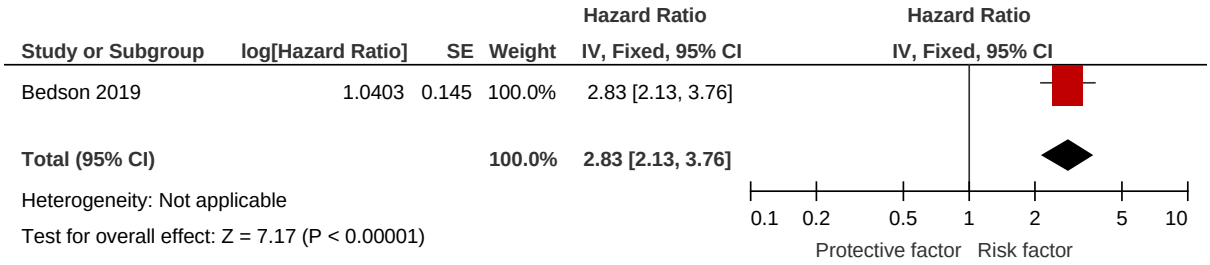



**Figure 47: Long-term opioid therapy (compared to short-term opioid therapy) for predicting opioid dependence**

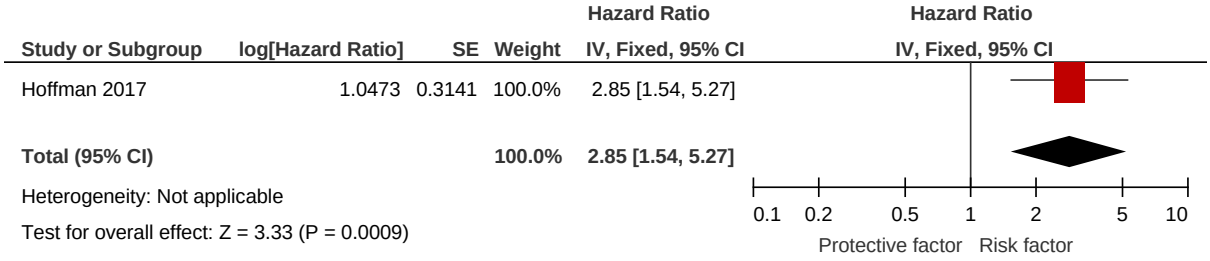
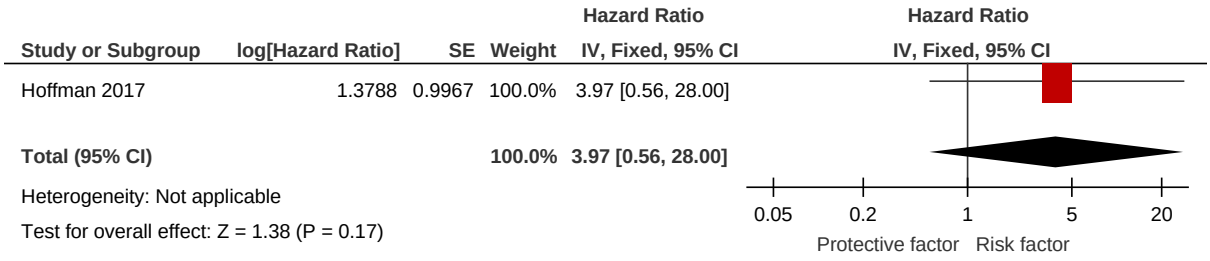



**Figure 48: Long-term opioid therapy (compared to short-term opioid therapy) for predicting opioid abuse**



## E.1.18 Opioid dosage

**Figure 49: Long-term episode at the following average daily dose (ADD) (compared to not being in an episode of long-term prescribing) for predicting incident addiction to opioids**

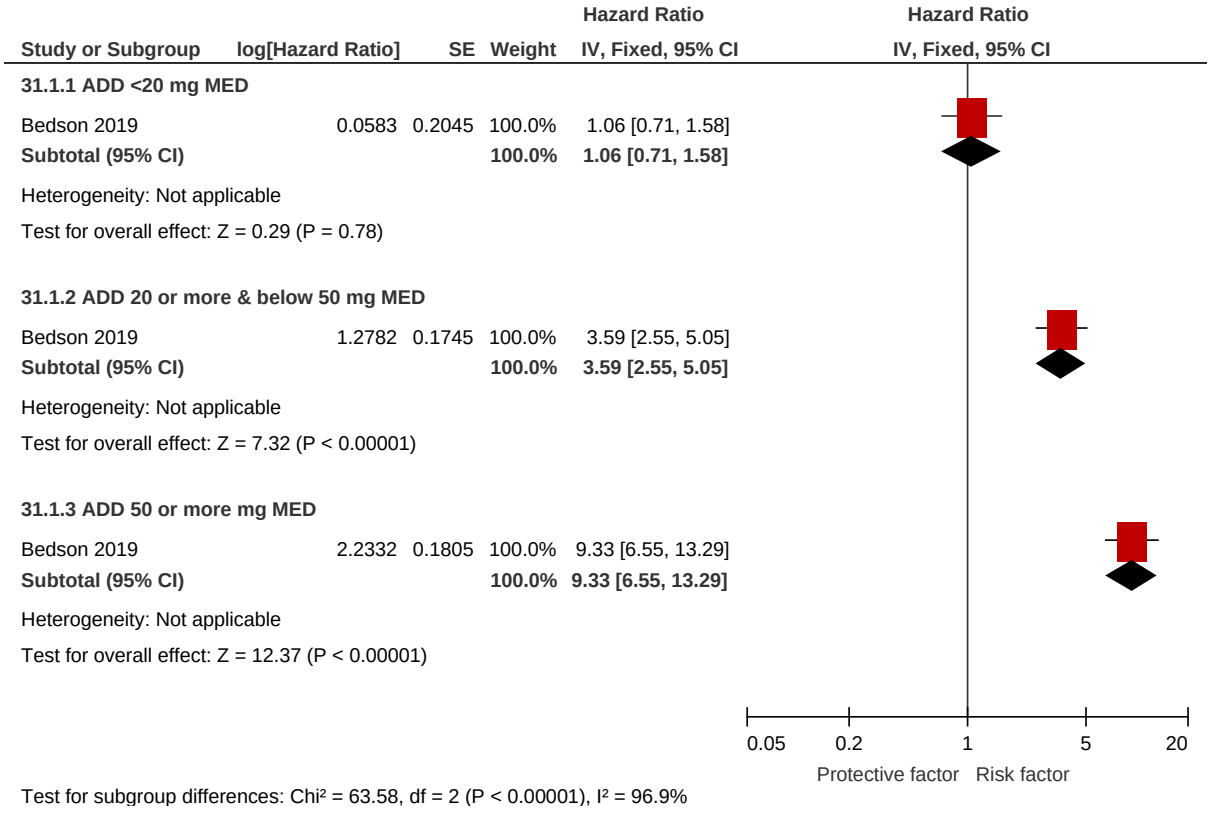
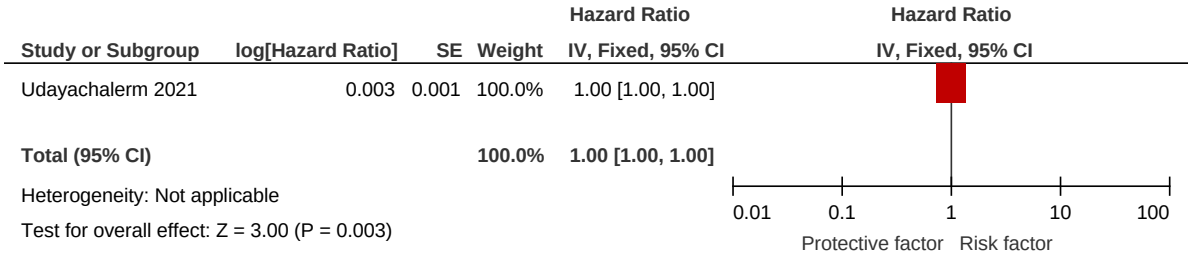
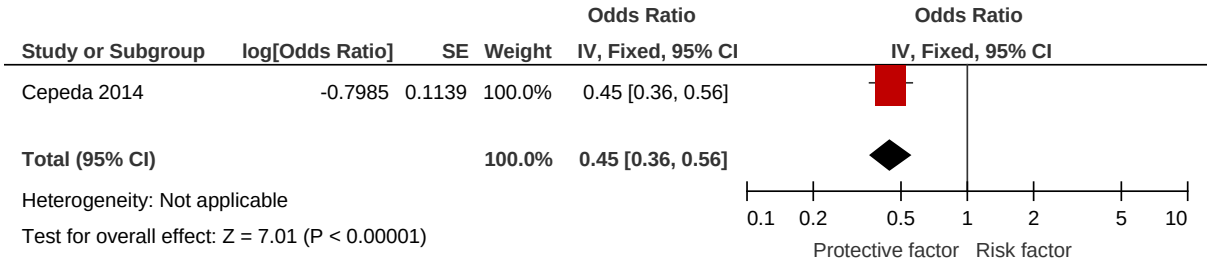



**Figure 50: Opioid dosage MME/d (continuous) for predicting composite outcome (any combination of opioid abuse, dependence or overdose)**

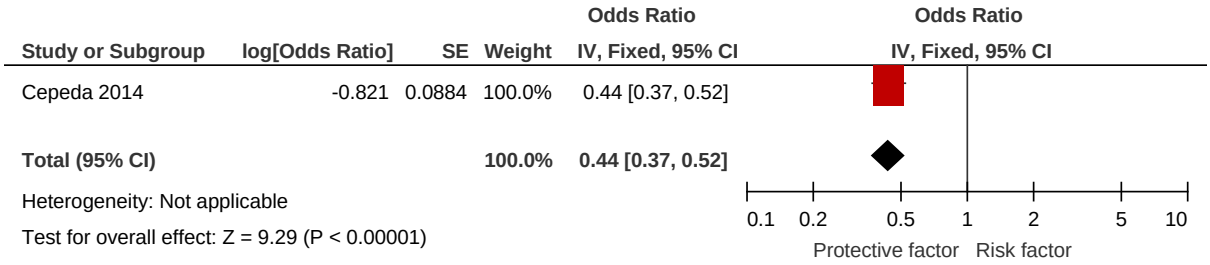


## E.1.19 Opioid formulation

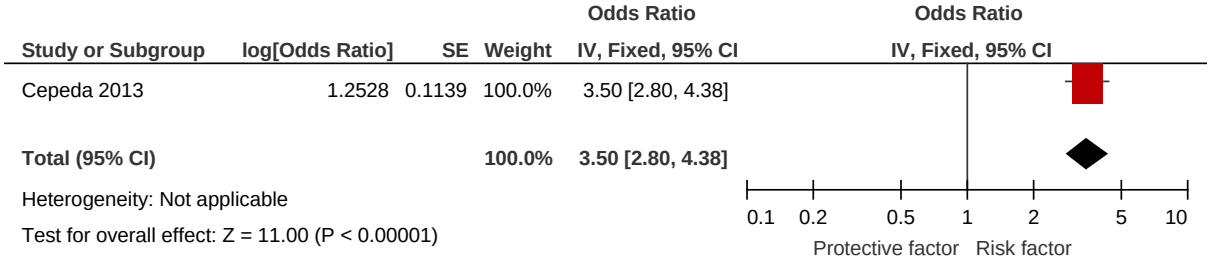
### Figure 51: Tapentadol IR (compared to oxycodone IR) for predicting shopping behaviour



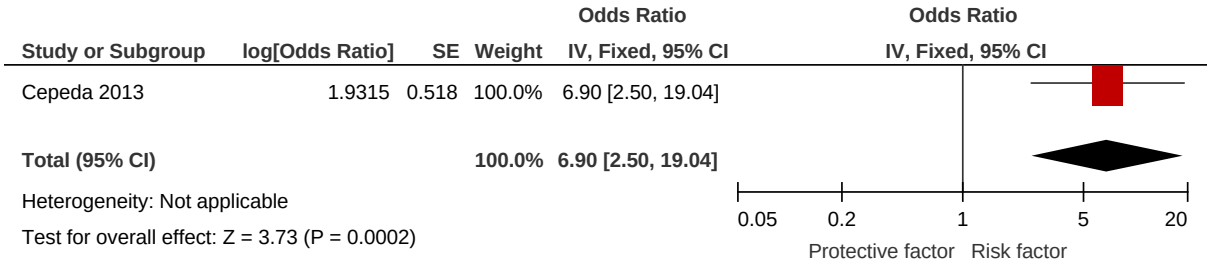

### Figure 52: Tapentadol IR (compared to oxycodone IR) for predicting opioid abuse




### Figure 53: Oxycodone IR (compared to tapentadol IR) for predicting shopping behaviour




### Figure 54: Oxycodone IR (compared to tapentadol IR) for predicting heavy shopping behaviour



## E.1.20 Duration of action in the first prescription

**Figure 55: Long-acting opioids (compared to short-acting) for predicting overlapping opioid prescriptions**

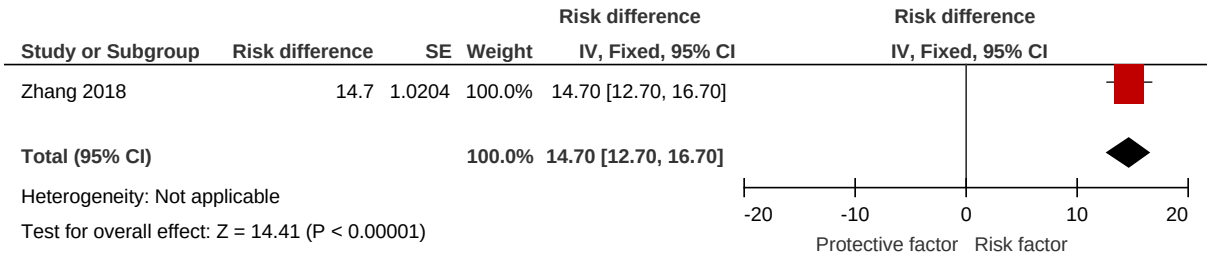



**Figure 56: Long-acting opioids (compared to short-acting) for predicting 3 or more opioid prescribers**

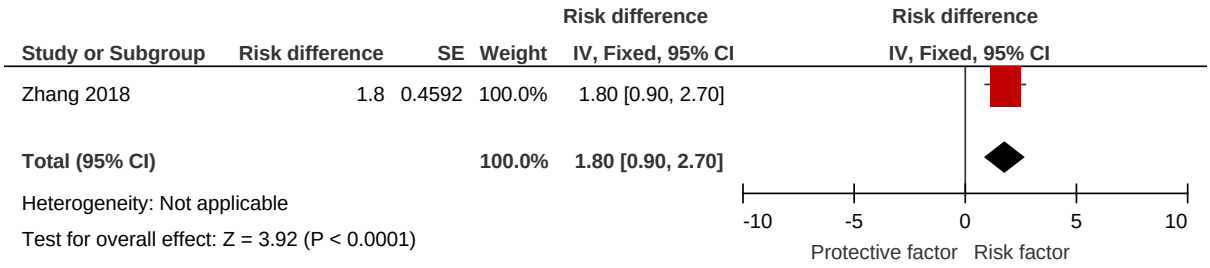
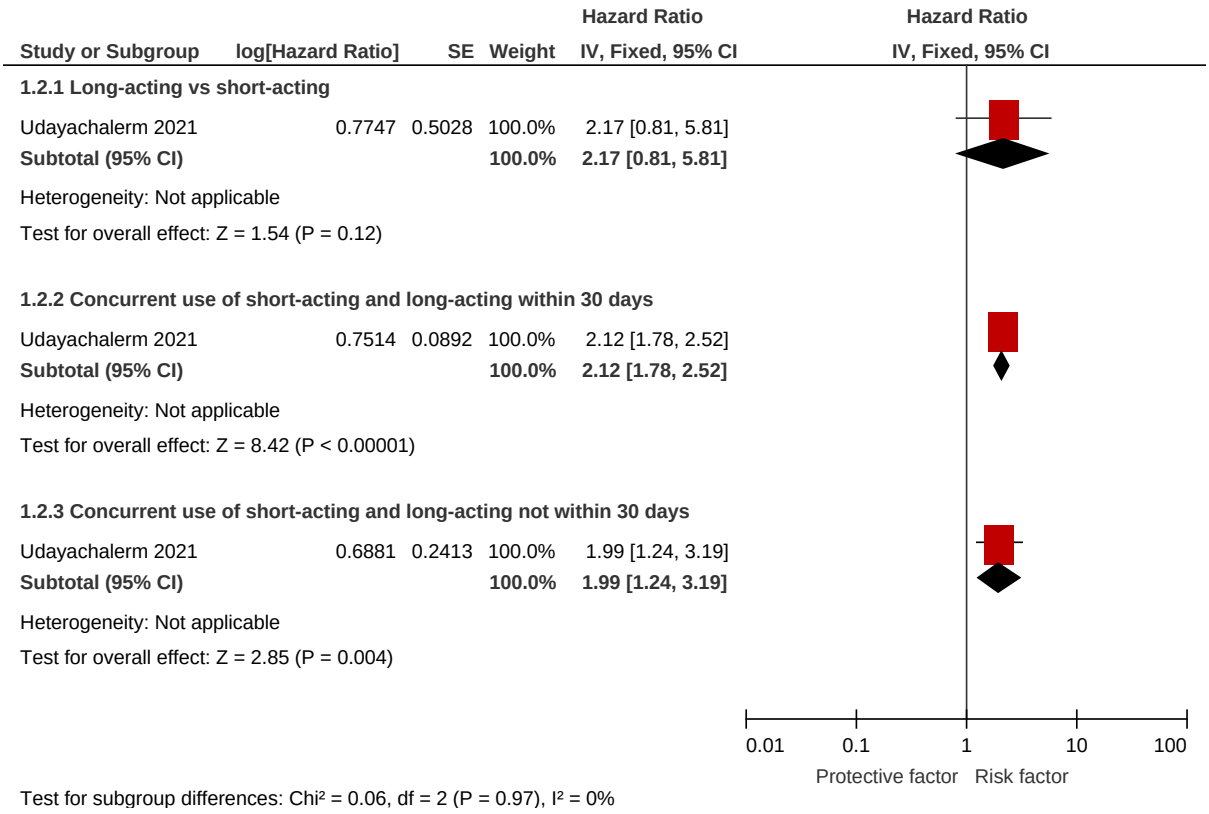


**Figure 57: Concurrent use of short-acting and long-acting opioids (compared to short-acting alone) for predicting composite outcome – any combination of opioid abuse, dependence or overdose**

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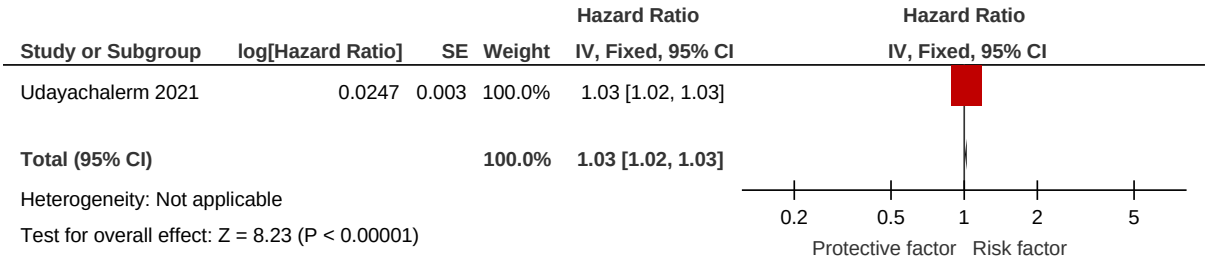
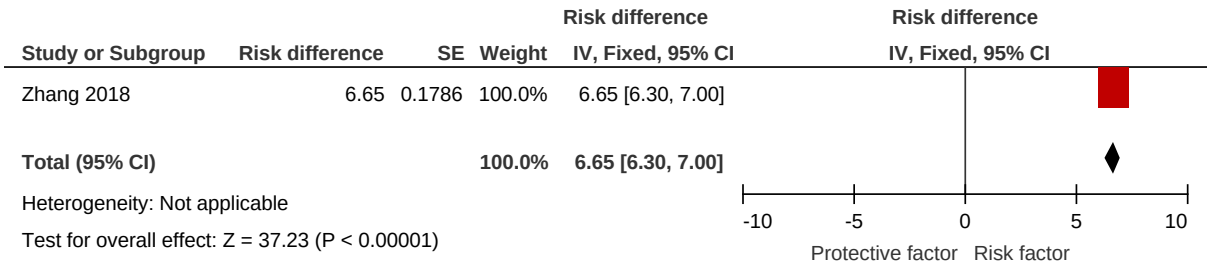
## 2 E.1.21 Days of opioid supply in the first prescription

**Figure 58: Number of days' supply (continuous) for predicting composite outcome (any combination of opioid abuse, dependence or overdose)**



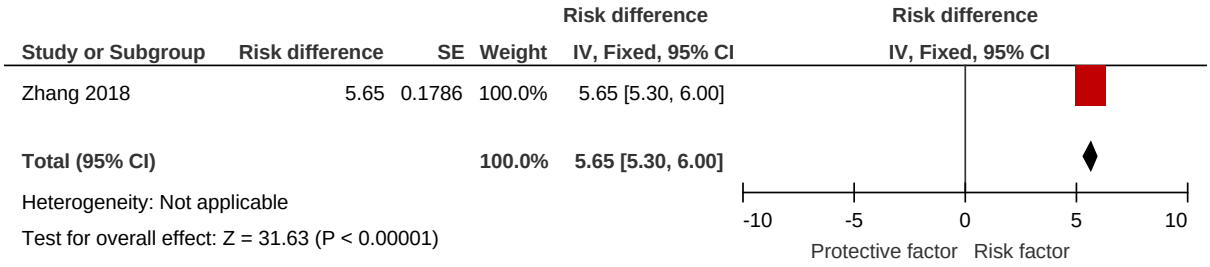

3

**Figure 59: >7 days opioid supply (compared to ≤3 days) for predicting overlapping opioid prescriptions**



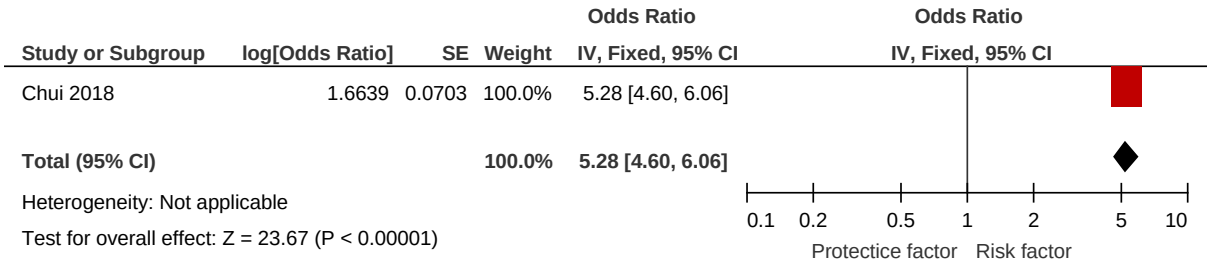

1

**Figure 60: >7 days opioid supply (compared to 4-7 days) for predicting overlapping opioid prescriptions**




2 **E.1.22 Dual use of Veterans health administration (VHA) pharmacy and Medicare part**
3 **D**

**Figure 61: Dual use of VHA and Medicare part D (compared to no dual use) for predicting overlapping concurrent opioids**




4

## E.1.23 Type of payment

**Figure 62: Type of payment (compared to cash) for predicting shopping behaviour**

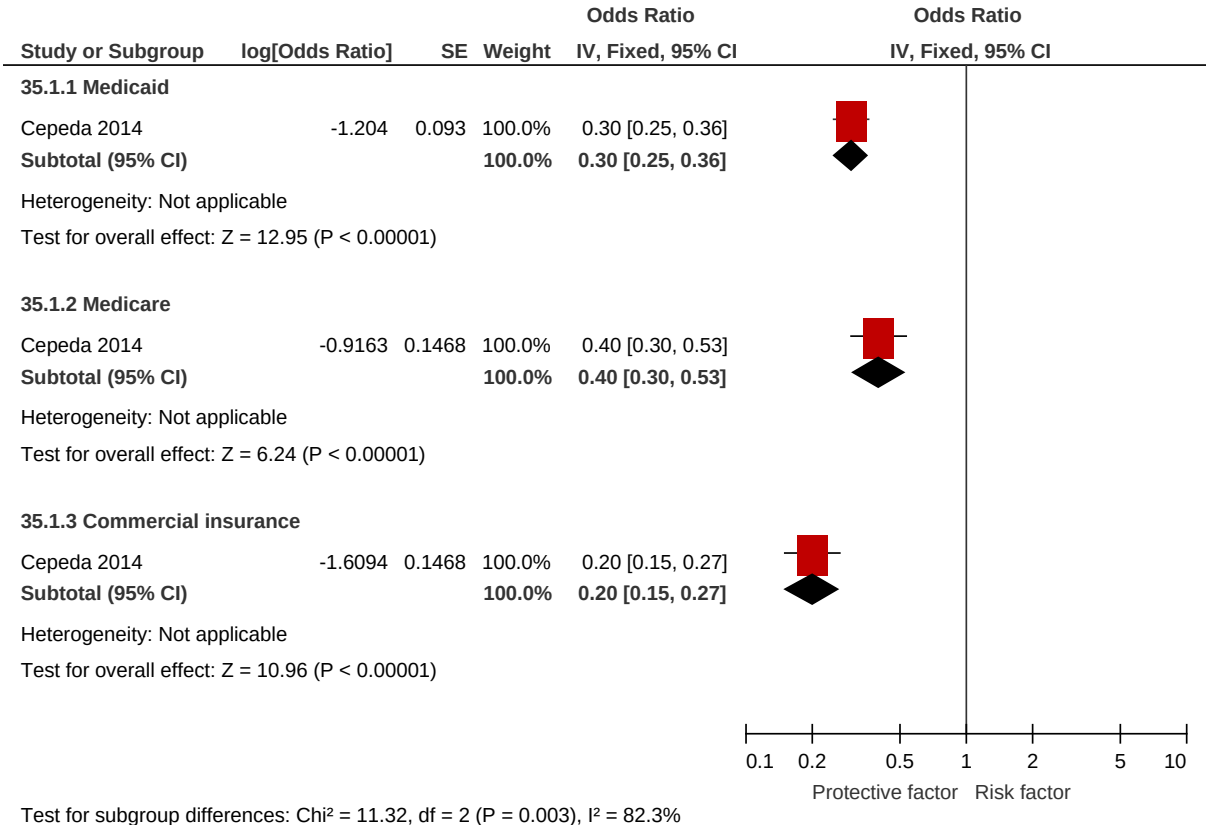
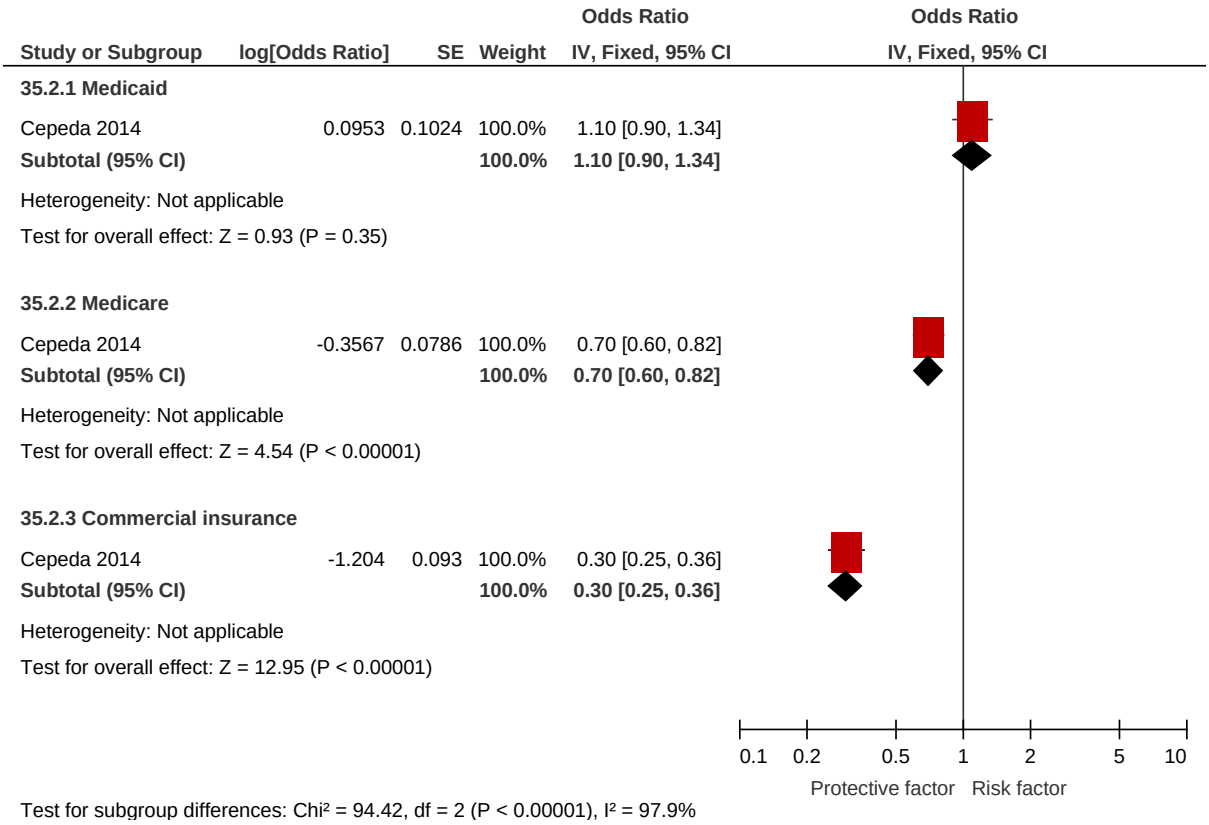


**Figure 63: Type of payment (compared to cash) for predicting opioid abuse**

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## E.1.24 Type of painful condition

**Figure 64: Painful condition (presence compared to absence) for predicting shopping behaviour**

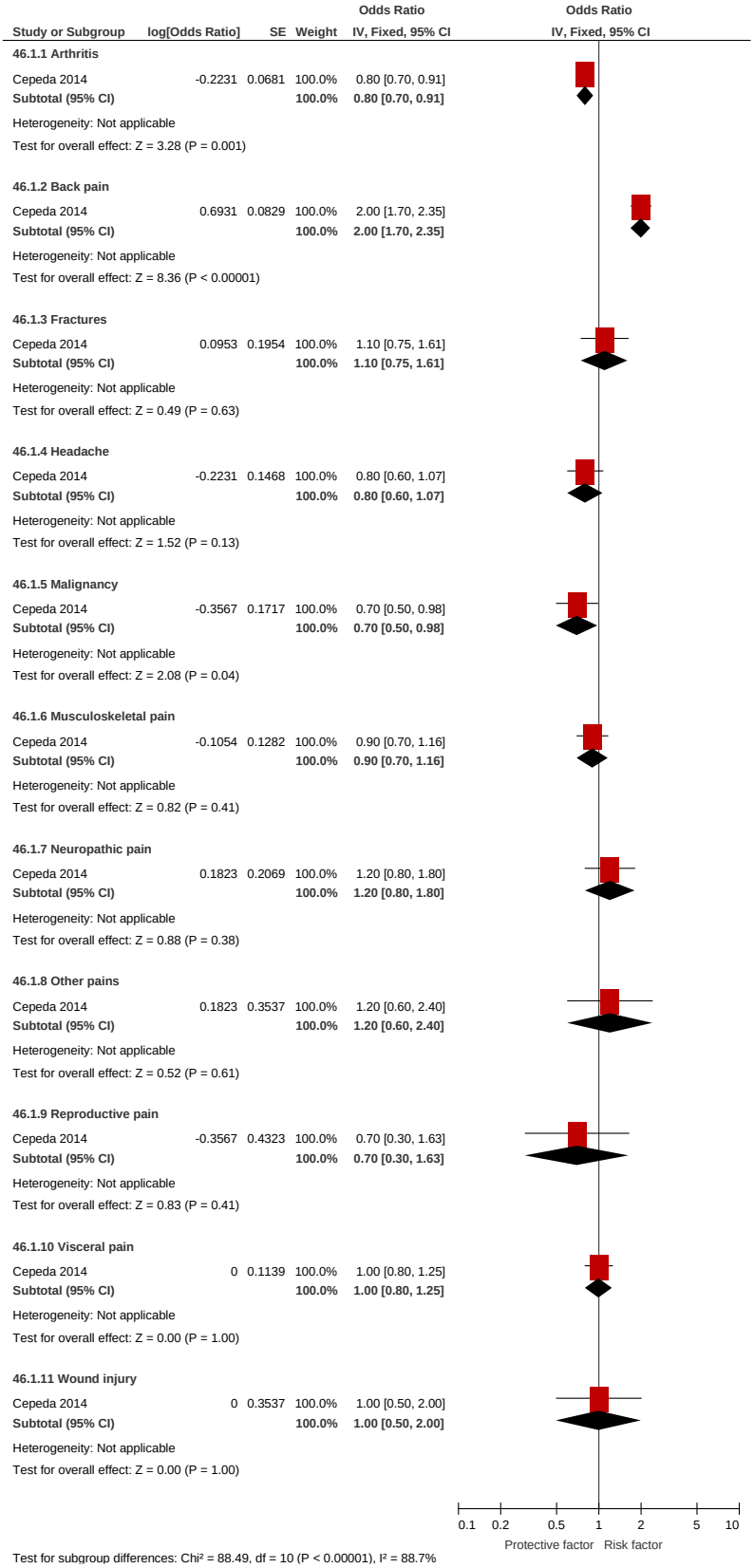
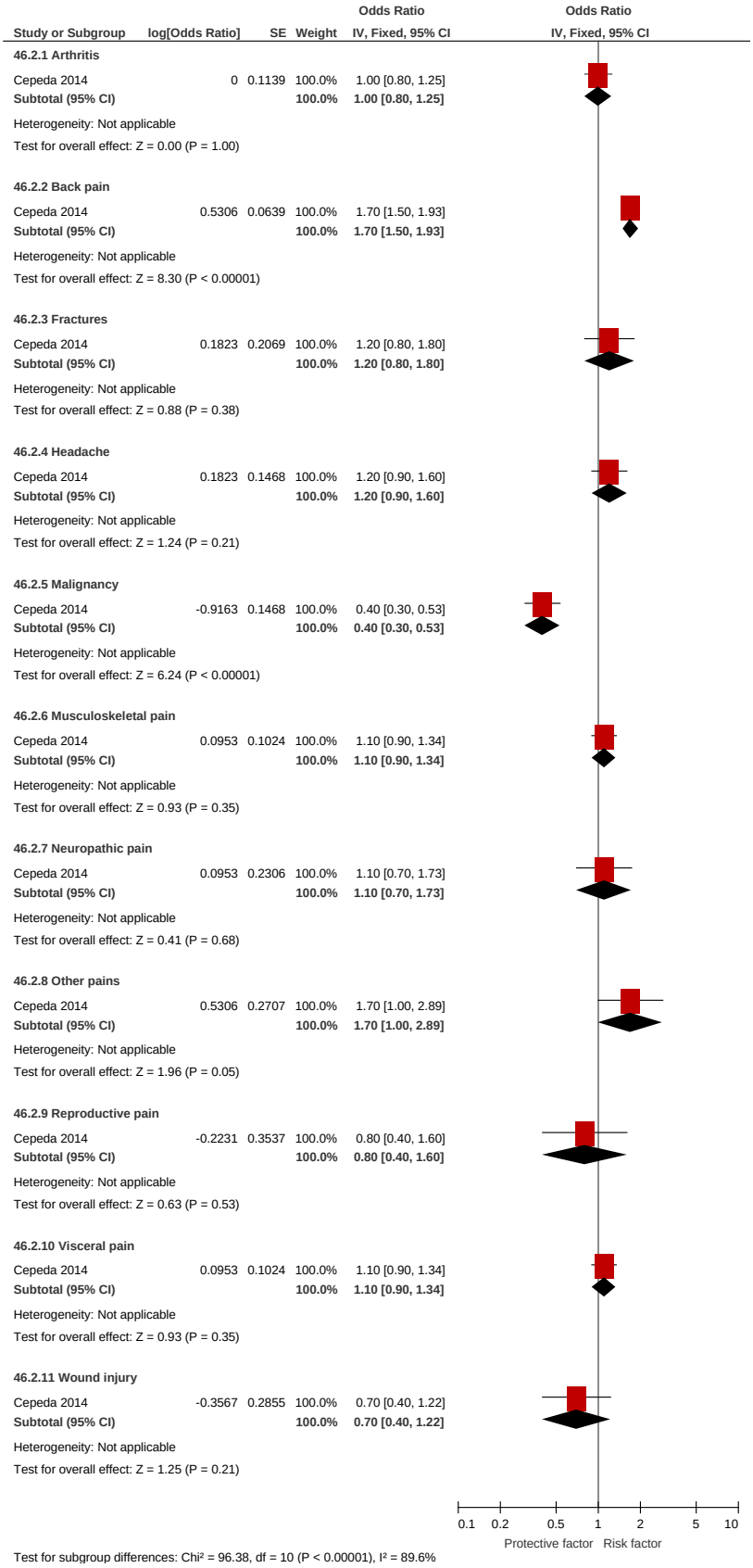


**Figure 65: Painful condition (presence compared to absence) for predicting opioid abuse**

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# E.2 Benzodiazepines

## E.2.1 Age

**Figure 66: Age (continuous) for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period)**

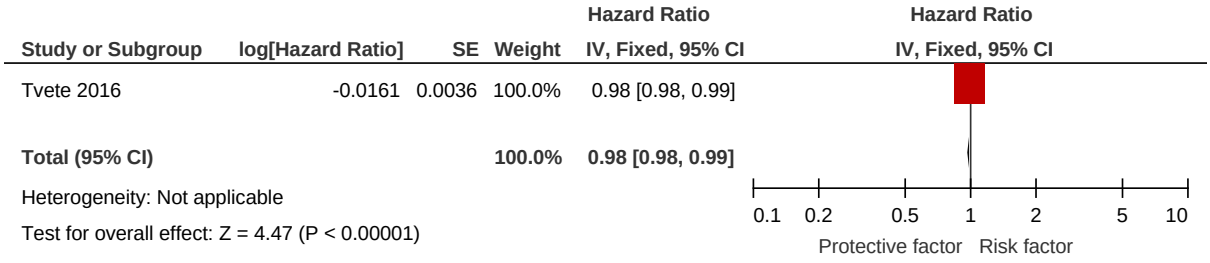
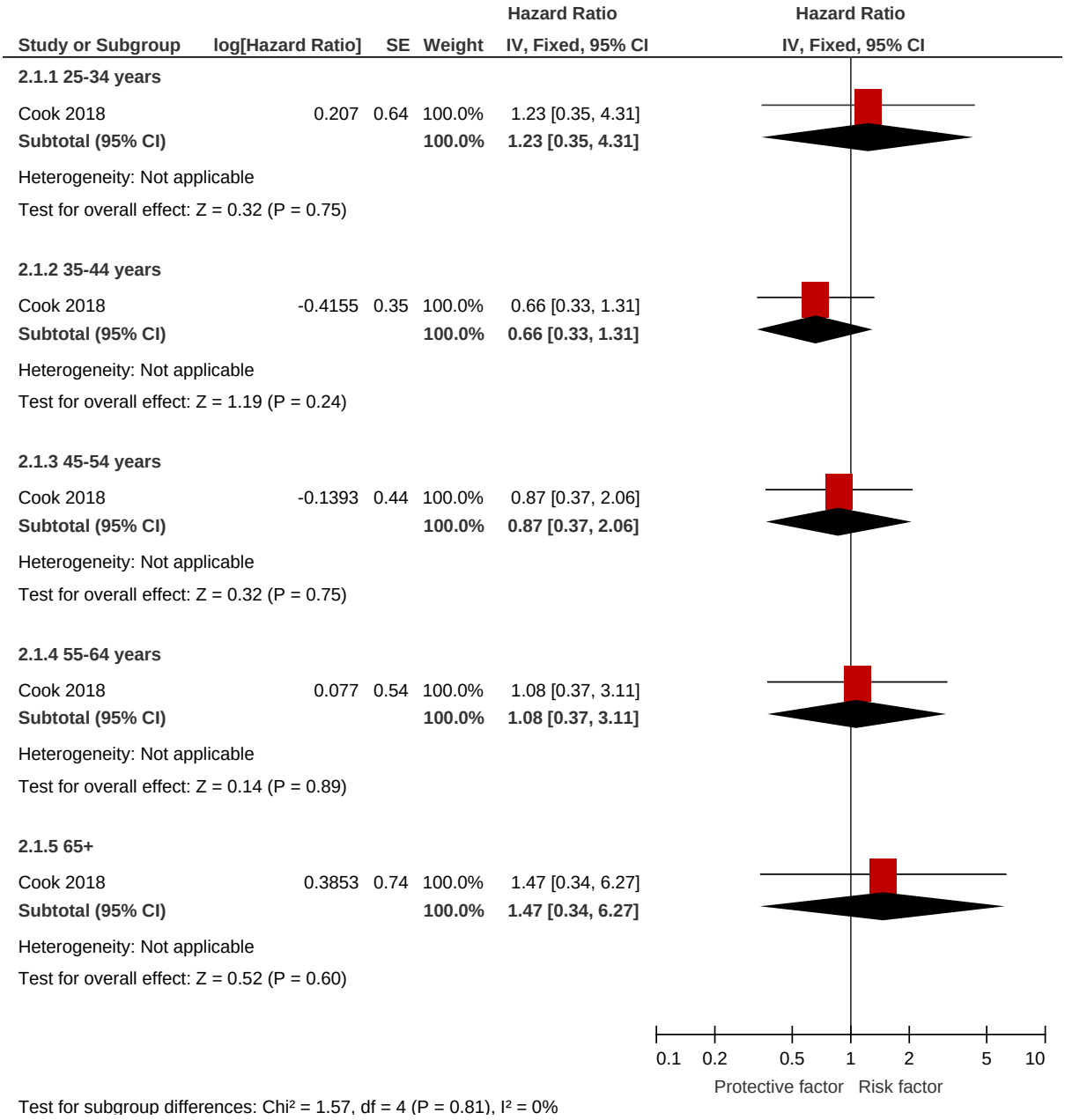


**Figure 67: Age (compared to 18-24) for predicting benzodiazepine dependence**




1

## E.2.2 Gender

**Figure 68: Gender: female (compared to male) for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period)**

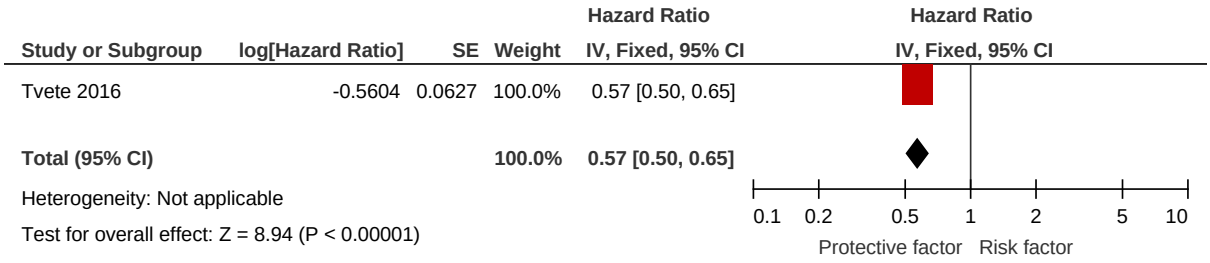
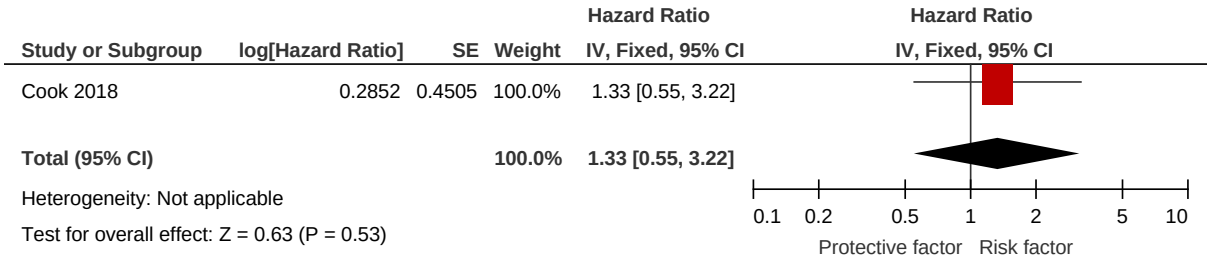
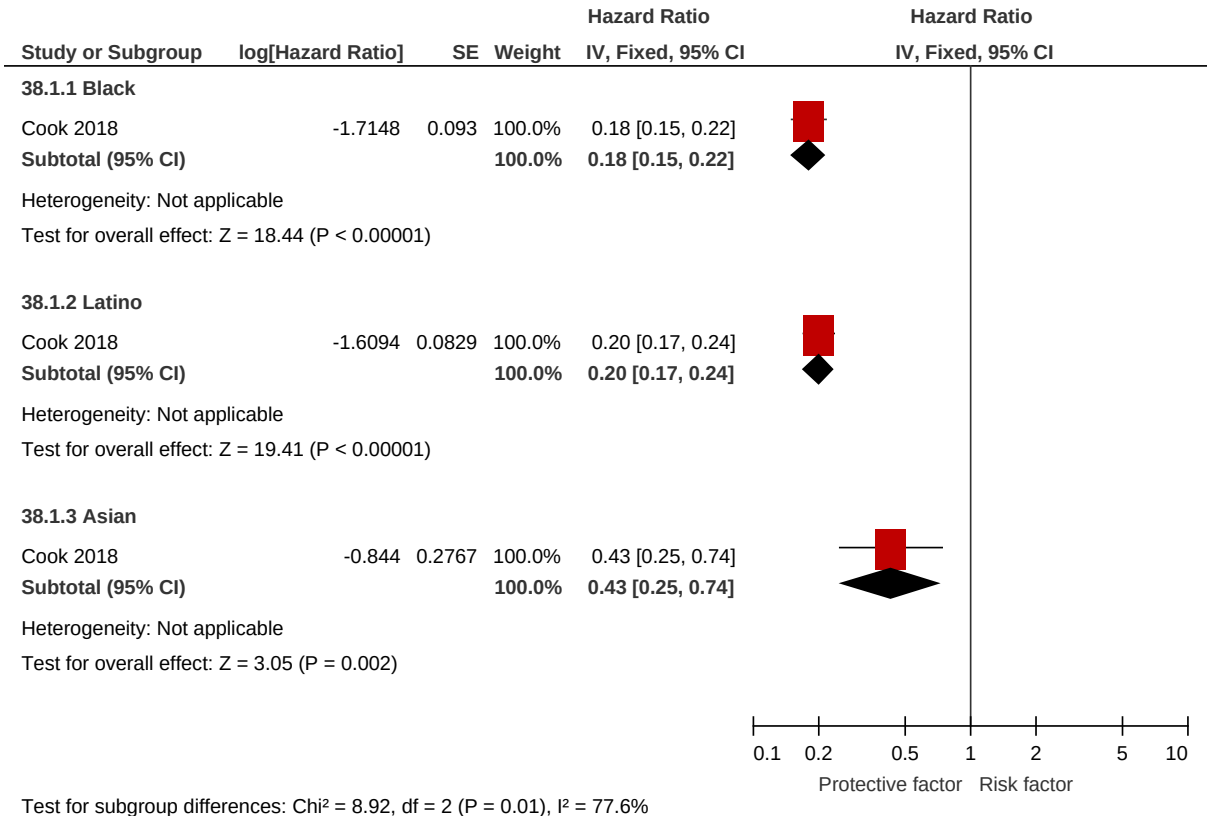



**Figure 69: Gender: male (compared to female) for predicting benzodiazepine dependence**



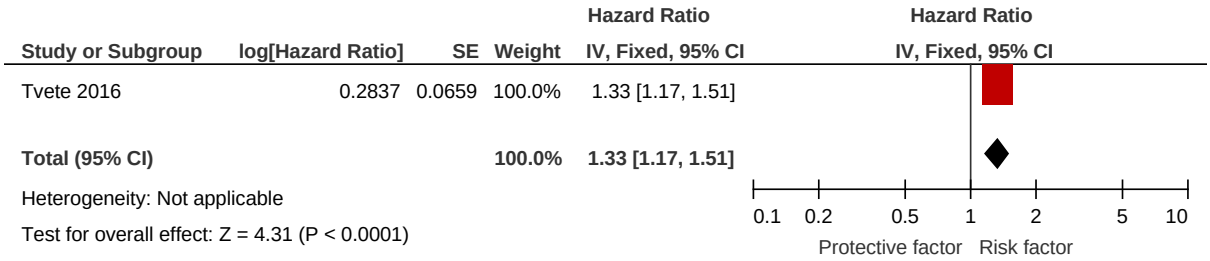
## E.2.3 Family Background

**Figure 70: Non-white (compared to white) for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period)**



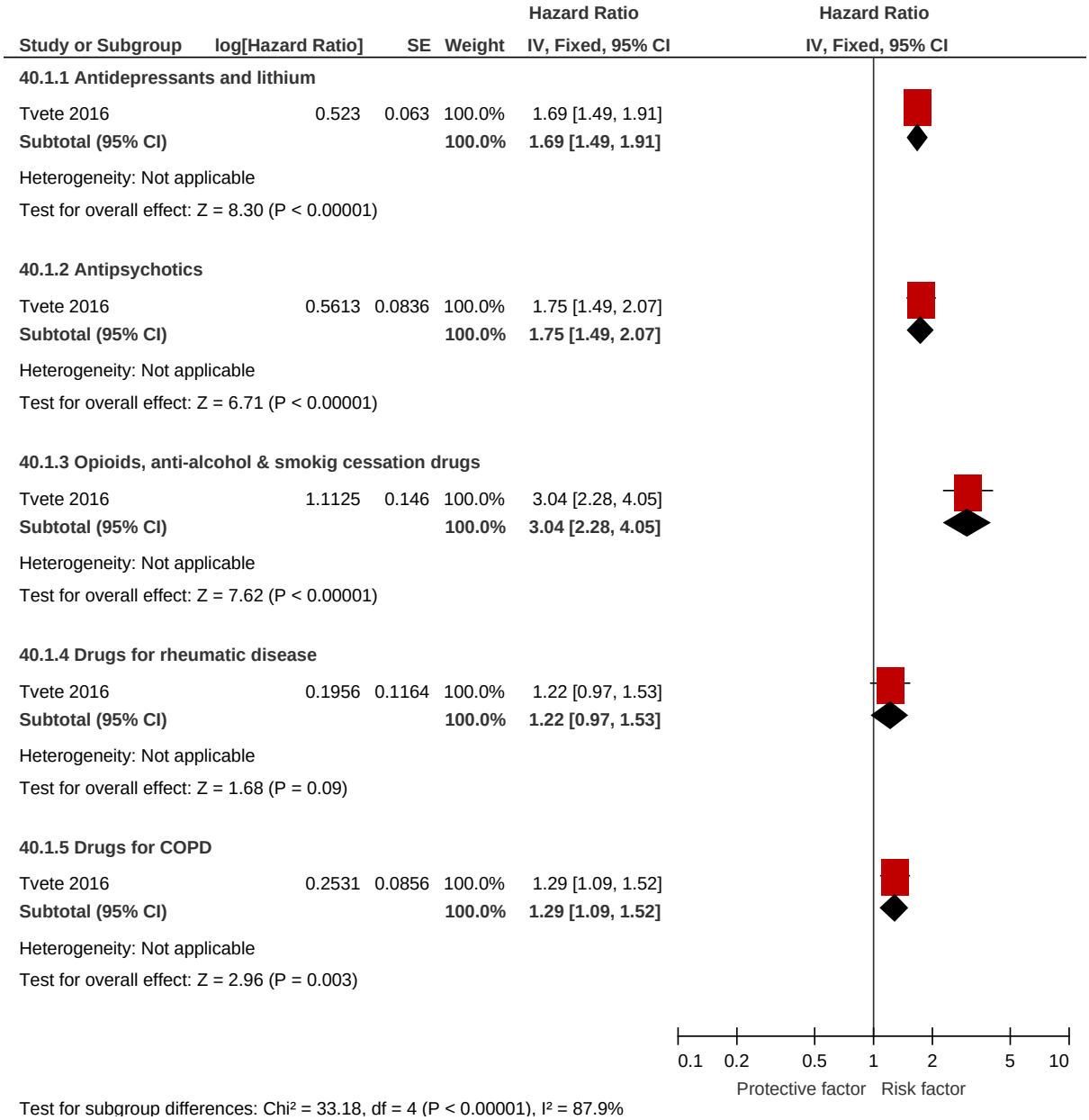

## E.2.4 First benzodiazepine dispensation

**Figure 71: First benzodiazepine dispensation: oxazepam (compared to diazepam) for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period)**



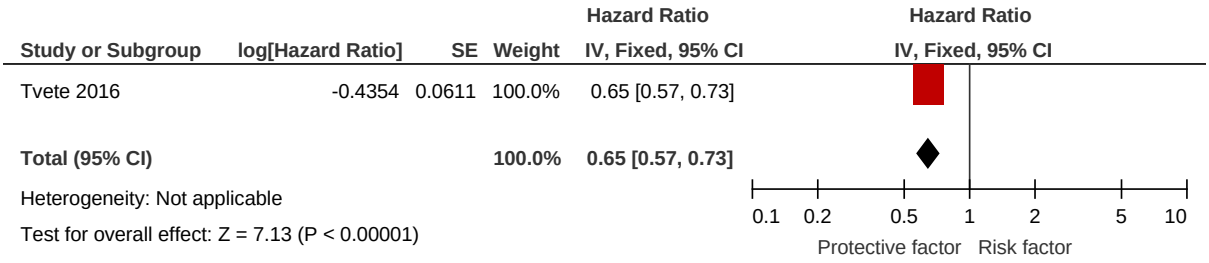
## E.2.5 Previous medication

**Figure 72: Previous medication (compared to no such medication) for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period)**



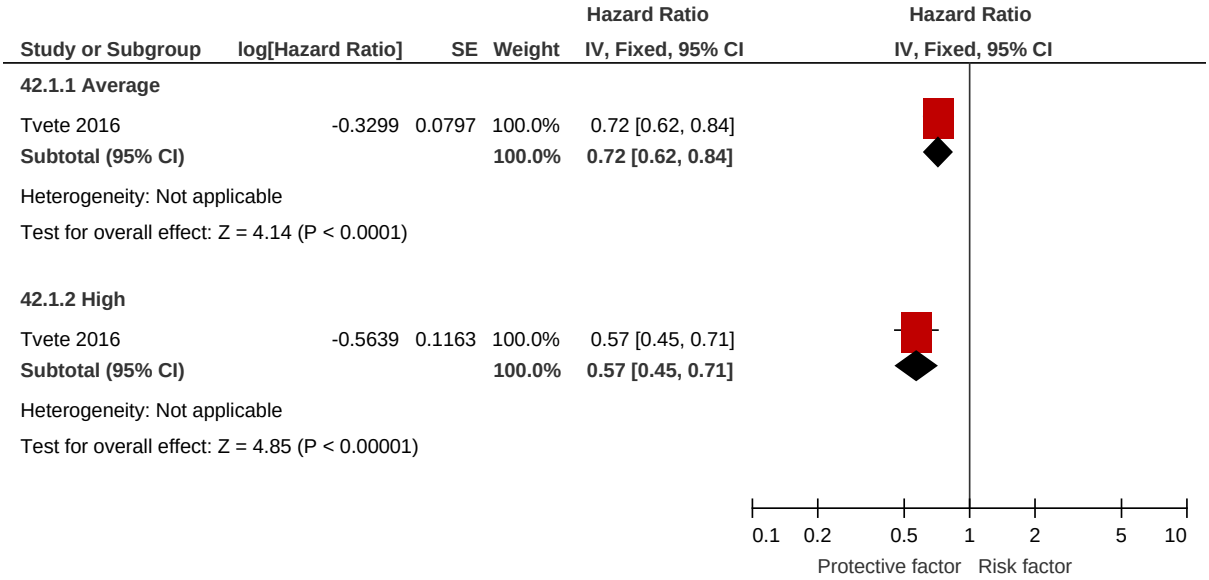
## E.2.6 Education

**Figure 73: Education: high (compared to low) for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period)**




## E.2.7 Income

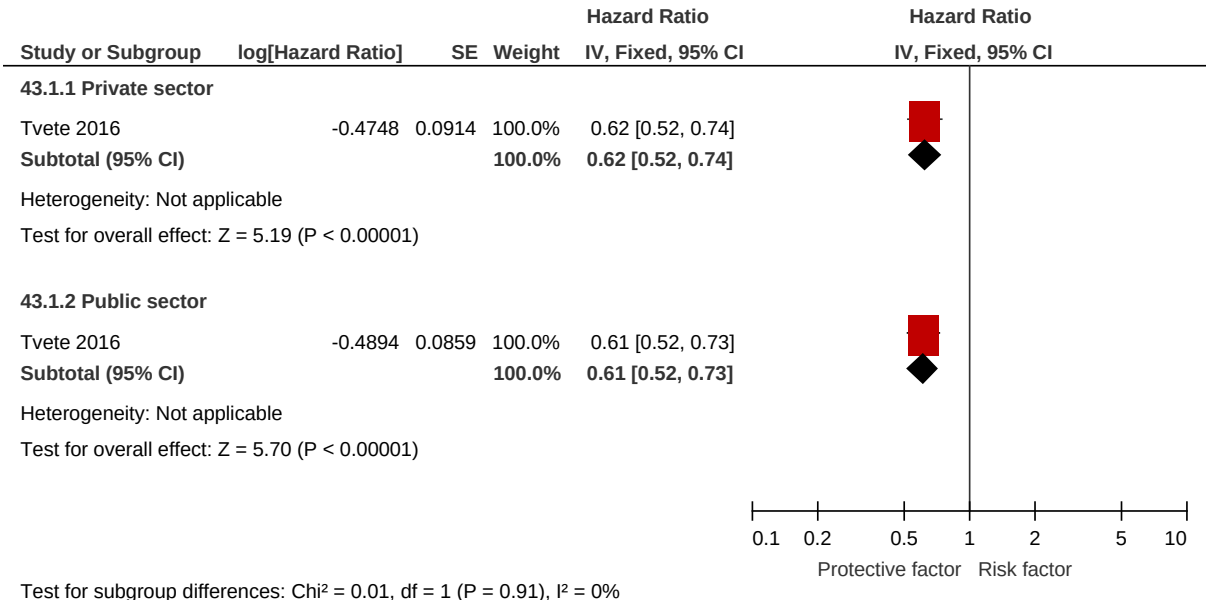
**Figure 74: Income (compared to low) for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period)**




Test for subgroup differences: Chi² = 2.75, df = 1 (P = 0.10), I² = 63.7%

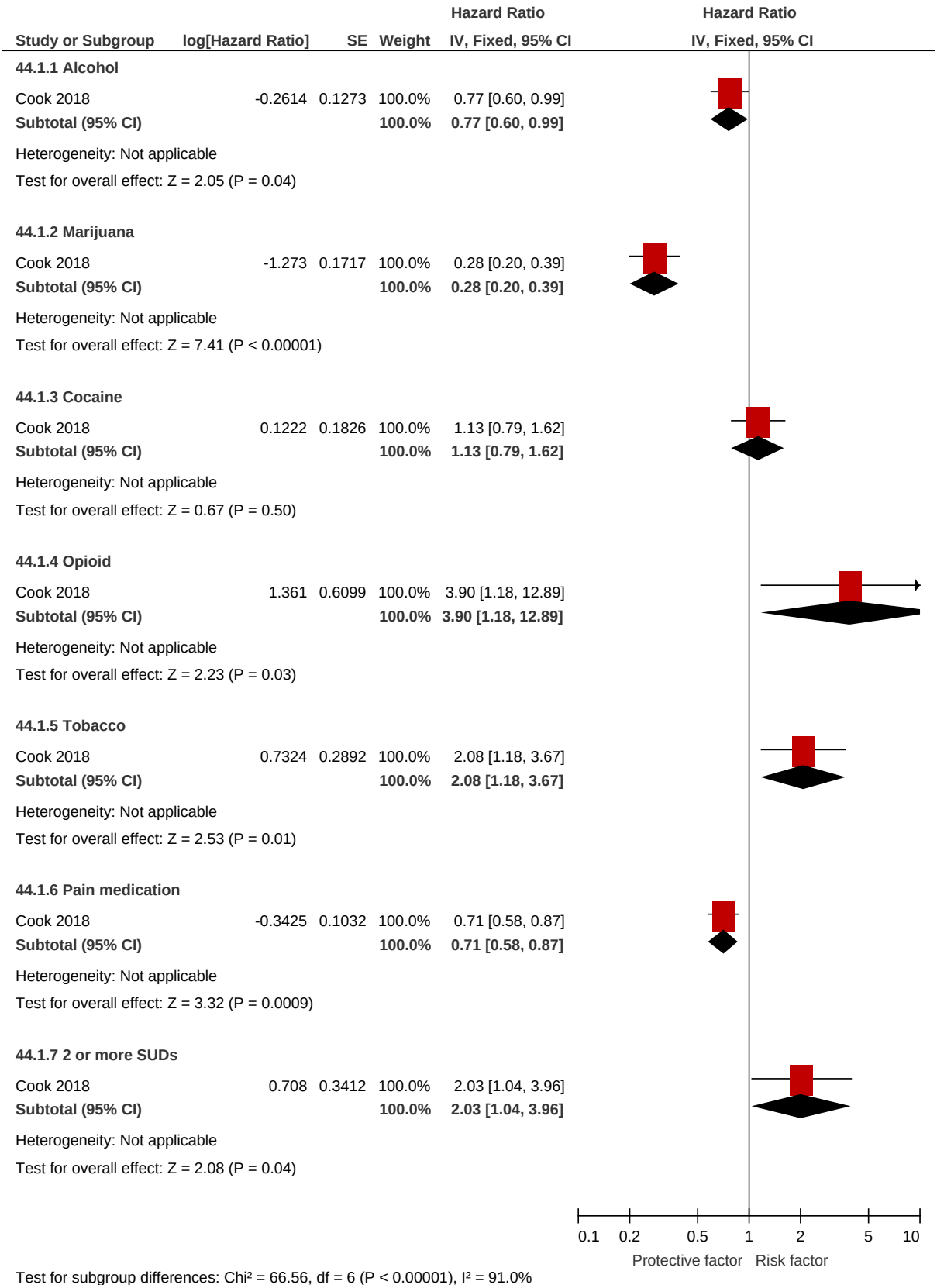
## E.2.8 Type of work

**Figure 75: Type of work (compared to no registration) for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period)**



## E.2.9 Substance use diagnosis

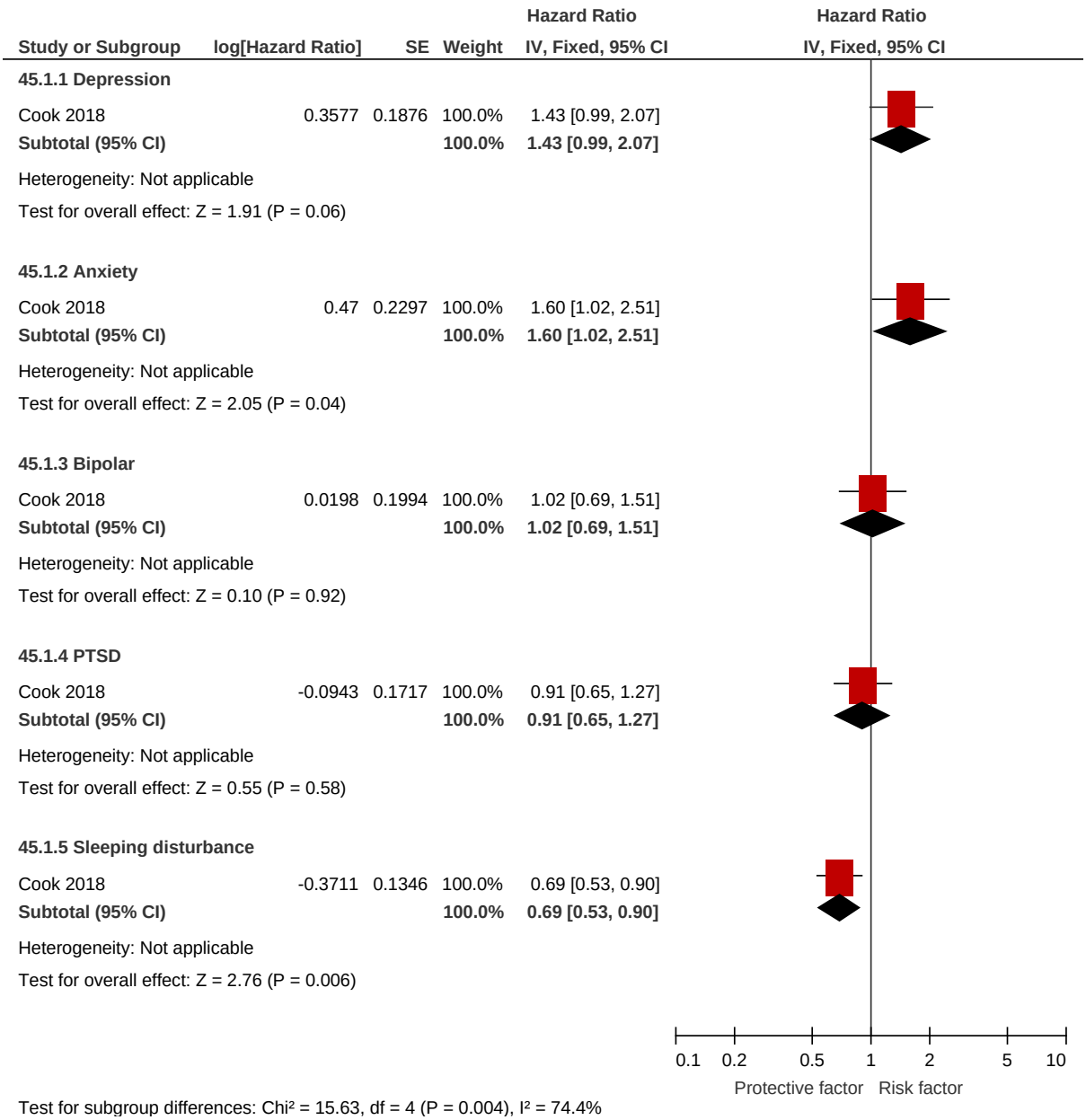
**Figure 76: Substance use diagnosis (compared to no such substance use diagnosis) for predicting benzodiazepine dependence**




Test for subgroup differences: $Chi^2 = 66.56$, df = 6 (P < 0.00001), $I^2 = 91.0\%$

## E.2.10 Mental health diagnosis

**Figure 77: Mental health diagnosis (compared to no diagnosis) for predicting benzodiazepine dependence**



# Appendix F GRADE tables

## F.1 GRADE tables for opioids

**Table 40: Clinical evidence profile: Age**

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations (including publication bias where possible) | Effect (95% CI) | |
| **Age ≤40 versus age >40 for predicting codeine shopping behaviour (HR) (CNCP patients treated with codeine)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | HR 7.29 (4.28 to 12.42) | MODERATE |
| **Age (continuous) for predicting prescription opioid misuse (OR) (adults aged 26–84 with CNCP)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[2] | no serious inconsistency | serious indirectness[3] | no serious imprecision | none | OR 0.94 (0.89 to 0.99) | LOW |
| **Age 75-84 versus 65-74 years old for predicting overlapping concurrent opioid prescriptions (OR) (Veterans aged ≥ 65 years with a new MSD diagnosis)** | | | | | | | | |
| 1 | Cohort study | no serious risk of bias[4] | no serious inconsistency | no serious indirectness | no serious imprecision | none | OR 0.81 (0.75 to 0.87) | HIGH |
| **Age 85+ versus 65-74 years old for predicting overlapping concurrent opioid prescriptions (OR) (Veterans aged ≥ 65 years with a new MSD diagnosis)** | | | | | | | | |
| 1 | Cohort study | no serious risk of bias[4] | no serious inconsistency | no serious indirectness | no serious imprecision | none | OR 0.83 (0.74 to 0.92) | HIGH |
| **Age <18 versus >64 for predicting shopping behaviour (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[5] | no serious inconsistency | very serious indirectness[6] | serious imprecision[7] | none | OR 0.9 (0.5 to 1.8) | VERY LOW |
| **Age <18 versus >64 for predicting opioid abuse (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | Cohort study | Very serious risk of bias[5] | no serious inconsistency | very serious indirectness[6] | serious imprecision[7] | none | OR 0.7 (0.3 to 1.4) | VERY LOW |
| **Age 18-39 versus >64 for predicting shopping behaviour (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[5] | no serious inconsistency | serious indirectness[6] | no serious imprecision | none | OR 9.8 (7.9 to 12) | VERY LOW |
| **Age 18-39 versus >64 for predicting opioid abuse (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[5] | no serious inconsistency | serious indirectness[6] | no serious imprecision | none | OR 13.9 (11.2 to 17.2) | VERY LOW |
| **Age 40-64 versus >64 for predicting shopping behaviour (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[5] | no serious inconsistency | serious indirectness[6] | no serious imprecision | none | OR 4.6 (3.8 to 5.6) | VERY LOW |
| **Age 40-64 versus >64 for predicting opioid abuse (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[5] | no serious inconsistency | serious indirectness[6] | no serious imprecision | none | OR 6.7 (5.5 to 8.3) | VERY LOW |
| **Age <40 versus ≥ 50 for predicting tramadol shopping behaviour (HR) (CNCP patients treated with tramadol (mean age (SD) 66.4 (14.7) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias [8] | no serious inconsistency | no serious indirectness | serious imprecision[7] | none | HR 7.4 (2.8 to 19.7) | VERY LOW |
| **Age 40-50 versus ≥ 50 for predicting tramadol shopping behaviour (HR) (CNCP patients treated with tramadol (mean age (SD) 66.4 (14.7) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias [8] | no serious inconsistency | no serious indirectness | No serious imprecision | none | HR 2.8 (1 to 7.7) | LOW |

*[1] Methods: multivariable analysis: cox proportional hazards model developed according to clinically relevant variables such as age and gender; downgraded by 1 increment due to serious risk of bias*
*[2] Methods: Multivariate logistic regression model with covariates not specified; downgraded by 1 increment due to serious risk of bias*
*[3] Downgraded by 1 increment due potential indirectness of the population as it was not clear if they were opioid naïve during baseline assessment*
*[4] Methods: multivariate logistic regression analysis adjusted for age, sex, ethnicity, pain intensity (NRS), co morbid diagnoses, overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and PTSD.*
*[5] Methods: multivariate analysis: logistic regression adjusted for age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date; downgraded by 2 increments due to very serious risk of bias*
*[6] Downgraded by 1 increment with the proportion of those being prescribed opioids for chronic pain being unclear, and by 1 more increment for results of participants in the <18 years age category*

*[7] Downgraded by 1 increment as the confidence interval crossed the null line or was judged to be very wide*
*[8] Methods: multivariate analysis: cox proportional hazard model; confounders not specified; downgraded by 2 increments due to very serious risk of bias*

### Table 41: Clinical evidence profile: Family Background

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Non-white versus white race for predicting overlapping concurrent opioid prescriptions (OR) (Veterans aged ≥ 65 years with a new MSD diagnosis)** | | | | | | | | |
| 1 | Cohort study | no serious risk of bias[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | OR 0.77 (0.71 to 0.84) | HIGH |

*[1] Methods: multivariate logistic regression analysis adjusted for age, sex, ethnicity, pain intensity (NRS), co morbid diagnoses, overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and PTSD*

### Table 42: Clinical evidence profile: Gender

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Female versus male for predicting codeine shopping behaviour (HR) (CNCP patients treated with codeine)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | no serious indirectness | serious imprecision[2] | none | HR 0.92 (0.53 to 1.58) | LOW |
| **Female versus male for predicting tramadol shopping behaviour (HR) (CNCP patients treated with tramadol)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias [3] | no serious inconsistency | no serious indirectness | serious imprecision[2] | none | HR 1.6 (0.7 to 3.8) | VERY LOW |
| **Female versus male for predicting overlapping concurrent opioid prescriptions (OR) (Veterans aged ≥ 65 years with a new MSD diagnosis)** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | Cohort study | no serious risk of bias[4] | no serious inconsistency | no serious indirectness | Serious imprecision[2] | none | OR 0.97 (0.75 to 1.24) | MODERATE |
| **Male versus female for predicting shopping behaviour (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[5] | no serious inconsistency | serious indirectness [6] | no serious imprecision | none | OR 1.6 (1.4 TO 1.7) | VERY LOW |
| **Male versus female for predicting opioid abuse (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[5] | no serious inconsistency | serious indirectness [6] | no serious imprecision | None | OR 1.5 (1.3 to 1.6) | VERY LOW |

*[1] Methods: multivariable analysis: cox proportional hazards model developed according to clinically relevant variables such as age and gender; downgraded by 1 increment due to serious risk of bias*
*[2] Downgraded by 1 increment as the CI crossed the null line*
*[3] Methods: multivariate analysis: cox proportional hazards model; co-variated not specified; downgraded by 2 increments due to very serious risk of bias*
*[4] Methods: multivariate logistic regression analysis adjusted for age, sex, ethnicity, pain intensity (NRS), co morbid diagnoses, overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and PTSD*
*[5] Methods: multivariate analysis: logistic regression adjusted for Age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date; downgraded by 2 increments due to very serious risk of bias*
*[6] Downgraded by 1 increment due to the proportion of those taking opioids for chronic pain being unclear*

### Table 43: Clinical evidence profile: Low-income status

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Low-income status for predicting codeine shopping behaviour (HR) (CNCP patients treated with codeine)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | no serious indirectness | serious imprecision[2] | none | HR 1.75 (0.96 to 3.21) | LOW |
| **Low-income status for predicting tramadol shopping behaviour (HR) (CNCP patients treated with tramadol)** | | | | | | | | |
| 1 | Cohort study | very serious risk of bias[3] | no serious inconsistency | no serious indirectness | serious imprecision[2] | none | HR 8.5 (3.6 to 20.5) | VERY LOW |

*[1] Methods: multivariable analysis: cox proportional hazards model developed according to clinically relevant variables such as age and gender; downgraded by 1 increment due to serious risk of bias*
*[2] Downgraded by 1 increment as the CI crossed the null line or was judged to be very wide*
*[3] Methods: multivariable analysis: cox proportional hazards mode; confounders not specified*

### Table 44: Clinical evidence profile: Pain intensity

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Moderate-to-severe pain intensity (pain scale 4-10) for predicting overlapping concurrent opioid prescriptions (OR) (Veterans aged ≥ 65 years with a new MSD diagnosis)** | | | | | | | | |
| 1 | Cohort study | no serious risk of bias[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | OR 1.40 (1.31 to 1.49) | HIGH |

*[1] Methods: multivariate logistic regression analysis adjusted for age, sex, ethnicity, pain intensity (NRS), co morbid diagnoses, overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and PTSD*

### Table 45: Clinical evidence profile: Clinical severity (Charlson comorbidity index (CCI))

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **CCI 2+ versus lower score for predicting overlapping concurrent opioid prescriptions (OR) (Veterans aged ≥ 65 years with a new MSD diagnosis)** | | | | | | | | |
| 1 | Cohort study | no serious risk of bias[1] | no serious inconsistency | no serious indirectness | serious imprecision[2] | none | OR 0.96 (0.90 to 1.03) | MODERATE |
| **Number of medical diseases (mean number of individual chronic medical diseases as per the unweighted CCI) for predicting prescription opioid misuse (OR) (adults aged 26–84 with CNCP)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[3] | no serious inconsistency | serious indirectness[2] | serious imprecision[4] | none | OR 0.72 (0.45 to 1.1) | VERY LOW |

*[1] Methods: multivariate logistic regression analysis adjusted for age, sex, ethnicity, pain intensity (NRS), co morbid diagnoses, overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and PTSD*
*[2] Downgraded by 1 increment as the confidence interval crossed the null line*
*[3] Methods: Multivariate logistic regression model with covariates not specified; downgraded by 1 increment due to serious risk of bias*
*[4] Downgraded by 1 increment due potential indirectness of the population as it was not clear if they were opioid naïve during baseline assessment*
*[5] Downgraded by 1 increment as the CI crossed the null line*

### Table 46:Clinical evidence profile: History of opioid use disorder

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations (including publication bias where possible) | Effect (95% CI) | |
| **History of opioid use disorder for predicting codeine shopping behaviour (HR) (CNCP patients treated with codeine)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | no serious indirectness | very serious imprecision[2] | none | HR 1.25 (0.19 to 8.40) | LOW |

*[1] Methods: multivariable analysis: cox proportional hazards model developed according to clinically relevant variables such as age and gender; downgraded by 1 increment due to serious risk of bias*
*[2] Downgraded by 1 increment as the confidence interval crossed the null line*

### Table 47: Clinical evidence profile: History of substance use disorder/abuse of non-opioids

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations (including publication bias where possible) | Effect (95% CI) | |
| **History of substance use disorder for predicting codeine shopping behaviour (HR) (CNCP patients treated with codeine; mean (SD) age 62.7 (16.1) years)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | No serious indirectness | serious imprecision[2] | none | HR 0.89 (0.21 to 3.83) | LOW |
| **Lifetime history of substance use disorder for predicting prescription opioid misuse (OR) (adults aged 26–84 with CNCP)** | | | | | | | | |
| 1 | Cohort study | very serious risk of bias[3] | no serious inconsistency | serious indirectness[4] | serious imprecision[5] | none | OR 3.8 (1.4 to 10.8) | VERY LOW |
| **Substance use disorder for predicting overlapping concurrent opioid prescriptions (Veterans aged ≥ 65 years with a new MSD diagnosis)** | | | | | | | | |
| 1 | Cohort study | no serious risk of bias[6] | no serious inconsistency | no serious indirectness | no serious imprecision | none | OR 1.18 (1.05 to 1.33) | HIGH |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **History of abuse of non-opioid drugs (such as alcohol & tobacco) for predicting shopping behaviour (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[7] | no serious inconsistency | serious indirectness[8] | no serious imprecision | none | OR 1.5 (1.0 to 2.2) | VERY LOW |
| **History of abuse of non-opioid drugs (such as alcohol & tobacco) mood for predicting opioid abuse (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[7] | no serious inconsistency | serious indirectness[8] | no serious imprecision | none | OR 1.5 (1.1 to 2.1) | VERY LOW |

*[1] Methods: cox proportional hazards model developed according to clinically relevant variables such as age and gender; downgraded by 1 increment due to serious risk of bias*
*[2] Downgraded by one increment as the CI crossed the null line*
*[3] Methods: Multivariate logistic regression model with covariates not specified; downgraded by 2 increments due to very serious risk of bias*
*[4] Downgraded by 1 increment due potential indirectness of the population as it was not clear if they were opioid naïve during baseline assessment*
*[5] Downgraded by 1 increment as the CI was judged to be very wide*
*[6] Methods: multivariate logistic regression analysis adjusted for age, sex, ethnicity, pain intensity (NRS), co morbid diagnoses, overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and PTSD*
*7 Methods: multivariate analysis: logistic regression adjusted for Age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date; downgraded by 2 increments due to very serious risk of bias*
*8 Downgraded by 1 due to the proportion of those taking opioids for chronic pain being unclear*

### Table 48: Clinical evidence profile: Active chronic liver disease

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Active chronic liver disease for predicting codeine shopping behaviour (HR) (adults with CNCP)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | no serious indirectness | serious imprecision [2] | none | HR 2.09 (95% CI 0.62 to 7.03) | LOW |

*[1] Methods: multivariable analysis: cox proportional hazards model developed according to clinically relevant variables such as age and gender; downgraded by 1 increment due to serious risk of bias*
*[2] Downgraded by 1 increment as the confidence interval crossed the null line*

**Table 49: Clinical evidence profile: Mental health disorders**

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations (including publication bias where possible) | Effect (95% CI) | |
| **Mental health disorders for predicting codeine shopping behaviour (HR) (adults with CNCP)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | HR 2.25 (1.08 to 4.67) | MODERAE |
| **PTSD with or without other mental health diagnosis for predicting early opioid refills (RR) (Iraq and Afghanistan veterans prescribed opioids within 1 year of a pain-related diagnosis)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | RR 1.64 (1.53 to 1.75) | LOW |
| **Mental health diagnosis without PTSD for predicting early opioid refills (RR) (Iraq and Afghanistan veterans prescribed opioids within 1 year of a pain-related diagnosis)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | RR 1.50 (1.39 to 1.62) | LOW |
| **PTSD with or without other mental health diagnosis for predicting overlapping opioids (>7 days) (RR) (Iraq and Afghanistan veterans prescribed opioids within 1 year of a pain-related diagnosis)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | RR 1.87 (1.70 to 2.06) | LOW |
| **Mental health diagnosis without PTSD for predicting overlapping opioids (>7 days) (RR) (Iraq and Afghanistan veterans prescribed opioids within 1 year of a pain-related diagnosis)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | RR 1.62 (1.44 to 1.81) | LOW |
| **PTSD for predicting overlapping concurrent opioid prescriptions (OR) (Veterans aged ≥ 65 years with a new MSD diagnosis)** | | | | | | | | |
| 1 | Cohort study | no serious risk of bias[3] | no serious inconsistency | no serious indirectness | serious imprecision[4] | none | OR 0.94 (0.82 to 1.05) | MODERATE |
| **Major depression for predicting overlapping concurrent opioid prescriptions (OR) (Veterans aged ≥ 65 years with a new MSD diagnosis)** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | Cohort study | no serious risk of bias[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | OR 1.32 (1.15 to 1.52) | HIGH |

*[1] Methods: multivariable analysis: cox proportional hazards model developed according to clinically relevant variables such as age and gender; downgraded by 1 increment due to serious risk of bias*
*[2] Methods: : Poison regression with robust error variance adjusted for sociodemographic factors (age, sex, race/ethnicity, marital status, VA facility type - medical centre vs community clinic) and military service characteristics ( component, rank, service branch, and number of deployments); downgraded by 2 increments due to very serious risk of bias*
*[3] Methods: multivariate logistic regression analysis adjusted for age, sex, ethnicity, pain intensity (NRS), co morbid diagnoses, overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and PTSD*
*[4]Downgraded by one increment as the confidence interval crossed the null line*

### Table 50: Clinical evidence profile: History of mood disorder

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **History of mood disorders for predicting shopping behaviour (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness[2] | no serious imprecision | none | OR 1.4 (1.1 to 1.8) | VERY LOW |
| **History of mood disorders for predicting opioid abuse (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness[2] | no serious imprecision | none | OR 1.9 (1.5 to 2.3) | VERY LOW |

*[1] Methods: multivariate analysis: logistic regression adjusted for Age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date; downgraded by 2 increments due to very serious risk of bias*
*[2] Downgraded by 1 due to the proportion of those taking opioids for chronic pain being unclear*

### Table 51: Clinical evidence profile: Concurrent use of antidepressants

| Quality assessment | Effect | Quality |
|---|---|---|

| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations (including publication bias where possible) | Effect (95% CI) | |
|---|---|---|---|---|---|---|---|---|
| **Concurrent use of antidepressants for predicting codeine shopping behaviour (HR) (adults with CNCP)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | no serious indirectness | serious imprecision[2] | none | HR 0.93 (0.53 to 1.63) | LOW |

*[1] Methods: multivariable analysis: cox proportional hazards model developed according to clinically relevant variables such as age and gender; downgraded by 1 increment due to serious risk of bias*
*[2] Downgraded by 1 increment as the confidence interval crossed the null line*

### Table 52: Clinical evidence profile: Previous use of antipsychotics

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Previous use of antipsychotics for predicting codeine shopping behaviour (HR) (adults with CNCP)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | no serious indirectness | serious imprecision [2] | none | HR 1.03 (0.42 to 2.53) | LOW |

*[1] Methods: multivariable analysis: cox proportional hazards model developed according to clinically relevant variables such as age and gender; downgraded by 1 increment due to serious risk of bias*
*[2] Downgraded by 1 increment as the confidence interval crossed the null line*

### Table 53: Clinical evidence profile: History of benzodiazepine use

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Previous use of hypnotic BZDs for predicting codeine shopping behaviour (HR) (adults with CNCP)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | no serious indirectness | serious imprecision [2] | none | HR 1.56 (0.70 to 3.49) | LOW |
| **Previous use of anxiolytic BZDs for predicting codeine shopping behaviour (HR) (adults with CNCP)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | no serious indirectness | serious imprecision [2] | none | HR 0.63 (0.32 to 1.26) | LOW |
| **History of BZD use for predicting shopping behaviour (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[3] | no serious inconsistency | serious indirectness[4] | no serious imprecision | none | OR 1.6 (1.1 to 2.2) | VERY LOW |
| **History of BZD use for predicting opioid abuse (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[3] | no serious inconsistency | serious indirectness[4] | no serious imprecision | none | OR 1.5 (1.3 to 1.5) | VERY LOW |

*[1] Methods: multivariable analysis: cox proportional hazards model developed according to clinically relevant variables such as age and gender; downgraded by 1 increment due to serious risk of bias*
*[2] Downgraded by 1 increment as the confidence interval crossed the null line*
*[3]Methods: multivariate analysis: logistic regression adjusted for Age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date; downgraded by 2 increments due to very serious risk of bias*
*[4] Downgraded by 1 increment due to the proportion of those taking opioids for chronic pain being unclear*

### Table 54: Clinical evidence profile: Concurrent use of benzodiazepine/ concurrent use of gabapentin/pregabalin

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Concurrent use of hypnotic BZD for predicting codeine shopping behaviour (HR) (adults with CNCP)** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | No serious indirectness | serious imprecision [2] | none | HR 0.89 (0.43 to 1.83) | LOW |
| **Concurrent use of anxiolytic BZD for predicting codeine shopping behaviour (HR) (adults with CNCP)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | No serious indirectness | serious imprecision [2] | none | HR 3.12 (1.55 to 6.26) | LOW |
| **Receipt of benzodiazepine prescription versus non-receipt of benzodiazepine prescription for predicting second early opioid refill (HR) (adults aged with CNCP)** | | | | | | | | |
| 1 | Cohort study | No serious risk of bias[3] | no serious inconsistency | serious indirectness[4] | No serious imprecision | none | HR: 1.54 (1.09 to 2.18) | MODERATE |
| **Concurrent use of BZD for predicting composite outcome – any combination of opioid abuse, dependence or overdose (hazard ratio) (opioid naïve patients aged 18 or over)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[5] | no serious inconsistency | serious indirectness[6] | No serious imprecision | None | HR: 1.38 (1.17 to 1.61) | LOW |
| **Concurrent use of gabapentin/ pregabalin for predicting composite outcome – any combination of opioid abuse, dependence or overdose (hazard ratio) (opioid naïve patients aged 18 or over)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[5] | no serious inconsistency | serious indirectness[6] | No serious imprecision | None | HR: 1.54 (1.29 to 1.84) | LOW |
| **Concurrent use of BZD and gabapentin/pregabalin within 30 days for predicting composite outcome – any combination of opioid abuse, dependence or overdose (hazard ratio) (opioid naïve patients aged 18 or over)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[5] | no serious inconsistency | serious indirectness[6] | No serious imprecision | None | HR: 1.68 (1.38 to 2.04) | LOW |
| **Concurrent use of BZD and gabapentin/pregabalin not within 30 days for predicting composite outcome – any combination of opioid abuse, dependence or overdose (hazard ratio) (opioid naïve patients aged 18 or over)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[5] | no serious inconsistency | serious indirectness[6] | No serious imprecision | none | HR: 1.66 (1.24 to 2.22) | LOW |

*[1]Methods: multivariable analysis: cox proportional hazards model developed according to clinically relevant variables such as age and gender; downgraded by 1 increment due to serious risk of bias*

*[2] Downgraded by 1 increment as the confidence interval crossed the null line*

*[3] Methods: cox proportional hazards model analysis, including key covariates used in analysis to assess if receipt of benzodiazepine prescription is an independent risk factor. Key covariates included: sex, age, race, medical insurance, medical comorbidities, pain, mental health and substance use disorders*

*[4] Downgraded by 1 increment due to potential indirectness of part of the population who may not have been opioid naïve or could have drug use disorder/ dependence that could include opioids at baseline*

*[5] Methods: multivariable analysis: cox proportional hazards with stepwise selection adjusted for age, sex and comorbidities; downgraded by 1 increment due to serious risk of bias*

[6] *Downgraded by 1 increment as the proportion of those treated for chronic pain unclear*

### Table 55: Clinical evidence profile: Previous use of strong opioids

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Previous use of antipsychotics for predicting codeine shopping behaviour (HR) (adults with CNCP)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | HR 2.94 (1.24 to 6.98) | MODERAE |
| **Prior use of strong opioids for predicting tramadol shopping behaviour (HR) (CNCP patients treated with tramadol)** | | | | | | | | |
| 1 | Cohort study | very serious risk of bias [2] | no serious inconsistency | no serious indirectness | serious imprecision [3] | none | HR 5.7 (1.9 to 17.0) | VERY LOW |

[1] *Methods: multivariable analysis: cox proportional hazards model developed according to clinically relevant variables such as age and gender; downgraded by 1 increment due to serious risk of bias*
[2] *Methods: multivariable analysis: cox proportional hazards mode; confounders not specified; downgraded by 2 increments due to serious risk of bias*
[3]*Downgraded by 1 increment as the confidence interval was judged to be very wide*

### Table 56: Clinical evidence profile: Long-term opioid therapy

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Periods on long-term opioids versus not being in an episode of long-term prescribing for predicting incident addiction to opioids (new long-term opioid users)** | | | | | | | | |
| 1 | Cohort study | No serious risk of bias[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | HR 2.83 (2.13 to 3.76) | HIGH |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Long term opioid therapy (≥90 days) vs shorter term opioid therapy (<90 days) for predicting opioid dependence (adj. HR) (patients with polyneuropathy)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | HR 2.85 (1.54-5.47) | LOW |
| **Long term opioid therapy (≥90 days) vs shorter term opioid therapy (<90 days) for predicting opioid abuse (adj. HR) (patients with polyneuropathy)** | | | | | | | | |
| *1* | *Cohort study* | *Very serious risk of bias[2]* | *no serious inconsistency* | *no serious indirectness* | *Very serious imprecision[3]* | *none* | *HR: 3.97 (0.87-28.9)* | *VERY LOW* |

*[1] Methods: multivariable analysis: Cox proportional hazards regression adjusted for age at baseline, gender, year of start of follow-up, ever smoking, ever alcohol drinking, overweight (BMI ≥25 kg/m2), geographical region, deprivation level, prior recorded depression, co-prescribing of NSAID and total number of co-morbid conditions*
*[2] Methods: multivariate logistic regressions adjusted for of Charlson Comorbidity Index comorbidities, sex, and use of non-opioid analgesics; downgraded by 2 increments due to very serious risk of bias*
*[3] Downgraded by 1 increment as the confidence interval crossed the null line and was judged to be very wide*

## Table 57: Clinical evidence profile: Opioid dosage

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Long-term episode at average daily dose (ADD) <20 mg MED versus not being in an episode of long-term prescribing for predicting incident addiction to opioids (new long-term opioid users)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | no serious indirectness | serious imprecision[2] | none | HR 1.06 (0.71 to 1.60) | LOW |
| **Long-term episode ADD ≥20 and <50 mg MED versus not being in an episode of long-term prescribing for predicting incident addiction to opioids (new long-term opioid users)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | HR 3.59 (2.55 to 5.06) | MODERATE |
| **Long-term episode ADD ≥ 50 mg MED versus not being in an episode of long-term prescribing for predicting incident addiction to opioids (new long-term opioid users)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | HR 9.33 (6.55 to 13.29) | MODERATE |
| **Opioid dosage, MME/d (continuous) for predicting composite outcome (any combination of opioid abuse, dependence or overdose) (hazard ratio) (opioids naïve patients aged 18 years and over)** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | Cohort study | serious risk of bias[3] | no serious inconsistency | serious indirectness[4] | no serious imprecision | none | HR 1.003 (1.001-1.006) | LOW |

[1] *Methods: multivariable analysis: Cox proportional hazards regression adjusted for age at baseline, gender, year of start of follow-up, ever smoking, ever alcohol drinking, overweight (BMI ≥25 kg/m2), geographical region, deprivation level, prior recorded depression, co-prescribing of NSAID and total number of co-morbid conditions; downgraded by 1 increment due to serious risk of bias*
[2] *Downgraded by 1 increment as the CI crossed the null line*
[3] *Methods: multivariate analysis: cox proportional hazards with stepwise selection adjusted for age, sex and comorbidities; downgraded by 1 increment due to serious risk of bias*
[4] *Downgraded by 1 increment as the proportion of those treated for chronic pain was unclear*

**Table 58: Clinical evidence profile: Opioid formulation (Oxycodone IR versus tapentadol IR)**

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Tapentadol IR vs oxycodone IR for predicting (opioid) shopping behaviour (OR) (opioid-naïve patients initiating opioid use)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | serious indirectness[2] | No serious imprecision | none | OR 0.45 (0.36 to 0.55) | LOW |
| **Tapentadol IR vs oxycodone IR for predicting incident opioid abuse (OR) (opioid-naïve patients initiating opioid use)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | serious indirectness[2] | no serious imprecision | none | OR 0.44 (0.37 to 0.54) | LOW |
| **Oxycodone IR vs tapentadol IR for predicting shopping behaviour (OR) (opioid-naïve patients initiating opioid use)** | | | | | | | | |
| 1 | Cohort study | no serious risk of bias[3] | no serious inconsistency | serious indirectness[2] | no serious imprecision | none | OR 3.5 (2.8 to 4.4) | MODERATE |
| **Oxycodone IR vs tapentadol IR for predicting heavy shopping behaviour (OR) (opioid-naïve patients initiating opioid use)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[4] | no serious inconsistency | serious indirectness[2] | serious imprecision [5] | none | OR 6.9 (2.5 to 19.3) | VERY LOW |

[1] *Methods: multivariable analysis: logistic regression adjusted for Age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date; downgraded by 1 increment due to risk of bias*
[2] *Downgraded by 1 increment due to proportion of participants taking opioids for chronic pain being unclear*
[3] *Methods: multivariate analysis: conditional logistic regression conducted using matched analysis, taking into account matching variables of time of opioid exposure, geographic area, specialty of the prescriber and age and adjusting for gender, benzodiazepine use and type of payment at the first opioid exposure.*

*[4] Downgraded by 1 increment due to risk of bias*
*[5] Downgraded by 1 increment as the confidence interval was judged to be very wide*

**Table 59: Clinical evidence profile: Duration of action in the first prescription**

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Long versus short acting opioids for predicting overlapping opioid prescriptions across the six following 3-month quarters (risk difference) (privately insured patients aged 18-64 years)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness[3] | no serious imprecision | none | Risk difference 14.70 (12.7 to 16.7) | VERY LOW |
| **Long versus short acting opioids for predicting having 3 or more opioid prescribers across the six following 3-month quarters (risk difference) (privately insured patients aged 18-64 years)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness[3] | Serious imprecision | none | Risk difference 1.8 (0.9 to 2.7%) | VERY LOW |
| **Long-acting opioids versus short-acting for predicting composite outcome – any combination of opioid abuse, dependence or overdose (hazard ratio) (opioid naïve patients aged 18 years or over)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[2] | no serious inconsistency | serious indirectness[3] | serious imprecision[4] | none | HR 2.17 (0.81 to 5.86) | VERY LOW |
| **Concurrent use of short-acting and long-acting opioids within 30 days (compared to short-acting alone) for predicting composite outcome – any combination of opioid abuse, dependence or overdose (hazard ratio) (opioid naïve patients aged 18 years or over)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[2] | no serious inconsistency | serious indirectness[3] | no serious imprecision | none | HR 2.12 (1.78 to 2.54) | LOW |
| **Concurrent use of short-acting and long-acting opioids not within 30 days (compared to short-acting alone) for predicting composite outcome – any combination of opioid abuse, dependence or overdose (hazard ratio) (opioid naïve patients aged 18 years or over)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[2] | no serious inconsistency | serious indirectness[3] | no serious imprecision | none | HR 1.99 (1.24 to 3.18) | LOW |

*[1] Methods: multivariate analysis: linear probability model adjusting for ordinal indicators of the quarters/3-month intervals following the first prescription (second, third, sixth, with the first quarter as the reference), calendar year indicators, patient demographics (age groups, sex); dichotomous indicators of back pain, neck pain, arthritis/joint pain and other pain, an indicator of any mental health disorder, alcohol use disorder, any drug use disorder and tobacco use disorder, socio-demographic profiles at the patient's residential ZIP codes; downgraded by 2 increments due to very serious risk of bias*
*[2] Methods: multivariate analysis: Cox proportional hazards with stepwise selection adjusted for age, sex and comorbidities; downgraded by 1 increment due to serious risk of bias*
*[3] Downgraded by 1 increment as the proportion of those treated for chronic pain was unclear*
*[4] Downgraded by 1 increment as the CI crossed the null line*

**Table 60: Clinical evidence profile: Duration of opioid supply in the first prescription**

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Number of days' supply for predicting composite outcome (any combination of opioid abuse, dependence or overdose) (hazard ratio) (opioid naïve patients aged 18 years and over)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias[1] | no serious inconsistency | serious indirectness[3] | no serious imprecision | none | HR 1.025 (1.019 to 1.032) | LOW |
| **>7 days' supply vs 3 ≤ days for predicting overlapping opioid prescriptions across the six following 3-month quarters (risk difference) (privately insured patients aged 18-64 years)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[2] | no serious inconsistency | serious indirectness[3] | no serious imprecision | none | Risk difference 6.65 (6.3 to 7) | VERY LOW |
| **>7 days' supply vs 4-7 days for predicting overlapping opioid prescriptions across the six following 3-month quarters (risk difference) (privately insured patients aged 18-64 years)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[2] | no serious inconsistency | serious indirectness[3] | no serious imprecision | none | Risk difference 5.65 (5.3 to 6) | VERY LOW |

*1 Methods: multivariate analysis: cox proportional hazards with stepwise selection adjusted for age, sex and comorbidities; downgraded by 1 increment due to serious risk of bias*
*2 Methods: multivariate analysis: linear probability model adjusting for ordinal indicators of the quarters/3-month intervals following the first prescription (second, third, sixth, with the first quarter as the reference), calendar year indicators, patient demographics (age groups, sex); dichotomous indicators of back pain, neck pain, arthritis/joint pain and other pain, an indicator of any mental health disorder, alcohol use disorder, any drug use disorder and tobacco use disorder, socio-demographic profiles at the patient's residential ZIP codes; downgraded by 2 increments due to very serious risk of bias*
*3 Downgraded by 1 increment as the proportion of those treated for chronic pain was unclear*

### Table 61: Clinical evidence profile: Dual use of Veterans health administration (VHA) pharmacy and Medicare part D

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations (including publication bias where possible) | Effect (95% CI) | |
| **Dual use of VHA and Medicare part D for predicting overlapping concurrent opioid prescriptions (OR) (Veterans aged ≥ 65 years with a new MSD diagnosis)** | | | | | | | | |
| 1 | Cohort study | No serious risk of bias | no serious inconsistency | serious indirectness[2] | no serious imprecision | none | OR 5.28 (4.60 to 6.05) | MODERATE |

[1] *Methods: multivariate logistic regression analysis adjusted for age, sex, ethnicity, pain intensity (NRS), co morbid diagnoses, overall clinical severity (CII), mental health diagnoses: depressive disorder, substance use disorder (alcohol and illicit drug use disorders) and PTSD*
[2] *Downgraded by 1 increment as the risk factor may be of limited relevance to the NHS setting.*

### Table 62: Clinical evidence profile: Type of payment

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations (including publication bias where possible) | Effect (95% CI) | |
| **Medicaid vs cash payment for predicting shopping behaviour (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | no serious imprecision | none | OR 0.3 (0.3 to 0.4) | VERY LOW |
| **Medicaid vs cash payment for predicting opioid abuse (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | serious imprecision[3] | none | OR 1.1 (0.9 to 1.2) | VERY LOW |
| **Medicare vs cash payment for predicting shopping behaviour (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | no serious imprecision | none | OR 0.4 (0.3 to 0.4) | VERY LOW |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Medicare vs cash payment for predicting opioid abuse (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | no serious imprecision | none | OR 0.7 (0.6 to 0.8) | VERY LOW |
| **Commercial insurance vs cash payment for predicting shopping behaviour (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | no serious imprecision | none | OR 0.2 (0.2 to 0.2) | VERY LOW |
| **Commercial insurance vs cash payment for predicting opioid abuse (OR) (opioid-naïve patients initiating opioid use (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | no serious imprecision | none | OR 0.3 (0.3 to 0.4) | VERY LOW |

*[1]Methods: multivariate analysis: logistic regression adjusted for Age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date; downgraded by 2 increments due to very serious risk of bias*
*[2]Downgraded by 1 increment due to the proportion of those being prescribed opioids for chronic pain being unclear and by 1 increment due the risk factor being of limited relevance to the NHS setting*
*[3] Downgraded by 1 increment as the confidence interval crossed the null line*

### Table 63: Clinical evidence profile: Painful condition (present vs absent)

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Arthritis for predicting shopping behaviour (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision[3] | none | OR 0.8 (0.7 to 1.0) | VERY LOW |
| **Arthritis for predicting opioid abuse (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision [3] | none | OR 1 (0.8 to 1.1) | VERY LOW |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Back pain for predicting shopping behaviour (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | no serious imprecision | none | OR 2 (1.7 to 2.3) | VERY LOW |
| **Back pain for predicting opioid abuse (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | no serious imprecision | none | OR 1.7 (1.5 to 2.0) | VERY LOW |
| **Fractures for predicting shopping behaviour (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision [3] | none | OR 1.1 (0.75 to 1.7) | VERY LOW |
| **Fractures for predicting opioid abuse (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision [3] | none | OR 1.2 (0.8 to 1.6) | VERY LOW |
| **Headache for predicting shopping behaviour (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision [3] | none | OR 0.8 (0.6 to 1.2) | VERY LOW |
| **Headache for predicting opioid abuse (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision [3] | none | OR 1.2 (0.9 to 1.5) | VERY LOW |
| **Malignancy for predicting shopping behaviour (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | no serious imprecision | none | OR 0.7 (0.5 to 0.9) | VERY LOW |
| **Malignancy for predicting opioid abuse (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | no serious imprecision | none | OR 0.4 (0.3 to 0.5) | VERY LOW |
| **Musculoskeletal pain for predicting shopping behaviour (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision [3] | none | OR 0.9 (0.7 to 1.1) | VERY LOW |
| **Musculoskeletal pain for predicting opioid abuse (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision [3] | none | OR 1.1 (0.9 to 1.3) | VERY LOW |
| **Neuropathic pain for predicting shopping behaviour (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision [3] | none | OR 1.2 (0.8 to 1.8) | VERY LOW |
| **Neuropathic pain for predicting opioid abuse (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision [3] | none | OR 1.1 (0.7 to 1.6) | VERY LOW |
| **Other pains for predicting shopping behaviour (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision [3] | none | OR 1.2 (0.6 to 2.3) | VERY LOW |
| **Other pains for predicting opioid abuse (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | no serious imprecision | none | OR 1.7 (1.0 to 2.8) | VERY LOW |
| **Reproductive pain for predicting shopping behaviour (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision [3] | none | OR 0.7 (0.3 to 1.8) | VERY LOW |
| **Reproductive pain for predicting opioid abuse (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision [3] | none | OR 0.8 (0.4 to 1.7) | VERY LOW |
| **Visceral pain for predicting shopping behaviour (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision [3] | none | OR 1.0 (0.8 to 1.2) | VERY LOW |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Visceral pain for predicting opioid abuse (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision [3] | none | OR 1.1 (0.9 to 1.3) | VERY LOW |
| **Wound injury for predicting shopping behaviour (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision [3] | none | OR 1.0 (0.5 to 1.8) | VERY LOW |
| **Wound injury for predicting opioid abuse (opioid-naïve patients initiating opioid use (OR) (mean age (SD): 53.1 (17.1) years))** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | serious indirectness [2] | serious imprecision [3] | none | OR 0.7 (0.4 to 1.4) | VERY LOW |

*[1]Methods: multivariate analysis: logistic regression adjusted for Age, sex and types of payments at the index date; benzodiazepine use in the 3 months before the index date; major depression, mood and anxiety disorders or abuse of nonopioid medications (such as alcohol or tobacco) and pain-related diagnoses in the 12 months before the index date; downgraded by 1 increment due to serious risk of bias*
*[2]Downgraded by 1 increment due to the proportion of those being prescribed opioids for chronic pain being unclear and by 1 increment due the risk factor being of limited relevance to the NHS setting*
*[3] Downgraded by 1 increment as the confidence interval crossed the null line*

# F.2 GRADE tables for Benzodiazepines

### Table 64: Clinical evidence profile: Age

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Age (continuous) for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (new BZD users with a first redemption for diazepam or oxazepam)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias [1] | no serious inconsistency | serious indirectness[2] | no serious imprecision | none | HR 0.984 (0.977 to 0.99) | LOW |
| **25-34 years vs 18-24 years for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | Cohort study | Very serious risk of bias[3] | no serious inconsistency | No serious indirectness | Serious imprecision[4] | none | HR 1.23 (0.35 to 4.31) | VERY LOW |
| **35-44 vs 18-24 years for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[3] | no serious inconsistency | No serious indirectness | Serious imprecision[4] | none | HR 0.66 (0.33 to 1.31) | VERY LOW |
| **45-54 years vs 18-24 years for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[3] | no serious inconsistency | No serious indirectness | Serious imprecision[4] | none | HR 0.87 (0.37 to 2.06) | VERY LOW |
| **55-64 years vs 18-24 years for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[3] | no serious inconsistency | No serious indirectness | Serious imprecision[4] | none | HR 1.08 (0.37 to 3.11) | VERY LOW |
| **65+ years vs 18-24 years for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[3] | no serious inconsistency | No serious indirectness | Serious imprecision[4] | none | HR 1.47 (0.34 to 6.27) | VERY LOW |

[1] *Methods: Cox proportional hazard regression model adjusted for socio-demographic status and previous drug use; unclear if the analysis adjusted for other covariates in addition to the aforementioned and those entered in the model as prognostic factors; downgrade by 1 increment due to serious risk of bias*
[2] *Downgraded by 1 increment due to outcome indirectness*
[3] *Methods: Cox proportional hazard regression model adjusted for substance use disorder diagnosis (alcohol, marijuana, cocaine, opioid, tobacco, pain medication), mental health disorder diagnosis, age, sex, race; model also included interactions between age and sex; downgraded by 2 increments due to very serious risk of bias*
[4] *Downgraded by 1 increment as the confidence interval crossed the null line*

### Table 65: Clinical evidence profile: Gender

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Female vs male for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (HR) (new BZD users with a first redemption for diazepam or oxazepam)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias [1] | no serious inconsistency | serious indirectness[2] | no serious imprecision | none | HR 0.571 (0.505 to 0.645) | LOW |
| **Male vs female for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias [3] | no serious inconsistency | No serious indirectness | serious imprecision[4] | None | HR 1.33 (0.55 to 3.21) | VERY LOW |

*[1] Methods: Cox proportional hazard regression model adjusted for socio-demographic status and previous drug use; unclear if the analysis adjusted for other covariates in addition to the aforementioned and those entered in the model as prognostic factors; downgrade by 1 increment due to serious risk of bias*
*[2] Downgraded by 1 increment due to outcome indirectness*
*[3] Methods: Cox proportional hazard regression model adjusted for substance use disorder diagnosis (alcohol, marijuana, cocaine, opioid, tobacco, pain medication), mental health disorder diagnosis, age, sex, race; model also included interactions between age and sex; downgraded by 2 increments due to very serious risk of bias*
*[4] Downgraded by 1 increment as the confidence interval crossed the null line*

## Table 66: Clinical evidence profile: Family Background

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Black vs white for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | No serious indirectness | No serious imprecision | none | HR 0.18 (0.15 to 0.21) | LOW |
| **Latino vs white for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | No serious indirectness | No serious imprecision | none | HR 0.2 (0.17 to 0.23) | LOW |
| **Asian vs white for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | No serious indirectness | No serious imprecision | none | HR 0.43 (0.25 to 0.74) | LOW |

*[1] Methods: Cox proportional hazard regression model adjusted for substance use disorder diagnosis (alcohol, marijuana, cocaine, opioid, tobacco, pain medication), mental health disorder diagnosis, age, sex, race; model also included interactions between age and sex; downgraded by 2 increments due to very serious risk of bias*

### Table 67: Clinical evidence profile: First benzodiazepine dispensation

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Diazepam vs oxazepam for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (HR) (new BZD users with a first redemption for diazepam or oxazepam)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias [1] | no serious inconsistency | serious indirectness[2] | no serious imprecision | none | HR 1.328 (1.167 to 1.512) | LOW |

*[1] Methods: Cox proportional hazard regression model adjusted for socio-demographic status and previous drug use; unclear if the analysis adjusted for other covariates in addition to the aforementioned and those entered in the model as prognostic factors; downgrade by 1 increment due to serious risk of bias*
*[2] Downgraded by 1 increment due to outcome indirectness*

### Table 68: Clinical evidence profile: Previous medication

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Antidepressants and lithium for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (HR) (new BZD users with a first redemption for diazepam or oxazepam)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias [1] | no serious inconsistency | serious indirectness[2] | no serious imprecision | none | HR 1.687 (1.491 to 1.91) | LOW |
| **Antipsychotics for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (HR) (new BZD users with a first redemption for diazepam or oxazepam)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias [1] | no serious inconsistency | serious indirectness[2] | no serious imprecision | none | HR 1.753 (1.488 to 2.066) | LOW |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Opioids, anti-alcohol and smoking cessation drugs and dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (HR) (new BZD users with a first redemption for diazepam or oxazepam)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias [1] | no serious inconsistency | serious indirectness[2] | no serious imprecision | none | HR 3.042 (95% CI 2.285 to 4.047) | LOW |
| **Drugs for rheumatic disease for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (HR) (new BZD users with a first redemption for diazepam or oxazepam)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias [1] | no serious inconsistency | serious indirectness[2] | serious imprecision [3] | none | HR 1.216 (0.968 to 1.529) | VERY LOW |
| **Drugs for COPD for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (HR) (new BZD users with a first redemption for diazepam or oxazepam)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias [1] | no serious inconsistency | serious indirectness[2] | no serious imprecision | none | HR 1.288 (1.089 to 1.523) | LOW |

*[1] Methods: Cox proportional hazard regression model adjusted for socio-demographic status and previous drug use; unclear if the analysis adjusted for other covariates in addition to the aforementioned and those entered in the model as prognostic factors; downgrade by 1 increment due to serious risk of bias*
*[2] Downgraded by 1 increment due to outcome indirectness*
*[3] Downgraded by 1 increment as the confidence interval crossed the null line*

## Table 69: Clinical evidence profile: Education

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **High vs low for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (HR) (new BZD users with a first redemption for diazepam or oxazepam)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias [1] | no serious inconsistency | serious indirectness[2] | no serious imprecision | none | HR 0.647 (0.574 to 0.73) | LOW |

*[1] Methods: Cox proportional hazard regression model adjusted for socio-demographic status and previous drug use; unclear if the analysis adjusted for other covariates in addition to the aforementioned and those entered in the model as prognostic factors; downgrade by 1 increment due to serious risk of bias*
*[2] Downgraded by 1 increment due to outcome indirectness*

## Table 70: Clinical evidence profile: Income

| Quality assessment | Effect | Quality |
|---|---|---|

| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations (including publication bias where possible) | Effect (95% CI) | |
|---|---|---|---|---|---|---|---|---|
| **Average vs low for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (HR) (new BZD users with a first redemption for diazepam or oxazepam)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias [1] | no serious inconsistency | serious indirectness[2] | No serious imprecision | none | HR 0.719 (0.615 to 0.841) | LOW |
| **High vs low for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (HR) (new BZD users with a first redemption for diazepam or oxazepam)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias [1] | no serious inconsistency | serious indirectness[2] | no serious imprecision | none | HR 0.569 (0.453 to 0.714) | LOW |

*[1] Methods: Cox proportional hazard regression model adjusted for socio-demographic status and previous drug use; unclear if the analysis adjusted for other covariates in addition to the aforementioned and those entered in the model as prognostic factors; downgrade by 1 increment due to serious risk of bias*
*[2] Downgraded by 1 increment due to outcome indirectness*

### Table 71: Clinical evidence profile: Type of work

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Private sector vs no registration for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (HR) (new BZD users with a first redemption for diazepam or oxazepam)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias [1] | no serious inconsistency | serious indirectness[2] | No serious imprecision | none | HR 0.622 (0.520 to 0.743) | LOW |
| **Public sector vs no registration for predicting dose escalation (daily average intake of ≥ 1 defined daily dose over a 3-month period) (HR) (new BZD users with a first redemption for diazepam or oxazepam)** | | | | | | | | |
| 1 | Cohort study | serious risk of bias [1] | no serious inconsistency | serious indirectness[2] | no serious imprecision | none | HR 0.613 (0.518 to 0.725) | LOW |

*[1] Methods: Cox proportional hazard regression model adjusted for socio-demographic status and previous drug use; unclear if the analysis adjusted for other covariates in addition to the aforementioned and those entered in the model as prognostic factors; downgrade by 1 increment due to serious risk of bias*
*[2] Downgraded by 1 increment due to outcome indirectness*

**Table 72: Clinical evidence profile: Substance use diagnosis**

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations (including publication bias where possible) | Effect (95% CI) | |
| **Alcohol vs no diagnosis for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | No serious indirectness | No serious imprecision | none | HR 0.77 (0.6 to 0.99) | LOW |
| **Marijuana vs no diagnosis for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | No serious indirectness | No serious imprecision | none | HR 0.28 (0.2 to 0.38) | LOW |
| **Cocaine vs no diagnosis for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | No serious indirectness | Serious imprecision[2] | none | HR 1.13 (0.79 to 1.61) | VERY LOW |
| **Opioid vs no diagnosis for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | No serious indirectness | Serious imprecision[2] | none | HR 3.9 (1.18 to 12.89) | VERY LOW |
| **Tobacco vs no diagnosis for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | No serious indirectness | No serious imprecision | none | HR 2.08 (1.18 to 3.67) | LOW |
| **Pain medications vs no diagnosis for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | No serious indirectness | No serious imprecision | none | HR 0.71 (0.58 to 0.86) | LOW |
| **2 or more substance use disorders vs no diagnosis for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | No serious indirectness | No serious imprecision | none | HR 2.03 (1.04 to 3.95) | LOW |

*[1] Methods: Cox proportional hazard regression model adjusted for substance use disorder diagnosis (alcohol, marijuana, cocaine, opioid, tobacco, pain medication), mental health disorder diagnosis, age, sex, race; model also included interactions between age and sex; downgraded by 2 increments due to very serious risk of bias*
*[2] Downgraded by 1 increment as the confidence interval crossed the null line or was judged to be very wide*

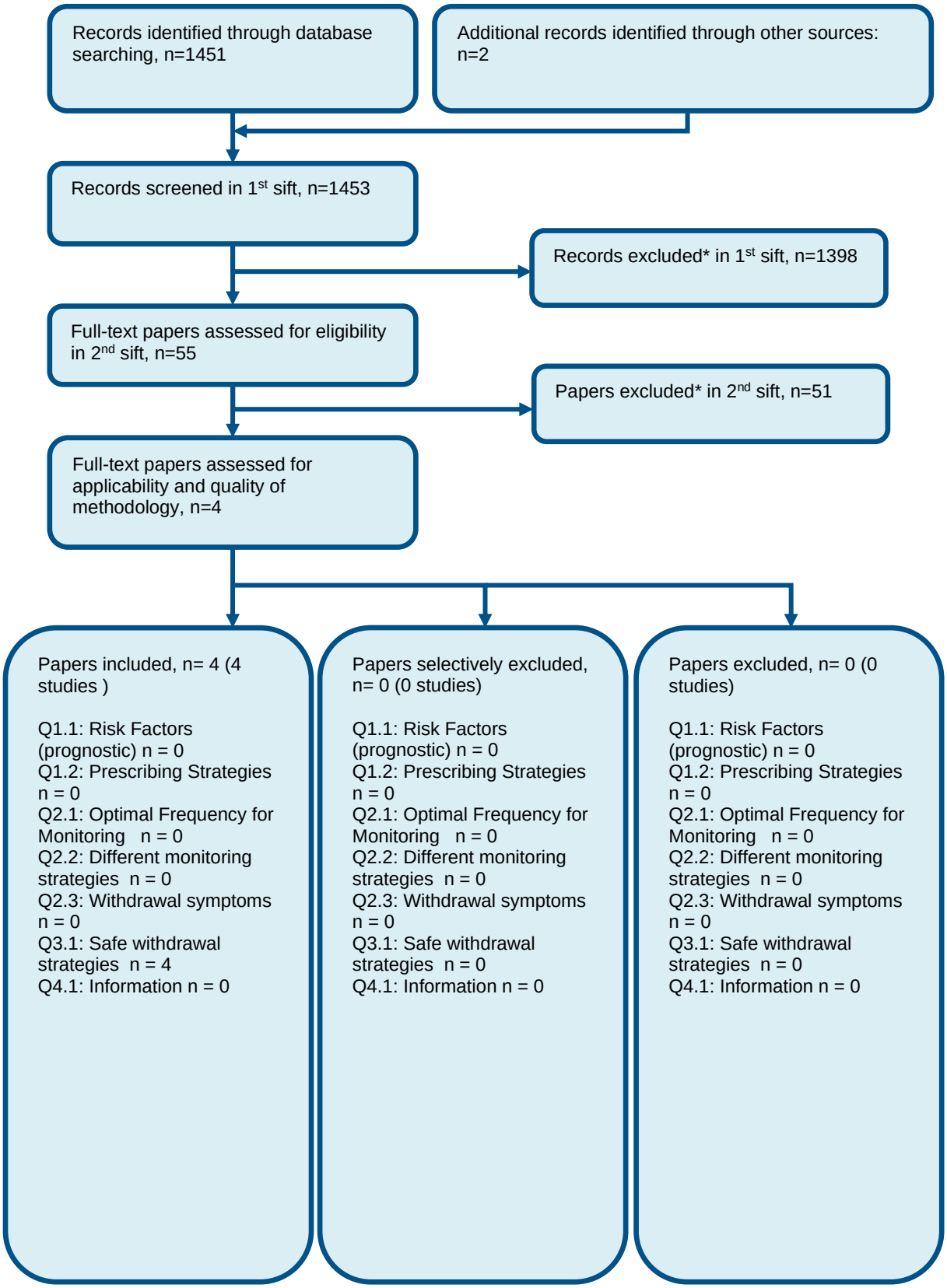
**Table 73: Clinical evidence profile: Mental health disorder diagnosis**

| Quality assessment | | | | | | | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations (including publication bias where possible)** | **Effect (95% CI)** | |
| **Depression vs no diagnosis for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | No serious indirectness | No serious imprecision | none | HR 1.43 (0.99 to 2.08) | LOW |
| **Anxiety vs no diagnosis for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | No serious indirectness | No serious imprecision | none | HR 1.6 (1.02 to 2.51) | LOW |
| **Bipolar vs no diagnosis for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | No serious indirectness | Serious imprecision[2] | none | HR 1.02 (0.69 to 1.51) | VERY LOW |
| **PTSD vs no diagnosis for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | No serious indirectness | Serious imprecision[2] | none | HR 0.91 (0.65 to 1.27) | VERY LOW |
| **Sleeping disturbance vs, no diagnosis for predicting benzodiazepine dependence (HR) (benzodiazepine users)** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | Cohort study | Very serious risk of bias[1] | no serious inconsistency | No serious indirectness | No serious imprecision | none | HR 0.69 (0.53 to 0.89) | LOW |

*[1] Methods: Cox proportional hazard regression model adjusted for substance use disorder diagnosis (alcohol, marijuana, cocaine, opioid, tobacco, pain medication), mental health disorder diagnosis, age, sex, race; model also included interactions between age and sex; downgraded by 2 increments due to very serious risk of bias*
*[2] Downgraded by 1 increment as the confidence interval crossed the null line*

# Appendix G Economic evidence study selection




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

# Appendix H Economic evidence tables

None.

# Appendix I Health economic model

This question was not prioritised for health economic modelling.

# Appendix J Excluded studies

## J.1 Clinical studies

**Table 73: Studies excluded from the clinical review**

| Study | Exclusion reason |
|---|---|
| Adejumo 2021[1] | Incorrect study design: cross-sectional |
| Adewumi 2018[2] | Systematic review. No relevant outcomes (severe opioid poisoning or mortality). |
| Airagnes 2019[3] | No relevant outcomes (outcome reported: long term use). |
| Al Dabbagh 2014[4] | No relevant outcomes (outcome reported: long term use). |
| Alam 2012[5] | No relevant outcomes (outcome reported: long term use). |
| Almakadma 2013[6] | No relevant outcomes (outcome reported: long term use). |
| Alzeer 2018[7] | Systematic review: protocol differs from review protocol |
| Anciano Granadillo 2018[8] | No relevant outcomes (outcome reported: long term use & post-operative complications). |
| Anderson 2015[9] | No relevant outcomes (outcome reported: long term use) |
| Atluri 2004[10] | Study design does not meet protocol: case-control study |
| Azad 2019[11] | No relevant outcomes (outcome reported: long term use). |
| Banerjee 2019[12] | Incorrect population: already prescribed opioids at baseline |
| Barnas 1993[13] | Incorrect population: already prescribed benzodiazepines at baseline |
| Barry 2018[14] | Incorrect population: already prescribed opioids at the baseline |
| Bartels 2018[15] | No relevant outcomes (outcome reported: long term use). |
| Beaudoin 2014[16] | Incorrect population meeting exclusion criteria: emergency department patients discharged with a prescription |
| Bedard 2017[18] | No relevant outcomes (outcome reported: prolonged use, increase in opioid use) |
| Bedard 2017[17] | No relevant outcomes (outcome reported: prolonged use) |
| Belgrade 2006[20] | No relevant outcomes (global impression of compliance: good, fair or poor with latter referring to various signs of misuse); incorrect population: people taking opioids at screening. |
| Ben-Joseph 2016[21] | No relevant outcomes: length of treatment, use of extended-release/long-acting opioids. |
| Berecki-Gisolf 2014[22] | No relevant outcomes: long-term use |
| Bertenthal 2018[23] | No relevant outcomes: long-term & short-term use |
| Beyer 2019[24] | Population does not meet protocol: only 40% being prescribed medicines associated with dependence at baseline |
| Bhashyam 2018[25] | Incorrect design: cross-sectional & no relevant outcomes: persistent use, duration of use, total prescribed opioids |
| Bicket 2019[26] | No relevant outcomes: new persistent opioid use |
| Birke 2017[27] | No relevant outcomes: long-term use |
| Birke 2016[28] | Incorrect design: two-gate cross-sectional study; no relevant outcomes: long-term use |
| Blanch 2015[29] | Systematic review not meeting protocol |
| Blanch 2018[30] | Incorrect design: cross-sectional; no relevant outcomes: opioid access |

| Study | Exclusion reason |
|---|---|
| Blanco 2016[31] | Population does not meet protocol: not being prescribed medicines associated with dependence at baseline. |
| Boscarino 2010[34] | Incorrect study design: cross-sectional |
| Boscarino 2011[35] | Incorrect study design: cross-sectional |
| Bonnet 2017[32] | Systematic review not meeting protocol |
| Booher[33] | Incorrect study design: integrative review |
| Brady 2017[36] | Systematic review of studies not meeting protocol |
| Brat 2018[37] | Population & setting do not meet protocol: people with post-surgery prescription i.e., acute pain setting |
| Broekmans 2010[38] | Incorrect study design: cross-sectional |
| Brummett 2017[39] | No relevant outcomes: new persistent opioid use (90-180 days post-surgery) |
| Bruneau 2021[40] | Incorrect population: already prescribed opioids at baseline |
| Burke 2020[41] | Incorrect population: people being prescribed opioids with no breakdown of chronic and acute pain. Breakdown is provided for the specialty that prescribed the opioid (17% in surgery and 10% in dental specialty), suggesting >20% had acute pain. |
| Bushnell 2017[42] | No relevant outcomes: long-term use & simultaneous new use of antidepressants and benzodiazepines |
| Calcaterra 2018[43] | No relevant outcomes: chronic opioid use |
| Calcaterra 2016[44] | No relevant outcomes: chronic opioid use |
| Callaghan 2019[45] | No relevant outcomes: opioid use, guideline-recommended opioid use, specialist visits; incorrect study design: cross-sectional |
| Campbell 2015[47] | Incorrect study design: article about study with no relevant outcomes |
| Campbell 2014[46] | No relevant outcomes such as pain, quality-of-life and physical health |
| Campbell 2015[48] | Incorrect population: Prospective cohort of people already on opioids |
| Campbell 2020[49] | Incorrect population: already prescribed opioids at the baseline |
| Capaldi 2019[50] | No relevant outcomes: opioid misuse (of prescribed drugs obtained from sources other than doctors) or taking more than prescribed that was different from prescribed opioid use |
| Carroll 2012[51] | No relevant outcomes: days to cessation, pain. |
| Cepeda 2013[53] | Incorrect population: >20% had malignancy |
| Chalmers 2019[55] | Incorrect population: current opioid users; no risk factors, screening tools for opioid misuse |
| Chaudhary 2019[56] | Incorrect study design: case-control; no relevant outcomes: sustained prescription use |
| Chaudhary 2017[57] | No relevant outcomes: discontinuation and sustained use |
| Chaudhary 2019[58] | No relevant outcomes: length of prescription |
| Cheatle 2019[59] | Population already on opioids; design: secondary analysis of cross-sectional study with no relevant outcome |
| Cheng 2008[62] | Incorrect study design: cross-sectional; no relevant outcomes |
| Cho 2020[63] | No relevant outcomes: opioid overdose |
| Chou 2009[65] | Systematic review not meeting protocol |
| Chou 2014[64] | Systematic review not meeting protocol |
| Chou 2015[67] | Systematic review not meeting protocol |

| Study | Exclusion reason |
|---|---|
| Chou 2020[66] | Systematic review not meeting protocol |
| Cicero 2019[69] | Population: on opioids at time of assessment |
| Ciesielski 2016[70] | People were on opioids prior to the baseline timepoint |
| Clarke 2014[71] | No relevant outcome: prolonged opioid use |
| Clift 1972[72] | 1/3 received drug not meeting protocol; no multivariate analysis |
| Cochran 2017[73] | Incorrect study design: cross-sectional |
| Cochran 2017[74] | Incorrect study design: cross-sectional |
| Connolly 2017[75] | No relevant outcomes: long-term opioid use |
| Coplan 2017[77] | Incorrect population: exposed to opioids; no relevant outcomes: study looking at prescription data- examining rate of intentional abuse, suicidal intents associated with exposure to buprenorphine transdermal system/patch |
| Coutinho 2018[78] | CART analysis for opioid abuse outcome, no multivariate analysis and exact ORs for risk factors not reported in the papers |
| Coyle 2018[79] | Narrative review: references checked |
| Cragg 2019[80] | Systematic review & meta-analysis |
| Cragg 2017[81] | Systematic review protocol |
| Driot 2019[82] | Incorrect population: new gabapentinoid users taking at least one of various other drugs at baseline e.g., antidepressants, antipsychotics, opioids and part of the population had a cancer diagnosis or other psychiatric diagnosis e.g., schizophrenia or anxiety disorder |
| Dufour 2014[83] | Incorrect study design: case-control study |
| Dunbar 1996[84] | Population already on opioids at time of assessment; no multivariate analysis; case-control design |
| Dy 2019[85] | Case-control study; no relevant outcomes: prolonged use |
| Edlund 2007[86] | Incorrect population: Already chronic opioid users |
| Elzey 2016[87] | Systematic review not meeting protocol |
| Fang 2009[88] | No relevant outcomes: long-term opioid use & discontinuation |
| Fiorio 1990[89] | No relevant outcomes: long-term use |
| Fishbain 2008[90] | Review not meeting protocol: reporting on the prevalence of addiction/ aberrant drug related behaviours |
| Ford 2015[91] | Population not meeting protocol: adolescents aged 12-17 |
| Foy 2016[92] | Incorrect study design: cross-sectional & no relevant outcomes |
| Frankenburg 2014[93] | No relevant outcomes: opioid use |
| Franklin 2009[94] | No relevant outcomes: long-term use |
| Fredheim 2014[95] | No relevant outcomes: persistent opioid use |
| Fresán 2011[96] | Study not in English |
| Fride Tvete 2015[97] | Population and design not meeting protocol: looking at prescription data of people already on opioids; no relevant outcomes: excessive use |
| Fritz 2018[98] | No relevant outcomes: long-term use |
| Furlan 2016[99] | Analysis not meeting protocol; no relevant outcomes: long-term use |
| Garvey 1986[100] | Incorrect population: approximately 50% on benzodiazepine not on guideline medicine list; incorrect analysis: no multivariate analysis |
| Glei 2020[101] | Incorrect population: population not being prescribed medicines associated with dependence |

| Study | Exclusion reason |
|---|---|
| Groenewald 2019[102] | Incorrect study design: Cross-sectional study |
| Gryczynski 2017[103] | No relevant outcomes: sensitivity and specificity of assessment tool for illicit drug use, alcohol use and prescription drug misuse with no multivariate analysis data on specific risk factors |
| Guerlais 2015[104] | Incorrect study design: cross-sectional study with no multivariate analysis |
| Gustafsson 2013[105] | Incorrect study design: cross-sectional study with no relevant outcomes |
| Hah 2017[106] | Incorrect time point: Not following up people from an initial prescription |
| Halbert 2016[107] | No relevant outcomes: long-term use |
| Haller 2017[108] | Incorrect population: already on opioids at time of assessment; no multivariate analysis |
| Hauser 2020[109] | Article not in English |
| Heo 2021[110] | Incorrect population: prescribed opioids for acute post-operative pain |
| Himei 2006[111] | No multivariate analysis (associations of characteristics with occurrence of discontinuation syndrome upon stopping antidepressants) |
| Hinther 2019[112] | Systematic review not meeting protocol |
| Hooten 2015[114] | No relevant outcomes: chronic use |
| Huffman 2015[115] | Population already on opioids at time of initial assessment; multivariate analysis for past non-opioid substance abuse but it is likely most were also on opioids at the time |
| Hur 2021[116] | Incorrect population: opioid use after surgery |
| Ives 2006[117] | Population already on opioids at study entry |
| Jamison 2010[118] | Population already on opioids at study entry; no multivariate analysis |
| Jamison 2016[28] | Population already on opioids; no multivariate analysis; no relevant outcomes |
| Jamison 2009[119] | Population already on opioids at study entry; no multivariate analysis |
| Jobert 2021[120] | Incorrect population: already prescribed benzodiazepines at the baseline |
| Kaplan 1988[121] | Incorrect study design: descriptive observational study with no multivariate analysis |
| Karhade 2019[122] | Incorrect study design: case-control study; no relevant outcomes: prolonged use |
| Katz 2013[123] | Not following people up from an initial prescription and participants are not limited to people being prescribed opioids |
| Klimas 2019[124] | Systematic review: protocol does not match review protocol |
| Knisely 2008[125] | Cross-sectional study: administration of questionnaire at a time the population was already on opioids & had or had not developed addiction with questions examining factors during the past year; no multivariate analysis |
| Lalic 2018[126] | Outcome not meeting protocol: persistent opioid use |
| Lawrence 2017[127] | Systematic review: references checked |
| Layton 2014[128] | Analysis does not meet protocol: univariate |
| Li 2020[129] | No relevant outcomes: opioid overdose |

| Study | Exclusion reason |
|---|---|
| Lobo 2020[130] | Incorrect population: people being prescribed opioids with no breakdown of chronic and acute pain. Breakdown is provided for the specialty that prescribed the opioid (4% in surgery and 20% in dental specialty), suggesting >20% had acute pain. |
| Lu 2015[131] | No multivariate analysis |
| Mackay 1997[132] | No multivariate analysis |
| Mahowald 2005[133] | Incorrect study design: cross-sectional; no relevant outcomes |
| Manchikanti 2006[134] | Incorrect study design: cross sectional study; no multivariate analysis |
| Manthey 2012[135] | Incorrect time point: recruited people already taking benzodiazepines; incorrect study design: cross-sectional |
| Maree 2016[136] | Systematic review of studies not meeting protocol |
| Martel 2014[137] | Incorrect study design: cross-sectional; no multivariate analysis |
| Martel 2013[138] | Incorrect study design: cross-sectional; no multivariate analysis |
| Morasco 2008[139] | Incorrect study design: cross-sectional |
| Morasco 2013[140] | Incorrect study design: cross-sectional |
| Morgan 2017[141] | No relevant outcomes: chronic use |
| Nam 2020[142] | No relevant outcomes: opioid overdose |
| Okumura[144] | Incorrect time point: recruited people already taking benzodiazepines |
| Padomanolakis 2021[146] | Incorrect population: >20% prescribed an opioid for acute pain (dental pain or surgical pain) |
| Page 2020[145] | Systematic review not meeting protocol |
| Passik[148] | Incorrect timepoint: baseline characteristics correspond to a time participants were already on opioids; no multivariate analysis |
| Peacock[149] | Incorrect timepoint: population on opioids at time of assessments |
| Portenoy[150] | Incorrect study design: observational study with no multivariate analysis or relevant outcomes |
| Raman 2019[145] | No multivariate analysis |
| Rickels 1983[153] | Incorrect population: non benzodiazepine naïve population |
| Robbins 1999[154] | No multivariate analysis: results for relevant outcome only reported narratively |
| Robisnon-Papp 2012[155] | No usable outcomes: study reports results narratively with no HRs or equivalent effect measure of multivariate analysis. |
| Rodriguez 2021[156] | Incorrect study design: cross-sectional |
| Saper 2004[157] | Correlation analysis with no examination of risk factors associated with relevant outcome |
| Skurtveit 2011[159] | No multivariate analysis |
| Smit 2020[160] | Population not followed up from initial point of prescription |
| Sridharan 2021[161] | Incorrect population: opioid use after surgery |
| Sullivan 2010[162] | No multivariate analysis; incorrect population: mixed drug classes (opioids and benzodiazepines) for which clinical evidence has been included |
| Szmulewicz 2021[163] | No relevant outcomes: opioid overdose |
| Timmerman 2016[164] | Systematic review of studies not meeting protocol |
| Tsao 2007[165] | Non-opioid naïve participants |
| Tsao 2010[166] | Non-opioid naïve participants; incorrect analysis: chi-square analysis results reported |

| Study | Exclusion reason |
|---|---|
| Turk 2008[167] | Systematic review of studies not meeting protocol |
| Tvete 2013[168] | No relevant data: results based on estimation modelling rather than actual data |
| Upadhye 2018[171] | Setting does not meet protocol: Emergency department (ED) thus, highly likely to include patients with acute pain. 23.7% ED injury visits having an opioid prescription. |
| Voyer 2009[173] | Incorrect study design: cross-sectional |
| Voyer 2011[172] | Incorrect study design: cross-sectional |
| Wasan 2012[175] | Incorrect time population: the patients had been prescribed opioid therapy for pain for > 6 months at study entry (inclusion criteria). |
| Wasan 2015[174] | Incorrect population: patients had previously been on short acting opioids and allowed changing between morphine and oxycodone. |
| Webster 2005[176] | Risk prediction tool for aberrant behaviours. No relevant outcomes for individual risk factors. |
| White 2009[177] | Mixed population (currently on opiates and people starting opiates). No separate results. |
| Yoshizawa 2015[178] | Incorrect outcomes |
| Ytterberg 1998[179] | Incorrect population: patients were taking opioids prior to start of study. |
| Zhou 2021[181] | No relevant outcomes: outcomes of opioid-use disorder and substance-use disorders appear to be related to heroin and other drugs and not dependence on the prescribed medicine |

## J.2 Health Economic studies

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

None.

# Appendix K Research recommendations

## K.1 Do individual circumstances such as social distress, low-income status, access to alternative sources of support, alter the risk of dependence on prescribed medicines?

### Why this is important

Medicines are often prescribed for conditions such as mental health disorders or chronic pain. These conditions and others are more common among those who have experienced established risk factors for health inequalities, such as social distress and economic deprivation. Access to sources of support may be both a risk factor for, and a consequence of, having these conditions. When offering medicines associated with dependence and withdrawal, prescribers should know whether these individual circumstances can also exacerbate these complications.

### Rationale for research recommendation

| | |
|---|---|
| Importance to 'patients' or the population | Dependence on prescribed medicines is a public health problem of policy interest, and may be increased among certain groups based on individual risk factors, which may also predispose people to the conditions for which these medicines are prescribed. Identification of factors that alter the risk of developing dependence, would help prescribers to tailor management plans to more appropriately support people who might be at a higher risk of developing problems associated with dependence. This would consequently improve patient outcomes when being prescribed these medicines, by reducing likelihood of problems associated with dependence. |
| Relevance to NICE guidance | This guideline explores individual risk assessment prior to prescribing, but there was a lack of evidence about whether individual circumstances increase risk of dependence on key groups of prescribed medicines. Further evidence in this area would therefore help inform future updates of this guideline. |
| Relevance to the NHS | Identification of people at increased risk of dependence on prescribed medicines can modify prescribing behaviour, support shared decision making, and may help resource allocation in proving people at higher risk with alternative or additional means of support. |
| National priorities | High<br>This is relevant to Public Health England's Prescribed medicines review, which recommends further research is required in this area: https://www.gov.uk/government/publications/prescribed-medicines-review-report<br>Reducing health inequalities is also an area of policy interest. |
| Current evidence base | There is poor quality evidence from retrospective studies, linking some individual factors to risk of benzodiazepine and opioid dependence, but the |

| | |
|---|---|
| | evidence is insufficiently strong or detailed to make decisions about public health or clinical approaches. |
| Equality considerations | This research would likely identify groups who already experience substantial health inequalities compared to the population as a whole. The findings could support measures to tackle these inequalities. |

### Modified PICO table

| | |
|---|---|
| Population | Adults (aged 18 years or older) with conditions for which medicines associated with dependence and withdrawal are prescribed (opioids, benzodiazepines, Z-drugs, gabapentinoids or antidepressants), at the point of initial prescribing or without dependence at baseline. |
| Intervention / Risk factor | • Indicators of social distress<br>• Low-income status<br>• Indicators of support networks (peer support / family support etc) |
| Comparator | N/A |
| Outcome | Dependence on the prescribed medicine |
| Study design | A longitudinal prospective cohort with multivariate analysis adjusting for key confounders would be required. |
| Timeframe | Long term follow up would be required to demonstrate an association between the risk factors and any future dependence. |
| Additional information | None |

## K.2 Do system level factors, such as prescriber training *alter* the risk of dependence on prescribed medicines?

### Why this is important

Healthcare professionals may prescribe medicines associated with dependence or withdrawal symptoms due to pressure to prescribe, distress, expectations to be prescribed a medicine for their condition, or lack of non-pharmacological alternatives, despite it not being in the best interests of the person concerned. Although system-level factors, such as availability of prescriber training may result in reducing the risk of developing dependence on prescribed medicines, there is currently no evidence available to support this.

### Rationale for research recommendation

| | |
|---|---|
| Importance to 'patients' or the population | Dependence on prescribed medicines can lead to significant morbidity and reduced quality of life and it is a cause of public and political concern. Identification of system-level factors that alter the risk of developing dependence, for example prescriber training, could have a significant and sustained impact on a large number of people. |
| Relevance to NICE guidance | System level factors were considered in this guideline and there was no evidence in this area, |

| | |
|---|---|
| | therefore further research would help inform future updates and may enable recommendations to be made on this topic. |
| Relevance to the NHS | Reducing the risk of developing dependence on prescribed medicines by altering system level factors could not only result in reduced morbidity and improved quality of life for large numbers of people but could also result in reduced costs to the NHS related to morbidity and ongoing prescribing and provide opportunities for strategic changes to service delivery. |
| National priorities | High<br>This is relevant to Public Health England's Prescribed medicines review, which recommends further research is required in this area: https://www.gov.uk/government/publications/prescribed-medicines-review-report |
| Current evidence base | The evidence review did not identify any available evidence for system-level factors that alter the risk of dependence on prescribed medicines. |
| Equality considerations | None known |

## Modified PICO table

| | |
|---|---|
| Population | Adults (aged 18 years or older) with conditions for which medicines associated with dependence and withdrawal are prescribed (opioids, benzodiazepines, Z-drugs, gabapentinoids or antidepressants) at the point of initial prescribing or without dependence at baseline. |
| Risk factor | System level factors, for example, level of training of prescribers in prescribing communication, competency of prescriber, supervision of prescribers. |
| Comparator | N/A |
| Outcome | Dependence on the prescribed medicine |
| Study design | A longitudinal prospective cohort with multivariate analysis adjusting for key confounders would be required. |
| Timeframe | Long term follow up would be required to demonstrate an association between the risk factors and any future dependence. |
| Additional information | None |

# Appendix L List of medicines to be included

This list refers to codes from BNF version 68.

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

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

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

List of medicines taken from the 2019 Public Health England review of prescribed medicines, and adapted where necessary.[151]

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

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

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

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