[Factors associated with concomitant prescribing of opioids and benzodiazepines in Primary Care]

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Abstract

Objective: This paper reviews studies that examine the factors that are associated with concurrent prescription of opioids and benzodiazepines in an outpatient setting with a focus on primary care.

Methods: We conducted a systematic review of any type of study, except case reports, until February 2021. We searched PubMed, Cochrane Library, Embase, CINAHL, PsycArticles, Web of Science and reference lists of selected articles. Two authors screened all articles independently, extracted data and appraised quality assessment following the GRADE system. Two investigators interpreted the extracted data according to their research question: the prevalence of co-prescribing benzodiazepines and opioids by researcher one, while the factors associated with co-prescription are described in this paper by researcher two.

Results: We included 42 articles. The majority of studies were conducted in the United States and had an observational study design. The co-prescription of benzodiazepines and opioids is more prevalent in patients who suffer from a mental health diagnosis (depression, anxiety disorder, substance use disorder, posttraumatic stress disorder, insomnia, panic attack disorder, have a lifetime reporting of a mental health condition) and chronic pain, especially if they had more than one pain condition, higher pain severity or lower pain self-efficacy. Concomitant use was more prevalent among middle-aged women, ranging from 35 till 64 years old. Opioid characteristics were also an important risk factor, as co-prescription was more prevalent in patients who used higher opioid doses, had long-term opioid use or early opioid refills.

Conclusion: Concomitant prescription seems to be associated with several patient-related factors. Physicians should be vigilant in co-prescribing this potentially harmful combination, especially in vulnerable patients if alternative treatment options are available.

Dutch Abstract:

Opzet: Deze masterproef onderzoekt de factoren die geassocieerd zijn met het concomitant voorschrijven van opioïden en benzodiazepines in een ambulante setting met een focus op eerstelijnszorg.

Methoden: Deze systematische review includeert studies van elke onderzoekmethode, behoudens casestudies, gepubliceerd tot februari 2021. Verscheidene databanken werden geraadpleegd aan de hand van vooraf geselecteerde zoektermen: PubMed, Cochrane Library, Embase, CINAHL, PsycArticles en Web of Science. Daarnaast werden artikels geïncludeerd via de referentielijst van andere studies. Screening, data-extractie en kwaliteitscontrole aan de hand van het GRADE systeem gebeurde onafhankelijk door twee auteurs. Hierna werden de data geïnterpreteerd door elke onderzoeker, afgestemd op zijn onderzoeksvraag. De prevalentie van concomitant voorschrijven van benzodiazepines en opioïden werd geanalyseerd door onderzoeker één. Onderzoeker twee beschrijft de factoren geassocieerd met het concomitant voorschrijven van benzodiazepines en opioïden, zoals neergeschreven in deze masterproef.

Resultaten: In totaal werden 42 artikels geïncludeerd. Het merendeel van de studies betreft een observationele onderzoeksmethode en werd uitgevoerd in de Verenigde Staten. Een hogere prevalentie van concomitant voorschrijven van benzodiazepines en opioïden komt voor bij patiënten die lijden aan een psychische aandoening (depressie, angststoornis, middelenmisbruik, posttraumatisch stresssyndroom, slaapstoornis, paniekstoornis of voorgeschiedenis van een psychische aandoening). De prevalentie is tevens hoger bij patiënten met chronische pijn, in het bijzonder bij meerdere pijndiagnoses, ernstigere pijn of verminderd vertrouwen in eigen-effectiviteit ten aanzien van de pijn. Concomitant gebruik komt hoofdzakelijk voor bij vrouwen van middelbare leeftijd, voornamelijk tussen 35 en 64 jaar oud. Daarnaast wordt een hogere prevalentie gezien bij patiënten die hogere dosissen of reeds langere tijd opioïden innemen, of bij patiënten die vervroegd consulteren voor een hernieuwd voorschrift.

Conclusie: Concomitant voorschrijven van benzodiazepines en opioïden is geassocieerd met verschillende patiënt-gerelateerde factoren. Artsen dienen waakzaam te zijn bij het simultaan voorschrijven van deze mogelijks gevaarlijke combinatie, in het bijzonder bij kwetsbare patiënten.

Introduction

Opioids and benzodiazepines are both well known as hazardous drugs, given their addictive potential and serious side effects. Both medications, especially in combination, are associated with risk of abuse, fatal and non-fatal overdoses, depression of the respiratory drive and central nervous system.[1] Therefore, they increase the risk of falling and traffic accidents.[1] Primary care physicians are common prescribers of these drugs.[2]

Apart from their individual harmful side effects, co-prescription of benzodiazepines and opioids leads to an even higher risk of fatal and nonfatal overdoses.[3] Prescribed opioids are responsible for more than half of overdose deaths, half of these prescriptions are written by a primary care physician.[4] Their risk for addiction and overdose is dose-dependent.[4] In 2011 the Centers for Disease Control and Prevention (CDC) reported that 31% of the opioid fatalities are contributed by benzodiazepines.[5] Whereas taking benzodiazepines without other drugs has a broader margin of safety, the risk of fatality overdose rises to 71% in association with opioids.[6]

Benzodiazepines are most commonly prescribed for anxiety and insomnia, given their calming and hypnotic effect.[7] Other useful properties are their anticonvulsant and antispastic effects. Common adverse effects are risk of fall, road accidents and disturbance of nocturnal respiratory control.[7] Opioids play a central role in treatment of pain, although there is lack of evidence for long-term use.[1] As the prevalence of chronic pain, healthcare costs and consequences of opioid use, misuse and abuse increases, opioid prescription has become a global problem.[8] Opioids are most safe and effective when prescribed for acute postoperative pain, procedural pain and pain relief in end-of-life care.[8] Despite their increased risk of misuse, patients with mental health problems or substance use disorders are more likely to receive opioid prescriptions and use higher daily doses.[4] Similarly, older adults are at increased risk of side effects, nonetheless they are more likely to receive a prescription for opioids or benzodiazepines by their physician because they experience pain more often and frequently visit a doctor.[3]

Patients using opioids are more likely to become excessive users of benzodiazepines, and patients using benzodiazepines are more likely to receive opioid prescriptions.[7] There are multiple factors associated with co-prescription of these drugs: sociodemographic, comorbidity-dependent and doctor-related.

Though it is estimated that misuse of these prescription drugs is common and increasing, there has not been much focus on the extent of prescription and the factors of concomitant use in primary care.

We conducted a systematic review to analyze the prevalence of concomitant prescription of opioids and benzodiazepines in different study populations (researcher 1, PK) and the factors associated with concomitant prescription (researcher 2, KH). Our objective is to provide relevant insights for the primary care physician.

Methods

We conducted an independent systematic search of all relevant articles using multiple databases following the PRISMA guidelines and search strategy.

Eligibility criteria

We included any type of study, apart from case reports. Most articles were English written, but French and Dutch articles were eligible too, or any other language if translation was available.

Every study with setting in primary care was included, defined as the first point of contact for care that can provide continuity of care; including general practice, family medicine and outpatient practices.[9]

Articles were selected if they studied adults with chronic or episodic use of an opioid or a benzodiazepine, chronic and episodic use as defined by the author. Requirements for inclusion were relevant data on co-prescribing in the presence or absence of a determinant, defined as the presence of an element that conditions an outcome.

Articles were excluded if they included patients younger than 18 years old. Exceptions were made if the minors in the study population accounted for less than 10% of the population.

We excluded studies that exclusively focused on a study population with abuse of abuse history, opioid maintenance therapy with methadone or buprenorphine, studies conducted in an inpatient setting (e.g. intensive care unit, preoperative setting; including small procedures) or specific outpatient settings (e.g. palliative care or cancer pain).

Lastly, we excluded studies focusing on severe psychiatric comorbidity and on severe alcohol or substance use disorder (as defined in Diagnostic and Statistical Manual of Mental Disorders 5 (DSM 5)).

First question (researcher 1, PK): To what extent do primary care physicians co-prescribe benzodiazepines and opioid related drugs?

P	Patients in primary care or general outpatient setting with acute or chronic use of benzodiazepines/ patients in primary care or general outpatient setting with acute or chronic use of opioids
I	Opioid co-prescribing/ benzodiazepine co-prescribing
C	No co-prescribing
O	The proportion of patients co-prescribed both drugs (%)

Second question (researcher 2, KH): Which factors are associated with coprescribing of benzodiazepines and opioids?

P	Patients in primary care or general outpatient setting with acute or chronic use of benzodiazepines/ patients in primary care or general outpatient setting with acute or chronic use of opioids
I	Prevalence of co-prescribing in the presence of a cofactor
C	Prevalence of co-prescribing in the absence of a cofactor
O	The proportion of patients with concomitant prescription in the presence of a cofactor in comparison to the proportion of patients with concomitant prescription in the absence of that cofactor (%)

Search strategy

Our systematic review was conducted using PubMed, Cochrane Library, Embase, CINAHL, PsycArticles and Web of Science. We screened all articles published before February 2021. We used the following search terms in a wide range of synonyms: benzodiazepines and derivatives, opioids and derivatives and primary care *(attachment A).* Additional articles were manually collected from screening the reference lists in the selected articles. We uploaded all of our articles in Endnote 20®. After removal of duplicates, two authors (KH, PK) used Rayyan QCRI® to screen all articles independently by title and abstract for eligibility using our predetermined criteria. Afterwards, the detected conflicts by Rayyan QCRI® were discussed by two authors (KH, PK) to decide whether the concerned articles were eligible. Disagreements were solved by interpretation of our predefined protocol. Remaining conflicts were discussed with the promotor (MC). Subsequently, remaining articles were independently screened based on their full text by two authors (KH, PK) for eligibility criteria. The inclusion of the resulting undecided articles was discussed by two authors. Many articles did not provide eligible data in outcome measurements but were used as background information.

Data charting process

A data extraction table was created containing data relevant for both research questions. The data collection happened independently, using the same extraction template. This included:

(1) General information and study characteristics: author, year of publication, study period, geographical location, study design, population subtype with age and gender distribution, sample size, recruitment, definition of concomitant use, outcome measurements

(2) Prevalence of benzodiazepine and opioid use, concomitant use and factors associated with co-prescription. Following factors were included: sex, age, country, socioeconomic status, residential care setting, co-morbidities (i.e. chronic pain and mental health problems), and opioid use characteristics.

Depending on the heterogeneity of the data, we decided for both research questions whether meta-analysis was feasible.

Outcome measurements

The primary outcome was investigated by the first researcher (PK) and analyses the number of patients receiving combined prescriptions of benzodiazepines and opioids.[51]

The secondary outcome is discussed in this paper by the second researcher (KH) and investigates the factors associated with concomitant prescription of opioids and benzodiazepines.

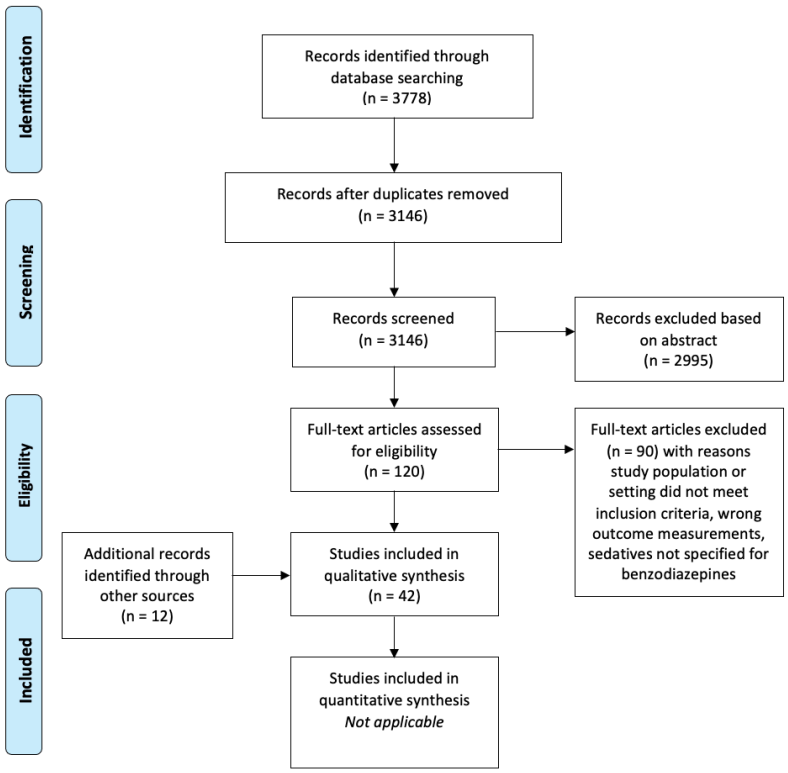
Quality assessment

The overall quality of the included articles will be assessed with the GRADE rating system *(Attachment B).*

Results

We found 3778 articles through screening the previously listed databases. Search strings can be found in attachment A. 617 duplicates were removed in Endnote 20® by both authors separately and inconsistencies were resolved in discussion. In Rayyan QCRI®, 15 duplicates were removed manually. The resulting 3146 articles were screened by abstract by both authors using Rayyan QCRI®. 2995 articles were excluded, 87 included and 64 taken into consideration. 31 articles were excluded because the full text was not available or provided by the author on request by email. Of the resulting 120 full-text articles, 30 met our inclusion criteria, 90 were excluded. 12 additional articles were found through snowball referencing.

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

After screening the resulting full-text articles, 42 studies met our eligibility criteria. Attachment C provides a detailed overview of the included articles in a data-extraction table.

Most studies were conducted in the United States of America (USA) (32 articles), 6 in Australia, 3 in Europe (Sweden, United Kingdom and Scotland) and one study in Canada. There was no time restriction, but the year of earliest publication starts from 2010. The earliest period of study originated in 1993.[10]

The study designs that were most common were retrospective cohort and cross-sectional studies. Several studies had a prospective cohort design and we included one case-control study. The majority of these studies used electronic health database information.

The number of included participants varied between studies (range several million patients to several hundred, except for one study which included only 55 patients).[11] Gender distribution differed between the articles: apart from the Veteran populations, where the majority is male, most studies included more women than men. Most articles had a study population from 34 till 60 years old. Two studies focused specifically on the elderly population.[12,13]

Quality and risk of bias assessment

We used the GRADE-system to each perform an independent quality assessment of the included articles. Inherent limitations and complexities of using observational evidence impacts the quality and availability of data.

Five studies were rated as 'moderate' quality. Eight studies were rated as 'very low' quality. Most studies were limited by their study sample, therefore not generalizable to a broader population. For example: observational data from veterans, conduction in a regional Health Plan. Another general finding was that observation of co-use inherently involves the risk of bias because adherence to prescription drugs is difficult to examine. The full GRADE-assessment is found in an additional file attached to this paper *(attachment B)*.

Factors associated with concomitant prescription

Mental Health Diagnosis

Mental health problems are associated with concomitant prescription of benzodiazepines and opioids despite the higher risk of misuse in this population.

Eight studies focused on mental health problems and co-prescription of opioids and benzodiazepines. Table 1 (additional file S1) shows all significant results ($p< 0.05$). Patients with co-use were more likely to be depressive, suffer from an anxiety disorder, have substance use disorder (SUD) or history of SUD, posttraumatic stress disorder (PTSD), insomnia, panic attacks or have a lifetime reporting of a mental health diagnosis in comparison to non-concomitant use.

One study found most of these mental health problems were more prevalent among patients with benzodiazepine monotherapy compared to co-prescription with opioids; namely depression, anxiety disorder and insomnia.[10] Only SUD diagnosis was associated with a higher percentage of visits when co-prescribing occurred.[10] (Hirschtritt et al., 2018, USA)

Patients with concomitant use often have a diagnosis of SUD or history of SUD compared to non-concomitant use (see table 1). Patients with SUD history are also at higher risk of co-use versus those without (38.9% vs. 28.7%).[14] (Saunders et al., 2012, USA)

Seven studies concluded depression to be more likely in the group of concomitant users compared to non-concomitant users. One study exclusively focused on a population diagnosed with depression. Prescribing an opiate is an important risk factor for benzodiazepine monotreatment for depression (OR

2.86, 95% CI: 2.01–4.06), while antidepressants and psychotherapy are first-line treatments recommended by practice guidelines.[15] (Soric et al., 2018, USA)

Gender and Age Distribution

Nine studies investigated gender differences between concomitant use of opioids and benzodiazepines (Table 2, additional file S2). Except for veteran studies, all studies had a gender distribution of mostly female. Overall, women represent a higher proportion of concomitant use compared to men (mean 28.8% compared to 20.8%).

Two veteran studies [16,17] investigated the differences of concomitant use between men and women. Because the study population was largely male, men made out the greatest proportion in the group with concomitant use and non-concomitant use (91% vs 94% (Park et al., 2015, USA); 87.7% vs 88.6% (Carlson et al., 2018, USA)). While women with opioid use were more likely to be prescribed a benzodiazepine (33% of females) than men (26% of males) as investigated by Park et al., there was just a slight difference by Carlson et al. (18.7% of females, 17.4% of males).[16,17]

Torrance et al. (2018, Scotland) describes national opioid prescription rates and co-prescription with benzodiazepines rates in Scotland. In all age categories (from under the age of 25y till more than 90y old), co-prescription was more common among women, except for a slightly higher rate in men under the age of 25 years old using strong opioids.[18] Co-prescribing a benzodiazepine was the highest in age category 35-49y (females: 19%, males:16%) for weak opioids and 40-59y (females: 38%, males: 29%) for strong opioids.[18] Other authors similarly found that the highest proportion of opioid users with concomitant benzodiazepine use were middle-aged and women (see Table 2).

Chronic Pain

Six studies investigated chronic pain as a cofactor of concurrent use or prescribing. Definition of pain characteristics differed among all studies. Chronic pain was defined by two authors as at least 3 months duration.[18,19] Other studies did not mention the duration of pain. Assessment of chronic pain mostly was obtained by using the International Classification of Diseases, Ninth or Tenth Revision (ICD-9 or ICD-10). Some studies used diagnoses from existing databases to obtain chronic pain diagnoses, others used survey forms by phone interviews or existing survey data. Some studies focused on pain severity or pain self-efficacy in relationship to concomitant use, which was obtained by the Chronic Pain Grade Questionnaire (CPGQ), respectively Pain Self-Efficacy Questionnaire (PSEQ).[18,19] Pain localization as a cofactor of co-prescribing was investigated by four authors.[10,17,19,20] Following diagnoses were investigated: neuropathy, musculoskeletal pain, arthritis, fibromyalgia, visceral pain, headache and low back and/or neck pain. Number of pain conditions was assessed by self-report past 12 months and 3 months.[14,19] Concomitant use is more prevalent if patients have more than one pain condition, higher pain severity, lower pain self-efficacy; if they are diagnosed with headache, back and/or neck pain or visceral pain.

Pain localization as a cofactor of concomitant use was investigated by four authors. Headache was more prevalent in a population of chronic opioid users if they were also co-prescribed a benzodiazepine (45% of concomitant use group versus 28% of non-concomitant use group[20] (Park et al., 2015, USA); 36% of patients with current daily benzodiazepine use concomitantly versus 23% with non-concomitant use[19] (Nielsen et al., 2015, Australia)). Similarly, in a veteran study of Carlson et al. (2018, USA) headache was more common in the group with concurrent prescription fills, compared to those without (23% versus 17.5%).[17]

Hirschtritt et al. (2018, USA) identified visits in which pain was listed as the primary reason for consultation. He compared six physical locations (head or neck, chest, abdomen or pelvis, back or hip, extremities, or unspecified). Only low back pain correlated with co-prescription of benzodiazepines and opioids, whereas other pain locations correlated with benzodiazepine or opioid only prescriptions.[10] A diagnosis of chronic back or neck pain was more common in an opioid taking population among patients with current daily benzodiazepine use compared to less than daily, past or never used a benzodiazepine (84% versus respectively 79%, 78%, 69%), as was visceral pain (28% versus respectively 24%, 25%, 16%).[19] (Nielsen et al.,2015, Australia)

Following pain diagnoses were investigated but were not associated with concomitant use: fibromyalgia and arthritis[19] ($p > 0,05$) (Nielsen et al.,2015, Australia), musculoskeletal pain and neuropathy[20] (both not significant, respectively $p = 0.73$, $p = 0.22$). (Park et al.,2015, USA)

Pain intensity and self-efficacy were associated with concomitant use of opioids and benzodiazepines. Torrance et al. (2018, Scotland) examined a population of chronic opioid users and found that higher pain levels persisting longer than three months, measured by the CPGQ, were significantly associated with higher prevalence of co-prescribing a benzodiazepine: 16% of patients with severe pain, whereas 8.8% of patients without chronic pain.[18] Similar results were found in Australia by Nielsen et al. (2015), as pain severity was the highest in the group with daily use of benzodiazepine (mean 5.5 (SD 1.7)), compared to patients with less than daily use, past or never used a benzodiazepine (respectively mean 5.0 (SD 1.7), 5.1 (SD 1.8), 4.9 (SD 1.8)).[19] Concurrent use of any benzodiazepine among patients with chronic opioid use significantly correlates with a lower pain self-efficacy score, explained as less confidence in coping with pain and the ability to do a range of activities (e.g. household chores, socializing, work), also after controlling for pain severity.[19] (Nielsen et al., 2015, Australia)

Two studies examined the positive correlation between number of pain conditions and concurrent use of benzodiazepines in an opioid taking population. Only Nielsen et al. (2015, Australia) specified types of pain past 12 months: arthritis (inc. rheumatoid arthritis), chronic back or neck pain, frequent or severe headache, visceral pain and fibromyalgia.[19] He found broadly comparable results between different categories of benzodiazepine-users (never used, past use, current less than daily use), except for the current daily users, who had the highest mean number of pain conditions (2.49 (SD 1.30) versus 2.1 (SD 1.09), 2.30 (SD 1.11), 2.30 (SD 1.13) respectively).[19] Similarly, Saunders et al. (2012, USA) established that 71.4% of patients with concurrent sedative use took opioids for more than one pain condition past 3 months, whereas 60% without concomitant use.[14]

Several studies examined a study population of patients with back and/or neck pain. Patients who co-used benzodiazepines for pain relief were more likely to have used opioids in the last year (OR = 6.02, 95% CI: 2.95–12.33).[21] (Weeks et al., 2018, USA) Another study investigated concurrent prescription fills in a study population of veterans post-9/11; veterans diagnosed with back or neck pain had twice the odds as those without to have concurrent prescription fills (OR= 2; 95% CI: 1.7-2.4), as were those with any pain diagnosis (OR = 1.9, 95% CI: 1.6-2.4).[17] (Carlson et al., 2018, USA). Fritz et al. (2018, USA) investigated patients with low back pain and concluded that concurrent use of opioids with benzodiazepines has a higher risk to become a long-term opioid user.[22] One study examined a population of patients with osteoarthritis. Only 1.8% of the study population was co-prescribed benzodiazepines and opioids.[23] (Alamanda et al., 2020, USA)

Opioid Use Characteristics

Opioid use characteristics in relationship to concomitant use were discussed in ten studies. Following characteristics were examined: opioid dose, long-term opioid use and early opioid refill.

Overall, a higher median opioid dose was significantly associated with co-use of a benzodiazepine. High-dose opioid differed among studies, ranging from 90mg to more than 200mg morphine equivalents daily (MED). Long-term opioid use was defined as continuous opioid therapy for at least 90 days. Only one study investigated the association between early opioid refill and concomitant use, defined as an opioid prescription written 7-25 days after the previous prescription for the same drug.[20]

Higher opioid doses (≥ 100mg MED) are associated with a higher rate of co-prescribing in a graded fashion and vice versa.[24] (Kobus et al., 2013, USA) Patients taking high-dose opioids (≥ 90mg MED) are at greater risk of being co-prescribed a benzodiazepine (RR 1.47, 95% CI 1.37 – 1.59) compared to lower doses.[25] (Richards et al., 2020, USA)

Nielsen et al. (2015, Australia) investigated patients taking opioids for chronic non-cancer pain. High-dose opioids, defined as > 200mg MED, was the highest in the group with daily benzodiazepine use (27.9%), and the lowest in the group who had never used any benzodiazepine (8.9%).[19] In contrast, almost half of patients with a high-dose opioid ≥ 200mg MED had concomitant use of benzodiazepines.[26] (Campbell et al., 2015, Australia). Similarly, Saunders et al. (2012, USA) found that 22.2% of concurrent sedative users took a daily opioid dose ≥ 120mg MED and had a mean daily opioid dose of 108.2mg, compared to 13% and 68.1mg in the non-concurrent group, respectively.[14] A veteran study (Morasco et al., 2010, USA) examined demographic and clinical characteristics associated with high-dose opioids, defined as ≥ 180 mg MED. Patients taking traditional dose opioids (ranging from 5 to 179 mg MED) had a lower rate of benzodiazepine prescription compared to high-dose opioid use (25% versus 32%), whereas only 9.6% in the group with no opioid use.[27] Musich et al. (2018, USA) found that patients with high doses (≥ 120mg MED) were more commonly diagnosed with low back pain (77%) and were often co-prescribed benzodiazepines (49%).[12]

Two studies investigated the positive correlation between long-term opioid use and co-prescription. Concomitant use was average 9.6 times higher among long-term opioid users compared to non-

chronic opioid users from study years 2002 till 2014.[28] (Hwang et al., 2016, USA) Patients with long-term opioid use had co-prescription of a benzodiazepine in 23.8%, compared to patients with short-term or no opioid use (respectively 15.7 and 11.5%).[29] (Dobschka et al., 2008, USA)

One study (Park et al., 2015, USA) investigated the association between benzodiazepine prescription and early opioid refill, suggesting opioid misuse. Receipt of a benzodiazepine has a higher risk of a second early opioid refill with a hazard ratio of 1.54 (95% CI: 1.09-2.18).[20]

Discussion

This part of the systematic review examined the factors associated with concomitant prescribing of benzodiazepines and opioids, using mostly observational data from studies performed in the USA.

In 2016, the U.S. Food and Drug Administration added a black box warning against co-prescribing benzodiazepines and opioids.[30] Despite this clear recommendation, co-prescription is ubiquitous and associated with multiple factors.

Several authors discussed the presence of a cofactor in association with concomitant prescription. Only mental health diagnosis, gender and age differences, chronic pain and opioid characteristics seem to be associated with this behavior.

Patients with concomitant prescription are more likely to suffer from depression, anxiety disorder, SUD use or history, PTSD, insomnia, panic attacks or have a lifetime reporting of a mental health condition. Although patients with mental health problems are at even greater risk of abuse and overdose, therefore more vulnerable for this drug combination. Physicians often co-prescribe benzodiazepines and opioids to treat pain and mental health problems simultaneously.[31] Although, benzodiazepine treatment for anxiety disorder in patients with chronic pain seems to be associated with even greater levels of pain scores.[31] The CDC-guidelines recommend clinicians to optimize mental health treatment to improve pain symptoms and decrease overdose risk of concomitant use.[1]

Overall, the prevalence of concomitant prescription seems to be the highest in middle-aged women, ranging from 35 till 64 years old. This finding could be explained by the higher prevalence of both chronic pain and mental health conditions among women, and because they seek medical care more frequently than men.[18,28] Women are indeed prescribed benzodiazepines and opioids more often compared to men, both individually as concomitantly.[14,26,28,30] However, men are at greater risk of misuse of these co-medications.[28]

Concomitant prescription of benzodiazepines and opioids are more prevalent among patients with chronic pain, especially if they had more than one pain condition, higher pain severity or lower pain self-efficacy. Following diagnoses were associated with co-prescription: headache, back and/or neck pain, visceral pain. These types of pain are common in primary care. There is limiting evidence for improved pain or function with long-term use of opioids for these pain conditions[1], also there is no clear role for benzodiazepines as pain reliever[18]. Physicians should prefer nonpharmacologic therapy and nonopioid pharmacologic therapy for chronic pain.[1] However, evidence supports short-term efficacy of opioids in non-cancer nociceptive and neuropathic pain.[1] Following explanations for co-prescribing benzodiazepines and opioids in chronic pain are described in literature. Benzodiazepine use is correlated to a higher pain severity in patients with chronic pain, therefore enhancing concomitant use.[20] Mental health conditions play an important role by influencing chronic pain and vice versa, as there is a bi-directional relationship.[20,24] Mental health disorders, often treated by

benzodiazepines, are associated with greater pain severity and less pain-tolerance, leading to a higher prevalence of opioid use.[20]

Some opioid use characteristics are associated with higher co-use of benzodiazepines and opioids; namely higher opioid dose, long-term opioid use and early opioid refill. This last factor could be explained by the enhancement of drug liking and euphoria of opioids by benzodiazepines, leading to early opioid refills.[20] Otherwise, patients with anxiety disorder often misuse opioids as an additive anxiolytic, therefore having early opioid refills.[20] As long-term opioid use usually starts with treatment of acute pain, the CDC-guidelines recommend physicians to prescribe the lowest effective dose for short duration (rarely more than seven days will be needed) and to avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.[1] While high-dose opioid is defined as ≥ 50mg MED by the CDC-guidelines, the definition of high-dose in this review ranged from 90mg to ≥200mg MED. Therefore, awareness by physicians should start at much lower doses than described in this review.

An objective of this study *(protocol in attachment D)* was to find reasons why prescribers choose to combine opioids and benzodiazepines. One study by Jeffery et al. (2019, USA) characterizes co-prescribing by the same physicians versus when a different physician co-prescribes. Against all expectations, the intensity of co-prescription increased when the same physician prescribed benzodiazepines and opioids.[31] One possible explanation for this finding was that treatment of co-occurring pain and mental health conditions often occurs by the same physician and therefore co-prescribing is not driven by lack of information.[31] But why do prescribers take the risk of causing iatrogenic harm? This complexity of prescribing behavior seems to be influenced by prescribers risk mitigation, patients expectations, availability of alternatives and gender differences.[32,33]

This study provides additional insight into the clinical factors that play an important role in co-prescribing of opioids and benzodiazepines. Future studies are needed to confirm the findings of this study, explore prescriber reasons for co-prescribing benzodiazepines and opioids and aware them for this potentially harmful combination.

Limitations

There are important limitations that influence the strength and relevance of the results in this review. Most studies had an observational design, limiting the quality of used data. Some studies had very low quality or small sample sizes, therefore limiting the withdrawal of relevant conclusions. Data from different study designs were compared with each other: observational data from health prescription databases, pharmacist prescription fills, patient queries... *(full overview in attachment C)*, limiting comparability. Because adherence to prescription drugs is not measurable, we should be cautious to interpret the given results. Comparability was further comprised because the eligible studies differed in several areas: sample size, generalizability to the general population (e.g. veteran studies, primarily men included), diagnosis (patients with chronic non-cancer pain, depression, osteoarthritis etc.), baseline drug use (only opioids/benzodiazepines or combined use), subgroup use, definition of concomitant use (e.g. overlap of one day versus one month), duration of opioid use (chronic use, short-term use), definition of high-dose opioids (ranging from 90mg to ≥200mg), assessment of chronic pain or other pain characteristics (pain localization, pain severity, number of pain diagnoses). Although we focused on outpatient settings, some studies did not exclusively used data from primary care. Our studies did not provide data eligible for a meta-analysis because of the heterogeneity of collected data. Further studies are needed to confirm the trends that we see in this review.

Conclusion

This paper provides additional insights into the clinical characteristics that influence co-prescribing of opioids and benzodiazepines. We found recurrent patterns that concomitant prescribing is more prevalent among middle-aged women, patients with mental health disorders, chronic pain and specific opioid characteristics. Further studies are needed to confirm these patterns. Physicians should be vigilant for co-prescribing this potentially harmful combination, especially in vulnerable patients if alternative treatment options are available. Education of primary care physicians could be beneficial.

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Authors	Participants	Study population with co-use	Mental Health Diagnosis (as defined by the author)							
			Depression	Anxiety	SUD use/history	PTSD	Insomnia	Panic attacks past 4 weeks	Lifetime reporting of any mental health condition	Comparison to non-concomitant use
Population of opioid users										*Opioids only without concurrent benzodiazepine use*
Park et al. (2015), USA (20)	847	196 patients with CNCP	73% (a)	61% (a)						47% vs 30%
Nielsen et al. (2015), Australia	1220	398 patients with CNCP	33% (b)	33% (b)	19% (c)	21% (d)		61.8%*	83.4%*	18.5% vs 18.4% vs 8.8% vs 11.4% vs 12.1% vs 69.7%
Saunders et al. (2012), USA	1848	590 patients with CNCP	72% (e)		23.8% (f)					55.1% vs 13%
Park et al. (2015), USA (16)	422.786	112.069 veterans with acute or chronic pain	38%*	20%*	13%*	22%*				19% vs 5% vs 10% vs 9%
Sun et al. (2017), USA	315.428	5425 patients	17% (a)		1.15% (a,g)					4.4% vs 0.22%
Part opioid use, part benzodiazepine use										*No concurrent benzodiazepine or opioid use*
Hirschtritt et al. (2018), USA	402.027	1350 encounters	3.5%*	1.2%*	6.4%*		1%*			Opioid only: 6.2% vs 7.4% vs 2.1% vs 1.5% Benzodiazepine only: 21.2% vs 25.8% vs 3.7% vs 3.2%
Carlson et al. (2018), USA	5882	1036 post-9/11 veterans	54.3% (a)	28.1% (a)	30.8% (a,h)	75% (a)				41.9% vs 21.8% vs 30.8% vs 58.7%
Hawkins et al. (2019), USA°	17.476	4369 veterans with PTSD	49.3% (a)	32.4% (a)	31.9% (a,i)					/

(a) Based on International Classification of Diseases, Ninth revision (ICD-9)
(b) As measured by the Patient Health Questionnaire-9 (PHQ-9) and generalized anxiety disorder-7 (GAD-7) modules. Symptoms indicating major depressive disorder were defined at a score of ≥10 on the PHQ-9 , symptoms of moderate to severe anxiety were defined as a score of ≥10 on the GAD-7
(c) Ever diagnosed/suffered substance abuse/dependence, ever used an illicit drug, ever injected a drug, met criteria for alcohol use disorder (ICD-10), daily nicotine use (past month)
(d) A score of ≥3 on the Primary Care Post Traumatic Stress Disorder screen (PC-PTSD) was used to indicate presence of PTSD
(e) Depression in the 3 years prior to the survey date, assessment through combination of automated data and self-report by Patient Health Questionnaire (PHQ ≥ 10) or according to electronic data
(g) Alcohol and drug abuse
(h) Any substance use disorder (excluding nicotine use disorder), opioid use disorder
(i) Comprises alcohol use disorder, opioid use disorder, stimulant use disorder, sedative use disorder and others substance use disorder
CNCP = chronic non-cancer pain
* Not specified
° Describs baseline characteristics of veterans with PTSD included in this study

Additional file S2: Table 2, 'Gender and Age in relationship to concomitant use'

Authors	Participants (% female)	Number of concomitant use (% female)	Number of non-concomitant use (% female)	Age category with highest percentage of concomitant use
Park et al. (2015), USA [20]	847 (42.9%)	197 (58%)	651 (38%)	No specific data
Torrance et al. (2018), Scotland	11.041 (63.7%)	264 (no specific data)*	No specific data	Weak opioids: 35-49y Strong opioids: 40-59y
Saunders et al. (2012), USA	1848 (62.7%)	590 (71.1%)	1153 (58.2%)	53.8y
Hirschtritt et al. (2018), USA	Not specified	1350 (54.9%)	24.764 (63%)	50-64y
Hwang et al. (2016), USA	177.079.757 (56.2%)	No specific data**	No specific data	45-64y
Park et al. (2015), USA [16]	422.786 (7%)	112.069 (9%)	310.717 (6%)	50-59y
Sun et al. (2017), USA	315.428 (57%)	5425 (65%)	53.389 (57%)	44.5y
Campbell et al. (2015), Australia [34]	43.796 (64%)	13.174 (70.5%)	30.622 (61.9%)	45-64y
Carlson et al. (2018), USA	5882 (11.5%)	1036 (12.3%)	4846 (11.4%)	36-45y

* In all age-categories co-prescription of weak and strong opioids with benzodiazepines was higher in females than males, except for strong opioids < 25y
** Every year from 2002-2014 women had a higher proportion of opioid recipients with concomitant benzodiazepine use

Attachment A: Search Strings

PUBMED

Concept 1

("Benzodiazepines"[Mesh] OR “Benzodiazepinone*”[tiab] OR “Zolpidem”[Mesh] OR “Eszopiclone”[Mesh] OR "Hypnotics and Sedatives"[Mesh] OR "Tranquilizing Agents"[Mesh] OR “benzodiazepine*”[tiab] OR “hypnotic*”[tiab] OR “sedative*”[tiab] OR “tranquiliz*”[tiab] OR “nitrazepam”[tiab] OR “flurazepam”[tiab] OR “central nervous system depressant*”[tiab] OR “alprazolam”[tiab] OR “alprazolam”[tiab] OR “brotizolam”[tiab] OR “bromazepam”[tiab] OR “clonazepam”[tiab] OR “diazepam”[tiab] OR “flumazenil”[tiab] OR “flunitrazepam”[tiab] OR “flurazepam”[tiab] OR “lorazepam”[tiab] OR “oxazepam”[tiab] OR “prazepam”[tiab] OR “temazepam”[tiab] OR “chlordiazepoxide”[tiab] OR “clobazam”[tiab] OR “chlorazepate”[tiab] OR “clotiazepam”[tiab] OR “cloxazolam”[tiab] OR “ethyl-loflazepate”[tiab] OR “ketazolam”[tiab] OR “loprazolam”[tiab] OR “lormetazepam”[tiab] OR “nordazepam”[tiab] OR “estazolam”[tiab] OR “medazepam”[tiab] OR “midazolam”[tiab] OR “triazolam”[tiab] OR “CNS depressant*”[tiab] OR “pharmaceutical sleep aid*”[tiab] OR “sleep promoting agent*”[tiab] OR “sleep inducer*”[tiab] OR “sleeping pill*”[tiab] OR “antianxiety agent*”[tiab] OR “anti anxiety agent*”[tiab] OR “anti anxiety drug*”[tiab] OR “anxiolytic*”[tiab] OR “zolpidem”[tiab] OR “zolirin”[tiab] OR “zolpi lich”[tiab] OR “afizagabar”[tiab] OR “arfendazam”[tiab] OR “cinolazepam”[tiab] OR “clorazepate”[tiab] OR “clorazepate dipotassium”[tiab] OR “clorazepate potassium”[tiab] OR “delorazepam”[tiab] OR “demoxepam”[tiab] OR “doxefazepam”[tiab] OR “loflazepate”[tiab] OR “fludiazepam”[tiab] OR “flutoprazepam”[tiab] OR “fosazepam”[tiab] OR “gidazepam”[tiab] OR “girisopam”[tiab] OR “halazepam”[tiab] OR “loflazepate”[tiab] OR “meclonazepam”[tiab] OR “metaclazepam”[tiab] OR “nerisopam”[tiab] OR “netazepide”[tiab] OR “nimetazepam”[tiab] OR “nitrazepam”[tiab] OR “noclobazam”[tiab] OR “nordazepam”[tiab] OR “phenazepam”[tiab] OR “pinazepam”[tiab] OR “quazepam”[tiab] OR “remimazolam”[tiab] OR “tifluadom”[tiab] OR “tofisopam”[tiab] OR “tuclazepam”[tiab] OR “uxepam”[tiab] OR “tranquilizing drug*”[tiab] OR “abercanil”[tiab] OR “chlorazepam”[tiab] OR “emapunil”[tiab] OR “haloxazolam”[tiab] OR “imidazenil”[tiab] OR “mexazolam”[tiab] OR “premazepam”[tiab] OR “zopiclone”[tiab])

Concept 2

(“Opiate Alkaloids”[Mesh] OR “Opioid Analgesic*”[tiab] OR “Opioid*”[tiab] OR “Partial Opioid Agonist*”[tiab] OR “Agonists, Partial Opioid*”[tiab] OR “Opioid Agonists, Partial”*[tiab] OR “Opioid Partial Agonists*”[tiab] OR “Agonists, Opioid Partial*”[tiab] OR “Partial Agonists, Opioid*”[tiab] OR “Full Opioid Agonist*”[tiab] OR “Agonists, Full Opioid*”[tiab] OR “Opioid Agonists, Full*”[tiab] OR “Opioid Full Agonists*”[tiab] OR “Agonists, Opioid Full*”[tiab] OR “Full Agonists, Opioidanalgesic*”[tiab] OR “opioid*”[tiab] OR “opiate*”[tiab] OR “narcotic*”[tiab] OR “morphine*”[tiab] OR “morphinan*”[tiab] OR “buprenorphine”[tiab] OR “hydrocodon*”[tiab] OR “ethylmorphine”[tiab] OR “thebaine”[tiab] OR “pentazocine”[tiab] OR “benzomorphans”[tiab] OR “phenazocine”[tiab] OR “Papaverine”[tiab] OR “antalgic agent*”[tiab] OR “tramadol”[tiab] OR “dihydrocodeine”[tiab] OR “opiate alkaloid*”[tiab] OR “pentazocine lactate”[tiab] OR “pentazocine hydrochloride”[tiab] OR “phenbenzorphan”[tiab] OR “pentazocine hydrobromide”[tiab] OR “buprenorphine hydrochloride”[tiab] OR “levorphanol tartrate”[tiab] OR “papaverine hydrochloride”[tiab] OR “isocodeine”[tiab] OR “dihydrocodeinone”[tiab] OR “hydrocodeinonebitartrate”[tiab] OR “dihydrohydroxycodeinone”[tiab] OR “oxycodeinon”[tiab] OR “oxycodone hydrochloride”[tiab] OR “ethomorphine”[tiab] OR “diacetylmorphine”[tiab] OR “heroin hydrochloride”[tiab] OR “diacetylmorphine hydrochloride”[tiab] OR “dihydromorphinone”[tiab] OR “hydromorphone hydrochloride”[tiab] OR “morphine chloride”[tiab] OR “Opiate agonist”[tiab] OR “Acetorphine”[tiab] OR “Acetylcodeine”[tiab] OR “Acetylmethadol”[tiab] OR “alphacetylmethadol”[tiab] OR “alphaprodine”[tiab] OR “amdakefalin”[tiab] OR “anileridine”[tiab] OR “apadoline”[tiab] OR “asalhydromorphone”[tiab] OR “azidomorphine”[tiab] OR “benzhydrocodone”[tiab] OR “bezitramide”[tiab] OR “bremazocine”[tiab] OR “buprenorphine”[tiab] OR “cebranopadol”[tiab] OR “ciramadol”[tiab] OR “codeine”[tiab] OR “codeine phosphate”[tiab] OR “codeine iodide”[tiab] OR “codeine sulfate”[tiab] OR “delta opiate receptor agonist”[tiab] OR “deltorphin”[tiab] OR “dermorphin”[tiab] OR “desmetramadol”[tiab] OR “dextromoramide”[tiab] OR “dextropropoxyphene”[tiab] OR “dextropropoxyphene napsilate”[tiab] OR “dezocine”[tiab] OR “diamorphine”[tiab] OR “diconal”[tiab] OR “dihydrocodeine”[tiab] OR “dihydroetorphine”[tiab] OR “dihydromorphine”[tiab] OR “dimethylthiambutene”[tiab] OR “dipipanone”[tiab] OR “drotebanol”[tiab] OR “fentanyl derivative”[tiab] OR “alfentanil”[tiab] OR “beta hydroxymefentanyl”[tiab] OR “brifentanil”[tiab] OR “carfentanil”[tiab] OR “carfentanil citrate”[tiab] OR “fentanyl”[tiab] OR “fentanyl citrate”[tiab] OR “hypnorm”[tiab] OR “lofentanil”[tiab] OR “lofentanil oxalate”[tiab] OR “mefentanyl”[tiab] OR “mirfentanil”[tiab] OR “ocfentanil”[tiab] OR “remifentanil”[tiab] OR “sufentanil”[tiab] OR “sufentanil citrate”[tiab] OR “trefentanil”[tiab] OR “frakefamide”[tiab] OR “hydrocodone”[tiab] OR “hydrocodone bitartrate”[tiab] OR “hydromorphone”[tiab] OR “ketazocine”[tiab] OR “ketobemidone”[tiab] OR “levorphanol”[tiab] OR “meptazinol”[tiab] OR “metazocine”[tiab] OR “metkephamid”[tiab] OR “morphine”[tiab] OR “morphine sulfate”[tiab] OR “morphinomimetic agent”[tiab] OR “morphinone”[tiab] OR “nalbuphine”[tiab] OR “nalfurafine”[tiab] OR “naltalimide”[tiab] OR “nicocodine”[tiab] OR “nicomorphine”[tiab] OR “nifalatide”[tiab] OR “norbuprenorphine”[tiab] OR “normorphine”[tiab] OR “oxycodon*”[tiab] OR “oxymorphone”[tiab] OR “Pentamorphone”[tiab] OR “tapentadol”[tiab] OR “tilidine”[tiab] OR “tonazocine”[tiab] OR “tramadol”[tiab] OR “trimeperidine”[tiab])

Concept 3

("Primary Health Care"[Mesh:NoExp] OR "Physicians, Primary Care"[Mesh] OR "Physicians, Family"[Mesh] OR "General Practitioners"[Mesh] OR “primary healthcare”[tiab] OR “primary health care”[tiab] OR “primary medical care”[tiab] OR “primary care”[tiab] OR “general practioner*”[tiab] OR “family physician*”[tiab] OR “GP”[tiab] OR “GPs”[tiab] OR “general physician*”[tiab] OR “general practice”[tiab] OR “family doctor*”[tiab]OR “family practitioner*”[tiab])

Results 12/11/2020 concept 1 + 2 + 3: 261

EMBASE

Concept 1

(‘benzodiazepine derivative’/de OR ‘benzodiazepine’/exp OR ‘benzodiazepin*’:ti,ab,kw OR 'benzodiazepine receptor stimulating agent'/de OR 'hypnotic sedative agent'/de OR ‘tranquilizer’/de OR ‘tranquiliz*’:ti,ab,kw OR 'anxiolytic agent'/de OR

'anxiolytic*':ti,ab,kw OR 'hypnotic*':ti,ab,kw OR 'sedativ*':ti,ab,kw OR 'afizagabar'/exp OR 'afizagabar':ti,ab,kw OR 'nitrazepam'/exp OR 'nitrazepam':ti,ab,kw OR 'flurazepam'/exp OR 'flurazepam':ti,ab,kw OR 'central nervous system depressant*':ti,ab,kw OR 'alprazolam'/exp OR 'alprazolam':ti,ab,kw OR 'arfendazam'/exp OR 'arfendazam':ti,ab,kw OR 'brotizolam'/exp OR 'brotizolam':ti,ab,kw OR 'bromazepam'/exp OR 'bromazepam':ti,ab,kw OR 'clonazepam'/exp OR 'clonazepam':ti,ab,kw OR 'cinolazepam'/exp OR 'cinolazepam':ti,ab,kw OR 'clobazam'/exp OR 'clobazam':ti,ab,kw OR 'clorazepate'/exp OR 'clorazepate':ti,ab,kw OR 'clorazepate dipotassium'/exp OR 'clorazepate dipotassium':ti,ab,kw OR 'clorazepate potassium'/exp OR 'clorazepate potassium':ti,ab,kw OR 'diazepam'/exp OR 'diazepam':ti,ab,kw OR 'delorazepam'/exp OR 'delorazepam':ti,ab,kw OR 'demoxepam'/exp OR 'demoxepam':ti,ab,kw OR 'devazepide'/exp OR 'devazepide':ti,ab,kw OR 'diazepam'/exp OR 'diazepam':ti,ab,kw OR 'doxefazepam'/exp OR 'doxefazepam':ti,ab,kw OR 'ethyl loflazepate'/exp OR 'ethyl loflazepate':ti,ab,kw OR 'flumazenil'/exp OR 'flumazenil':ti,ab,kw OR 'flunitrazepam'/exp OR 'flunitrazepam':ti,ab,kw OR 'flurazepam'/exp OR 'flurazepam':ti,ab,kw OR 'fludiazepam'/exp OR 'fludiazepam':ti,ab,kw OR 'flutoprazepam'/exp OR 'flutoprazepam':ti,ab,kw OR 'lorazepam'/exp OR 'fosazepam'/exp OR 'fosazepam':ti,ab,kw OR 'gidazepam'/exp OR 'gidazepam':ti,ab,kw OR 'girisopam'/exp OR 'girisopam':ti,ab,kw OR 'halazepam'/exp OR 'halazepam':ti,ab,kw OR 'loflazepate'/exp OR 'loflazepate':ti,ab,kw OR 'lorazepam'/exp OR 'lorazepam':ti,ab,kw OR 'lormetazepam'/exp OR 'lormetazepam':ti,ab,kw OR 'meclonazepam'/exp OR 'meclonazepam':ti,ab,kw OR 'clonazepam':ti,ab,kw OR 'medazepam'/exp OR 'medazepam':ti,ab,kw OR 'metaclazepam'/exp OR 'metaclazepam':ti,ab,kw OR 'midazolam'/exp OR 'midazolam':ti,ab,kw OR 'nerisopam'/exp OR 'nerisopam':ti,ab,kw OR 'netazepide'/exp OR 'netazepide':ti,ab,kw OR 'nimetazepam'/exp OR 'nimetazepam':ti,ab,kw OR 'nitrazepam'/exp OR 'nitrazepam':ti,ab,kw OR 'norclobazam'/exp OR 'norclobazam':ti,ab,kw OR 'nordazepam'/exp OR 'nordazepam':ti,ab,kw OR 'oxazepam'/exp OR 'oxazepam':ti,ab,kw OR 'phenazepam'/exp OR 'phenazepam':ti,ab,kw OR 'pinazepam'/exp OR 'pinazepam':ti,ab,kw OR 'prazepam'/exp OR 'prazepam':ti,ab,kw OR 'temazepam'/exp OR 'temazepam':ti,ab,kw OR 'quazepam'/exp OR 'quazepam':ti,ab,kw OR 'remimazolam'/exp OR 'remimazolam':ti,ab,kw OR 'tifluadom'/exp OR 'tifluadom':ti,ab,kw OR 'tofisopam'/exp OR 'tofisopam':ti,ab,kw OR 'tuclazepam'/exp OR 'tuclazepam':ti,ab,kw OR 'uxepam'/exp OR 'uxepam':ti,ab,kw OR 'chlordiazepoxide'/exp OR 'chlordiazepoxide':ti,ab,kw OR 'chlorazepate':ti,ab,kw OR 'clotiazepam'/exp OR 'clotiazepam':ti,ab,kw OR 'cloxazolam'/exp OR 'cloxazolam':ti,ab,kw OR 'clotiazepam'/exp OR 'clotiazepam':ti,ab,kw OR 'cloxazolam'/exp OR 'cloxazolam':ti,ab,kw OR 'ketazolam'/exp OR 'ketazolam':ti,ab,kw OR 'loprazolam':ti,ab,kw OR 'estazolam':ti,ab,kw OR 'triazolam':ti,ab,kw OR 'tranquilizing drug*':ti,ab,kw OR 'CNS depressant*':ti,ab,kw OR 'pharmaceutical sleep aid*':ti,ab,kw OR 'sleep promoting agent*':ti,ab,kw OR 'sleep inducer*':ti,ab,kw OR 'sleeping pill*':ti,ab,kw OR 'antianxiety':ti,ab,kw OR 'anti anxiety':ti,ab,kw OR 'abecarnil'/exp OR 'abecarnil':ti,ab,kw OR 'adinazolam'/exp OR 'adinazolam':ti,ab,kw OR 'adinzolam mesilate'/exp OR 'adinazolam mesilate':ti,ab,kw OR 'alpidem'/exp OR 'alpidem':ti,ab,kw OR 'bretazenil'/exp OR 'bretazenil':ti,ab,kw OR 'brotizolam'/exp OR 'brotizolam':ti,ab,kw OR 'chlorazepam'/exp OR 'chlorazepam':ti,ab,kw OR 'emapunil'/exp OR 'emapunil':ti,ab,kw OR 'estazolam'/exp OR 'estazolam':ti,ab,kw OR 'eszopiclone'/exp OR 'eszopiclone':ti,ab,kw OR 'haloxazolam'/exp OR 'haloxazolam':ti,ab,kw OR 'imidazenil'/exp OR 'imidazenil':ti,ab,kw OR 'ketazolam'/exp OR 'ketazolam':ti,ab,kw OR 'loprazolam'/exp OR 'loprazolam':ti,ab,kw OR 'mexazolam'/exp OR 'mexazolam':ti,ab,kw OR 'premazepam'/exp OR 'premazepam':ti,ab,kw OR 'triazolam'/exp OR 'triazolam':ti,ab,kw OR 'zolpidem'/exp OR 'zolpidem':ti,ab,kw OR 'zopiclone'/exp OR 'zopiclone':ti,ab,kw OR 'benzodiazepinone*':ti,ab,kw OR 'hypnotics and sedative*':ti,ab,kw OR 'tranquilizing agent*':ti,ab,kw)

Concept 2

('opioid*':ti,ab,kw OR 'oxynorm':ti,ab,kw OR 'opiate*':ti,ab,kw OR 'morphine derivative'/de OR 'narcotic agent'/de OR 'ethylmorphine':ti,ab,kw OR 'thebaine':ti,ab,kw OR 'benzomorphan*':ti,ab,kw OR 'benzomorphan derivative'/de OR 'pentazocine':ti,ab,kw OR 'phenazocine':ti,ab,kw OR 'papaverine':ti,ab,kw OR 'opiate agonist'/de OR 'acetorphine':ti,ab,kw OR 'acetorphine'/exp OR 'acetylcodeine':ti,ab,kw OR 'acetylcodeine'/exp OR 'acetylmethadol':ti,ab,kw OR 'acetylmethadol'/exp OR 'alphacetylmethadol':ti,ab,kw OR 'alphacetylmethadol'/exp OR 'alphaprodine':ti,ab,kw OR 'alphaprodine'/exp OR 'amdakefalin':ti,ab,kw OR 'amdakefalin'/exp OR 'anileridine':ti,ab,kw OR 'anileridine'/exp OR 'apadoline':ti,ab,kw OR 'apadoline'/exp OR 'asalhydromorphone':ti,ab,kw OR 'asalhydromorphone'/exp OR 'azidomorphine':ti,ab,kw OR 'azidomorphine'/exp OR 'benzhydrocodone':ti,ab,kw OR 'benzhydrocodone'/exp OR 'bezitramide':ti,ab,kw OR 'bezitramide'/exp OR 'bremazocine':ti,ab,kw OR 'bremazocine'/exp OR 'buprenorphine':ti,ab,kw OR 'buprenorphine'/exp OR 'cebranopadol':ti,ab,kw OR 'cebranopadol'/exp OR 'ciramadol':ti,ab,kw OR 'ciramadol'/exp OR 'codeine':ti,ab,kw OR 'codeine'/exp OR 'codeine phosphate':ti,ab,kw OR 'codeine phosphate'/exp OR 'codeine iodide':ti,ab,kw OR 'codeine iodide'/exp OR 'codeine sulfate':ti,ab,kw OR 'codeine sulfate'/exp OR 'delta opiate receptor agonist':ti,ab,kw OR 'delta opiate receptor agonist'/exp OR 'deltorphin':ti,ab,kw OR 'deltorphin'/exp OR 'dermorphin':ti,ab,kw OR 'dermorphin'/exp OR 'desmetramadol'/exp OR 'desmetramadol':ti,ab,kw OR 'desmetramadol'/exp OR 'dextromoramide':ti,ab,kw OR 'dextromoramide'/exp OR 'dextropropoxyphene':ti,ab,kw OR 'dextropropoxyphene'/exp OR 'dextropropoxyphene napsilate':ti,ab,kw OR 'dextropropoxyphene napsilate'/exp OR 'dezocine':ti,ab,kw OR 'dezocine'/exp OR 'diamorphine':ti,ab,kw OR 'diamorphine'/exp OR 'diconal':ti,ab,kw OR 'diconal'/exp OR 'dihydrocodeine'/exp OR 'dihydrocodeine':ti,ab,kw OR 'dihydroetorphine':ti,ab,kw OR 'dihydroetorphine'/exp OR 'dihydromorphine'/exp OR 'dihydromorphine':ti,ab,kw OR 'dimethylthiambutene':ti,ab,kw OR 'dimethylthiambutene'/exp OR 'dipipanone':ti,ab,kw OR 'dipipanone'/exp OR 'drotebanol':ti,ab,kw OR 'drotebanol'/exp OR 'fentanyl derivative':ti,ab,kw OR 'fentanyl derivative'/exp OR 'alfentanil':ti,ab,kw OR 'alfentanil'/exp OR 'beta hydroxymefentanyl':ti,ab,kw OR 'beta hydroxymefentanyl'/exp OR 'brifentanil':ti,ab,kw OR 'brifentanil'/exp OR 'carfentanil':ti,ab,kw OR 'carfentanil'/exp OR 'carfentanil citrate':ti,ab,kw OR 'carfentanil citrate'/exp OR 'fentanyl':ti,ab,kw OR 'fentanyl'/exp OR 'fentanyl citrate':ti,ab,kw OR 'fentanyl citrate'/exp OR 'hypnorm':ti,ab,kw OR 'hypnorm'/exp OR 'lofentanil':ti,ab,kw OR 'lofentanil'/exp OR 'lofentanil oxalate':ti,ab,kw OR 'lofentanil oxalate'/exp OR 'mefentanyl':ti,ab,kw OR 'mefentanyl'/exp OR 'mirfentanil':ti,ab,kw OR 'mirfentanil'/exp OR 'ocfentanil':ti,ab,kw OR 'ocfentanil'/exp OR 'remifentanil':ti,ab,kw OR 'remifentanil'/exp OR 'sufentanil':ti,ab,kw OR 'sufentanil'/exp OR 'sufentanil citrate':ti,ab,kw OR 'sufentanil citrate'/exp OR 'trefentanil':ti,ab,kw OR 'trefentanil'/exp OR 'frakefamide':ti,ab,kw OR 'frakefamide'/exp OR 'hydrocodone':ti,ab,kw OR 'hydrocodone'/exp OR 'hydrocodone bitartrate':ti,ab,kw OR 'hydrocodone bitartrate'/exp OR 'hydromorphone':ti,ab,kw OR 'hydromorphone'/exp OR 'ketazocine':ti,ab,kw OR 'ketazocine'/exp OR 'ketobemidone':ti,ab,kw OR 'ketobemidone'/exp OR 'levorphanol':ti,ab,kw OR 'levorphanol'/exp OR 'meptazinol':ti,ab,kw OR 'meptazinol'/exp OR 'metazocine':ti,ab,kw OR 'metazocine'/exp OR 'metkephamid':ti,ab,kw OR 'metkephamid'/exp OR 'morphine':ti,ab,kw OR 'morphine'/exp OR 'morphine sulfate':ti,ab,kw OR 'morphine sulfate'/exp OR 'morphinomimetic agent':ti,ab,kw OR 'morphinomimetic agent'/exp OR 'morphinone':ti,ab,kw OR 'morphinone'/exp OR 'nalbuphine':ti,ab,kw OR 'nalbuphine'/exp OR 'nalfurafine':ti,ab,kw OR 'nalfurafine'/exp OR 'naltalimide':ti,ab,kw OR 'naltalimide'/exp OR 'nicocodine':ti,ab,kw OR 'nicocodine'/exp OR 'nicomorphine':ti,ab,kw OR 'nicomorphine'/exp OR 'nifalatide':ti,ab,kw OR

'nifalatide'/exp OR 'norbuprenorphine':ti,ab,kw OR 'norbuprenorphine'/exp OR 'normorphine':ti,ab,kw OR 'normorphine'/exp OR 'oxycodon*':ti,ab,kw OR 'oxycodon*'/exp OR 'oxymorphone':ti,ab,kw OR 'oxymorphone'/exp OR 'Pentamorphone':ti,ab,kw OR 'pentamorphone'/exp OR 'tapentadol':ti,ab,kw OR 'tapentadol'/exp OR 'tilidine':ti,ab,kw OR 'tilidine'/exp OR 'tonazocine':ti,ab,kw OR 'tonazocine'/exp OR 'tramadol':ti,ab,kw OR 'tramadol'/exp OR 'trimeperidine':ti,ab,kw OR 'trimeperidine'/exp OR 'opioid anagelsic*':ti,ab,kw OR 'partial opioid agonist*':ti,ab,kw OR 'full opioid agonist*':ti,ab,kw OR 'opioid full agonist*':ti,ab,kw OR 'narcotic*':ti,ab,kw OR 'morphinan':ti,ab,kw OR 'opiate alkaloid*':ti,ab,kw OR 'pentazocine lactate':ti,ab,kw OR 'pentazocine hydrochloride':ti,ab,kw OR 'phenbenzorphan':ti,ab,kw OR 'pentazocine hydrobromide':ti,ab,kw OR 'buprenorphine hydrochloride':ti,ab,kw OR 'levorphanol tartrate':ti,ab,kw OR 'papaverine hydrochloride':ti,ab,kw OR 'isocodeine':ti,ab,kw OR 'dihydrocodeinone':ti,ab,kw OR 'dihydrocodeinonebitartrate':ti,ab,kw OR 'dihydrocodeinone':ti,ab,kw OR 'oxycodeinon':ti,ab,kw)

Concept 3

('Primary health care'/exp OR 'primary health care':ti,ab,kw OR 'first line care':ti,ab,kw OR 'health care':ti,ab,kw OR 'primary healthcare':ti,ab,kw OR 'primary care':ti,ab,kw OR 'medical care, primary':ti,ab,kw OR 'General practitioner'/exp OR 'general practitioner*':ti,ab,kw OR 'family doctor*':ti,ab,kw OR 'family physician*':ti,ab,kw OR 'family practitioner*':ti,ab,kw OR 'general physician*':ti,ab,kw OR 'general practice physician*':ti,ab,kw OR 'GP':ti,ab,kw OR 'primary care doctor*':ti,ab,kw OR 'primary care physician*':ti,ab,kw)

Results 20/10/2020 concept 1 + 2 + 3: 2023

CINAHL

Concept 1

(MH "Antianxiety Agents, Benzodiazepine+") OR (MH "Zolpidem") OR (MH "Eszopiclone") OR AB ("Benzodiazepines" OR "Benzodiazepinone*" OR "Zolpidem" OR "Eszopiclone" OR "Hypnotics and Sedatives" OR "Tranquilizing Agents" OR "benzodiazepine*" OR "hypnotic*" OR "sedative*" OR "tranquiliz*" OR "nitrazepam" OR "flurazepam" OR "central nervous system depressant*" OR "alprazolam" OR "alprazolam" OR "brotizolam" OR "bromazepam" OR "clonazepam" OR "diazepam" OR "flumazenil" OR "flunitrazepam" OR "flurazepam" OR "lorazepam" OR "oxazepam" OR "prazepam" OR "temazepam" OR "chlordiazepoxide" OR "clobazam" OR "chlorazepate" OR "clotiazepam" OR "cloxazolam" OR "ethyl-loflazepate" OR "ketazolam" OR "loprazolam" OR "lormetazepam" OR "nordazepam" OR "estazolam" OR "medazepam" OR "midazolam" OR "triazolam" OR "CNS depressant*" OR "pharmaceutical sleep aid*" OR "sleep promoting agent*" OR "sleep inducer*" OR "sleeping pill*" OR "antianxiety agent*" OR "anti anxiety agent*"[tiab] OR "anti anxiety drug*" OR "anxiolytic*" OR "zolpidem" OR "zolirin" OR "zolpi lich" OR "afizagabar" OR "arfendazam" OR "cinolazepam" OR "clorazepate" OR "clorazepate dipotassium" OR "clorazepate potassium" OR "delorazepam" OR "demoxepam" OR "doxefazepam" OR "loflazepate" OR "fludiazepam" OR "flutoprazepam" OR "fosazepam" OR "gidazepam" OR "girisopam" OR "halazepam" OR "loflazepate" OR "meclonazepam" OR "metaclazepam" OR "nerisopam" OR "netazepide" OR "nimetazepam" OR "nitrazepam" OR "noclobazam" OR "nordazepam" OR "phenazepam" OR "pinazepam" OR "quazepam" OR "remimazolam" OR "tifluadom" OR "tofisopam" OR "tuclazepam" OR "uxepam" OR "tranquilizing drug*" OR "abercanil" OR "chlorazepam" OR "emapunil" OR "haloxazolam" OR "imidazenil" OR "mexazolam" OR "premazepam" OR "zopiclone") OR TI ("Benzodiazepines" OR "Benzodiazepinone*" OR "Zolpidem" OR "Eszopiclone" OR "Hypnotics and Sedatives" OR "Tranquilizing Agents" OR "benzodiazepine*" OR "hypnotic*" OR "sedative*" OR "tranquiliz*" OR "nitrazepam" OR "flurazepam" OR "central nervous system depressant*" OR "alprazolam" OR "alprazolam" OR "brotizolam" OR "bromazepam" OR "clonazepam" OR "diazepam" OR "flumazenil" OR "flunitrazepam" OR "flurazepam" OR "lorazepam" OR "oxazepam" OR "prazepam" OR "temazepam" OR "chlordiazepoxide" OR "clobazam" OR "chlorazepate" OR "clotiazepam" OR "cloxazolam" OR "ethyl-loflazepate" OR "ketazolam" OR "loprazolam" OR "lormetazepam" OR "nordazepam" OR "estazolam" OR "medazepam" OR "midazolam" OR "triazolam" OR "CNS depressant*" OR "pharmaceutical sleep aid*" OR "sleep promoting agent*" OR "sleep inducer*" OR "sleeping pill*" OR "antianxiety agent*" OR "anti anxiety agent*"[tiab] OR "anti anxiety drug*" OR "anxiolytic*" OR "zolpidem" OR "zolirin" OR "zolpi lich" OR "afizagabar" OR "arfendazam" OR "cinolazepam" OR "clorazepate" OR "clorazepate dipotassium" OR "clorazepate potassium" OR "delorazepam" OR "demoxepam" OR "doxefazepam" OR "loflazepate" OR "fludiazepam" OR "flutoprazepam" OR "fosazepam" OR "gidazepam" OR "girisopam" OR "halazepam" OR "loflazepate" OR "meclonazepam" OR "metaclazepam" OR "nerisopam" OR "netazepide" OR "nimetazepam" OR "nitrazepam" OR "noclobazam" OR "nordazepam" OR "phenazepam" OR "pinazepam" OR "quazepam" OR "remimazolam" OR "tifluadom" OR "tofisopam" OR "tuclazepam" OR "uxepam" OR "tranquilizing drug*" OR "abercanil" OR "chlorazepam" OR "emapunil" OR "haloxazolam" OR "imidazenil" OR "mexazolam" OR "premazepam" OR "zopiclone")

Concept 2

(MH "Analgesics, Opioid+") OR (MH "Tramadol") OR (MH "Sufentanil") OR (MH "Remifentanil") OR (MH "Pentazocine") OR (MH "Oxycodone") OR (MH "Naltrexone") OR (MH "Nalbuphine") OR (MH "Methadone") OR (MH "Fentanyl") OR (MH "Dihydromorphinone") OR (MH "Codeine") OR (MH "Butorphanol") OR (MH "Buprenorphine") OR (MH "Alfentanil") OR AB ("Opioid Analgesic*" OR "Opioid*" OR "Partial Opioid Agonist*" OR "Agonists, Partial Opioid*" OR "Opioid Agonists, Partial"* OR "Opioid Partial Agonists*" OR "Agonists, Opioid Partial*" OR "Partial Agonists, Opioid*" OR "Full Opioid Agonist*" OR "Agonists, Full Opioid*" OR "Opioid Agonists, Full*" OR "Opioid Full Agonists*" OR "Agonists, Opioid Full*" OR "Full Agonists, Opioidanalgesic*" OR "opioid*" OR "opiate*" OR "narcotic*" OR "morphine*" OR "morphinan*" OR "buprenorphine" OR "hydrocodon*" OR "ethylmorphine" OR "thebaine" OR "pentazocine" OR "benzomorphans" OR "phenazocine" OR "Papaverine" OR "antalgic agent*" OR "tramadol" OR "dihydrocodeine" OR "opiate alkaloid*" OR "pentazocine lactate" OR "pentazocine hydrochloride" OR "phenbenzorphan" OR "pentazocine hydrobromide" OR "buprenorphine hydrochloride" OR "levorphanol tartrate" OR "papaverine hydrochloride" OR "isocodeine" OR "dihydrocodeinone" OR "hydrocodeinonebitartrate" OR "dihydrohydroxycodeinone" OR "oxycodeinon" OR "oxycodone hydrochloride" OR "ethomorphine" OR "diacetylmorphine" OR "heroin hydrochloride" OR "diacetylmorphine hydrochloride" OR "dihydromorphinone" OR "hydromorphone hydrochloride" OR "morphine chloride" OR "Opiate agonist" OR "Acetorphine" OR "Acetylcodeine" OR "Acetylmethadol" OR "alphacetylmethadol" OR "alphaprodine" OR "amdakefalin" OR "anileridine" OR "apadoline" OR "asalhydromorphone" OR "azidomorphine" OR "benzhydrocodone" OR "bezitramide" OR "bremazocine" OR "buprenorphine" OR "cebranopadol" OR "ciramadol" OR "codeine" OR "codeine phosphate" OR "codeine iodide" OR "codeine sulfate" OR "delta opiate receptor agonist" OR "deltorphin" OR "dermorphin" OR "desmetramadol" OR "dextromoramide" OR "dextropropoxyphene" OR "dextropropoxyphene napsilate" OR

“dezocine” OR “diamorphine” OR “diconal” OR “dihydrocodeine” OR “dihydroetorphine” OR “dihydromorphine” OR “dimethylthiambutene” OR “dipipanone” OR “drotebanol” OR “fentanyl derivative” OR “alfentanil” OR “beta hydroxymefentanyl” OR “brifentanil” OR “carfentanil” OR “carfentanil citrate” OR “fentanyl” OR “fentanyl citrate” OR “hypnorm” OR “lofentanil” OR “lofentanil oxalate” OR “mefentanyl” OR “mirfentanil” OR “ocfentanil” OR “remifentanil” OR “sufentanil” OR “sufentanil citrate” OR “trefentanil” OR “frakefamide” OR “hydrocodone” OR “hydrocodone bitartrate” OR “hydromorphone” OR “ketazocine” OR “ketobemidone” OR “levorphanol” OR “meptazinol” OR “metazocine” OR “metkephamid” OR “morphine” OR “morphine sulfate” OR “morphinomimetic agent” OR “morphinone” OR “nalbuphine” OR “nalfurafine” OR “naltalimide” OR “nicocodine” OR “nicomorphine” OR “nifalatide” OR “norbuprenorphine” OR “normorphine” OR “oxycodon*” OR “oxymorphone” OR “Pentamorphone” OR “tapentadol” OR “tilidine” OR “tonazocine” OR “tramadol” OR “trimeperidine”) OR TI (“Opioid Analgesic*” OR “Opioid*” OR “Partial Opioid Agonist*” OR “Agonists, Partial Opioid*” OR “Opioid Agonists, Partial”* OR “Opioid Partial Agonists*” OR “Agonists, Opioid Partial*” OR “Partial Agonists, Opioid*” OR “Full Opioid Agonist*” OR “Agonists, Full Opioid*” OR “Opioid Agonists, Full*” OR “Opioid Full Agonists*” OR “Agonists, Opioid Full*” OR “Full Agonists, Opioidanalgesic*” OR “opioid*” OR “opiate*” OR “narcotic*” OR “morphine*” OR “morphinan*” OR “buprenorphine” OR “hydrocodon*” OR “ethylmorphine” OR “thebaine” OR “pentazocine” OR “benzomorphans” OR “phenazocine” OR “Papaverine” OR “antalgic agent*” OR “tramadol” OR “dihydrocodeine” OR “opiate alkaloid*” OR “pentazocine lactate” OR “pentazocine hydrochloride” OR “phenbenzorphan” OR “pentazocine hydrobromide” OR “buprenorphine hydrochloride” OR “levorphanol tartrate” OR “papaverine hydrochloride” OR “isocodeine” OR “dihydrocodeinone” OR “hydrocodeinonebitartrate” OR “dihydrohydroxycodeinone” OR “oxycodeinon” OR “oxycodone hydrochloride” OR “ethomorphine” OR “diacetylmorphine” OR “heroin hydrochloride” OR “diacetylmorphine hydrochloride” OR “dihydromorphinone” OR “hydromorphone hydrochloride” OR “morphine chloride” OR “Opiate agonist” OR “Acetorphine” OR “Acetylcodeine” OR “Acetylmethadol” OR “alphacetylmethadol” OR “alphaprodine” OR “amdakefalin” OR “anileridine” OR “apadoline” OR “asalhydromorphone” OR “azidomorphine” OR “benzhydrocodone” OR “bezitramide” OR “bremazocine” OR “buprenorphine” OR “cebranopadol” OR “ciramadol” OR “codeine” OR “codeine phosphate” OR “codeine iodide” OR “codeine sulfate” OR “delta opiate receptor agonist” OR “deltorphin” OR “dermorphin” OR “desmetramadol” OR “dextromoramide” OR “dextropropoxyphene” OR “dextropropoxyphene napsilate” OR “dezocine” OR “diamorphine” OR “diconal” OR “dihydrocodeine” OR “dihydroetorphine” OR “dihydromorphine” OR “dimethylthiambutene” OR “dipipanone” OR “drotebanol” OR “fentanyl derivative” OR “alfentanil” OR “beta hydroxymefentanyl” OR “brifentanil” OR “carfentanil” OR “carfentanil citrate” OR “fentanyl” OR “fentanyl citrate” OR “hypnorm” OR “lofentanil” OR “lofentanil oxalate” OR “mefentanyl” OR “mirfentanil” OR “ocfentanil” OR “remifentanil” OR “sufentanil” OR “sufentanil citrate” OR “trefentanil” OR “frakefamide” OR “hydrocodone” OR “hydrocodone bitartrate” OR “hydromorphone” OR “ketazocine” OR “ketobemidone” OR “levorphanol” OR “meptazinol” OR “metazocine” OR “metkephamid” OR “morphine” OR “morphine sulfate” OR “morphinomimetic agent” OR “morphinone” OR “nalbuphine” OR “nalfurafine” OR “naltalimide” OR “nicocodine” OR “nicomorphine” OR “nifalatide” OR “norbuprenorphine” OR “normorphine” OR “oxycodon*” OR “oxymorphone” OR “Pentamorphone” OR “tapentadol” OR “tilidine” OR “tonazocine” OR “tramadol” OR “trimeperidine”)

Concept 3

(MH "Primary Health Care") OR AB ("Primary Health Care" OR "Physicians, Primary Care" OR "Physicians, Family" OR "General Practitioners" OR “primary healthcare” OR “primary health care” OR “primary medical care” OR “primary care” OR “general practioner*” OR “family physician*” OR “GP” OR “GPs” OR “general physician*” OR “general practice” OR “family doctor*”OR “family practitioner*”) OR TI ("Primary Health Care" OR "Physicians, Primary Care" OR "Physicians, Family" OR "General Practitioners" OR “primary healthcare” OR “primary health care” OR “primary medical care” OR “primary care” OR “general practitioner*” OR “family physician*” OR “GP” OR “GPs” OR “general physician*” OR “general practice” OR “family doctor*”OR “family practitioner*”)

Results 3/11/2020 concept 1 + 2 + 3: 141

COCHRANE

Concept 1

[mh "Benzodiazepines"] OR “Benzodiazepin*” OR [mh “Zolpidem”] OR [mh “Eszopiclone”] OR [mh "Hypnotics and Sedatives"] OR [mh "Tranquilizing Agents"] OR (“eszopiclone” OR “hypnotic*” OR “sedative*” OR “tranquiliz*” OR “nitrazepam” OR “flurazepam” OR (central NEXT nervous NEXT system NEXT depressant*) OR “alprazolam” OR “alprazolan” OR “brotizolam” OR “bromazepam” OR “clonazepam” OR “diazepam” OR “flumazenil” OR “flunitrazepam” OR “flurazepam” OR “lorazepam” OR “oxazepam” OR “prazepam” OR “temazepam” OR “chlordiazepoxide” OR “clobazam” OR “chlorazepate” OR “clotiazepam” OR “cloxazolam” OR “ethyl-loflazepate” OR “ketazolam” OR “loprazolam” OR “lormetazepam” OR “nordazepam” OR “estazolam” OR “medazepam” OR “midazolam” OR “triazolam” OR “CNS depressant*” OR (pharmaceutical NEXT sleep NEXT aid*) OR (sleep NEXT promoting NEXT agent*) OR (sleep NEXT inducer*) OR (sleeping NEXT pill*) OR (antianxiety NEXT agent*) OR (anti NEXT anxiety NEXT agent*) OR (anti NEXT anxiety NEXT drug*) OR “anxiolytic*” OR “zolpidem” OR “zolirin” OR “zolpi lich” OR “afizagabar” OR “arfendazam” OR “cinolazepam” OR “clorazepate” OR “delorazepam” OR “demoxepam” OR “doxefazepam” OR “loflazepate” OR “fludiazepam” OR “flutoprazepam” OR “fosazepam” OR “gidazepam” OR “girisopam” OR “halazepam” OR “loflazepate” OR “meclonazepam” OR “metaclazepam” OR “nerisopam” OR “netazepide” OR “nimetazepam” OR “nitrazepam” OR “noclobazam” OR “nordazepam” OR “phenazepam” OR “pinazepam” OR “quazepam” OR “remimazolam” OR “tifluadom” OR “tofisopam” OR “tuclazepam” OR “uxepam” OR (tranquilizing NEXT drug*) OR “abercanil” OR “chlorazepam” OR “emapunil” OR “haloxazolam” OR “imidazenil” OR “mexazolam” OR “premazepam” OR “zopiclone”):ti,ab,kw

Concept 2

[mh "Analgesics, Opioid"] OR [mh “Opiate Alkaloids”] OR (“Opioid*” OR “opiate*” OR “narcotic*” OR “morphin*” OR analgesic* OR “buprenorphin*” OR “hydrocodon*” OR “ethylmorphin*” OR “thebain*” OR “pentazocin*” OR “benzomorphan*” OR “phenazocin*” OR “Papaverin*” OR “antalgic*” OR “tramadol” OR “dihydrocodein*” OR “phenbenzorphan” OR “levorphanol tartrate” OR “isocodein*” OR “dihydrocodeinone” OR “hydrocodeinonebitartrate” OR “dihydrohydroxycodeinone” OR “oxycodeinon” OR “oxycodon*” OR “ethomorphin*” OR “diacetylmorphin*” OR “heroin hydrochloride” OR “diacetylmorphine hydrochloride” OR “dihydromorphinone” OR “Acetorphine” OR “Acetylcodeine” OR “Acetylmethadol” OR “alphacetylmethadol” OR “alphaprodine” OR “amdakefalin” OR “anileridine” OR “apadoline” OR “asalhydromorphone” OR “azidomorphine” OR

“benzhydrocodone” OR “bezitramide” OR “bremazocine” OR “buprenorphine” OR “cebranopadol” OR “ciramadol” OR “codeine” OR “deltorphin” OR “dermorphin” OR “desmetramadol” OR “dextromoramide” OR “dextropropoxyphene” OR “dezocine” OR “diamorphine” OR “diconal” OR “dihydrocodeine” OR “dihydroetorphine” OR “dihydromorphine” OR “dimethylthiambutene” OR “dipipanone” OR “drotebanol” OR “alfentanil” OR “beta hydroxymefentanyl” OR “brifentanil” OR “carfentanil” OR “fentanyl” OR “hypnorm” OR “lofentanil” OR “mefentanyl” OR “mirfentanil” OR “ocfentanil” OR “remifentanil” OR “sufentanil” OR “trefentanil” OR “frakefamide” OR “hydrocodone” OR “hydromorphone” OR “ketazocine” OR “ketobemidone” OR “levorphanol” OR “meptazinol” OR “metazocine” OR “metkephamid” OR “nalbuphine” OR “nalfurafine” OR “naltalimide” OR “nicocodine” OR “nicomorphine” OR “nifalatide” OR “norbuprenorphine” OR “normorphine” OR “oxymorphone” OR “Pentamorphone” OR “tapentadol” OR “tilidine” OR “tonazocine” OR “trimeperidine”):ti,ab,kw

Concept 3

[mh "Physicians, Primary Care"] OR [mh "Physicians, Family"] OR [mh "General Practitioners"] OR (“primary healthcare” OR “primary health care” OR “primary medical care” OR “primary care” OR (general NEXT practioner*) OR (family NEXT physician*) OR “GP” OR “GPs” OR (general NEXT physician*) OR “general practice” OR (family NEXT doctor*) OR (family NEXT practitioner*)):ti,ab,kw

Results 12/11/2020 concept 1 + 2 + 3: 34

PSYCARTICLES

Concept 1

MAINSUBJECT.EXACT.EXPLODE(“Benzodiazepines”) OR MAINSUBJECT.EXACT(“Zolpidem”) OR MAINSUBJECT.EXACT(“Eszopiclone”) OR MAINSUBJECT.EXACT("Hypnotics and Sedatives") OR MAINSUBJECT.EXACT(“Tranquilizing Agents") OR Ab,TI(“Benzodiazepin*” OR “eszopiclone” OR “hypnotic*” OR “sedative*” OR “tranquiliz*” OR “nitrazepam” OR “flurazepam” OR “central nervous system depressant*” OR “alprazolam” OR “alprazolan” OR “brotizolam” OR “bromazepam” OR “clonazepam” OR “diazepam” OR “flumazenil” OR “flunitrazepam” OR “flurazepam” OR “lorazepam” OR “oxazepam” OR “prazepam” OR “temazepam” OR “chlordiazepoxide” OR “clobazam” OR “chlorazepate” OR “clotiazepam” OR “cloxazolam” OR “ethyl-loflazepate” OR “ketazolam” OR “loprazolam” OR “lormetazepam” OR “nordazepam” OR “estazolam” OR “medazepam” OR “midazolam” OR “triazolam” OR “CNS depressant*” OR “pharmaceutical sleep aid*” OR “sleep promoting agent*” OR “sleep inducer*” OR “sleeping pill*” OR “antianxiety agent*” OR “anti anxiety agent*” OR “anti anxiety drug*” OR “anxiolytic*” OR “zolpidem” OR “zolirin” OR “zolpi lich” OR “afizagabar” OR “arfendazam” OR “cinolazepam” OR “clorazepate” OR “delorazepam” OR “demoxepam” OR “doxefazepam” OR “loflazepate” OR “fludiazepam” OR “flutoprazepam” OR “fosazepam” OR “gidazepam” OR “girisopam” OR “halazepam” OR “loflazepate” OR “meclonazepam” OR “metaclazepam” OR “nerisopam” OR “netazepide” OR “nimetazepam” OR “nitrazepam” OR “noclobazam” OR “nordazepam” OR “phenazepam” OR “pinazepam” OR “quazepam” OR “remimazolam” OR “tifluadom” OR “tofisopam” OR “tuclazepam” OR “uxepam” OR “tranquilizing drug*” OR “abercanil” OR “chlorazepam” OR “emapunil” OR “haloxazolam” OR “imidazenil” OR “mexazolam” OR “premazepam” OR “zopiclone”)

Concept 2

MAINSUBJECT.EXACT(“Analgesics, Opioid") OR MAINSUBJECT.EXACT(“Opiate Alkaloids”) OR Ab,TI(“Opioid*” OR “opiate*” OR “narcotic*” OR “morphin*” OR analgesic* OR “buprenorphin*” OR “hydrocodon*” OR “ethylmorphin*” OR “thebain*” OR “pentazocin*” OR “benzomorphan*” OR “phenazocin*” OR “Papaverin*” OR “antalgic*” OR “tramadol” OR “dihydrocodein*” OR “phenbenzorphan” OR “levorphanol tartrate” OR “isocodein*” OR “dihydrocodeinone” OR “hydrocodeinonebitartrate” OR “dihydrohydroxycodeinone” OR “oxycodeinon” OR “oxycodon*” OR “ethomorphin*” OR “diacetylmorphin*” OR “heroin hydrochloride” OR “diacetylmorphine hydrochloride” OR “dihydromorphinone” OR “Acetorphine” OR “Acetylcodeine” OR “Acetylmethadol” OR “alphacetylmethadol” OR “alphaprodine” OR “amdakefalin” OR “anileridine” OR “apadoline” OR “asalhydromorphone” OR “azidomorphine” OR “benzhydrocodone” OR “bezitramide” OR “bremazocine” OR “buprenorphine” OR “cebranopadol” OR “ciramadol” OR “codeine” OR “deltorphin” OR “dermorphin” OR “desmetramadol” OR “dextromoramide” OR “dextropropoxyphene” OR “dezocine” OR “diamorphine” OR “diconal” OR “dihydrocodeine” OR “dihydroetorphine” OR “dihydromorphine” OR “dimethylthiambutene” OR “dipipanone” OR “drotebanol” OR “alfentanil” OR “beta hydroxymefentanyl” OR “brifentanil” OR “carfentanil” OR “fentanyl” OR “hypnorm” OR “lofentanil” OR “mefentanyl” OR “mirfentanil” OR “ocfentanil” OR “remifentanil” OR “sufentanil” OR “trefentanil” OR “frakefamide” OR “hydrocodone” OR “hydromorphone” OR “ketazocine” OR “ketobemidone” OR “levorphanol” OR “meptazinol” OR “metazocine” OR “metkephamid” OR “nalbuphine” OR “nalfurafine” OR “naltalimide” OR “nicocodine” OR “nicomorphine” OR “nifalatide” OR “norbuprenorphine” OR “normorphine” OR “oxymorphone” OR “Pentamorphone” OR “tapentadol” OR “tilidine” OR “tonazocine” OR “trimeperidine”)

Concept 3

MAINSUBJECT.EXACT(“Primary Health Care") OR MAINSUBJECT.EXACT(“Physicians, Primary Care") OR MAINSUBJECT.EXACT(“Physicians, Family”) OR MAINSUBJECT.EXACT(“General Practitioners") OR Ab,TI(“primary healthcare” OR “primary health care” OR “primary medical care” OR “primary care” OR “general practioner*” OR “family physician*” OR “GP” OR “GPs” OR “general physician*” OR “general practice” OR “family doctor*” OR “family practitioner*”)

Results 12/11/2020 concept 1 + 2 + 3: 0

WEB OF SCIENCE

Concept 1

TS=(“benzodiazepin*”OR “tranquiliz*” OR “anxiolytic*” OR “hypnotic*” OR “sedativ*” OR “afizagabar” OR “nitrazepam” OR “flurazepam” OR “central nervous system depressant*” OR “alprazolam” OR “arfendazam” OR “brotizolam” OR “bromazepam”

OR “clonazepam”OR “cinolazepam”OR “clobazam” OR “clorazepate”OR “diazepam”OR “delorazepam”OR “demoxepam”OR “devazepide”OR “doxefazepam”OR “ethyl loflazepate”OR “flumazenil”OR “flunitrazepam”OR “flurazepam”OR “fludiazepam”OR “flutoprazepam” OR “fosazepam”OR “gidazepam”OR “girisopam”OR “halazepam”OR “loflazepate”OR “lorazepam”OR “lormetazepam”OR “meclonazepam”OR “clonazepam”OR “medazepam”OR “metaclazepam”OR “midazolam”OR “nerisopam”OR “netazepide”OR “nimetazepam”OR “nitrazepam”OR “norclobazam”OR “nordazepam”OR “oxazepam”OR “phenazepam”OR “pinazepam”OR “prazepam”OR “temazepam”OR “quazepam”OR “remimazolam”OR “tifluadom”OR “tofisopam”OR “tuclazepam”OR “uxepam”OR “chlordiazepoxide”OR “chlorazepate”OR “clotiazepam”OR “cloxazolam”OR “clotiazepam”OR “cloxazolam”OR “ketazolam”OR “loprazolam”OR “estazolam”OR “triazolam”OR “tranquilizing drug*”OR “CNS depressant*”OR “pharmaceutical sleep aid*”OR “sleep promoting agent*”OR “sleep inducer*”OR “sleeping pill*”OR “antianxiety”OR “anti anxiety”OR “abecarnil”OR “adinazolam”OR “alpidem”OR “bretazenil”OR “brotizolam”OR “chlorazepam”OR “emapunil”OR “estazolam”OR “eszopiclone”OR “haloxazolam”OR “imidazenil”OR “ketazolam”OR “loprazolam”OR “mexazolam”OR “premazepam”OR “triazolam”OR “zolpidem”OR “zopiclone”OR “benzodiazepinone*”)

Concept 2

TS=(“opioid*”OR “oxynorm”OR “opiate*”OR “ethylmorphine”OR “thebaine”OR “benzomorphan*”OR “pentazocine”OR “phenazocine”OR “papaverine”OR “acetorphine”OR “acetylcodeine”OR “acetylmethadol”OR “alphacetylmethadol”OR “alphaprodine”OR “amdakefalin”OR “anileridine”OR “apadoline”OR “asalhydromorphone”OR “azidomorphine”OR “benzhydrocodone”OR “bezitramide”OR “bremazocine”OR “buprenorphine”OR “cebranopadol”OR “ciramadol”OR “codeine”OR “deltorphin”OR “dermorphin”OR “desmetramadol”OR “dextromoramide”OR “dextropropoxyphene”OR “dextropropoxyphene napsilate”OR “dezocine”OR “diamorphine”OR “diconal”OR “dihydrocodeine”OR “dihydroetorphine”OR “dihydromorphine”OR “dimethylthiambutene”OR “dipipanone”OR “drotebanol”OR “alfentanil”OR “beta hydroxymefentanyl”OR “brifentanil”OR “carfentanil”OR “fentanyl”OR “hypnorm”OR “lofentanil”OR “mefentanyl”OR “mirfentanil”OR “ocfentanil”OR “remifentanil”OR “sufentanil”OR “trefentanil”OR “frakefamide”OR “hydrocodone”OR “hydromorphone”OR “ketazocine” OR “ketobemidone”OR “levorphanol”OR “meptazinol”OR “metazocine”OR “metkephamid”OR “morphin*”OR “nalbuphine”OR “nalfurafine”OR “naltalimide”OR “nicocodine”OR “nicomorphine”OR “nifalatide”OR “norbuprenorphine”OR “normorphine”OR “oxycodon*”OR “oxymorphone”OR “Pentamorphone”OR “tapentadol”OR “tilidine”OR “tonazocine”OR “tramadol”OR “trimeperidine”OR “narcotic*”OR “pentazocin*”OR “phenbenzorphan”OR “buprenorphine hydrochloride”OR “levorphanol tartrate”OR “papaverin*”OR “isocodeine”OR “dihydrocodeinon*”OR “oxycodeinon”)

Concept 3

TS=(“primary health care”OR “first line care”OR “primary healthcare” OR “primary care”OR “primary medical care”OR “general practitioner*”OR “family doctor*”OR “family physician*”OR “family practitioner*”OR “general physician*”OR “general practice physician*”OR “GP”OR “GPs”OR “primary care doctor*”OR “primary care physician*”)

Results 12/11/2020 concept 1 + 2 + 3: 324

Attachment B: Quality Assessment (GRADE-system)

Author, Year, Location	Reviewer	Design	Number Included	GRADE: Risk of bias	Inconsistency inbetween studies	Indirectness of Evidence	Impression	Publication Bias	Other Considerations	Overall Quality
				Lack of clearly randomized allocation sequence Lack of blinding Lack of allocation concealment Failure to adhere to intention-to-treat analysis Trial is cut short Large losses to follow-up	When there is significant and unexplained variability in results from different trials	An indirect comparison of two drugs. An indirect comparison of population, outcome or intervention.	When wide confidence intervals mark the quality of the data	When studies with "negative" findings remain unpublished	Large effect, Dose-response relationship	High-moderate-low-very low
Campbell et al. (2015), Austral	Heleen			low: data from automated health care data, no data	High (compared to general population surveys)	Low; ot generalize to other types of health plans	n/a	/	Large health plans	Low
	Karen	Observational study	43.796	serious, relies on automated health care data	n/a	Serious: no data on pain severity and function, other factors	n/a	None	Large health plan, but may not be generalized to other types of health plans	Low
Katzman et al. (2019), USA	Heleen			Low: selection bias	n/a	Low: not generalizable (veterans)	n/a	/	Very large sample	Very low
	Karen	Observational cohort	1,240,886	Serious, selection bias, baseline demographics no representation of general population	n/a	Serious: veteran population	n/a	None	Large population	Very low
Weeks et al. (2018), USA	Heleen			Low: information bias (self-report), respons bias, neck and back pain were not able to be distinguished in the analysis	n/a	Low	n/a	/	Head and neck pain not distinguished	Very low
	Karen	Observational, self-reported survey data	1.608	Serious, selection bias; response rate < 50%	n/a	Serious	n/a	None		Very low
Park et al. (2015), USA	Heleen			Low: missing data, selection bias	n/a	/	n/a	/	/	Low
	Karen	Retrospective cohort study on medical record data	847	Serious	n/a	Very serious	n/a	None		Very low
Torrance et al. (2018), Scotlan	Heleen			Moderate	n/a	Not generalizable for rest of Scotland or Europe (participants mostly from Tayside and Glasgow)	n/a	/	/	Moderate
	Karen	Observational, descriptive analysis on health care data	938674	Moderate	n/a	Serious	n/a	Not all numbers mentioned (e.g. absolute number weak and strong opioids)		Moderate
Fritz et al. (2018), USA	Heleen			Low: inclusion of higher risk population, confounding	Serious; % of patients progressed to LTO use after a new LBP consultation differed from other studies (effect in this study was much higher)	Low: conducted in a single regional health plan located in Salt Lake City, Utah -> large generalizability to other populations, inclusion of higher risk population	n/a	/	/	Very low
	Karen	Observational, health care data	707	Very serious, contributing factors/variables not discussed	n/a	Very serious, population no representation of general population	n/a	None		Very low
Soric et al. (2018), USA	Heleen			Low: - No information about duration of bzd-use (cross-sectional design) - Only single data use (NAMCS) - Missing factors taking into account	n/a	/	n/a	/	/	Low
	Karen	Cross-sectional study	9426	Serious	n/a	Serious	n/a	None		Low
Nielsen et al. (2015), Australia	Heleen			Moderate: - No data from non-participating pharmacies - Information bias (self-report) - Indication not always known	n/a	/	n/a	/	All pharmacies approached	Low
	Karen	Observational study, prospective	1.220	Serious: no data on pharmacies that did not participate, self-report data	n/a	Serious	n/a	None	Strength: alle community pharmacies approached	Low
Tong et al. (2019), USA	Heleen			Moderate: - Prescribed, not filled, opioid prescriptions - Overcounting of discrete opioid prescriptions compared with other medications	n/a	Not generalizable despite large sample	n/a	/	Low power	Low
	Karen	Observational study, retrospective	902 of 84.929	Serious (EHR data, potential opioid overcounting)	n/a	Serious (state of Virginia)	n/a	None		Very low
Saunders et al. (2012), USA	Heleen			Serious: - Information bias: SUD history (self-report, administrative data) - Respons rate 60% - Definition of concurrent use differs	n/a	/	n/a	/	/	Low
	Karen	Telephone survey and electronic health care data		Very serious: (response rate 60%, bias in self-report, various definitions)	n/a	Moderate	n/a	None		Low
Musich et al. (2020), USA	Heleen			Moderate - Prescription purchases, but not adherence - Underreport of depression, insomnia and anxiety; medication-related adverse effects	n/a	Low; not generalize to all older adults or other Medicare, Medicare Advantage or Medicare Supplement beneficiaries	n/a	/	- Large study population - Funded by the AARP Medicare Supplement Insurance Program	Moderate
	Karen	Observational study	209.947	Moderate (database prescription purchases; mental health issues potentially underreported)	n/a	Moderate	n/a	None	Large population, 50 states, 30 days overlap in concurrent use	Moderate
Paulozzi et al. (2015), USA	Heleen			Moderate: data from pharmacies not complete, identifying unique patients differed between states; number of days' supply is necessarily an estimate, no information about diagnosis or prescriber specialty	n/a	Generalizable for USA (8 states)	n/a	/		Low
	Karen	Observational study, pharmacy data	No absolute data	Serious (data from pharmacies not accurate or complete, different methods in different states, various potential confounders)	n/a	Moderate	n/a	Some numbers not mentioned	8 Different states	Low
Kobus et al. (2013), USA	Heleen			Moderate: - Lack of reason for high opioid prescription and risk-reduction-effectiveness - No causality	n/a	Low; Representative of the racial and ethnic composition of the general population; however, not generalizable to regions with higher concentrations of minority populations.	Reliable confidence intervals	/	Strenghts: large study population, use of electronic records, and nearly complete capture of health care utilization	Low
	Karen	Observational study, retrospective	5268	Serious: results may not be generalizable to regions with higher concentrations of minority populations	n/a	Moderate	n/a	None	Large study population, use of electronic records, and nearly complete capture of health care utilization	Low
Dobscha et al. (2008), USA	Heleen			Serious: confounders (only administrative data: adherence to prescribed medication, concurrent use, reason for adjunctive medications)	n/a	Low; generalizability: Participants were predominantly male, white veterans receiving VA healthcare in the Pacific Northwest portion of the U.S.	n/a	/		Very low
	Karen	Observational study, prospective	5961	Very serious: Veterans, generalizability limited, various confounders	n/a	Various confounders	n/a	None		Very low

Author, Year, Location	Reviewer	Design	Number Included	GRADE						
				Risk of bias	Inconsistency inbetween studies	Indirectness of Evidence	Imprecision	Publication Bias	Other Considerations	Overall Quality
				Lack of clearly randomized allocation sequence Lack of blinding Lack of allocation concealment Failure to adhere to intention-to-treat analysis Trial is cut short Large losses to follow-up	When there is significant and unexplained variability in results from different trials	An indirect comparison of two drugs. An indirect comparison of population, outcome or intervention.	When wide confidence intervals mark the quality of the data	When studies with "negative" findings remain unpublished	Large effect, Dose-response relationship	High-moderate-low-very low
Richards et al. (2020), USA, Au	Heleen			Moderate: no causal or temporal relationship, only a few studies, no standard or consensus definition of what constitutes high dose	n/a	Moderate: most studies in USA ->. less generalizable to parts of Europe and Oceania and are not applicable to low- and middle-income countries where access to opioids is inadequate	n/a	/		Moderate
	Karen	Systematic Review with Meta-analysis	4.248.119	Serious: heterogenity in data, definitions, generalizability not clear	Moderate	No causal conclusion	n/a	None		Moderate
Campbell et al. (2015), Austral	Heleen			Moderate: - Recall and social desirability bias (self report) - The proportion of participants on higher OME doses may have been underestimated	Data collected from pharmacists similar	/	n/a	/	Large national sample	Moderate
	Karen	Observational study, prospective cohort study	1424	Moderate self report, social desirability bias	n/a	Moderate: confounders discussed	n/a	None	Large sample, specific data	Moderate
Hooper et al. (2009), Tasmania	Heleen			Serious: Confounders - No monthly follow-up - Not distiguished for - Relative contributions of each intervention - Prescribers who did the intervention compared to who did not - External influences	n/a	/	n/a	/		Low
	Karen	Observational study, intervention	19.228	Serious (multiple confounders)	n/a	Serious	n/a	None		
Baldwin et al. (2020), USA	Heleen			Serious: selection bias	n/a	/	n/a	Moderate: unknown if the prescriptions were truly concurrently.	Funded by grants from the National Institute on Drug Abuse, CTSA	Very low
	Karen	Observational study, EHR query	561.017	serious (participants not represantative (volunteered for study, underrepresentation of rural studies, definition of concomitant use not specific enough)	n/a	Moderate	n/a	None		Low
Carlson et al. (2018), USA	Heleen			Serious: several confounders (eg pharmacy data alone, diagnostic categories, Medicaid eligibility, comorbidity index)	n/a	Serious: lack of generalizability of trends observed in Oregon to other states, veterans	n/a	/		Very low
	Karen	Observational study, retrospective cohort	19.959	very serious (veterans, 1 state, several important variables that were not accounted for)	n/a	Several important variables that were not accounted for	n/a	None		Very low
Maust et al. (2016), USA	Heleen			Serious: - Information bias: -Visit diagnoses are limited to three, also in patients with more diagnoses -Patient-level clinical assessments of current symptoms and function are not available. - No information about prescribed medication is taken regularly versus as needed - Only 8 medications are recorded, benzodiazepine use may also be underestimated.	n/a	Moderate: NAMCS is a survey of office-based practice, it does not include physicians practicing in other settings	n/a	/		Low
	Karen	Observational study, retrospective	98.818	Serious (information bias that affects, only psychiatrists, not representative)	n/a	Moderate	n/a	None		low
Hirschtritt et al. (2018), USA	Heleen			Serious - The variable non response - Possibly other prescribers - Does not contain information regarding medication adherence, strength, duration of treatment, or whether the medication is taken on a scheduled or as-needed basis.	n/a	/	n/a	/		Low
	Karen	Observational study, cross-sectional, survey-based	402.027	Serious (non responders, several confounders not accounted for)	n/a	Several confounders not accounted for	n/a	None		low
Agarwal et al. (2019), USA	Heleen			Serious: confounding: lacks detail on dosage, dosing frequency, refills, and long-term use of a prescription	n/a	/	n/a	Moderate: minor changes in survey design and data collection procedures for the NAMCS occur from year to year.		Very low
	Karen	Observational study, cross-sectional	386.457	Serious: confounding factors, changes in data collection during study period	n/a	Confounders	Wide confidence interval	None	Wide-spread database	low
Jeffery et al. (2019), USA	Heleen			/	Serious: another study showed coprescribing across all patient populations was declining both before and after the CDC guidelines	/	n/a	Moderate: missing prescriptions filled by beneficiaries who paid cash at the pharmacy -> changing outcome	Association, no causal effect	low
	Karen	Observational study, retrospective cohort study (adminis	3598322 + 1299142	Serious: data collection (influence of cash payers not included), confounders?	n/a	No causal effect	n/a	None		low
Murphy et al. (2018), USA	Heleen			Moderate: Underfitting: underestimating prevalence of polypharmacy in survivors	n/a	/	Serious: total unique prescriptions: true effect at the lower end of confidence interval	/	Large sample (mostly large control sample)	very low
	Karen	Observational study, retrospective cohort study	5216 survivors 19.588 controls	Serious: cancer survivors <-> chronic non cancer pain, no data about indication of prescription	n/a	Several confounders discussed but not accounted for	Small confidence intervals	None	Large, nationally representative sample	low
Price-Haywood et al. (2018), U	Heleen			Serious: no data from pharmacies	n/a	Serious: study in an urban federally qualified health center with a high proportion of low-income patients -> generalizability	n/a	Moderate: unable to prospectively follow all patients prior and after the protocol was implemented -> possibility patients treated before implementation systematically differed from those seen after implementation		

Author, Year, Location	Reviewer	Design	Number Included	GRADE						
				Risk of bias	Inconsistency inbetween studies	Indirectness of Evidence	Imprecision	Publication Bias	Other Considerations	Overall Quality
				Lack of clearly randomized allocation sequence Lack of blinding Lack of allocation concealment Failure to adhere to intention-to-treat analysis Trial is cut short Large losses to follow-up	When there is significant and unexplained variability in results from different trials	An indirect comparison of two drugs. An indirect comparison of population, outcome or intervention.	When wide confidence intervals mark the quality of the data	When studies with "negative" findings remain unpublished	Large effect, Dose-response relationship	High-moderate-low-very low
	Karen	Observational study, retrospective	250.000	Very serious: no data from pharmacies (filled/ not filled), low generalizability of population	n/a	Confounders not accounted for	n/a	None		low
Musich et al. (2018), USA	Heleen			Moderate: - no indication of whether patients actually consumed the drugs as directed.	n/a	Serious: study population of AARP Medicare Supplement insureds may not generalize to all older adults or other Medicare or Medicare Supplement beneficiaries.	n/a	/	Moderate: no measurements of pain severity, interference, causes or sites Strenth: a large study population that identified high dose opioid users, as well as selected characteristics associated with these older adults.	Low
	Karen	Observational study, retrospective cohort	2.502.830	Serious: population (again Medicare) not generalizable, cancer not excluded. depression and anxiety underreported	n/a	/	n/a	None	Also pharmacy data (filled/ not filled), large study population	low
Lalic et al. (2019), Australia	Heleen			Serious: underfitting (underestimating of actual use)	n/a	Moderate: random sample but no opioid initiation in an inpatient setting	n/a	/		Low
	Karen	Observational study, retrospective cohort	769.334	Moderate: generalizable population	n/a	Moderate	n/a	None		low
Hwang et al. (2016), USA	Heleen			Serious: confounding: data from dispensed prescriptions rather than actual medication use	n/a	Moderate: -Unable to restrict the study cohort to patients whose prescription data were continuously captured throughout the study period. -Inclusion of both cash and Medicaid transactions in this study greatly improves the generalizability	n/a	/		low
	Karen	Observational study, retrospective cohort	177.079.757	Serious (dispensing data)	n/a	Confounders not accounted for	No confidence intervals	None		low
Park et al. (2015), USA	Heleen			Low: adjusted for a range of potential confounders, including demographic, socioeconomic, and medical and mental health diagnostic data.	Low: the findings of this study were largely consistent with studies that have suggested that there are risks associated with concurrent benzodiazepine and opioid use	Serious: generalizability: US Veterans, most were men	n/a	/	Large nationwide sample	low
	Karen	Case-cohort study	422.786	Very serious: Veterans (low generalizability)	n/a	Confounders not accounted for	No confidence intervals	None	Large sample	very low
Bohnert et al. (2018), USA	Heleen			Moderate: observing trends without comparison group	n/a	/	n/a	n/a	Large sample: average of 19.1 million	moderate
	Karen	Interrupted time series analysis (on health care data)	19.100.000	Intermediate: no comparison population	n/a	Moderate	No confidence intervals	None	Large, generalizable sample	moderate
Lin et al. (2017), USA	Heleen			Moderate: confounding because lack of control group, lack of information about consulting another health care system during the study	n/a	Moderate: - A study of patients receiving care in the VHA -> results may not be generalized to a different health care system - veterans	n/a	n/a		low
	Karen	Observational study, retrospective analysis	2012: 571.476 to 2014: 514.883	Serious: veterans	n/a	Several potential confounders discussed	No confidence interval	None		very low
Breeden et al. (2020), USA	Heleen			Moderate: data from pharmacies not included	n/a	Serious; an urban federally qualified health center with a high proportion of low-income patients, limiting generalizability	n/a	Moderate: possibility that patients treated before implementation systematically differed from those seen after implementation		very low
	Karen	Observational study, retrospective	2607	Serious (no data from pharmacies, population not generalizable	n/a	Confounders not discussed	No confidence interval	None		very low
Buonora et al. (2019), USA	Heleen			/	n/a	Moderate: - Limitation of generalizability to other settings and time periods. Single institution during a time of evolving OPR prescribing practices. - Unable to draw conclusions about OPR dose reductions among patients not retained in care	Low: some narrow confidence intervals	n/a		low
	Karen	Observational study, retrospective cohort	1097	Serious: low generalizability	n/a	Confounders not discussed	No confidence interval	None		very low
Sun et al. (2017), USA	Heleen			Moderate. Confounding: unobservable differences between opioid users who did and did not use benzodiazepines, adjusting for an extensive set of covariates and comorbidities. Moderate: survival bias, adjusted by sensitivity analyses Severe: underfitting; underestimation the true risk of opioid overdose (only counted if the patient received emergency room/hospital care and ultimately survived)	Different magnitude of results in other studies	/	n/a	Low: does not take into account changes in prescribing/patient behaviors that could evolve in response to reduced concurrent benzodiazepine/opioid prescribing.	Strength: The research conducted was independent of any involvement from the sponsors of the study. Study sponsors were not involved in study design, data interpretation, writing, or the decision to submit the article for publication.	Moderate
	Karen	Observational study, retrospective	315.428	intermediate: large population, representation of population	n/a	Possibility of confounding discussed, adjusted	No confidence interval	None		Moderate
Hawkins et al. (2019), USA	Heleen			Moderate: confounding: cohorts were matched according to propensity scores calculated from demographic and clinical characteristics, medications, and utilization variables possibly linked to mortality risk	Garge et al had a larger effect relative to those p rescribed opioids only (explained as survival bias)	Severe: - A focus on PTSD limits the generalizability of results - Baseline psychiatric and medical comorbidity were more severe among patients in the concurrent cohort, inherently study cohort may differ from typical patients receiving these medications.	n/a	n/a	Moderate: Insufficient power	low
	Karen	Propensity score–matched cohorts, incident-user design	256.572	Serious: veterans, generalizability limited	n/a	Serious	No confidence interval	None		very low
Macey et al. (2011), USA	Heleen			/	n/a	Moderate: white OEF/OIF veterans receiving VA healthcare in the Pacific Northwest portion of the U.S. who had a high rate of service-connected disabilities; generalizability to other groups is therefore limited.	n/a	Low: prescription medication information was obtained from administrative data, patient adherence to prescribed medications cannot be confirmed.	The NRS (rating of pain intensity) were obtained as part of routine clinical care, and as such, may not have been administered systematically.	very low
	Karen	Observational study, retrospective o	762	Very serious: veterans in several states: low generalizability, adherence not confirmed.	n/a	Not adjusted for confounders	No confidence interval	None		very low

Author, Year, Location	Reviewer	Design	Number Included	GRADE						
				Risk of bias	Inconsistency inbetween studies	Indirectness of Evidence	Imprecision	Publication Bias	Other Considerations	Overall Quality
				Lack of clearly randomized allocation sequence Lack of blinding Lack of allocation concealment Failure to adhere to intention-to-treat analysis Trial is cut short Large losses to follow-up	When there is significant and unexplained variability in results from different trials	An indirect comparison of two drugs. An indirect comparison of population, outcome or intervention.	When wide confidence intervals mark the quality of the data	When studies with "negative" findings remain unpublished	Large effect, Dose-response relationship	High-moderate-low-very low
Gustavsson et al. (2012), Swec	Heleen			/	n/a	/	n/a	Moderate: conflict of interest: two authors were consultants to the pharmaceutical industry	Strength: no sampling uncertainty	Low
	Karen	Observational study, retrospective	10.799	Serious	n/a	Not adjusted for confounders	No confidence intervals	None	Large, randomised sample of the population	low
Shmagel et al. (2018), UK	Heleen			Serious: recall bias, measurement error Moderate; confounding	n/a	Data collection took place during 2009–2010, and was limited to non-institutionalized subjects between 20 and 69 years of age,thus results may not be extrapolated on other populations and other time periods.	n/a	Severe: study does not directly infer that the studied medications were used to treat back pain	Strength: large nationally-representative sample.	Low
	Karen	Observatinonal study, cross-sectional survey (through question	700	Serious: measurement error and recall bias	n/a	Serious	No confidence interval	None	Nationally representative sample	low
Morasco et al. (2010), USA	Heleen			/	n/a	Limitations about generalizability: participants included were veterans receiving medical care in the Pacific Northwest portion of the United States and results may not be generalizable to non-veterans or to veterans seeking care elsewhere. Mostly male; results cannot be extended to females	n/a	n/a	No reason for high-dose opioid therapy or effectiveness of treatment. No consideration of severity of comorbidity.	Low
	Karen	Observational study, retrospective cohort study	1.478	Serious	n/a	several confounders discussed but not adjusted for	No confidence interval	None		very low
Alamanda et al. (2020), USA	Heleen			Moderate: selection bias (population not defined if opioid naive or not)	n/a	Moderate. Not representative of national trends, because the data are limited to one health care system	n/a	n/a	Strength: large sample Benzodiazepine and opioid may be prescribed for a future surgical encounter during the patients' preoperative clinic visit	Low
	Karen	Observational study, retrospective cohort study	31.123	Serious	n/a	Serious	No confidence interval	None		low
Tilli et al. (2020), Canada	Heleen		Control: 20 Intervention: 35	Serious: confounding	n/a	Low	Not generalizable (sample of 55)			Very low
	Karen	Observational study, retrospective		Serious: small study population	n/a	Serious	Small study sample	None		low

Study characteristics				***Study Population***				***Definition of concomitant use***	***Outcome measurements***
Author, Year, Location	*Title*	*Period of study*	*Type of Study*	*Population characteristics*	*Number of patients*	*Gender distribution*	*Age distribution*		
Campbell et al. (2015), Australia	Age and gender trends in long-term opioid analgesic use for noncancer pain	1997-2005	Observational	Chronic noncancer pain	43.796	KNPC: 64% Female GHC: 65% Female	3 age groups: 18–44y (n = 7.686) 45–64y (n = 18.595) ≥65y (n = 11.300)	Not specified	Trends and risks for long-term opioid therapy
Katzman et al. (2019), USA	Army and Navy ECHO Pain Telementoring Improves Clinician Opioid Prescribing for Military Patients: an Observational Cohort Study	2013-2016	Observational	Veterans	1.187.945 (comparison group), 52.941 (ECHO group)	Comparison vs Echo group: 39,9% vs 54,6% Female	Comparison vs Echo group 18–24y 27,1% vs 19,7% 25–34y 33,7% vs 30,6% 35–44y 19,0% vs 21,4% 45–64y 20,2% vs 28,3%	Not specified	1. Decline in opioid prescribing after voluntary PCC participation in ECHO Pain 2. Evaluation of MME-dose and coprescribing
Weeks et al. (2018), USA	Association Among Opioid Use, Treatment Preferences, and Perceptions of Physician Treatment Recommendations in Patients With Neck and Back Pain	2017	Survey	Neck and back pain	1.608	53% Female	18-34y 127 (7,6%) 35-49y 324 (19,3%) 50-64y 683 (40,7%) 65y or older 543 (32,4%)	Not specified	Explore the relationship between self-reported use of opioids by patients with neck and back pain and their demographic characteristics, pain characteristics, treatment preferences, and recollection of their physicians' opinions regarding treatment options
Park et al. (2015), USA	The association between benzodiazepine prescription and aberrant drug behaviors in primary care patients receiving chronic opioid therapy	2011-2012	Observational, Retrospective, cohort study	Opoid use for chronic noncancer pain	847	42,9% Female	18-89y	Receive at least one benzodiazepine prescription during study period	1. Time to a patient's second early opioid refill prescription. Early opioid refills were defined as an opioid prescription written 7–25 days after the previous prescription for the same drug. 2. Any positive cocaine test by urine drug screen
Torrance et al. (2018), Scotland	Association of opioid prescribing practices with chronic pain and benzodiazepine co-prescription: a primary care data linkage study	2003-2012	Observational (Descriptive analysis)	Not specified	938.674	63,7% Female	< 25y: 993 (9%) 25-44y: 3.324 (30,1%) 45-64y: 5.286 (47,9%) ≥ 65y: 1.438 (13%)	Not specified	Describe national opioid prescription rates in Scotland, seeking sociodemographic factors associated with variations in prescribing and indicators of quality of prescribing, specifically co-prescribing of benzodiazepines

Fritz et al. (2018), USA	Associations Between Early Care Decisions and the Risk for Long-term Opioid Use for Patients With Low Back Pain With a New Physician Consultation and Initiation	2012-2015	Observational, Retrospective	Low back pain	707	68% Female	Mean age 38,1y (± 11,6) 18-64y	Not specified	Indication of long-term opioid use in 1-year period following the index visit: quantified the number of unique opioid prescriptions filled and total days of supply provided by the opioid fills
Soric et al. (2018), USA	Benzodiazepine monotherapy in patients with depression: A national cross-sectional study	2012-2015	Observational, Cross-sectional	Depression	9.426	Not specified	> 18y	Not specified	Percentage of adults treated for depression who are prescribed benzodiazepine monotherapy and which variables predict this usage pattern
Nielsen et al. (2015), Australia	Benzodiazepine Use among Chronic Pain Patients Prescribed Opioids: Associations with Pain, Physical and Mental Health, and Health Service Utilization	2012-2014	Observational, Prospective Cohort	Chronic noncancer pain	1.220	65,5% Female	Mean age 57y	Not specified	1. To describe patterns of BZD use amongst a sample of CNCP patients prescribed opioids 2. To examine demographic, physical, and mental health and substance correlates of BZD use 3. To examine if negative health outcomes, including emergency health care utilization, were independently associated with BZD use, after controlling for other patient characteristics
Tong et al. (2019), USA	Chronic Opioid Prescribing in Primary Care: Factors and Perspectives	2016	Observational, Retrospective	Chronic opioid use	902	Not specified	> 18y	Not specified	Compare those receiving chronic opioids with those not (in terms of their demographics, prescribing clinician characteristics, and risk factors for opioid-related harms), as identified by the Centers

Saunders et al. (2012), USA	Concurrent use of alcohol and sedatives among persons prescribed chronic opioid therapy: Prevalence and risk factors	2008-2009	Observational	Chronic opioid use for chronic noncancer pain	1.848	62,3% Female	21-80y Mean age 55,7y	Concurrent sedative use was defined by receiving sedatives for 45+ days of the 90 days preceding the interview. We limited analyses to patients who reported taking opioids everyday in the last 2 weeks to establish simultaneous use with sedatives.	To assess the prevalence and predictors of concurrent use of sedatives and alcohol among persons receiving chronic opioid therapy for noncancer pain, among patients with and without a substance use disorder history
Musich et al. (2020), USA	Concurrent Use of Opioids with Other Central Nervous System-Active Medications Among Older Adults	2017	Observational	Older adults with opioid use	209.947	69% Female	>65y	Concurrent use of opioids with other CNS-active medications was defined as an overlap by prescription dates and days of supply for at least 30 days for both opioids and at least one of the other CNS medications (benzodiazepines, non-benzodiazepine hypnotics, muscle relaxants, antipsychotics, or	1. To determine the prevalence and characteristics of older adults concurrently using opioids and other central nervous system (CNS)-active medications, and the specialties of providers who ordered the medications. 2. To document medication-related adverse effects associated with such concurrent drug use
Paulozzi et al. (2015), USA	Controlled Substance Prescribing Patterns--Prescription Behavior Surveillance System, Eight States , 2013	2013	Observational	Not specified	Not specified	Not specified	Not specified	Overlapping prescribing is calculated as the percentage of prescribed days for a particular class of drugs that overlap with a prescription for another class of drugs.	Rates of population-based prescribing and behavioral measures of drug misuse in the general population that have not been available previously for comparison among demographic groups and states

Kobus et al. (2013), USA	Correlates of high-dose opioid medication use for low back pain in primary care	2003-2004	Observational, Retrospective	Opioid use for chronic pain	5.268	62,6% Female	≥ 18y Mean age 50,3y (SD 16,6)	Sedative-hypnotic Rx 6 months before/after index visit (%)	Prevalence of high-dose opioid use, as well as associated demographic, clinical, and health service utilization correlates among low back pain patients
Dobscha et al. (2008), USA	Correlates of prescription opioid initiation and long-term opioid use in veterans with persistent pain	2008	Observational, Prospective	Veterans with chronic noncancer pain	5.961	10% Female	56y	Not specified	The objectives of the current study were to 1) describe patterns of prescription opioid initiation, 2) identify correlates of prescription opioid initiation, and 3) identify correlates of chronic opioid therapy (>90 consecutive days) use among Veterans with persistent noncancer pain who received care in a VA regional healthcare network.
Richards et al. (2020) USA, Australia, UK	Factors associated with the prescribing of high-dose opioids in primary care: A	up to 2019	Systematic Review with Meta-analysis	Opioid use	4.248.119	61,7% Female	≥ 18y	Not specified	Explore factors associated with the prescribing of high-dose opioids in primary care
Campbell et al. (2015), Australia	Pharmaceutical opioid use and dependence among people living with chronic pain: associations observed within the pain and opioids in Treatment (POINT) Cohort	Not specified	Observational, Prospective Cohort	Chronic opioid use for chronic pain	1.424	55% Female	Mean age 58y	Opioid use > 6 weeks	Examine pharmaceutical opioid dose and dependence and examine the correlates of each
Hooper et al. (2009), Tasmania	Alprazolam prescribing in Tasmania: a two-fold intervention designed to reduce inappropriate prescribing and concomitant opiate prescription	2000-2008	Intervention	Not specified	1.345	Not specified	Not specified	Three groups: 1. alprazolam but no opioid 2. alprazolam and an opioid < 1m 3. alprazolam and an opioid = or > 1m	A two-fold intervention, comprising GP education coupled with changes to prescribing regulations, was designed with the intention to decrease inappropriate prescribing of alprazolam and thereby reduce adverse outcomes
Baldwin et al. (2020), USA	Increasing collaboration on substance use disorder research with primary care practices through the National Drug Abuse Treatment Clinical Trials Network	2015-2017	EHR query	Not specified	561.017	Not specified	Not specified	A sedative and opioid prescribed in the same year	Identify the percent of adult patients with an office visit who were prescribed an opioid medication and, of those, the percent also prescribed a sedative in that year

Carlson et al. (2018), USA	Linkage of VA and State Prescription Drug Monitoring Program Data to Examine Concurrent Opioid and Sedative-Hypnotic Prescriptions among Veterans	2014-2016	Retrospectrive Cohort	Veterans	19.959	Not specified	Not specified	Not specified	Examine concurrent prescriptions among post-9/11 veterans, by year (2014–2016) and by patient demo- graphic and clinical characteristics
Maust et al. (2016), USA	No End in Sight: Benzodiazepine Use in Older Adults in the United States	2007-2010	Observational	Not specified	125.029 *encounters*	Not specified	Not specified	Not specified	Percentage of benzodiazepine visits of all outpatient encounters according to patient age and corresponding annual visit rate per 1,000 population
Hirschtritt et al. (2018), USA	Outpatient, combined use of opioid and benzodiazepine medications in the United States 1993-2014	1993-2014	Cross-sectional survey	Not specified	402.027 *encounters*	Not specified	18-64 y	Prescribed on same visit	Examine the probability of a visit including an opioid, benzodiazepine, or their combination, in addition to clinical and demographic correlates
Agarwal et al. (2019), USA	Patterns in Outpatient Benzodiazepine Prescribing in the United States	2003-2015	Cross-sectional survey	Not specified	386.457 *encounters*	Not specified	>18y	Different definitions	Calculate the annual coprescribing rate of benzodiazepines with other sedating medications
Jeffery et al. (2019), USA	Rates of physician coprescribing of opioids and benzodiazepines after the release of the Centers for Disease Control and Prevention guidelines in 2016	2014-2018	Retrospective Cohort	Not specified	Population 1: 3.598.322 ; population 2: 1.299.142 patients	Population 1: 54,9 ; population 2: 59,3% Female	Population 1: 51 (41-58) y ; Population 2: 70 (61-77) y	Any overlapping days of prescription of opioids and benzodiazepines. opioid use was defined as a period when the patient went no more than 30 days without using opioids	Extent (proportion of person-months with any overlapping days of prescription of opioids and benzodiazepines) and intensity (proportion of days with opioids prescribed where benzodiazepines were also available) of coprescription
Murphy et al. (2018), USA	Polypharmacy and patterns of prescription medication use among cancer survivors	2008-2014	Retrospective Cohort	Cancer survivors and controls	5.216 survivors, 19.588 controls	Cancer survivors 59,4% Female, noncancer controls 62,9%	Cancer survivors: age 18-39y 8,8%, 40-49 10,4%, 50-59 19,3%, 60-69y 25%,	Not specified	Estimate the percentage of respondents prescribed medications within therapeutic classes and total prescription
Price-Haywood et al. (2018), USA	Clinical Effectiveness of Decision Support for Prescribing Opioids for Chronic Noncancer Pain: A Prospective Cohort Study	2013-2016	Observational, Retrospective	Opioid use	250.000	Not specified	Not specified	Both on active medication list	Change in the average morphine equivalent daily dose and rates of opioid risk mitigation, hospitalization, and emergency department use
Musich et al. (2018), USA	Prevalence and characteristics associated with high dose opioid users among older adults	2016	Retrospective Cohort	Opioid use	2.502.830	68,5% Female	>65 y	Not specified	Determine the prevalence and characteristics of high dose opioid users among older adults

Lalic et al. (2019), Australia	Prevalence and incidence of prescription opioid analgesic use in Australia	2013-2017	Retrospective Cohort	Opioid use	769.334	53,1% Female	Mean age 49,5 y	Prior benzodiazepine use use in the 3 months prior to, and on the day of, opioid initiation	Determine the prevalence and incidence of prescription opioid analgesic use
Hwang et al. (2016), USA	Trends in the Concomitant Prescribing of Opioids and Benzodiazepines, 2002-2014	2002-2014	Retrospective Cohort	Opioid use	177.079.757	56,2% Female	Not specified	Benzodiazepine episode that overlapped an opioid episode by at least 7 consecutive days	Describe nationally projected trends of patients receiving opioids and benzodiazepines in the U.S. outpatient retail setting; proportion of patients with concomitancy receiving opioids and benzodiazepines from the same prescriber
Park et al. (2015), USA	Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: Case-co	2004-2009	Case-Cohort	Veterans with opioid use	422.786	Primarily male	Not specified	Receipt of benzodizepines for those who used opioids in that year	Association between benzodiazepine prescribing patterns including dose, type, and dosing schedule and the risk of death from drug overdose among US veterans receiving opioid analgesics
Bohnert et al. (2018), USA	Opioid Prescribing in the United States Before and After the Centers for Disease Control and Prevention's 2016 Opioid	2012-2015 -2017	Observational, Interrupted time series analysis	Opioid use	average of 19.1 million	Not specified	Not specified	Percentage of patients with an opioid and a benzodiazepine prescription	Prescriptions population-level estimates based on retail pharmacy data
Lin et al. (2017), USA	Impact of the Opioid Safety Initiative on opioid-related prescribing in veterans	2012-2014	Observational, Retrospective	Veterans with opioid use	2012: 571.476; 2014: 514.883	Not specified	Not specified	Opioids (100 MEQ and 200 MEQ) and co-prescriptions of benzodiazepines	Examine changes associated with OSI implementation among all adult patients who filled outpatient opioid prescriptions
Breeden et al. (2020), USA	Prescribing Patterns and Use of Risk-Reduction Tools After Implementing an Opioid-Prescribing Protocol	2013-2016	Observational, Retrospective	Opioid use	2.607	68,1% Female	Mean age 45,7 y	Not specified	Estimate change in opioid prescribing, morphine-equiva-lent dose, comedication prescribing, and number and type of protocol elements utilized
Buonora et al. (2019), USA	Race and Gender Are Associated with Opioid Dose Reduction among Patients on Chronic Opioid Therapy	2007-2012	Observational, Retrospective Cohort	Opioid use	1.097	55.2% female	Mean age 51,8 y	At least two unique benzodiazepine prescriptions (of any duration, with or without refills) during the baseline period.	Opioid dose reduction within two years
Sun et al. (2017), USA	Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis	2001-2013	Observational, Retrospective	Opioid use	315.428	57% Female	Not specified	An overlap of at least one day in the time periods covered by prescriptions for each drug	Annual percentage of opioid users with concurrent benzodiazepine use; annual incidence of visits to emergency room and inpatient admissions for opioid overdose

Hawkins et al. (2019), USA	New coprescription of opioids and benzodiazepines and mortality among veterans affairs patients with posttraumatic stress disorder	2009-2011	Observational, Propensity score–matched cohorts, incident-user design	Veterans with post-traumatic stress disorder	256.572	Not specified	Not specified	Prescriptions for opioid and benzodiazepine medications filled within 30 days of each other, with no more than 15 days of cumulative supply from either medication class in the prior 6 months	One-year total and cause-specific mortality was assessed by hazard ratios and subhazard ratios, adjusted for propensity score, age, baseline psychiatric and medical comorbidity, and daily medication dose
Macey et al. (2011), USA	Patterns and Correlates of Prescription Opioid Use in OEF/OIF Veterans with Chronic Noncancer Pain	Not specified	Observational, Retrospective	Veterans with chronic pain	762	15% Female	Mean age 34y (SD 8,8)	Not specified	Describe the prevalence of prescription opioid use, types, and doses of opioids received and to identify correlates of receiving prescription opioids for CNCP among OEF/OIF veterans
Gustavsson et al. (2012), Sweden	Pharmaceutical treatment patterns for patients with a diagnosis related to chronic pain initiating a slow-release strong opioid treatment in Sweden	2005-2009	Observational, Retrospective	Opioid use for chronic noncancer pain	10.799	60% Female	71 y On average	Not specified	Describe the present pharmacological pain treatment patterns and patient selection in connection with initiating slow release strong opioid treatment in Swedish clinical practice
Shmagel et al. (2018), UK	Prescription Medication Use Among Community-Based US Adults With Chronic Low Back Pain: A Cross-Sectional Population Based Study	2009-2010	Observational, Cross-sectional survey	Chronic low back pain	700	55,8% Female	20-69y	Not specified	Examined patterns of prescription medication use among Americans with chronic low back pain
Morasco et al. (2010), USA	Clinical characteristics of veterans prescribed high doses of opioid medications for chronic non-cancer pain	2008	Retrospective Cohort	Veterans with chronic pain	1.478	9,3% Female	Mean age 55,1 (SD 12,6) y	Prescribed opioids for at least 90 consecutive days	Prevalence of high-dose opioid use and associated demographic and clinical characteristics among veterans treated in a regional healthcare network
Alamanda et al. (2020), USA	Prevalence of Opioid and Benzodiazepine Prescriptions for Osteoarthritis	2016	Retrospective Cohort	Osteoarthritis	31.123	Not specified	Not specified	Not specified	Prevalence of opioid and benzodiazepine prescribing for osteoarthritis. Additionally, Characterize risk factors for prescription drug misuse, abuse, and diversion among this population
Tilli et al. (2020), Canada	Opioid stewardship: implementing a proactive, pharmacist-led intervention for patients coprescribed opioids and benzodiazepines at an urban academic primary care centre	2017-2018	Observational, Retrospective	Co-prescribed opioids and benzodiazepines	20 control, 35 intervention	65,7% Female	Mean age 60 (SD 8,4) y - 57y (SD 12,3)	Concurrent opioid and benzodiazepine prescriptions prescribed within the last 12 months	Mean daily opioid dose decrease

Study characteristics		Concomitant use			Cofactors						
Author, Year, Location	Title	Prevalence opioids	Prevalence benzodiazepines	Prevalence concomitant use	Population subgroup		Comorbidity		Pharmacotherapy		
					Sex	Age	Chronic pain	Mental health problem	Opioid dose	Number of prescriptions	Long-term opioid use
Campbell et al. (2015), Australia	Age and gender trends in long-term opioid analgesic use for noncancer pain	KNPC: 30,7% (11.541) GHC: 69,2% (4303)	KNPC: 30,1% (11.217) GHC: 28,5% (1774)	No data	> or =180 opioid+sedative KNPC: Female: 33% (7982) Male: 24,9% (3335) GHC: Female: 31,7% (1286) Male: 22,6% (488)	KNPC: -18–44 (n = 7.686) : opioids: 31,1%, bzd 30,6% -45–64 (n = 18.595) : opioids 33,2%, bzd 32,9% -65+ (n = 11.300): opioids 26,6%, bzd 25,6% GHC: 18–44 (n = 1.205): opioids 68,6%, bzd 31,7% 45–64 (n = 3.277) : opioids 70%, bzd 31,6% 65+ (n = 1.734): opioids 68,2%, bzd 23,4%	No data	No data	No data	No data	No data
Katzman et al. (2019), USA	Army and Navy ECHO Pain Telementoring Improves Clinician Opioid Prescribing for Military Patients: an Observational Cohort Study	Comparison group: 53,6% (63626) Echo group: 13,68% (7248)	No data	Comparison group: 6,02% (3830) Echo group: 8,92% (646)			No data	No data	No data	No data	No data
Weeks et al. (2018), USA	Association Among Opioid Use, Treatment Preferences, and Perceptions of Physician Treatment Recommendations in Patients With Neck and Back Pain	4,9% (82)	2,7% (46)	OR 6,02	No data	No data	Back and neck pain: OR 6,02	No data	No data	No data	No data
Park et al. (2015), USA	The association between benzodiazepine prescription and aberrant drug behaviors in primary care patients receiving chronic opioid therapy	100% (847)	23% (196)	23% (196)	Female 58% Male 42%	Not significant (p = 0,09)	Headache 45% (89) p < 0,001 Neuropathy: p = 0,73 Musculosceletal: p = 0,22	Any depressive disorder 73% (144) p< 0,001 Any anxiety disorder 61% (120) p< 0,001 Any other psychiatric disorder (bipolar disorder and any psychotic disorder): 13% (26) p = 0,01 Any alcohol use disorder (Includes alcohol abuse or dependence): not significant	No data	22% (183) had two or more early opioid refills	No data
Torrance et al. (2018), Scotland	Association of opioid prescribing practices with chronic pain and benzodiazepine co-prescription: a primary care data linkage study	18,9% (2082) Weak opioid 17,9% (1976) Strong opioid 1% (106)		Weak opioid + bzd: 12,2% (241) Strong opioid + bzd: 21,7% (23) Total opioid (weak+strong) + bzd : 12,7% (264) 264	Female 30-45y, weak opioid: 19% (1.336) Female 45-49y, strong opioid: 38% (2.672) < 25y, strong opioids: men > women	Weak opioids: 35-49y Strong opioids: 40-59y	No chronic pain (weak + strong opioid): 8,8% (58) Mild pain (weak+strong opioid): 9,3% (35) Severe pain (weak + strong opioid): 16% (171)	No data	No data	No data	No data
Fritz et al. (2018), USA	Associations Between Early Care Decisions and the Risk for Long-term Opioid Use for Patients With Low Back Pain With a New Physician Consultation and Initiation of Opioid Therapy	100% (707)	8,3% (59)	Acute/episodic opioid 76% (535): 6,9% (37) Long-term opioid use 24% (172): 12,8% (22)	No data	No data	No data	No data	No data	No data	No data
Soric et al. (2018), USA	Benzodiazepine monotherapy in patients with depression: A national cross-sectional study	No data	9,3% (877)	OR 2,93	No data	No data	No data	OR 2,86: Risk factor of coprescribing an opiate	No data	No data	No data

Nielsen et al. (2015), Australia	Benzodiazepine Use among Chronic Pain Patients Prescribed Opioids: Associations with Pain, Physical and Mental Health, and Health Service Utilization	100% (1.220)	32,6% (396)	398 (32,6%)	No data	No data	Headache: 36% vs 23% not Back or neck pain: 84% Visceral pain: 28% Fibromyalgia, arthritis: p>0,05 Pain severity: mean 5.5 Self-efficacy: mean 14,86 Pain conditions: mean 2,49	Substance use history: 19% (75) Lifetime reporting of any mental health condition: 83,4% (332) Moderate to severe depresion: 33% (134) Moderate to severe generalized anxiety disorder: 33% (132) PTSD: 21% (84) Panic attacks past 4 weeks: 61,8% (246)	≥200 MMED BZD-users with"high risk" opioid doses - Less than daily use: 21,4% (40) - Daily use: 27,9% (59) - Never BZD-use: 8,9%	No data	No data
Tong et al. (2019), USA	Chronic Opioid Prescribing in Primary Care: Factors and Perspectives	100% (902)	24% (216)	24% (216)	No data	No data	No data	No data	No data	No data	No data
Saunders et al. (2012), USA	Concurrent use of alcohol and sedatives among persons prescribed chronic opioid therapy: Prevalence and risk factors	100% (1.848)	31,9% (590)	31,9% (590) No current use 68,1% (1258)	Female 71,1% (419) Male 28,9% (171)	Mean age 53,8y (p < 0,05) No concurrent use: mean age 56,6y	> 1 Pain condition: 71,4% (421) vs 60% (755) with no concurrent sedative use (p < 0,05)	Concurrent sedative use <-> no concurrent use Depressed: 72% (429) <-> 55,1% (692) p < 0,05 SUD (any SUD diagnosis from electronic data-drug or alcohol): 23,8% (140) <-> 13% (163) p < 0,05 Diagnosis from electronic data - drug: 21% (123) <-> 9,9% (163) p < 0,05 Rates of concurrent sedative use were higher among subjects with a SUD history vs. those without: 38,9% people with SUD history had concurrent sedative use, vs 28,7% people with no SUD.	Mean daily opioid dose: 108,2 MMED <-> 68,1 MMED no concomitant use Daily opioid dose ≥ 120 MMED (%): *Concurrent use: 22,2% (130)* *Non-concurrent use 13% (163)*	No data	No data
Musich et al. (2020), USA	Concurrent Use of Opioids with Other Central Nervous System-Active Medications Among Older Adults	100% (209.947)	18,4% (38.630)	18,4% (38.630)	No data	No data	No data	No data	≥120 MMED: 49%	No data	No data
Paulozzi et al. (2015), USA	Controlled Substance Prescribing Patterns--Prescription Behavior Surveillance System, Eight States , 2013	7,70%	46,30%	13,6%: mean percentage of overlapping days of treatment	No data	No data	No data	No data	No data	No data	No data
Kobus et al. (2013), USA	Correlates of high-dose opioid medication use for low back pain in primary care	100% (5268) - 91,4% (4815): ≥100 mg/day - 8,6% (453) : 1-99mg/day morphine equivalent	43% (2296)	43% (2296) Lower-dose opioid group: 42% (2022) Higer-dose opioid group: 60,5% (274) Compared to no opioid group (10.184): only 10% (1018) has a sedative-hypnotic 6m before /after index visit	No data	No data	No data	No data	≥ 100 MMED: 60,5%	No data	No data
Dobscha et al. (2008), USA	Correlates of prescription opioid initiation and long-term opioid use in veterans with persistent pain	34% (2.040) Chronic opioid therapy 5% (273) Short-term opioid 29% (1.767)	11,5% (450) (without opioids)	16,7% (342) Chronic opioid therapy: 23% (65) received bzd Short-term opioid use: 15,7% (277) received bzd No-opioid group 11,5% (450)	No data	No data	No data	No data	No data	No data	23,8% vs 11,5% not

Richards et al. (2020) USA, Australia, UK	Factors associated with the prescribing of high-dose opioids in primary care: A systematic review and meta-analysis	100% (4.248.119) High-dose opioids (≥ 90 mg/day): 3,6% (154.470) Low-dose opioids: 96,4% (4.093.649)	9,1% (388.340)	Coprescription of bzd in high-dose opioids: 41% (63.297) Coprescription of bzd in low-dose opioids: 7,9% (325.043)	No data	No data	No data	Anxiety was not associated with high doses of opioids despite people taking high doses to be three times more likely to have benzodiazepines co-prescribed.	≥90 MMED: RR 1,47	No data	No data
Campbell et al. (2015), Australia	Pharmaceutical opioid use and dependence among people living with chronic pain: associations observed within the pain and opioids in Treatment (POINT) Cohort	100% (1.085)	31,4% (340)	31,4% (340) prevalence dependent on OME dose: OME in mg/d: 1-20mg/d (n= 95): 22,1% (20) 21-90mg/d (n = 565): 26,2% (148) 91-199mg/d (n=264): 36% (95) ≥ 200mg/d (n= 161): 47,8%) (77)	No data	No data	No data	No data	1-20 MMED (n= 95): 22,1% (20) 21-90 MMED(n = 565): 26,2% (148) 91-199 MMED (n=264): 36% (95) ≥ 200 MMED (n= 161): 47,8%) (77)	No data	No data
Hooper et al. (2009), Tasmania	Alprazolam prescribing in Tasmania: a two-fold intervention designed to reduce inappropriate prescribing and concomitant opiate prescription	15% (205)	100% (1.345)	Alprazolam + opioid <1m: 14,4% (195) Alprazolam + opioid = or > 1m: 0,7% (10)	No data	No data	No data	No data	No data	No data	No data
Baldwin et al. (2020), USA	Increasing collaboration on substance use disorder research with primary care practices through the National Drug Abuse Treatment Clinical Trials Network	22,90%	No data	8,3% of population 52,1% of opioid users	No data	No data	No data	No data	No data	No data	No data
Carlson et al. (2018), USA	Linkage of VA and State Prescription Drug Monitoring Program Data to Examine Concurrent Opioid and Sedative-Hypnotic Prescriptions among Veterans	4.385 (22%)	8,3% (1.649)	8,8 %	Concomitant use: 1.036 Females: 12,3% Non-concomitant use: 4.846 Females: 11,4%	36-45y	Back or neck pain: OR 2 Any pain: 1,9	Depression: 54,3% Anxiety: 28,1% SUD: 30,8% PTSD: 75%	No data	No data	No data
Maust et al. (2016), USA	No End in Sight: Benzodiazepine Use in Older Adults in the United States	No data	5,6% (95% CI = 5,2–6,0%)	10,0% (95% CI = 7,2– 13,3)	No data	No data	No data	No data	No data	No data	No data
Hirschtritt et al. (2018), USA	Outpatient, combined use of opioid and benzodiazepine medications in the United States 1993-2014	1993: 1,5% 2014: 24,7% (OR = 5.63, 95% CI = 3,17–10,02)	1993 28,8% 2014 68,2% (OR = 8,18, 95% CI = 4,12, 16,25)	1993 0,98% 2014 6,25% (OR = 9,23, 95% CI = 5,45–15,65)	Concomitant use: 1.350 Females: 54,9% (1993-2014) Non-concomitant use: 24.764 (63%)	18-34y: 15,6%, 35-49y: 35,3% , 50-64y: 49,1%	Low back pain: 19,7%	Depression: 3,5% Anxiety: 1,2% SUD: 6,4% Insomnia: 1%	No data	No data	No data
Agarwal et al. (2019), USA	Patterns in Outpatient Benzodiazepine Prescribing in the United States	2003: 3,8%, 2015: 7,4%	2003: 919 (2,4%) 2015: 1.672 (4,3%)	Benzodiazepines: 2015: 19,2% (95% CI, 16,3% -21,0%) of visits in which there was also an opioid. Opioids: 26,4% (95% CI, 20,8%-33,7%) of visits in which there was also a benzodiazepine.	No data	No data	No data	No data	No data	No data	No data
Jeffery et al. (2019), USA	Rates of physician coprescribing of opioids and benzodiazepines after the release of the Centers for Disease Control and Prevention guidelines in 2016	No data	No data	Population 1: 23% population 2: 25,7%	No data	No data	No data	No data	No data	No data	No data

Murphy et al. (2018), USA	Polypharmacy and patterns of prescription medication use among cancer survivors	Newly Diagnosed survivors 43% (CI 39;3-46,8), Previously diagnosed survivors 13.4% (CI 11,8-14,9) Noncancer Controls 9,0% (CI 8,3-9,6)	Newly diagnosed survivors 15,1% (CI 12,4-17,9), Previously diagnosed survivors 15,9% (CI 14,3-17,5), Noncancer Controls 14.0% (CI 13,4-14,7)	Newly Diagnosed Survivors (N=5.962) 6,1% (CI 5,1-7,2), Previously Diagnosed Survivors (N=53.258) 10,0% (CI 7,7-12,3), Noncancer Controls (N= 55.926) 3,9% (CI 3,4-4,3)	No data	No data	No data	No data	No data	No data	No data
Price-Haywood et al. (2018), USA	Clinical Effectiveness of Decision Support for Prescribing Opioids for Chronic Noncancer Pain: A Prospective Cohort Study	4,6% (54.200)	No data	1,6 % of population 36% of opioid users	No data	No data	No data	No data	No data	No data	No data
Musich et al. (2018), USA	Prevalence and characteristics associated with high dose opioid users among older adults	High dose: 3% (7.616) lower dose opioid: 97% (242.667)	No data	High dose opioid: 49% Low dose opioid: 34,5%	No data	No data	No data	No data	No data	No data	No data
Lalic et al. (2019), Australia	Prevalence and incidence of prescription opioid analgesic use in Australia	No data	No data	13.0%	No data	No data	No data	No data	No data	No data	No data
Hwang et al. (2016), USA	Trends in the Concomitant Prescribing of Opioids and Benzodiazepines, 2002-2014	100%	65.276.802,00	2002: 7% (11.864.343) 2014: 10% (15.405.938)	Opioid users: 56.3% female Benzodiazepine users: 63.8% female Concomitancy 2002-2014: women always higher proportion	45-64y	No data	No data	No data	No data	9,6 Times higher
Park et al. (2015), USA	Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: Case-co	100%	27% (112.069)	27% (112.069)	Concomitant use: 112.069 Females: 9% Non-concomitant use: 310.717 Females: 6%	50-59y	No data	Anxiety disorder: 20% vs 5% not Depression: 38% vs 19% not SUD: 13% vs 10% not PTSD: 22% vs 9% not	No data	No data	No data
Bohnert et al. (2018), USA	Opioid Prescribing in the United States Before and After the Centers for Disease Control and Prevention's 2016 Opioid Guideline	100%	No data	2012: 21,04%	No data	No data	No data	No data	No data	No data	No data
Lin et al. (2017), USA	Impact of the Opioid Safety Initiative on opioid-related prescribing in veterans	100%	No data	2012: 19,8% (112.907) 2014 (post-intervention): 17% (89.564)	No data	No data	No data	No data	No data	No data	No data
Breeden et al. (2020), USA	Prescribing Patterns and Use of Risk-Reduction Tools After Implementing an Opioid-Prescribing Protocol	100%	No data	Pre-intervention 25,9% (489) Pst intervention 24,5% (375)	No data	No data	No data	No data	No data	No data	No data
Buonora et al. (2019), USA	Race and Gender Are Associated with Opioid Dose Reduction among Patients on Chronic Opioid Therapy	100%	No data	19,2% (211)	No data	No data	No data	No data	No data	No data	No data
Sun et al. (2017), USA	Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis	100%	No data	2001: 9% 2013: 17%	Concomitant use: 5.425 Female: 65% Non-concomitant use: 53.389 Female: 57%	44,5y (44.4 to 44.7) vs 42,4 no benzo	no data	Depression 915 (17%; 16 to 18) vs 4,4% no benzo SUD: 1,15% vs 0,22% no benzo	No data	No data	No data

Hawkins et al. (2019), USA	New coprescription of opioids and benzodiazepines and mortality among veterans affairs patients with posttraumatic stress disorder	15,7% (65.042)	25,3% (40.494)	1,7% (4.415)	No data	No data	No data	Depression: 49,3% Anxiety: 32,4% SUD: 31,9%	No data	No data	No data
Macey et al. (2011), USA	Patterns and Correlates of Prescription Opioid Use in OEF/OIF Veterans with Chronic Noncancer Pain	64% (485)	14%: without opioids	Short term opioid: 26% Long term opioid: 33%	No data	No data	No data	No data	No data	No data	No data
Gustavsson et al. (2012), Sweden	Pharmaceutical treatment patterns for patients with a diagnosis related to chronic pain initiating a slow-release strong opioid treatment in Sweden	2-3% on average	No data	22% (2.327)	No data	No data	No data	No data	No data	No data	No data
Shmagel et al. (2018), UK	Prescription Medication Use Among Community-Based US Adults With Chronic Low Back Pain: A Cross-Sectional Population Based Study	18,80%	5% (vs 1,2% without back pain)	2,60%	No data	No data	No data	No data	No data	No data	No data
Morasco et al. (2010), USA	Clinical characteristics of veterans prescribed high doses of opioid medications for chronic non-cancer pain	No data	No data	high dose opioid: 32,0% traditional dose opioid: 25,2%	No data	No data	No data	No data	180 MMED: 32,0% 5-179 MMED: 25,2%	No data	No data
Alamanda et al. (2020), USA	Prevalence of Opioid and Benzodiazepine Prescriptions for Osteoarthritis	27%: opioid or benzodiazepine	27%: opioid or benzodiazepine	1,8% (148)	No data	no data	No data	No data	No data	No data	No data
Tilli et al. (2020), Canada	Opioid stewardship: implementing a proactive, pharmacist-led intervention for patients coprescribed opioids and benzodiazepines at an urban academic primary care centre	No data	no data	20 Control 35 Intervention patients	No data	No data	No data	No data	No data	No data	No data

Attachment D: Protocol Systematic Review: 'Co-prescription of opioids and benzodiazepines with a focus on primary care'.

Review team

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Rationale

Opioids and benzodiazepines are both potentially dangerous drugs because of their addictive potential, risk of severe sleepiness, coma and death by respiratory depression.[1,2] Co-prescription of these drugs creates a higher risk of fatal and nonfatal overdoses.[3] Although combined use of these prescription drugs is common, there has not been much focus on the extent of prescribing and the determinants of concomitant prescribing in primary care and outpatient setting.

The aim of this review is to analyse the prevalence and factors associated with concomitant prescription of benzodiazepines, opioids and partial opioid agonists, such as buprenorphine. Finally, we will discuss the relevance of these findings for general practice.

Research question

Firstly: To what extent do primary care physicians co-prescribe benzodiazepine and opioid related drugs?

Secondly: Identify the determinants of concomitant prescribing for these types of medications.

After data-extraction in November 2020, the second research question changed into the following: Identify the factors that are associated with concomitant prescribing of these types of medications.

*Primary care could be defined as:
> immediately accessible, ambulatory, generalistic care of non-specified health problems of physical, psychological or social nature;
> the first contact with professional care;
> can offer diagnostic, curative, rehabilitating and palliative care for most health problems;
> offers prevention for individuals and groups at risk within near populations;
> considers both personal and social context of patients;
> assures continuity of care over time and between care professionals;
> supports informal care of the patient/client.

PICO

First question (PK)

- P: patients in primary care or general outpatient setting with acute or chronic use of benzodiazepines/ patients in primary care or general outpatient setting with acute or chronic use of opioids
- I: benzo co-prescribing/ opioid co-prescribing
- C: no co-prescribing
- O: the proportion of patients co-prescribed both drugs (%)

Second question (KH)

- P: patients in primary care or general outpatient setting with acute or chronic use of benzodiazepines/ patients in primary care or general outpatient setting with acute or chronic use of opioids
- I: presence of determinants affecting the describing behaviour of the general practitioner *(Table A)*
- C: absence of determinants affecting the describing behaviour of the general practitioner *(Table A)*
- O: relative risk of presence of a determinant

After data-extraction in November 2020, the second PICO changed into the following:

- P: patients in primary care or general outpatient setting with acute or chronic use of benzodiazepines/ patients in primary care or general outpatient setting with acute or chronic use of opioids
- I: prevalence of concomitant prescription in the presence of a cofactor *(Table A)*
- C: prevalence of concomitant prescription in the absence of a cofactor *(Table A)*
- O: the proportion of patients with concomitant prescription in the presence of a cofactor in comparison to the proportion of patients with concomitant prescription in the absence of that cofactor (%)

*Determinants are defined as:

- The presence of an element that conditions an outcome

*Chronic use as defined by the authors

Population subgroup	Sex
	Age
Demographic	Country
	Socioeconomic status Employment/unemployment Level of education
	Residential care center
Pharmacotherapy	Subgroup use of benzodiazepines/opioids
	Number of prescriptions
	History of prescription drug misuse
Comorbidity	Chronic pain Chronic headache Lower back pain Fibromyalgia Neuropathic pain
	Mental health problems: a*s defined by the author* Depressive disorder Anxiety disorder, panic disorder Obsessive-compulsive disorder Insomnia disorder Substance use disorder Post-traumatic stress disorder *(in primary care, exclusion of psychiatric patients)*
Pharmacotherapy	Subgroup use of benzodiazepines/opioids
	Number of prescriptions
	History of prescription drug misuse

Table A: Overview of determinants, as mentioned in the second research question

Methods:

A systematic review will be conducted with the following inclusion/exclusion criteria.

Type of study

Inclusion

- Any type of study, excluding case reports
- English, French, Dutch language, or any relevant article if translation available.

Exclusion

- Case reports

Type of patients

Inclusion

- Age: Adults (18 years or older)
- Sex: No restrictions
- Ethnicity: No restrictions
- Indication: Chronic use of an opioid/ of a benzodiazepine.
- Setting: Primary care
- Treatment: Benzodiazepine co-prescribing/ opioid co-prescribing
- Specification: Patients who are co-prescribed benzodiazepine and one or more opioids/ patients who are co-prescribed opioid(s) and (a) benzodiazepine(s) in the presence or absence of a factor as defined by the author

Exclusion

- Age: Minors (< 18 years)
- Studies exclusively based on a study population with abuse or abuse history
- Setting: Use of opioids and benzodiazepines
    - In an inpatient setting e.g. intensive care unit, preoperative setting (including small procedures)
    - Specific outpatient setting: palliative care, cancer pain
- Comorbidity
    - Studies exclusively focussing on severe psychiatric comorbidity (as defined in DSM 5)
    - Studies exclusively focussing on severe alcohol or substance use disorder (as defined in DSM 5)

Type of outcome

- Research question 1:
  The proportion of opioid-users who are co-prescribed at least once benzodiazepines, the proportion of benzodiazepine-users who are co-prescribed at least once opioids
- Research question 2:
  The relative risk of a determinant *(Table A)* in co-prescribing of benzodiazepines and opioids

After data-extraction in November 2020, the second research question changed into the following: Which factors are associated with concomitant prescription of opioids and benzodiazepines.

Databases

The following databases will be systematically searched for articles published before February 2021: PubMed, Cochrane Library, Embase, CINAHL, PsycArticles and Web of Science. All search terms are synonyms of or comparable to the concepts listed below.

Concept 1: Benzodiazepines and derivatives
Concept 2: Opioids and derivatives
Concept 3: Primary care

Study selection

We will independently conduct a search of all relevant articles using multiple databases (PubMed, Cochrane Library, Embase, CINAHL, PsycArticles and Web of Science) following principles according to the PRISMA guidelines. Additional articles will be manually collected from screening the reference lists in the selected articles.
Firstly, we will collect all of our articles into Endnote 20®. After removal of the duplicates, we will use Rayyan QCRI® to compare independently and detect conflicts.

This process will be shown in a PRISMA Flow Diagram.

Data Charting Process

A data extraction table will be created containing the data relevant for both research questions. Two reviewers will extract the data independently, using the same extraction table template.

We will collect all data necessary for this systematic review in a pre-determined data extraction form, including

- Title of the article
- Author names
- Country
- Journal, year of publication, duration of the study, original language of the article
- Characteristics of the population: baseline characteristics (mean of median age, sex, current benzodiazepine and/or opioid use, mental health problems, abuse or abuse history, reason for current benzodiazepine or opioid use, subgroup of benzodiazepine or opioid), inclusion- and exclusion criteria.
- Outcome measurements: following the research questions

Research question 1:
Number of patients receiving prescriptions for benzodiazepines or opioids; combined prescription of benzodiazepines and opioids; number of patients who do not receive prescription for either of these medications.

Research question 2:
Regarding each determinant (Table A) separately: number of patients receiving co-prescription of opioids and benzodiazepines with or without the determinant. A relative risk ratio will be calculated if the data obtained allow the calculation.

After data-extraction in November 2020, the second research question changed into the following: the proportion (%) of patients receiving co-prescription of opioids and benzodiazepines in the presence and absence of a clinical cofactor.

Reporting the results

Depending on the heterogeneity of the data we will decide for both research questions whether meta-analysis is feasible.
If the data collected are of sufficient homogeneity and quality, the risk ratio will be calculated (second research question).

Quality assessment (risk of bias)

The overall quality of the included articles will be assessed with the GRADE rating system.

References

1. Torrance N, Mansoor R, Wang H, Gilbert S, Macfarlane GJ, Serpell M, et al. Association of opioid prescribing practices with chronic pain and benzodiazepine co-prescription: a primary care data linkage study. Br J Anaesth. 2018, 120(6): 1345-55.
2. McDonald JV, Ayers V, Paquin J. Practical Considerations for Prescribing Benzodiazepines and Opioids. R I Med J (2013). 2017, 100(7): 30-2.
3. Maree RD, Marcum ZA, Saghafi E, Weiner DK, Karp JF. A Systematic Review of Opioid and Benzodiazepine Misuse in Older Adults. Am J Geriatr Psychiatry. 2016, 24(11): 949-63.

Het concomitant voorschrijven van opioïden en benzodiazepines en de determinanten van het gelijktijdige gebruik.

Dossiernr.:	MP012739
Stage:	Masterproef I HAIO
Faculteit/opleiding:	Faculteit Geneeskunde - Master in de huisartsgeneeskunde
Studiefase:	eerste fase
Academiejaar:	2019-2020
Korte omschrijving / abstract:	Benzodiazepines and Z-drug hypnotics have many uses, but also important side effects: most importantly sedation and risk of addiction. They became the subject of increasing vigilance because of their abuse potential. Evidence suggests that these drugs have modulatory effects on one another, by changing another's pharmacokinetics and metabolism. Benzodiazepines can intensify and prolong the effects of opioids and opioid agonists, and can therefore reinforce addictive behaviour. On the other hand, opioids interact with mu receptors and benzodiazepines will work on the GABAA sites, which increases the risk of respiratory depression and overdose-related death. Therefore, contemporary use of these drugs can be dangerous, in particular among patients with psychiatric and somatic comorbidity. Though it is estimated that misuse of these prescription drugs is common, there has not been much focus on the extent of prescription and the determinants of concomitant use. Our objective is to analyse concomitant prescription of benzodiazepine (and non-benzodiazepine hypnotics), full opioid agonists and partial opioid agonists such as buprenorphine. We will focus on the determinants of concomitant prescription and hope to create insights that are useful in primary practice.
Toegepaste technieken:	Systematische literatuurstudie
Gewenste taal van communicatie:	nl
Promotor:	Professor Cathy Matheï (u0009104)
Organisatie:	KU Leuven
Dienst:	Academisch Centrum voor Huisartsgeneeskunde
Discipline:	Masterproef
Extra groepsleden:	Karen Poels karen.poels@student.kuleuven.be r0372237 Heleen Knuts heleen.knuts@student.kuleuven.be r0296241

De verstrekte informatie toont aan dat het onderzoek in het kader van de masterproef een zuivere literatuurstudie betreft en dat er op geen enkele wijze gebruik wordt gemaakt van proefdieren, proefpersonen of menselijk lichaamsmateriaal.

Dit type onderzoek vereist geen goedkeuring van een gemachtigde commissie voor medische ethiek.

Onder voorbehoud van de volledigheid en correctheid van de door u verstrekte gegevens, krijgt u hierbij het akkoord om het onderzoek in het kader van de masterproef te starten. Deze mail dient als bewijs van goedkeuring mocht u uw onderzoek wensen te publiceren.

Wij willen u erop attent maken dat u zelf verantwoordelijk blijft voor uw onderzoek. Bovendien doet elke wijziging aan de door u verstrekte gegevens omtrent de onderzoeksopzet deze goedkeuring vervallen. U dient in dat geval een amendement te maken aan uw huidig dossier.