Evidence-Based Practice Group
Answers to Clinical Questions

Tramadol and Acetaminophen Combination for Chronic non-Cancer Pain

A Rapid Systematic Review

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WorkSafeBC

About this report

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About the Evidence-Based Practice Group

The Evidence-Based Practice Group was established to address the many medical and policy issues that WorkSafeBC officers deal with on a regular basis. Members apply established techniques of critical appraisal and evidence-based review of topics solicited from both WorkSafeBC staff and other interested parties such as surgeons, medical specialists, and rehabilitation providers.

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Background

- The Evidence-Based Practice Group (EBPG) was requested to investigate adverse effects associated with the use of a combination of tramadol and acetaminophen in treating chronic pain patients. Specific topics of interest included drug safety, dependence, addiction, substance use disorder (SUD), and overdose deaths.
- Tramadol acts centrally as a μ-opioid agonist and serotonin-norepinephrine reuptake inhibitor. It is used to treat moderate to severe pain. Due to the need for slow dose titration, it is not ideal for acute pain, and its effectiveness for neuropathic pain remains unclear. Since CYP2D6 is required to convert tramadol into its active metabolite, individuals who metabolize CYP2D6 poorly or take CYP2D6 inhibitors may not experience the expected analgesic effect. Conversely, ultra-rapid metabolizers of CYP2D6 may experience adverse effects due to elevated levels of the active metabolite.
- Tramadol is available both as a stand-alone analgesic and in combination with acetaminophen. The combination formulation (tramadol/acetaminophen) is believed to have a synergistic effect and may reduce adverse events.
- Due to its potential for psychological and physical dependence, tramadol (in all formulations) is monitored under the Narcotic Safety and Awareness Act and is classified as a Schedule I controlled substance in Canada.

Objectives

- To determine whether sufficient evidence exists regarding the serious adverse effects of tramadol/acetaminophen combination therapy — specifically focusing on deaths, addiction, and SUDs — when compared to placebo or other active comparators in the clinical management of patients with chronic pain.

Methods

- A rapid systematic literature search was conducted on May 27, 2025.
- The search was undertaken using selected commercial medical literature databases on the OVID platform, including the Joanna Briggs Institute Evidence-Based Practice Database (JBI EBP) (current to May 14, 2025), Cochrane Central Register of Controlled Trials (April 2025), Cochrane Database of Systematic Reviews (2005 to May 21, 2025), Cochrane Clinical Answers (May 2025), Ovid MEDLINE® and Epub Ahead of Print, In-Process, In-Data-Review, & Other Non-Indexed Citations, Daily, and Versions (1946 to May 23, 2025).
- A combination of keywords was used in this search, which included:
    - ["tramadol and paracetamol" OR "tramadol/paracetamol" OR "tramadol and acetaminophen" OR "tramadol/acetaminophen" OR Tramacet OR Ultracet OR Tramcet OR Ramcet OR Tramapap]
      AND
    - [mortality OR (all-cause mortality) OR death* OR overdose* OR (overdose death*) OR (overdose mortality) OR overdosed* OR (over dose*) OR (over dose death*) OR (over dosed) OR over-dosed* OR substance-use-disorder* OR SUD OR misuse* OR abuse* OR dependence* OR addict*]
- Studies involving humans and those in English language were included. No date limitations were applied.
- A manual search was also conducted on the references of selected articles and other relevant sources.

- Predetermined inclusion criteria included studies that were:
    - randomized controlled trials (RCTs), comparative studies, high-quality observational studies, and systematic reviews (with or without a meta-analysis)
    - focusing on the efficacy and safety of tramadol/paracetamol combination therapy for chronic pain (regardless of the route or dosage)
    - comparing tramadol/acetaminophen combination with placebo or other active treatments
    - focusing on drug safety, dependence, addiction, substance use disorder (SUD), and overdose deaths
    - involving adult populations
    - covering relevant chronic pain conditions (e.g., musculoskeletal non-cancer pain, such as low back pain and knee/hip osteoarthritis pain)
- Predetermined exclusion criteria included studies:
    - published as conference abstracts/posters, editorials, opinion/position papers, reprints in other journals, narrative reviews, qualitative interviews, study proposals, pilot studies, case reports, and practice guidelines
    - written in languages other than English
    - with low methodological quality
    - unavailable as full-text articles
    - animal or laboratory-based
    - involving child/adolescent populations
    - involving hospital inpatients
    - involving obstetrics and gynecology patients
    - focusing on cancer pain
    - on dental procedures related pain
    - on pre- and postoperative pain

Results

- Search results:
    - A total of 50 relevant citations were captured.
    - After deduplication, the number of citations was 49.
    - When limited to studies involving humans and written in English, the number of citations was reduced to 40.
    - Upon examining the titles, two additional duplicates were identified and removed. There were 38 articles remaining.[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38]
    - Due to the limited number of articles focusing solely on tramadol/paracetamol combination therapy, we broadened our inclusion criteria to include studies focusing on tramadol monotherapy during the abstract review.
    - After reviewing the abstracts of the 38 articles, 18 were selected for full-text review.[6, 8, 10, 11, 12, 13, 14, 17, 18, 19, 21, 23, 24, 27, 32, 33, 38, 39]
    - The full-text review led to the inclusion of six more studies.[6, 8, 12, 18, 32, 33] Additionally, other articles were identified through hand searches and were included.[40, 41, 42, 43, 44, 45, 46, 47, 48, 49]
    - Although they did not fully meet the inclusion criteria (e.g., case reports, expert opinions, conference abstracts), nine excluded studies[3, 7, 10, 11, 13, 14, 19, 23, 38] were briefly mentioned with the hope that they might still contribute valuable insights into the topic.
    - Three other studies were briefly mentioned. These studies focused on opioid prescriptions (including tramadol) for pain relief after surgery, and their effects

on future opioid use and long-term clinical and social consequences, rather than focusing on tramadol for chronic non-cancer pain management.[50, 51, 52]

- In addition to the aforementioned studies that were published in peer-reviewed journals, three important reports were also worth highlighting.[53, 54, 55] These reports were from well-recognized organizations: Canadian Agency for Drugs and Technologies in Health (CADTH)[53], UBC Therapeutics Initiative (54), and The Morbidity and Mortality Weekly Report (MMWR) of the Centers for Disease Control and Prevention (CDC).[55]
- Of the six studies selected, three were Cochrane systematic reviews,[8, 32, 33] one was a Bayesian network meta-analysis,[6] one was a case fatality study,[18] and one was a death investigation study.[12]
- The systematic reviews and meta-analysis were high-quality Cochrane reviews with level 1 evidence.[8, 32, 33]
- In the case fatality study, data was analyzed using paracetamol as the reference group, level of evidence 3.[18]
- The remaining level 4 study was a death investigation study, which also included impaired driving data.[12]
- For most of the additional studies reviewed the level of evidence was 3;[42, 45, 46, 47, 48, 49] however, there were a few level of evidence 1 systematic reviews,[40, 41, 43] and one level of evidence 2 study.[44]

Included Studies

- In 2021, Boya et al.[6] conducted a network meta-analysis (NMA) of randomized controlled trials (RCTs) to study the efficacy and safety of 13 opioid analgesics (including tramadol) used for treating chronic low back pain. Out of 3,835 citations, they selected 150 articles for full-text review, and 23 RCTs were included in their NMA, comprising data from 8,420 patients. Osteoarthritis patients were excluded based on the predetermined study selection criteria. The outcome of interest for efficacy was a '30% or 50% pain reduction from baseline to follow-up', and for safety, it was 'total withdrawal due to any reason'. A random effects model was used to compare two similar treatments via pairwise meta-analysis (PMA) and multiple treatments simultaneously via a network meta-analysis (NMA). The dropout rate was similar in the intervention and control groups, 34.5% and 37.9%, respectively. The PEDro score for the 23 RCTs included was 8.6, indicating a lower risk of bias. The heterogeneity between studies (for both efficacy and safety-focused studies) was moderate (SD:0.39 to 0.69). The majority of the RCTs allowed the use of rescue medications such as acetaminophen (AP), oxymorphone, oxycodone, hydrocodone/AP, and diclofenac. Of the 23, eight RCTs focused on the effect of tramadol in comparison with placebo or an active comparator. Five of these eight studies focused on tramadol alone, and three studied tramadol plus acetaminophen (AP). The findings from the NMA showed that for all opioid interventions, relative efficacy over placebo was superior, except for tramadol alone (as a monotherapy). The NMA results also indicated that, compared to placebo, oxymorphone, tramadol/AP, and buprenorphine showed a higher efficacy than other opioids. Both the PMA and NMA results demonstrated that tramadol alone was less effective than placebo in reducing chronic back pain. However, the tramadol/AP combination was significantly more effective than placebo for both a 30% pain reduction (OR:2.37) and 50% pain reduction (OR:2.11). The corresponding Odds Ratios (ORs) for oxymorphone were OR:5.36 and OR:5.10, respectively. When considering safety (as measured by total withdrawal from a clinical trial), there was no statistically significant differences between opioids and placebo, except for hydrocodone (OR:

0.33). This study showed that, among the 13 opioids studied, oxymorphone was the most effective in reducing chronic low back pain, but with a high withdrawal rate. (Level of evidence 1. Appendix 1)

- Hawton et al.[18] (2019) investigated the relative toxicity of analgesics in England, during the period 2005–2012. They calculated case fatalities for selected analgesics (i.e., paracetamol (acetaminophen), aspirin (acetylsalicylic acid), codeine, dihydrocodeine, tramadol, paracetamol with codeine (co-codamol), paracetamol with dihydrocodeine (co-dydramol) and ibuprofen). They also studied co-proxamol (paracetamol plus dextropropoxyphene), which was withdrawn in 2008 due to its high toxicity. The authors stated that, in the UK, the most commonly used agents for self-poisoning—fatal or non-fatal—were analgesic drugs. Data on deaths due to intentional self-poisoning and undetermined intent (open verdict) was obtained from the Office for National Statistics. Non-fatal self-poisoning data were obtained from the Multicentre Study of Self-harm in England. The rates of suicide by self-poisoning per 100,000 person-years were calculated using the mid-year population estimates of England for 2005–2012. The rates of non-fatal self-poisoning episodes per 100,000 person-years were calculated using the mid-year population estimates from the geographical areas covered by the Multicentre Study of Self-Harm (Oxford City, the City of Manchester, and Derby Unitary Area) for 2005–2012. For each analgesic, the case fatality was calculated as the ratio between "the number of deaths involving each drug to the total number of episodes of non-fatal self-poisoning with each drug". The authors chose paracetamol as the reference drug to compare the fatality of other analgesics they studied. They conducted two analyses: one for single-drug and one for multiple-drug case fatalities. Combination drugs (e.g., paracetamol and codeine) were counted as single drug treatments. Throughout the study period (2005-2012) there were 1462 single-drug suicide deaths due to poisoning involving the studied analgesics (excluding co-proxamol). The reference drug paracetamol, which was most frequently involved in these deaths, was followed by tramadol, dihydrocodeine, and co-codamol. For non-fatal self-poisoning cases, the highest rates were again associated with paracetamol, but this time, followed by ibuprofen and co-codamol. When the ratios of suicide poisonings to non-fatal poisonings for each studied analgesics was compared to the reference drug (paracetamol), the ratio was 13 times higher for dihydrocodeine and four times higher for tramadol. This was also the case for multiple-drug deaths, where dihydrocodeine or tramadol were the first-named drugs in overdoses (i.e., 17 and six times, respectively, more deaths compared to overdosing with paracetamol). The authors stated that "overdoses of dihydrocodeine and tramadol were both considerably more likely to result in death compared to paracetamol". They also examined the effect of alcohol and suggested that in overdoses that may lead to respiratory depression, alcohol may exacerbate the risk of death. The authors stated that, according to the calculated case fatalities for each analgesic, dihydrocodeine and tramadol were more toxic than the others when overdosed during fatal and/or non-fatal self-poisoning. Although they acknowledged the role of these two drugs in pain management, the authors cautioned the prescribers, especially when treating a patient at risk of self-poisoning. (Level of evidence 3. Appendix 1)
- A Cochrane review conducted by Toupin April et al.[32] (2019) focused on tramadol use in patients with knee and/or hip osteoarthritis. They included 22 RCTs that evaluated the effect of tramadol, or tramadol in combination with acetaminophen, versus placebo or other comparators used by osteoarthritis patients. Generally, the RCTs that were included were multicentre studies, and the follow-up period was two months on average. Of the 22 RCTs, 21 were eligible for a meta-

analysis. Altogether, there were 3,871 participants in the treatment group (tramadol or tramadol combined with acetaminophen) and 2,625 participants in the control group (placebo or other comparators). The quality of the RCTs indicated moderate-quality evidence, after being downgraded due to a high risk of biases, and imprecision. In particular, the high risk of bias due to a lack of sufficient sequence generation and allocation concealment in 18 of 22 RCTs, and incomplete outcome data in 10 of 22 RCTs, were major concerns. Another red flag raised by the authors was pharmaceutical industry funding for the majority of the included trials. When compared to placebo, 15 out of 100 people in the tramadol group improved by 20%, compared to 10 people in the placebo group. The authors stated that they "found moderate-quality evidence that tramadol alone had a small and probably not clinically important pain reduction compared to placebo control interventions". The comparative results for effectiveness of tramadol and placebo on physical function of the OA patients (as assessed with WOMAC Physical Function) were similar to pain improvement results. On the other hand, the number of participants experiencing any adverse events, serious adverse events, and withdrawing due to adverse events was significantly higher in the tramadol group compared to placebo group (RR: 1.34, 1.78, and 2.64, respectively). When tramadol/acetaminophen combination therapy was compared to placebo, the rates and patterns of the pain outcome was similar to the findings with tramadol alone, except for being somewhat more pronounced. When tramadol alone was compared with NSAIDs relative risk was 0.71 for pain and 0.71 for physical function, indicating better results with NSAIDs. The number of participants experiencing any adverse events and withdrawing due to adverse events was significantly higher with tramadol (RR 1.31 and 1.88, respectively) compared to NSAIDs. However, serious adverse events were higher in the NSAID group (RR: 0.21). The quality of the evidence was even lower (moderate to very low) in tramadol versus NSAID trials. The tramadol versus acetaminophen comparison displayed an RR of 0.78 for pain and 5.00 for withdrawal outcomes. When compared to other opioids, tramadol improved both pain and physical function, with relative risks of 1.13 and 1.32, respectively. The number of participants experiencing any adverse event were compatible in both groups. However, withdrawal due to adverse effects and serious adverse effects were higher in the tramadol group compared to other opioids (RR: 2.26 and 7.42, respectively). The quality of evidence with these studies was low. The authors concluded that based on moderate-quality evidence, their analysis did not show important clinical benefits of tramadol alone or when combined with acetaminophen for pain and function in osteoarthritis patients. They called for high-quality, long-term RCTs to clarify the safety risks of tramadol and tramadol/acetaminophen in osteoarthritis patients, compared to placebo, NSAIDs, and other opioids. (Level of evidence 1. Appendix 1)

- In a 2014 a Cochrane review by Chapparo et al.,[8] including 15 RCTs, explored the effectiveness of opioids in improving pain and function in chronic low back pain (CLBP) patients. This was an update of a 2007 Cochrane review on the same topic, which included only four RCTs. Of the 15 included trials, five compared tramadol with placebo, studying a total of 1,378 patients. In two of these studies, tramadol was combined with acetaminophen. In five tramadol vs. placebo studies, tramadol outperformed placebo for both pain and function outcomes (standardized mean difference (SMD) -0.55 and SMD -0.18, respectively). However, the level of evidence was low for pain and was moderate for functional outcomes. One study included an active comparator. Involving 1,583 patients, this study compared tramadol with celecoxib in reducing pain in CLBP patients. Using only one study, a meta-analysis was not possible, and the quality of

evidence for this study was very low. In general, evaluating the biases in the RCTs comparing tramadol with placebo was challenging due to insufficiently reported information. Overall, the risk of attrition bias was high, with performance and detection biases also present. Funnel plots did not capture publication bias. The authors stated that none of these trials reported on concurrent treatment use. The authors concluded that there was moderate-quality evidence supporting that strong opioids (morphine, hydromorphone, oxycodone, oxymorphone, tapentadol) and tramadol performed better in the short term compared to placebo for both pain and functional outcomes in CLBP patients. However, they highlighted the dropout rates and short follow-up periods as limitations of the 15 included trials. Except for the two studies with a 15-week follow-up period, the rest of the studies lasted only four to 12 weeks. The authors also stated that other parameters that might influence the outcome (e.g., pain history and response to treatments before enrolling in the trial, prior employment and compensation status) were not—or underreported. (Level of evidence 1. Appendix 1)

- The Cochrane review by Whittle et al.[33] (2011) focused on the efficacy and safety of opioids for rheumatoid arthritis. Codeine, tramadol, (dextro)propoxyphene, pentazocine and tilidine were considered 'weak opioids', while morphine, oxycodone, methadone, fentanyl, hydromorphone, buprenorphine and diamorphine were considered 'strong opioids'. Comparators included placebo, other opioid analgesics, non-opioid analgesics, non-pharmacological analgesic modalities, and the same opioid medication via a different route, formulation, or dosing interval. The authors identified 33 studies and 11 of these, with a total of 672 participants, were selected for the review. Of the 11 included studies, 10 used weak opioids, and one study used oral morphine, a strong opioid. Primary outcomes included 'patient reported pain relief of 30% or greater' (for efficacy), and 'number of withdrawals due to adverse events' (for safety). Secondary outcomes for pain included 'patient-reported pain relief of 50% or greater', 'patient-reported global impression of clinical change (PGIC)', 'proportion of patients achieving pain score below 30/100 mm on a visual analogue scale (VAS)', and 'mean change in pain score on a visual analogue scale or numerical rating scale'. Other secondary outcomes included 'number and type of adverse events (AEs) and serious adverse events (fatal, life-threatening, or require hospitalization AEs)', 'function (measured by the Health Assessment Questionnaire (HAQ) or modified HAQ)', 'quality of life (measured by generic instruments or disease-specific tools)' and 'participant withdrawals due to inadequate analgesia'. Overall, the selected studies had methodological concerns, such as questionable treatment assignment (inadequate randomization and allocation concealment) and exclusion of the subjects with missing data. The duration of interventions varied significantly across studies. Only one of the selected studies included tramadol as the intervention (tramadol/paracetamol combination). For this study, random sequence generation and allocation concealment were not sufficiently described, outcome data were incomplete and there was selective reporting. The authors' overall conclusion was: "Treatment of RA patients with weak oral opioids for up to six weeks may offer clinically relevant improvement in pain, but adverse effects are common and limit the utility of this class of analgesics". (Level of evidence 1. Appendix 1)
- A forensic report by Clarkson et al.[12] (2004) from Washington State Toxicology Laboratory investigated 66 deceased individuals with tramadol present in their blood, all of whom died while driving between 1995 and 2000. The authors aimed to ascertain the causal significance of tramadol in these deaths, patterns of other drugs' presence, and any potential drug interactions. Although blood tramadol

concentrations were higher than the therapeutic limits (0.28–0.61 mg/L) in many cases, tramadol was often accompanied by other drugs such as analgesics, muscle relaxants, and CNS depressants. Of the 66 deaths with tramadol present in blood, 20 were due to natural causes, accidents, or suicides that were not drug related. Fifteen deceased individuals had tramadol at therapeutic doses along with other drugs in high concentrations, which were accountable for death; thus, tramadol was regarded as an incidental finding. However, in another 27 cases, the presence of tramadol (within or above therapeutic concentrations) was identified as the main contributing factor to death (contributory cause of death), as the other present drugs alone or any anatomical factors could not account for these deaths. The remaining four deaths were attributed solely to tramadol (as the primary cause of death), with concentrations above the therapeutic range and no other drug or anatomical cause contributing. These four cases were discussed in detail in the paper. The authors also studied a set of 83 cases of impaired drivers from the same 1995–2000 period. Fifty-seven of these cases had tramadol detected in their blood. Again, most of these cases involved other CNS acting drugs alongside with tramadol. The authors emphasized the increased risk when driving after taking an excessive tramadol dosage or starting a new course of tramadol therapy. The authors stated that "tramadol may be a significant contributor to lethal intoxication when taken in excess with other drugs" through potential drug interactions, such as increased serotonergic activity (possibly leading to Serotonin Syndrome), inhibition of tramadol metabolism (via CYP2D6 isoenzyme inhibition), and with additional CNS depression. (Level of evidence 4. Appendix 1)

<u>Additional studies included</u>

- Given the broad use of tramadol in managing various pain conditions and the limited number of studies comparing its adverse effects with other opioids, Xie et al.[48] (2021) conducted a retrospective cohort study comparing tramadol and codeine with regard to the risks associated with a new prescription of either drug. Codeine was chosen as a comparator as both tramadol and codeine are weak opioids, frequently prescribed for similar indications in Spain. The cohort consisted of patients who were first prescribed either tramadol or codeine during a 10-year period (2007–2017). Data was obtained by linking routinely collected, anonymized primary healthcare records (including ICD-10 disease classification codes) with national pharmacy claims data for community pharmacy dispensations. The identified opioid prescription indications included cancer, back pain, neck/shoulder pain, osteoarthritis, cough, migraine, musculoskeletal diseases, chronic obstructive pulmonary disease, fibromyalgia, dyspnea, peripheral vascular disease, angina, transient ischemic attack, osteoporosis, diarrhea, rheumatoid arthritis, malabsorption disorders, pulmonary edema, diabetes, chronic liver disease, chronic kidney disease, Alzheimer's disease, and Parkinson's disease. The outcomes of interest were all-cause mortality, cardiovascular events (stroke, cardiac arrhythmia, myocardial infarction, and heart failure), fractures (hip, vertebral, and others), constipation, delirium, falls, opioid abuse/dependence (within one year), and sleep disorders. A logistic regression model was used to calculate propensity scores for tramadol vs. codeine dispensation, for each study year. Person-years of follow-up were computed for each member of the cohort for each outcome (from the index date to the end). The Kaplan-Meier method was used to compute one-year cumulative incidences, and survival curves were drawn. Cox proportional hazards regression was used to estimate hazard ratios (HRs). In total, 839,489 people were initiated tramadol or codeine during the study period. After exclusions and propensity

score matching, there were 184,480 people in each of the tramadol, and codeine cohorts. The two cohorts were similar at baseline. The mean age was 52.7 years in the tramadol cohort, 53.5 years in the codeine cohort. The diagnosis of back pain was 47.5% in the tramadol cohort, and 48.5% in the codeine cohort, neck/shoulder pain was 28.6% vs. 29.5%, and osteoarthritis was 15.3% vs. 15.5%, respectively. Medications most frequently dispensed included ibuprofen and paracetamol/acetaminophen, 34.4% vs. 34.3%, and 37.1% vs. 36.8%, respectively, in the tramadol and codeine cohorts. At the 1-year follow-up, participants with a tramadol prescription had a significantly higher risk of all-cause mortality, cardiovascular disease, and fractures. The 1-year cumulative incidence (calculated using the Kaplan-Meier method) for all-cause mortality was 12.86 vs. 5.59 per 1000; cardiovascular disease was 9.97 vs. 8.19 per 1000; and fractures were 12.07 vs. 8.08 per 1000 in the tramadol and codeine cohorts, respectively. Within one year, incidence rates, absolute rate differences (ARDs), and adjusted hazard ratios (HRs) were calculated and compared for tramadol and codeine cohorts. The tramadol cohort experienced significantly higher mortality (13.00 vs. 5.61 per 1000 person years, HR 2.31, ARD 7.37 per 1000 person years), cardiovascular events (10.03 vs. 8.67 per 1000 person years, HR 1.15, ARD 1.36 per 1000 person years), and significantly higher number of fractures (12.26 vs. 8.13 per 1000 person years, HR 1.50, ARD 4.10 per 1000 person years) compared to the codeine cohort. However, the authors did not find any significant difference between the tramadol and codeine cohorts regarding the risks of constipation, delirium, falls, opioid abuse/dependence, or sleep disorders. The authors concluded that "a new prescription dispensation of tramadol, compared with codeine, was significantly associated with a higher risk of subsequent all-cause mortality, cardiovascular events, and fractures". However, they cautioned against overinterpreting these findings due to potential residual confounding. (Level of evidence 3. Appendix 1)

- In 2019 Thiels et al.[47] published an observational study on the risk of transitioning from acute to prolonged tramadol use in opioid-naive patients treated with tramadol for pain following a surgical procedure. The authors suggested that while data supporting tramadol's safety and lower dependence risk was lacking, it was considered to have a favorable side effect profile due to its lower affinity for the μ-opioid receptor. The study used a retrospective cohort of de-identified Medicare Advantage enrollees. Medicare Advantage covers 33% of Medicare beneficiaries in the US. The study included 20 common surgical procedures with varying post-operative pain levels. This cohort was designed to minimize clinical complexity and confounding. Discharge opioid prescriptions (for 357,884 patients) were expected to last a minimum of 30 days, and the total morphine milligram equivalents (MME) had to be less than 1400. Following surgery, no other surgeries within 180 days and a 90-day insurance enrollment period were required. Discharge opioid prescription status was categorized in five groups: short acting opioids only (excluding the reference, tramadol); tramadol only; tramadol with other short acting opioids; any long-acting opioids; and no opioids. The primary outcome was the 'risk of prolonged opioid use after surgery', where 'prolonged opioid use' was defined by three criteria. One of these three, the CONSORT definition, was the strictest as "an opioid use episode lasting at least 90 calendar days and including either 10 or more opioid fills or 120 or more days' supply". Logistic regression analysis was used to adjust proportions for 'prolonged opioid use' for patients who received tramadol at discharge and for those who did not. Then, these adjusted proportions were used to calculate the risk ratios and risk differences. Larger discharge prescription volumes (higher total MME) were "associated with a higher risk of prolonged opioid use across all

three definitions of prolonged use". 'Tramadol alone' prescription was linked to an increased risk of additional opioid use compared to other short-acting opioids (incidence rate: 1.00 to 1.13) and persistent opioid use (incidence rate: 1.25 to 1.69). The adjusted risk of a CONSORT chronic opioid use episode was 1.08 to 1.75 percentage points. The authors concluded that tramadol posed a similar or slightly increased risk of prolonged opioid use after surgery compared to other short-acting opioids. They invited FDA to consider "rescheduling tramadol to a level that better reflects its risks of prolonged use". (Level of evidence 3. Appendix 1)

- Zeng et al.[49] (2019) conducted a study exploring the relationship between tramadol use and all-cause mortality, which has been rarely investigated. The study was a sequential, propensity score–matched cohort design that analyzed all-cause mortality within one year after tramadol initiation and compared it to the all-cause mortality with five other analgesics (naproxen, diclofenac, celecoxib, etoricoxib, and codeine) which were also initiated during the study period. The study period spanned from January 2000 to December 2015 and was divided into 16 one-year time blocks. The main exposure was the initial drug prescription, and the primary outcome was death from any cause in one year. Initially, the tramadol group differed from the NSAID prescribed patients in terms of the baseline characteristics, but after propensity score matching, the tramadol cohort and the five other analgesic cohorts were similar in terms of sociodemographic factors (i.e., age at index date, sex, Townsend Deprivation Index), body mass index (BMI), lifestyle factors (i.e., drinking habits and smoking status), osteoarthritis duration, comorbidities and prescriptions prior to the index date, and health care utilization in the 2-year period prior to the index date. Data were obtained from the UK's Health Improvement Network (THIN) database, linked to the National Health Service (NHS), ensuring immediate and accurate death date tracking. The study analyzed data from 88,902 patients, including those prescribed tramadol. All-cause mortality rates for tramadol were compared to those for naproxen, diclofenac, celecoxib, etoricoxib, and codeine using Kaplan-Meier survival curves. The hazard ratios for all-cause mortality in the tramadol cohort compared to NSAIDs were: Naproxen: HR = 1.71, Diclofenac: HR = 1.88, Celecoxib: HR = 1.70, Etoricoxib: HR = 2.04. However, there was no statistically significant difference in all-cause mortality between tramadol and codeine cohorts (HR = 0.94 [95% CI, 0.83–1.05]). A unique finding was the higher cancer-related mortality in the tramadol cohort compared to NSAID cohorts, which indicated potential "confounding by indication" due to presence of more severe comorbidities in the tramadol cohort. This provides an example for likely residual confounding, despite the efforts to control for confounders (i.e., with propensity score matching). The authors invited future studies to establish whether there was a causal association between initiation of tramadol treatment and higher all-cause mortality risk in osteoarthritis patients, in the following year compared to the initiation of other pain treatments. (Level of evidence 3. Appendix 1)
- Els et al.[41] (2017) conducted a Cochrane overview reviewing all Cochrane reviews on the adverse effects of medium- and long-term opioid use (two weeks or longer) in patients with chronic non-cancer pain (CNCP). The authors focused on various adverse events associated with all opioids, regardless of dose, frequency, or route of administration. The overview included 16 Cochrane reviews, of which 14 provided unique quantitative data on 14 different opioids: buprenorphine, codeine, dextropropoxyphene, dihydrocodeine, fentanyl, hydromorphone, levorphanol, methadone, morphine, oxycodone, oxymorphone, tapentadol, tilidine, and tramadol, drawn from 61 studies involving 18,679 randomized patients. [*Two[8,33] of these 16 Cochrane reviews are included in our review*]. The

equivalent milligrams of morphine (MME) per 24 hours were calculated for each opioid in the studies. Five of the selected Cochrane reviews included tramadol as one of the opioids studied. While the Cochrane reviews scored highly according to AMSTAR (A Measurement Tool to Assess Systematic Reviews), the individual studies had a high risk of bias and imprecision. The level of evidence for adverse event outcomes (e.g., addiction, cognitive dysfunction, constipation, depressive symptoms, hypogonadism, infection, respiratory depression, sexual dysfunction, sleep apnea, xerostomia, and other events such as anorexia, dizziness, fatigue, nausea, pruritus, etc.) was graded as low according to the GRADE assessment tool. Comparison groups in the studies included either a placebo or an active (non-opioid) pharmacological comparator. In some reviews, outcome data was only presented for the treatment group, not for the control group. According to the GRADE rating, when opioids were compared to placebo, the quality of evidence was moderate for 'any adverse event', 'any serious adverse event', and 'withdrawal due to adverse events'. However, when opioids were compared to an active comparator, the quality of evidence for 'any serious adverse event' was very low. Only one study compared opioids to non-pharmacological interventions, and the quality of evidence for 'any adverse event' in this study was very low. When opioids were compared to placebo, the risk ratio (RR) for 'any adverse event' was 1.42, for 'any serious adverse event' was 2.75, and for 'withdrawal due to adverse events' was 3.40, all favoring placebo. Placebo was also favored for all other adverse effect outcomes (e.g., constipation, dizziness, fatigue, hot flashes, nausea, pruritus, vomiting). When opioids were compared to other active pharmacological comparators, the risk ratio (RR) for 'any adverse event' was 1.21, for 'any serious adverse event' was 5.0, and for 'withdrawal due to adverse events' was 3.23, all favoring the active pharmacological comparator. The authors noted that the research relied heavily on "earlier studies with less robust methodology", which might have "contributed to the current opioid use epidemic, opioid overdoses, and deaths". The authors concluded that their overview suggested "the occurrence of adverse events with opioids for CNCP is both common and clinically relevant". Although tramadol or combined tramadol/acetaminophen's effect on CNCP patients was not explicitly reported in the overall conclusion of this Cochrane overview, it was included in our report as an additional study due to its focus on the adverse effects of medium- and long-term opioid use. (Level of evidence 1. Appendix 1)

- Fournier et al.[42](2015) conducted a large-scale, population-based study in non-cancer patients to investigate whether there was an increased risk of hospitalization due to tramadol-induced hypoglycemia. The authors compared hospitalization rates between patients treated with tramadol and those treated with codeine. Since, as a weak opioid, codeine was not previously linked to hypoglycemia, the 'codeine use' group was assigned as the reference group. The study utilized the Clinical Practice Research Datalink (CPRD), which includes records of 13 million individuals, and the Hospital Episode Statistics (HES) database, which contains records of all hospitalizations in the UK. These two databases were linked, and patients who had an initial prescription of either tramadol or codeine between April 1, 1998, and March 1, 2012, were included in the cohort. The exposure was defined by the participants' status on the index date, and there were three mutually exclusive groups: The 'codeine use' group had "the first prescription within 30 days before the index date, with no prior prescriptions of codeine or tramadol in the year before the index date". The 'tramadol use' group had "a prescription within 30 days before the index date, but no codeine prescriptions in the previous year." The 'other patterns and combinations' group included participants with concurrent use, previous use, or

no use of either medication. A nested case-control study design was chosen by the authors to analyze the data. Cases consisted of patients who were first-time hospitalized due to hypoglycemia, with the index time set as the hospital admission date. Controls (up to 10 per case) were randomly selected from the risk sets and were matched on age, sex, and follow-up duration. The authors considered various baseline covariates in their analysis, including calendar year of cohort entry, body mass index, excessive alcohol use, comorbidities, prescription drug use, opioid-related indications, number of GP visits, hospitalizations, and number of prescribed drugs prior to cohort entry. Poisson distribution was used to calculate the incidence of hospitalization for hypoglycemia, while conditional logistic regression was used to calculate and compare odds ratios (ORs) for hospitalization due to hypoglycemia, following the tramadol versus codeine treatment. Two secondary analyses explored the effect of the timing of the first tramadol prescription (≤30 days versus >30 days before the index date) and the presence of antidiabetic medication at baseline as a covariate on the association between tramadol use and hospitalization for hypoglycemia. The analysis was restricted to first-time tramadol and codeine users, and a high-dimensional propensity score, which included the aforementioned covariates, was computed. The authors compared the cumulative incidence of hospitalization due to hypoglycemia (up to 30 days after treatment initiation) in tramadol versus codeine treatment groups using Kaplan-Meier curves, and the hazard ratios (HRs) using Cox proportional hazards models. For 1105 patients who were hospitalized for hypoglycemia and matched with 11,1019 controls, the primary analysis employing nested case-control design revealed that prior 'tramadol use' increased the risk of being hospitalized for hypoglycemia (adjusted OR: 1.52), and the secondary analysis showed that this risk was even higher for the group whose treatment was initiated within 30 days of the index date (adjusted OR: 2.61). Antidiabetic drug use modified these results, with the OR being higher in nonusers compared to users of antidiabetics (adjusted OR: 2.12 vs. 1.11, respectively). The cumulative incidence of hospitalization due to hypoglycemia was higher in the tramadol group compared to the codeine group. Of the 1,105 hospitalized cases due to hypoglycemia, 112 (10.1%) were fatal. The authors highlighted a significant two-fold increased risk of hospitalization due to hypoglycemia (which is a rare but potentially fatal adverse event) with initiation of tramadol therapy, compared to initiation of codeine therapy. (Level of evidence 3. Appendix 1)

- Park et al.[45] (2015) investigated the efficacy of tramadol/acetaminophen (APAP) and NSAIDs as continuous maintenance therapies (for 8 weeks) after achieving reduced pain levels in patients with knee osteoarthritis (OA) lasting over a year. Patients experienced moderate knee pain (≥5 on the Numerical Rating Scale, NRS), which did not improve with 4 weeks of NSAID therapy. A total of 143 patients were enrolled in the study across six outpatient clinics. As an add-on therapy, the tramadol/APAP combination (37.5 mg tramadol/325 mg acetaminophen) was titrated from one tablet per day to between three and eight tablets per day, as needed. Of the 143 patients, 112 completed the add-on therapy phase, and 97 of them (67.8%) reduced their knee pain NRS to <4. Their total WOMAC score, as well as scores for pain, stiffness, and physical function, also improved. In the comparative study phase, these 97 patients were randomized to receive either tramadol/APAP or NSAID monotherapy. Eighty-three patients completed the 56-day monotherapy phase. At the time of randomization, the demographic and clinical characteristics of the two groups were similar. To study efficacy, the primary outcome of interest was the WOMAC OA index score (Korean version), while secondary outcomes included pain intensity (measured by

NRS), pain relief score, and both patient and investigator assessments of the medication. Measurements were taken on days 29 and 57, and no significant changes in WOMAC index scores or pain intensity were observed for either treatment group. Patient-reported pain relief at the study's end was similar in both groups. Regarding adverse effects (e.g., nausea, dizziness, heartburn, constipation), there was no significant difference between the monotherapy groups. Only one withdrawal due to adverse effects occurred in the tramadol/APAP group. The authors emphasized that a large portion of knee OA patients, who were initially resistant to NSAID therapy, became responsive when tramadol/APAP was added to their NSAID therapy for four weeks. Later, the patients responsive to add-on therapy were randomized to either tramadol/APAP or NSAID for eight weeks of maintenance therapy. No statistically significant difference was found between the two groups in maintaining a reduced pain state (WOMAC total score: 36.11±13.22 for tramadol/APAP vs. 33.32±14.39 for NSAID). This study was funded by a grant from Janssen Korea, a pharmaceutical company. (Level of evidence 3. Appendix 1)

- Roussin et al.[46] (2015) studied abuse and addiction patterns in France, using tramadol (and its combined version, tramadol/acetaminophen) as an example. The authors selected tramadol due to its dual pharmacokinetic mechanism: a greater affinity than the parent molecule for μ-opioid receptors through its metabolite O-desmethyl and inhibition of serotonin and noradrenaline reuptake. This unique mechanism increases the risk of adverse effects, as well as the potential for abuse and dependency, particularly when taken in excessive doses. In France, the Centres of Evaluation and Information on Pharmacodependence-Addictovigilance (CEIP-A) was tasked by the French Drugs Security Agency (ANSM) in 2010 to oversee the surveillance system for tramadol. The CEIP-A network involved collecting and analyzing 'spontaneous notifications of abuse and dependence cases' (reported by healthcare professionals, with no personal identifiers) and conducting various pharmaco-epidemiological surveys annually. The surveys included OSIAP (suspicious prescriptions indicating possible abuse), OPPIDUM (observatory for illegal psychotropic substances or diverted medications), OPEMA (observatory for pharmacodependence in ambulatory medicine), and DRAMES (deaths related to medication and substance abuse). Beginning with the first survey in 2010, three major themes emerged from the notifications on problematic tramadol use: signs of withdrawal syndrome at therapeutic or higher-than-recommended doses (above 400 mg/day), diversion or misuse of tramadol for non-clinical purposes (e.g., psychoactive effects), and tramadol abuse (in 2013, 25% of notifications involved tramadol use above the recommended dose, with nine cases involving doses from 1g/day to 6g/day). In addition to the spontaneous notifications and survey results, the authors reported a 2008 descriptive/cross-sectional study conducted by the Toulouse CEIP-A. The study surveyed the purpose, methods of taking, and undesirable effects of tramadol on users' health, social, and work life. Of the 465 questionnaires, 55% were completed. Tramadol misuse was reported by 6.2%, abuse by 1.6%, and each of 'tolerance', 'signs of withdrawal', and 'use of larger doses than recommended' were reported by 30%. Another 13% of patients reported experiencing 'undesirable effects' from tramadol. Roussin et al. also reported that, based on insurance reimbursement data and pharmacy dispensed amounts, ANSM determined that between 2007 and 2012, tramadol and tramadol-acetaminophen use increased by 47% and 67%, respectively. They emphasized the importance of monitoring addiction and conducting yearly data analysis to identify potential signals. The authors concluded that data from the CEIP-A network indicated tramadol abuse and dependence had "clinically significant

consequences" and stressed the need to "inform health professionals about tramadol's abuse and dependence potential to prevent routine prescriptions". (Level of evidence 3. Appendix 1)

- Since no head-to-head comparison studies existed for tramadol and tapentadol, Mercier et al.[44] (2014) performed a model-based meta-analysis to indirectly compare the efficacy and tolerability of these two opioids in treating chronic non-cancer pain. The indirect comparison of the risk-benefit tradeoff between tramadol and tapentadol was made using publicly available data. In this simulation study, the authors systematically screened clinical trial registries for trials involving tramadol and/or tapentadol as analgesic treatments for non-cancer pain, extracting data from 45 Phase II and Phase III trials, totaling approximately 13,000 patients. The majority of trials were placebo-controlled. For active-controlled trials, data were retained only from the tramadol or tapentadol arms if other comparators were involved. They described the treatment effects over time. They also included other differences across trials and treatment arms, such as disease severity, age, gender, and concomitant medications, as covariates in their analysis. Pain intensity measurement varied widely across studies. As a result, they compared tramadol and tapentadol through simulation of typical time profiles. The typical doses for tramadol and tapentadol were considered to be 300 mg daily (qd) and 100–250 mg twice daily (bid), respectively. The typical trial duration was 12 weeks. They simulated 1000 patients in each group, with a baseline pain intensity of 7 out of 10. A significantly higher risk of constipation and vomiting was observed in the tramadol group, while the tapentadol group showed a slightly higher risk of dizziness. Drop-out frequencies were as expected for each group: 7.1%, 18.7%, and 20.5% for drop-outs due to adverse effects, and 18.5%, 6.1%, and 7.8% for drop-outs due to lack of efficacy, in the placebo, tapentadol, and tramadol groups, respectively. A large and clinically significant reduction in pain was observed with placebo treatment: at week 12, the pain intensity in the placebo group was 4.8, a reduction of 2.1 points. At week 12, pain intensity was estimated at 3.7 for the tramadol group and 4.3 for the tapentadol group, both reduced from a baseline value of 6.9. The final pharmacodynamic model retained one significant covariate: baseline pain intensity, as higher baseline pain intensity led to a larger treatment effect. This was true for both active and placebo groups. Since, in the past, treatment schedules, doses, comparators, and conditions were different across studies and most trials were small with short-term study periods, conclusions from these heterogenous data were erroneous, incomplete, or imprecise. Although this simulation and indirect analysis of Phase II and Phase III trials was also subject to the heterogeneity of the studies, the authors stated that the "mathematical framework not only gives the possibility to summarize the information in a clear and concise way, but also to predict the response in various hypothetical clinical scenarios". They also noted that most of the 45 included trials were funded by the pharmaceutical industry and highlighted "bias in the quality of results reported in the literature. In particular, less than adequate reporting of adverse events information". The authors concluded that their meta-analysis suggested that the benefit-risk ratios for tramadol (300 mg daily) and tapentadol (100–250 mg twice daily) were comparable, with tramadol showing slightly higher efficacy and tapentadol offering a better safety profile. The authors advocated for "broad and open access to clinical trial data" to facilitate the evaluation of the clinical utility of opioids as analgesics. (Level of evidence 2. Appendix 1)
- Manchikanti et al.[43] (2011) conducted a systematic review focused on long-term opioid management for chronic non-cancer pain patients, requiring a minimum

12-week follow-up. This high-quality review included 21 RCTs evaluating treatments such as transdermal fentanyl, buprenorphine, oral morphine, tramadol, oxycodone, oxymorphone, tapentadol, and hydromorphone, with six studies focusing on tramadol. Four of the tramadol RCTs were placebo-controlled. A meta-analysis was conducted for each opioid when at least five studies were available. When fewer than five studies were available, general quantitative and qualitative methods were used to assess the magnitude and direction of treatment effects. A clinically meaningful change in pain score was defined as a 2-point reduction on a 0 to 10 scale. There were enough studies on tramadol to perform a meta-analysis. The tramadol studies evaluated chronic pain, low back pain, and osteoarthritis (OA). Except for osteoarthritis, the clinical efficacy of tramadol in managing other chronic pain conditions showed poor evidence, ranging from weak positive to indeterminate or negative results. For osteoarthritis, the authors concluded that the evidence was "fair" for tramadol administration in both multiple joint and knee osteoarthritis. Following this systematic review, the authors concluded that there was poor evidence for using opioids in the clinical management of pain conditions other than OA. (Level of evidence 3. Appendix 1)

- Cepeda et al.[40] (2006) conducted a Cochrane review investigating the analgesic and functional effectiveness of oral tramadol in osteoarthritis patients. They also examined the duration of any existing benefits and the safety of tramadol. The review included 11 RCTs, with nine studies on tramadol monotherapy and two studies on tramadol/paracetamol combination therapy. The trials included both placebo-controlled (six studies) and active treatment-controlled (five studies) groups. Primary outcomes of interest were pain, physical function, safety outcomes, patient global assessment of improvement, and joint imaging reports. The secondary outcome was the duration of any benefits. The total number of participants was 1,019 in the treatment group (tramadol or tramadol/paracetamol) and 920 in the control group (placebo or active control). All but one of the included RCTs were supported by the pharmaceutical industry. The effectiveness and safety of tramadol alone and the tramadol/paracetamol combination therapy were similar. In placebo-controlled trials, tramadol reduced pain intensity by 8.5 units (out of 100), compared to a 2.5-unit reduction in active treatment-controlled trials. The analgesic effect of tramadol was similar to diclofenac but inferior to paracetamol. In terms of global assessment of improvement, tramadol led to more favorable results in both placebo and active control trials. In placebo trials, tramadol led to a larger reduction in WOMAC score (a measure of physical activity), compared to the control (placebo). Whereas the WOMAC score was similar when tramadol was compared to diclofenac (an active control treatment). When evaluating the proportion of subjects with at least moderate improvement by follow-up duration, the risk ratio (RR) was 1.38 for short-term follow-up (up to 8 weeks) and 1.36 for long-term follow-up. Patients receiving tramadol alone or tramadol/paracetamol combination treatments experienced adverse events, including nausea, vomiting, dizziness, constipation, somnolence, tiredness, and headache. The risk ratio (RR) for developing major adverse events was 2.67 in placebo-controlled trials and 2.31 in active-controlled trials, both favoring the control groups. The authors stated that tramadol was more effective than placebo in reducing pain intensity and improving function in OA patients. However, they could not determine whether tramadol's effectiveness would decrease with long-term use. There was also limited evidence suggesting that traditional opioids had a larger effect than tramadol for OA. Generally, opioids were less effective than NSAIDs in OA patients. One in eight patients receiving tramadol or tramadol/paracetamol therapy discontinued treatment due

to adverse effects. The authors concluded that "benefits of tramadol are comparable with those obtained with paracetamol and these benefits are coupled with a less favorable safety profile". (Level of evidence 1. Appendix 1)

- Three additional studies are briefly highlighted. These studies were not on opioids used for clinical management of chronic non-cancer pain, rather, they focused on opioid prescriptions (including tramadol) following surgery for pain relief, examining their effects on future opioid use and long-term clinical and social outcomes.
    - Ladha et al.[52] (2019) conducted a retrospective cohort study on opioid prescribing patterns following surgery in the United States, Canada, and Sweden. The study analyzed three large administrative datasets from these countries, including patients who underwent laparoscopic cholecystectomy, laparoscopic appendectomy, knee meniscectomy, or breast excision, and were prescribed postoperative opioid analgesics (e.g., codeine, fentanyl, hydrocodone, hydromorphone, ketobemidone, levorphanol, meperidine, morphine, oxycodone, oxymorphone, pentazocine, tramadol, tapentadol). The study included 461,846 patients across the three countries, with 223,834 eligible for analysis: 129,379 from the U.S., 84,653 from Canada, and 9,802 from Sweden. The primary outcome was the number of patients who filled a prescription within the first 7 days following surgery (with day 0 defined as the day of hospital discharge or, if no hospitalization, the day of surgery). Secondary outcomes included: the amount of opioid dispensed in the first prescription, total opioids dispensed in the first 30 days, the type of opioid in the first prescription, the postoperative day of dispensing, use of combination opioid products, and morphine milligram equivalents (MME) of the first prescription. When examining the distribution of opioid types in first prescriptions, tramadol accounted for 18.5% of prescriptions in Canada, 29% in Sweden, and only 3.5% in the U.S. When codeine was also included, tramadol and codeine together accounted for approximately 58% and 45% of postoperative opioid prescriptions in Canada and Sweden, respectively, compared to only 7% in the U.S. However, when comparing the total amount and frequency of opioid prescriptions across the three countries, the authors concluded that "patients treated in the United States and Canada received opioids after surgery more often and in higher doses compared with patients treated in Sweden." (Level of evidence 3. Appendix 1)
    - The impact of first prescriptions and refills of opioid analgesics after surgery on the future likelihood of opioid misuse was unknown. Brat et al.[51] (2018) investigated various opioid prescription patterns following surgery in relation to dependence, overdose, and abuse, as determined by ICD-9 diagnostic codes. This retrospective cohort study used data from a commercially insured patient population and included 1,015,116 opioid-naïve patients (defined as those who had not used opioids in the 60 days prior to surgery) who underwent surgery between 2008 and 2016. The median follow-up period was 2.67 years. The study considered prescriptions for opioid drugs containing codeine, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, and tramadol. The authors developed a composite primary outcome consisting of opioid dependence, abuse, and overdose. The results demonstrated that the strongest predictor of misuse was the total duration of opioid use (including refills and each additional week of use), while dosage was a weaker predictor. For example, patients who had one refill had more than

double the rate of misuse compared to those with no refills. Also, an average increase of 34.2% in the rate of misuse was observed with each additional week of opioid use. The associated adjusted increase in the rate of misuse was 44.0%, and the increase in hazard was 19.9%. The authors noted that risk profiles for misuse may differ among patients with chronic opioid use. When considering misuse cases per 100,000 person-years in this insured patient cohort from the U.S., tramadol had the second-highest rate with 221.1 cases, following hydromorphone with 427.6 cases per 100,000 person-years. Mixed opioids had 339.7 misuse cases per 100,000 person-years. (Level of evidence 3. Appendix 1)

- Bicket et al.[50](2017) conducted a systematic review to identify studies on the over-supply of opioids prescribed to adults post surgery or procedures. They registered the study protocol with PROSPERO and searched the medical literature for cross-sectional and cohort studies and randomized controlled trials. The authors defined 'over-supply' as the "number of patients with either filled prescriptions with unused opioids or unfilled opioid prescriptions". They reviewed six articles, incorporating findings from a total of 810 patients. Of the patients who were prescribed opioids after surgery, the percentage of patients who did not fill their prescriptions ranged from 0% to 21%, while those who filled their prescriptions but reported unused opioids ranged from 7% to 14%. Secondary outcomes included the amount (number or volume) of unused opioids, the morphine-equivalents of unused opioids, reasons for non-use or discontinuation, and how opioids were stored or disposed of. Due to substantial differences across the studies, quantitative data pooling was not possible, so the authors conducted a qualitative review. They found that unused opioid rates were high for all seven surgical procedures studied, ranging from 67% to 92%. The authors concluded that "the majority of patients undergoing surgery in these studies had unused prescription opioids, while safe storage and disposal of unused medicines rarely occurred." They emphasized the need for increased efforts to develop and disseminate best practices to reduce opioid over-supply after surgery, especially since opioids prescribed by clinicians are often diverted for non-medical use. (Level of evidence 1. Appendix 1)

- In addition to the aforementioned studies published in peer-reviewed journals, three important reports are worth highlighting:
  - Morbidity and Mortality Weekly Report (MMWR) Vol. 66 / No. 10 March 17, 2017 — Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use - United States, 2006-2015 (Shah A. et al. 2017)[55] The summary of the report read: "In a representative sample of opioid naïve, cancer-free adults who received a prescription for opioid pain relievers, the likelihood of chronic opioid use increased with each additional day of medication supplied starting with the third day, with the sharpest increases in chronic opioid use observed after the fifth and thirty-first day on therapy, a second prescription or refill, 700 morphine milligram equivalents cumulative dose, and an initial 10- or 30-day supply. The highest probability of continued opioid use at 1 and 3 years was observed among patients who started on a long-acting opioid followed by patients who started on tramadol." The authors also stated, "approximately 10% of patients were prescribed tramadol, which might indicate intentional chronic opioid prescribing."
  - The Therapeutics Letter 131, 2021. Therapeutics Initiative / UBC — Tramadol. Where do we go from here? (Perry T, 2021).[54]

The conclusions from this report were: "- Compared with acetaminophen, NSAIDs or other opioids, tramadol has no therapeutic advantage but some disadvantages. -Tramadol's unpredictable metabolism and complex pharmacology are associated with unique and serious adverse effects. -As with other opioids, even short prescriptions for tramadol can engender tolerance, dependence, withdrawal, and abuse. -Tramadol (+/- acetaminophen) significantly increases costs to patients and insurers."

- Canadian Agency for Drugs and Technologies in Health (CADTH) Rapid Response Report — Tramadol for the Management of Pain in Adult Patients: A Review of Clinical Effectiveness - An Update (Chen S, Argáez C., 2018).[53]
  The authors concluded: "Systematic reviews and individual RCTs suggest greater pain reduction and more adverse events with tramadol and tramadol combination products compared with placebo, however the differences were not always statistically significant. Network meta-analysis between tramadol and other active treatments for pain relief suggests similar efficacy between tramadol and NSAIDs, acetaminophen and other opioids." "However, the quality of these trials may have been compromised due to small sample sizes, lack of rigorous statistical analyses and short study duration. The generalizability of the findings may be limited to Canadian population."

<u>Excluded studies mentioned</u>

- Lösch et al.[23] (2022) were concerned with the increase in the number of opioid-related adverse drug reaction (ADR) reports submitted to the Netherlands Pharmacovigilance Centre Lareb database, notably since 2014/2015. To investigate the ADR patterns for opioids, they analyzed the reports submitted to the Lareb Database between 1991 and December 2020. During that period, the pharmacovigilance database included 3,069 unique reports, either directly submitted by patients or healthcare professionals using the online reporting form or indirectly received via the Marketing Authorization Holder (MAH), i.e., the drug company. The majority of the information in the Lareb database was structured and coded according to the Medical Dictionary for Regulatory Activities (MedDRA). However, there was also a large amount of unstructured or semi-structured information in the database, which was not utilized for analysis. The authors aimed to utilize this information and employed an automated text analysis method, Structural Topic Modelling (STM), to uncover drug safety/adverse event-related information. Using STM, the authors detected patterns of themes and groupings in the reports, which helped them identify potential drug safety issues for opioids. The number of relevant topics identified in the reports submitted directly by patients and healthcare professionals was 11, and the number of topics identified through MAH reports was 12. The topics relating to tramadol, detected through the patients' and healthcare professionals' direct reports, were included in the results table. For example, under the 'Topics in both MAH and direct Report' section of the table, it was stated that "ADRs related to the use of tramadol with paracetamol, specifically changes in the international normalized ratio (INR) and drug interactions are mentioned in the MAH reports and a dry mouth and sweating in the direct reports". In the 'Topics in direct reports only' section of the table, it was stated: "Timing of intake and occurrence of ADRs for tramadol and paracetamol, for example, 'This side effect also occurs at night when a tablet is taken for the night". Another statement included in this section was "Nausea; sometimes described in combination with other ADRs such as

migraines, dizziness and vomiting. Mostly occurs with tramadol, for pain relief diclofenac was sometimes given". The authors concluded that Structural Topic Modelling, as an innovative approach, can be helpful in analyzing and utilizing substantial amounts of unstructured text data available on adverse drug reactions in the narrative reports submitted to a pharmacovigilance database.

- A conference abstract by Bannuru et al.[3] (2020) is worth mentioning. In this study, the authors investigated post-marketing data from the FDA Adverse Event Reporting System (FAERS) for analgesics used in osteoarthritis pain. Serious adverse events (AEs) were defined as death, life-threatening AEs, hospitalization, disability and/or permanent damage (or AEs requiring intervention to prevent these events), as well as congenital anomalies and birth defects. Among all adverse events observed with acetaminophen, the percentage of serious AE was 55.7% (83/149). The same percentage was 63.8% (598/938) for Drug Enforcement Administration (DEA) class II/III opioids, 75.4% (5,371/7,128) for NSAIDs, and 90.5% (268/296) for tramadol. The authors acknowledged the lack of control groups in their study, the possibility of confounding with other medications, and called for further studies on the AEs they had included.
- Another study worth mentioning is a case report by Bynum et al.[7] (2005), which aimed to document concentrations of tramadol, amitriptyline, and their metabolites after a multidrug overdose death. The enzyme Cytochrome P450 2D6 is responsible for the metabolism of tramadol and also participates in the metabolism of other compounds, including amitriptyline. The authors stated, "The presence of amitriptyline, which is a substrate for 2D6, may result in competitive inhibition of the isoenzyme thus disallowing it to fully bind to tramadol resulting in incomplete metabolism and high parent drug concentrations". The authors found that, in this case of multidrug overdose death, central blood and other tissue levels of tramadol were remarkably high, whereas the concentrations of amitriptyline were as expected.
- One relevant report was identified through the Cochrane Clinical Answers database. Ciapponi[10] (2019) reviewed and summarized, including forest plots of each outcome, the Cochrane systematic review by Toupin April et al. titled "Tramadol for Osteoarthritis". [This study was one of the studies selected for full-text review in our report]. The key point highlighted by Ciapponi was: "For people with knee or hip osteoarthritis, tramadol was slightly less effective than non-steroidal anti-inflammatory drugs (NSAIDs) regarding pain, physical function, and adverse events. Compared with other opioids, tramadol slightly improved physical function but resulted in little to no difference in pain and increased withdrawals due to adverse events."
- In 2017, Duehmke et al.[13] updated a 2006 Cochrane review to study the efficacy of tramadol and its associated adverse effects in chronic neuropathic pain. They compared tramadol with placebo or other active treatments in adult patients suffering from neuropathic pain for at least three months. However, the six studies they selected included patients with cancer and experiencing neuropathic pain due to cancer and cancer treatment. Hence, we excluded this study. Nevertheless, based on the three studies available for data pooling, they found tramadol to be effective in reducing pain intensity by 50% (RR: 2.2), but associated with higher adverse events (RR: 1.6) and higher 'adverse event withdrawal' rates (RR: 4.1) compared to placebo. The authors stated that the studies were mostly inadequate, with small sample sizes and a potential risk of bias and concluded: "Evidence of benefit from tramadol was of low or very low quality, meaning that it does not provide a reliable indication of the likely effect, and the likelihood is very high that the effect will be substantially different from the estimate in this systematic review".

- Yoshizawa et al.[38] published the results from a 12-week observation period of a post-marketing survey in Japan, in 2015. The data on tramadol hydrochloride and acetaminophen (TA) combination used for patients suffering from non-cancer pain and not responding to non-opioid drugs was collected through a multicenter (204 institutions), prospective, longitudinal registry that was set up for a 52-week follow-up period. Information on socio-demographics, treatment information, incidence of adverse drug reactions (ADRs), numerical rating scale for intensity of pain, EuroQol-5D (EQ-5D) scale, and physician's global impression (PGI) were collected. Initially, 1,316 patients who were prescribed tramadol hydrochloride 37.5 mg/acetaminophen 325 mg orally (one tablet four times a day) registered for the survey. After exclusions, the dataset for safety was down to 1,262 and for efficacy down to 1,063. The diagnoses included musculoskeletal pain, such as lumbago, osteoarthritis, spinal stenosis, and neck, shoulder, and arm syndrome, and post-herpetic neuralgia. The study was initiated due to the increased use of TA in Japan, and the anticipated increase in concerning adverse drug reactions (ADRs) typical to opioid use (e.g., respiratory depression, constipation, nausea, vomiting, and sleepiness, and the risk of drug dependence and/or abuse). Out of the studied patients, 47.1% had at least one concomitant disease and 84.7% were using a concurrent medication, of which 63.8% was other analgesics. Adverse drug reactions (ADRs) were seen in 20.5%, and serious ADRs were seen in 0.6% of the patients. The patients taking concurrent medication encountered ADRs more than the patients on TA therapy alone (22.6% versus 8.8%). Gastrointestinal disorders were the most common ADRs (14.3%), followed by nervous system disorders (4.9%). The patients who previously used analgesic medication experienced ADRs more often. This descriptive study had no control group, and the clinical effectiveness of TA was measured by physician- and patient-reported parameters (e.g., physician's global impression (PGI)). The authors noted the insufficiency of the 12-week period to evaluate opioid dependency (including withdrawal symptoms) in patients with chronic non-cancer pain. They also underlined that "manageable, expected, nonserious ADRs and AEs" were underreported in surveys compared to clinical trials. However, their overall conclusion was favorable for use of TA in chronic non-cancer patients who were unresponsive to non-opioid drugs for pain treatment. One important concern for this study is the pharmaceutical sponsorship of the survey registry, as well as the full-time employment of the authors in the related pharmaceutical company.
- A comprehensive narrative review/expert opinion article on tramadol and acetaminophen combination (T/A) for chronic non-cancer pain, by Farquhar-Smith and Gubbay,[14] was published in 2013. The authors explained the pharmacodynamics and pharmacokinetics of both tramadol and acetaminophen and mentioned the two brands available: Tramacet® and Ultracet®. Then, they explored the clinical efficacy of this combination medication in specific types of chronic non-cancer pain (e.g., chronic low back pain, fibromyalgia, osteoarthritis, ankylosing spondylitis, rheumatoid arthritis, and diabetic neuropathy). Even though the existing studies displayed statistically significant results, most of the time, the magnitude of the analgesic effect was modest when compared to the effect in control group. The clinical significance (the improvement of 2 points on a 0-10 scale) was achieved only in a few studies. There was no consistency across studies in reporting adverse events, and particularly, long-term adverse events data was missing. Up to 20% of the study subjects did not continue the treatment due to adverse effects. Since the duration of the studies was short, no information was available on long-term side effects (whereas this had been shown in studies with other opioids). The authors noted that data comparing

efficacy and adverse effects of T/A with similar medications used in chronic non-cancer pain were lacking. This was the case when T/A was compared to codeine/acetaminophen. The only two studies they found compared T/A with a codeine and acetaminophen combination in treating chronic low back pain and did not demonstrate strong efficacy or favourable adverse effect profile for the T/A group. The authors also stated that when used in chronic pain, T/A was not explicitly advantageous in comparison to tramadol or acetaminophen monotherapies.

- Inciardi et al.[19] (2006) published a short narrative report to communicate the level of diversion for Ultram®, Ultracet®, and generic Tramadol HCl, in public settings. This study was sponsored by Ortho-McNeil Pharmaceutical (OMP) which produced Ultram® and the authors were paid consultants to the company. An independent steering committee began to monitor the abuse of Ultram via a comprehensive risk-management program, which they developed and implemented, and was funded by OMP. The mandate of the steering committee was extended to include monitoring the tramadol/acetaminophen combination product Ultracet (2001), the generic tramadol (2002), and to undertake a quarterly survey on the diversion of these tramadol products. They surveyed 102 drug diversion investigators from police agencies in 50 states quarterly. There is no information about the selection of these investigators; however, it was stated that they (or their agencies) were paid. They collected data on the total number of prescription drug diversion investigations, the numbers on Ultram, and the top 10 diverted drugs (including the number of cases for each and street prices for each). The authors reported that the investigations mentioned hydrocodone, benzodiazepines, and oxycodone more often (40.1%, 27.9%, and 20.2%, respectively), while tramadol products (Ultram, Ultracet, and generics) were mentioned in only 1.5% of the investigations. The authors concluded that "the diversion of tramadol is very limited in comparison to other opioid pain relievers". However, they also acknowledged the limitations of their study, referring to the limited number of agencies participating in the diversion survey and underreporting of the studied drugs, prioritization of monitoring other criminal activities by the involved agencies, and the agency dropouts from the quarterly surveys.
- One other study not included in this review is the surveillance report by Cicero et al.[11] (2005). This surveillance report (as also explained in the Inciardi et al.'s paper) tracked the change in the abuse and diversion rates of tramadol after the introduction of cheaper generic tramadol (2002) and the tramadol/acetaminophen combination (2001) which increased tramadol use in acute pain. The surveillance was initiated in 1995 as a risk-management program by Ortho-McNeil Pharmaceutical (OMP) (the company producing Ultram®) and was approved by the FDA and overseen by an independent steering committee (ISC). Although the composition of the ISC is not fully explained in their report, the authors indicated that a questionnaire, acquired by the ISC, was distributed quarterly to a network of 309 experts and 100 police agencies to collect data on the diversion of Ultram, Ultracet, and generic tramadol. It is unclear how these key informants/experts were selected. At the end of their study, the authors reported that the "introduction of generic tramadol had no effect on abuse or withdrawal rates", and "tramadol products were diverted much less frequently" compared to other diverted pain medications. Nonetheless, the authors mentioned the limitations of this surveillance program, such as the "anecdotal nature of the information provided", the "uncertainty about the actual number of cases or rate of abuse and withdrawal of branded, generic tramadol, and tramadol/acetaminophen", and possible underestimation of tramadol diversion due to its "non-scheduled drug

situation, the possession of which may not lead to an arrest in some jurisdictions". It should be noted that this study was not only sponsored by the pharmaceutical company OMP, but the authors were also paid as consultants to the company.

Summary

- Currently, studies specifically focusing on the efficacy/effectiveness and safety of tramadol and acetaminophen combination are scarce.
- Most of the currently available studies focus on the efficacy/effectiveness of 'tramadol alone' compared to placebo and/or other analgesics, with few including safety outcomes.
- Rarely, if a statistically significant analgesic effect (improvement in pain outcomes) is observed with tramadol in an efficacy/effectiveness study, this treatment effect is at most modest when compared to the effect in the control group.
- Current available studies are insufficient to determine whether any observed clinical effectiveness of tramadol (typically defined as an improvement of 2 points on a 0-10 scale) would decrease when used for longer periods.
- The safety studies on tramadol typically come from the early marketing years, funded by the pharmaceutical industry, and peaked in the late 90s and early 2000s. Many of these studies were methodologically flawed and lacked sufficient follow-up periods to ascertain drug safety beyond common adverse effects (e.g., nausea, vomiting, constipation, dizziness, headache) and withdrawals due to these effects. As a result, they often cited a lack of substantial serious adverse effects and a low risk of addiction for tramadol. However, newer studies refer to more serious adverse effects (e.g., hypoglycemia, seizure, hospitalization, disability/permanent damage, and all-cause mortality).
- Exploring clinical safety outcomes such as serious adverse effects, drug dependence, addiction, substance use disorder (SUD), overdose deaths, as well as social safety outcomes such as drug abuse and diversion requires studies with longer follow-up periods.
- When tramadol or tramadol/acetaminophen combination is compared to placebo or other active treatments, the follow-up periods range from four to 12 weeks, and very rarely exceed six months; hence, evidence on serious adverse effects of tramadol in the clinical management of chronic pain patients (especially with a specific focus on deaths, addiction, and SUDs) is inadequate.
- Based on the limited evidence regarding serious adverse effects with tramadol use for non-cancer pain, two conditions appeared to increase the likelihood of experiencing adverse drug reactions (ADRs): previous use of analgesic medication and taking other concurrent medications.
- Even though some evidence from high-level studies (e.g., systematic reviews, meta-analyses) supports the clinical effectiveness of tramadol or the tramadol/acetaminophen combination in treating non-cancer chronic pain compared to placebo, the quality of the primary studies informing these high-level studies is generally low. For example, short-term follow-ups, biases (e.g., selection, performance, and attrition biases), and confounding (including confounding by indication). Several of the reviewed studies attempted to address these shortcomings by using the propensity score approach, conducting stratified analyses, or acknowledging the issues through sensitivity and subgroup analyses.
- A number of studies included in this review (one study selected through the database search and four additional studies found through hand-searching) involved osteoarthritis patients. When tramadol alone or combined with acetaminophen statistically improved pain or function in osteoarthritis patients, the observed beneficial effect was not clinically significant.

- When compared to placebo, tramadol alone was less effective in reducing chronic back pain, but tramadol-acetaminophen combination was significantly more effective than placebo.
- Compared to other weak opioids, efficacy of tramadol for non-cancer pain was compatible. However, its safety profile measured by adverse effects, serious adverse effects, and withdrawals due to these adverse effects was unfavorable.
- Most of the included studies did not report on drug dependence, addiction, substance use disorder (SUD), and overdose deaths, likely due to short study follow-up periods.
- A few studies that compared tramadol to other analgesics with regard to relative toxicity and the risk of overdose and death found higher rates with tramadol. Withdrawals due to adverse effects were also higher with tramadol, with some studies reporting rates as high as 20% of the study subjects.
- In general, when compared to nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol was somewhat less effective in improving pain and physical function and led to more adverse events.
- When tramadol was compared to other opioids, it displayed a slightly improved physical function. However, little to no difference was observed in pain improvement. Additionally, withdrawals due to adverse events were increased.
- One major challenge in using tramadol for non-cancer pain is its unpredictable clinical effect on certain individuals. Based on substantial genetic variability in the population, one can be an ultrarapid or poor metabolizer of CYP2D6 (the enzyme required to metabolize tramadol into its principal metabolite, O-desmethyltramadol). Hence, depending on the individual's CYP2D6 phenotype, tramadol can lead to extreme or low opioid and serotonergic effects; either potentially reducing pain, or being ineffective, or even harmful. Considering this phenomenon, prescribing tramadol for the first time is challenging.
- Some studies suggest that, compared to other short-acting opioids, the risk of long-term opioid use is increased when the initial prescription is tramadol.
- Long-term tramadol use increases the risk of abuse, and better monitoring is recommended for individuals with a history of substance abuse, means of easy access (e.g., health professionals), and living with chronic pain.
- Since the pharmacokinetics of tramadol involves multiple mechanisms of action (μ-opioid receptor agonism and both serotonin and norepinephrine reuptake inhibition), stopping tramadol therapy abruptly may cause patients to suffer from both opioid and serotonin–norepinephrine reuptake inhibitor withdrawal syndromes.
- These multiple mechanisms of action in tramadol can also become problematic and lead to serotonin syndrome when tramadol is prescribed concurrently with other serotonergic medications.
- Recent literature on clinical efficacy/effectiveness/safety of tramadol includes observational studies (e.g., retrospective cohort studies) with potential confounders in the data. One technique used to control these potential confounders is propensity score matching. Despite this effort, study findings may be subject to residual confounding. Especially when comparing different clinical treatments (e.g., comparing tramadol with other analgesics, such as NASAIDs or other opioids) 'confounding by indication' becomes a problem. This means that the comorbidity burden of the patients who had tramadol as their initial prescription was higher compared to the burden of those whose initial prescription was a NSAID.

Conclusion

- The findings from this review on efficacy, effectiveness, and safety of tramadol and tramadol/acetaminophen combination for non-cancer pain remain mixed, and due to insufficient evidence, drawing conclusions on its use for longer than six weeks is difficult.

- Even if there is some evidence from high level studies (systematic reviews and meta-analyses), the findings from these studies should be interpreted with caution because the quality of primary studies was low and subject to various biases and confounding effects.
- The short follow-up duration of the primary studies impedes any inferences regarding an association between tramadol and serious adverse reactions, dependence, abuse, addiction, divergence, and overdose deaths. Any estimates of safety outcomes require long-term adverse events data, which was missing in most of the reviewed studies.
- Regarding the tramadol/acetaminophen combination, the evidence for the assumed beneficial synergistic effect between these two pharmaceutical substances is scarce.
- Tramadol is a Schedule I controlled substance in Canada, which includes "drugs and substances considered to be the most harmful and having a high potential for abuse." However, its status as a Schedule IV controlled substance in the U.S. leads prescribers to perceive tramadol as a relatively safe opioid with a low potential for abuse and dependence.

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Appendix 1

WorkSafeBC — Evidence-Based Practice Group levels of evidence (adapted from 1-6)

1	Experimental, randomized controlled trial (RCT), systematic review RTCs with or without meta-analysis.
2	Evidence from controlled trials without randomization (quasi-experimental studies) or systematic reviews of observational studies.
3	Evidence from cohort or case-control analytic studies, preferably from more than 1 centre or research group.
4	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments.
5	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees based on scientific evidence.

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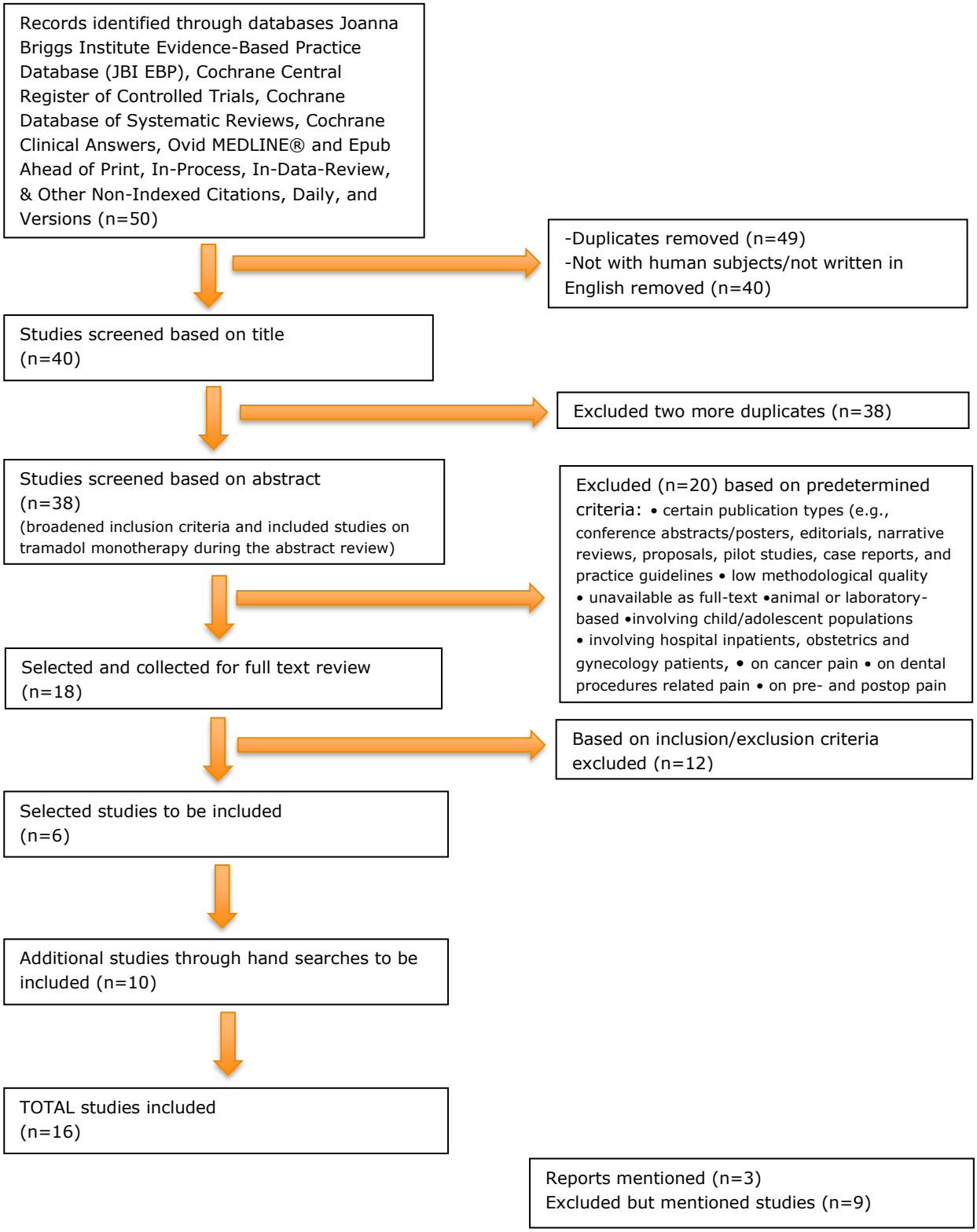
Appendix 2

Flow chart