"Safety and abuse potential of oral analgesic tramadol: a systematic review"

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Master of Family Medicine

Masterproef Huisartsgeneeskunde
Academiejaar: [2021– 2022]

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INDEX

1 ABSTRACT 5

2 INTRODUCTION 7

2.1 Background 7

2.2 Objective 8

3 MATERIALS AND METHODS 9

3.1 Literature search strategy 9

3.2 Selection criteria and process 9

3.3 Data Management 10

3.4 Study risk of bias assessment 11

3.5 Data synthesis 11

4 RESULTS 11

5 RESULTS: serious adverse events with tramadol use 13

5.1 Study selection 13

5.2 Study characteristics 13

5.2.1 Characteristics by study design 13

5.3 Risk of bias characteristics 14

5.4 Synthesis of results 14

5.4.1 Serious adverse events 14

5.4.2 Determinants 15

6 DISCUSSION: serious adverse events with tramadol use 19

6.1 Summary of results 19

6.2 Comparison of results to other studies 21

6.3 Strengths and limitations 21

6.4 Future recommendations 22

7 RESULTS: abuse, misuse, aberrant behaviour and chronic use of tramadol 23

7.1 Study selection 23

7.2 Study characteristics 23

7.3 Risk of bias 24
7.3.1 Healthcare databases 24
7.4 Synthesis of results 25
8 DISCUSSION: abuse, misuse, aberrant behaviour and chronic use of tramadol 31
8.1 Summary of results 31
8.2 Strengths and limitations 32
9 Conclusion 33
10 Acknowledgements 33
11 Conflict of interest & funding 33
12 Bibliography 34
13 Appendix 38
13.1 Full search strategy 38
13.2 Expanded outcomes: serious adverse events 38
13.3 Risk of bias assessment using Newcastle-Ottawa scale 38
13.4 Favourable advice ethical committee 38

1 ABSTRACT

ACHTERGROND: Er is een tekort aan data die de veronderstelde veiligheid en het lagere afhankelijkheidsrisico van tramadol ondersteunt. Er zijn aanwijzingen voor toenemend gebruik in België waardoor verder onderzoek naar het potentiële misbruik van tramadol aangewezen is. Het opzet van deze literatuurstudie bestaat uit het systematisch overzicht weer te geven van het veiligheidsprofiel en het verslavingspotentieel van tramadol in vergelijking met andere opioïden.

METHODE: Voor deze literatuurstudie werd gebruik gemaakt van Medline, Embase en Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled trials. Er werd geen tijdslimiet vooropgesteld. De inclusiecriteria bestonden uit 1) Vergelijkende studies waarbij tramadol vergeleken werd met een ander opioïd, 2) een volwassen bevolking met een minimum leeftijd van 18 jaar en 3) analgetisch tramadol gebruik per os. Er werden twee onderzoeksvragen opgesteld: Wat is het veiligheidsprofiel en wat is het verslavingspotentieel van tramadol? Het veiligheidsprofiel werd onderzocht op basis van ernstige neveneffecten zoals 1) ziekenhuisopname, 2) overdosis, 3) sterfte en 4) respiratoire depressie. Voor het verslavingspotentieel werd er geen strikte definitie gebruikt. Zowel wangebruik, misbruik en afwijkend gedrag werden aanvaard. Naast het verslavingspotentieel werd er ook aandacht besteed aan het risico op chronisch gebruik. Determinanten die beide onderzoeksvragen in de hand zouden kunnen werken werden onderzocht. Om de kwaliteit van de studies te beoordelen, werd er gebruik gemaakt van de Newcastle Ottawa scale (NOS). Om de data te vergelijken werd gebruik gemaakt van een descriptieve analyse.

RESULTATEN: In totaal werden 17 studies geïncludeerd die aan de inclusiecriteria voldeden. Voor de uitkomst ziekenhuisopname door tramadol was er een grote variatie van de resultaten gaande van 3.6% tot 93.6%, wat vergelijkbaar was met andere opioïden (3.1 – 98.6%). Resultaten voor overdosis werden gepresenteerd als twee verschillende verhoudingen (0.34 overdosis per 100 000g afgeleverd medicijn en 0.015 overdosis per 100 000mg orale morfine equivalenten (OME)). Sterfte werd geregistreerd bij 0.1% en 1.5% voor andere opioïden in vergelijking met 0.1%-0.3% voor tramadol. Respiratoire depressie werd gezien bij 1.6% van de studiepopulatie voor tramadol en 8.8% voor tapentadol. Het wangebruik werd in twee artikelen weergegeven als vaker voorkomend bij tramadol in vergelijking met andere opioïden (5.6%, 23.78% en 22.90%). Het misbruik van tramadol werd omschreven als minder dan het misbruik van hydrocodon (2.7% vs. 4.9%, $P < 0.01$) en codeïne (15.90% vs. 40.9%). tramadol was significant geassocieerd met een verminderd risico op afwijkend gedrag (OR 0.06 – 0.38; $P < 0.05$). Het risico op chronisch gebruik was in vijf van de zes artikelen groter bij de inname van tramadol in vergelijking met de andere opioïden ((ARR 1.06, 95% CI (1.00-1.13); p= 0.049, 4.2%, 11%, 48.71%, 43.43%, OR 1.23, 95% CI (1.13-1.35)).

CONCLUSIE: Op basis van deze resultaten lijken ernstige nevenwerkingen niet meer voor te komen dan bij andere opioïden. Er is echter onvoldoende data om met zekerheid te stellen dat ze minder voorkomen. Verder suggereren onze resultaten dat de algemene perceptie van het lage risico op misbruik van tramadol moet heroverwogen worden. Verder vergelijkend onderzoek en statistische analyse met gebruik van uniforme, welomschreven uitkomsten is vereist om het veiligheidsprofiel en risico op misbruik van tramadol in kaart te brengen. Op deze manier zou in de toekomst een klinische richtlijn voor huisartsen tot stand kunnen komen.

BACKGROUND: There is a shortage of data supporting the presumed safety and lower dependence risk concerning tramadol. There is also an indication for growing usage in Belgium wherefore further evaluation of the potential misuse of tramadol seems necessary. In this systematic review an attempt was made to provide an overview of the existing literature regarding the safety profile and the abuse potential of tramadol and its position compared to other opioids.

METHOD: A literature search strategy was conducted without limitation in time using Medline and Embase as well as the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled trials. The following inclusion criteria were applied: 1) comparative study design in which another opioid is compared, 2) adult population defined as age above 18 years, 3) use of oral opioids for analgesic purpose only. The outcomes to assess the safety profile of tramadol were defined as 1) hospital admission, 2) overdose, 3) death or 4) respiratory depression. To determine the abuse potential of tramadol no stringent definition was wielded: misuse, abuse as well as aberrant behaviour were accepted. The determinants that could facilitate serious events and chronicity were assessed for both review questions. The Newcastle Ottawa Scale (NOS) was applied in order to study the risk of bias. For comparison of the data a descriptive analysis was made.

RESULTS: 17 studies were included in total. The range for hospital admission regarding tramadol was stated between 3.6 and 93.6% compared to other opioids (3.1% and 98.3%). Results for overdose were presented as two different rates in two articles (0.34 overdoses per 100 000g drug dispensed and 0.015 overdoses per 100 000mg oral morphine equivalents (OME)). The range for death was reported between 0.1% and 1.5% for other opioids, compared to 0.1% to 0.3% for tramadol. Respiratory depression was registered as 1.6% for tramadol compared to 8.8% for tapentadol by one article. tramadol was described in two articles as more contributing for misuse in comparison with other opioids. (5.6%, 23.87% and 22.90%) The abuse potential was stated as lower for tramadol in comparison to hydrocodone (2.7% vs 4.9%, P <0.01) and codeine (15.9% vs 40.9%) Aberrant behaviour was associated with significantly reduced odds compared to the other opioids. (OR 0.06 – 0.38; P < 0.05). tramadol was found to comprise a greater risk of evolving into chronic use compared to other opioids in five of the six articles (ARR 1.06, 95% CI (1.00-1.13); p= 0.049, 4.2%, 11%, 48.71%, 43.43%, OR 1.23, 95% CI (1.13-1.35)).

CONCLUSION: Serious adverse events did not seem to occur more in tramadol compared to other opioids, but there is insufficient data to state that they occur less. Furthermore our results suggest that the overall perception of the low abuse potential of tramadol should be reconsidered. Further comparative clinical studies and statistical research with more uniform data should be conducted to assess the safety profile and abuse potential of tramadol. In this way a clinical guideline could be achieved for the general practitioner (GP) in the future.

2 INTRODUCTION

2.1 Background

Tramadol is a weak agonist of the μ-opioid receptor, categorized level two on the World Health Organization cancer pain treatment ladder.[1] It is being used for mild to moderate pain and is structurally equal to morphine and codeine, although their mechanisms of action are somewhat different.[2] Its low affinity for the μ-opioid receptor was initially thought to be more beneficial when it comes to side-effects, for instance less constipation, less respiratory depression, fewer cases of overdoses and lower chance of addiction.[3] The last couple of years there has been a strong rise in tramadol usage, which caused it to be one of the most prescribed opioids in the US.[4, 5] Tramadol is now frequently used in treating acute postoperative pain, as an alternative for strong μ-opioid receptor agonists (when there is an apprehension for misuse).[6]

The long-term use of opioids is associated with numerous side-effects, including the possibility to develop tolerance, dependence and misuse.[7] In response to the recent increase in usage of opioids especially in the US - their role in chronic pain was examined, both nationally and internationally. In the US in 2016, on average 115 people died on a daily basis in circumstances related to opioid usage.[8] In spite of the evolving knowledge of health care professionals and the general population, and an economic cost of 504 billion US dollars in 2015 (including healthcare costs, lost earnings from employment and higher costs to the criminal justice system), ratings of prescribed opioids in the US did not decrease.[9] Regular investigations commissioned by the RIZIV in Belgium led to the discovery that more often than not, a prescription of these drugs was issued without medical justification.[10] Adding to that, these investigations found the number of these prescriptions to be very high. Although the situation overseas is not the same as in Belgium, there is still reason for concern due to the overall growth and non-medical justification for usage in this country, in which youngsters also have a fair share.[10] The use of tramadol has more than doubled in Belgium between 2006 and 2017, where it is currently the most used opioid, from 20.550.181 DDD (defined daily dose) to 43.930.499 DDD.[11] Besides, Belgium is the number five leading country of opioid consumption worldwide per million inhabitants. Although the use of opioids in the regions with highest consumption remains clearly dominant, there seems to be a trend of stagnation or even decline in North America, West and Central Europe, and Oceania over the last ten years. An upward trend could however be seen in South-Eastern Europe, South America, South Asia and Eastern Europe.[12]

Historically, tramadol was already prescribed in Europe for over 20 years before appearing in the US market. Back then, there was little evidence for potential misuse, and initial epidemiological studies also indicated a low share of misuse compared to stronger opioids (e.g. oxycodone).[3, 13] Nowadays, the potential risk concerning misuse and abuse of tramadol has been repeatedly questioned. [14] Recent investigations show that the risk of abuse regarding oral administration has been underestimated for a long time, as earlier studies kept focusing on parenteral dosages.[15] Since the supply of the opioid-agonist depends on liver metabolism, these concentrations are much higher after oral administration compared to parenteral use, causing the agonistic effects to be larger when given orally.[15] These effects were also seen in lighter users with therapeutic doses.[16]

There is a shortage of data supporting the presumed safety and lower dependence risk concerning tramadol. Due to the dramatic increase in prescribed opioid misuse and overdose in the US together

with indications for growing usage in Belgium, further evaluation of the potential misuse of tramadol seems necessary. It is also important to expand our knowledge of the safety risks associated with atypical opioids, to estimate the need for renewed vigilance regarding these drugs, which have long been thought to be relatively safe.[17]

2.2 Objective

Based on the observations above, we focus on two research questions:

1. In the general adult population, what is the safety profile of analgesic orally administered tramadol use regarding death, hospital admission, overdose and respiratory depression compared to other opioids?

2. Within the same population, compared to other opioids, what is the abuse potential of analgesic orally administered tramadol use? Hereby, we focus on and assess the determinants that could facilitate chronicity such as sex, age, comorbidities, or duration of usage.

3 MATERIALS AND METHODS

3.1 Literature search strategy

This systematic review was registered at PROSPERO (CRD42021198801). A search was conducted by two independent groups of two reviewers for each research question. In June 2020 a search was conducted in MEDLINE (using PubMed) and Embase as well as in the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled trials. Tramadol, tramundin and K-315 were used as title and abstract search terms **(see Appendix 13.1 for full search strategy)**. An additional Medical Subjects Headings (Mesh) was applied to PubMed for tramadol. Clinical Trials.gov. was scanned with tramadol as search term and a filter was applied to only select subjects older than 18 years. Micromedex and Equator were searched for additional grey literature to supplement extra data for the first research question the safety of tramadol. Conference abstracts eligible for inclusion in the systematic review were searched in later publication or if not available the author was written to through ResearchGate. A new search of the above-mentioned databases was completed at the end of December 2021 in order to find additional articles.

3.2 Selection criteria and process

The databases were searched without limitation in time. Results of the search were reviewed based on title and abstract by two independent groups of two reviewers for each research question. If there was any disagreement that couldn't be resolved between two reviewers a decision was made in consultation with the other group of two independent reviewers.

The full text review was done between October 2021 and December 2021. The following three inclusion criteria were applied **(See box 1)**: Firstly, only comparative study designs in which other opioids were compared with tramadol. All clinical used opioids were defined as 'other opioid' for comparison with tramadol, regardless of their strength or place on the WHO pain treatment ladder. Combination drugs with tramadol e.g. tramadol/paracetamol were enrolled with the tramadol group. Secondly, the search was limited to an adult population defined as aged above 18 years. Lastly, use of oral opioids for analgesic purpose only were included.

Exclusion criteria were a population of more than fifty percent (ex-)addicts, cancer or palliative patients, children or adolescents less than 18 years old, case reports, in vitro, animal or pharmacokinetics/pharmacogenomics studies, parenteral drug administration, opioid use for other reasons than analgesia, comparative studies which only compared tramadol uniquely with a placebo or with non-opioid drugs e.g., paracetamol or non-steroidal anti-inflammatory (NSAID) drug and studies using only single dose ingestion.

The outcomes to assess the safety profile of tramadol were defined as hospital admission, overdose, death or respiratory depression. Overdose was defined as the use of any drug in such an amount that acute adverse physical or mental effects are produced.[18] To determine the abuse potential of tramadol no stringent definition was wielded: misuse, abuse as well as aberrant behaviour were accepted. Misuse was interpreted as every use that does not conform to the prescription. For the definition of abuse various interpretations were accepted such as DSM-IV, DSM-V and every definition implemented in ICD-10. Nevertheless, any other term used in a particular study was

defined and categorized. Aberrant behaviour was defined as medical shopping, fulfilling early prescriptions, or obtaining prescriptions illegally. To obtain the determinants that could facilitate chronicity, the latter was defined as usage of more or equal to 90 days whit the first prescription counting as the index day. **(See box 1)**

Box 1. Tramadol serious adverse events and abuse potential (systematic review): inclusion criteria for literature

- Time period:
  - No limitation
- Comparative study design
  - Other opioids in comparison with tramadol
    - Combination drug with tramadol covered by tramadol group
    - Other opioid covered by all clinical used opioids regardless of strength of place on the WHO pain treatment ladder
- Adult population
  - Above 18 years
- Oral opioids for analgesic use only
- Outcome
  - Serious adverse events
    - Hospital admission
    - Overdose
    - Death
    - Respiratory depression
  - The abuse potential
    - Misuse
      - Every use not conform prescription
    - Abuse
      - DSM-IV
      - DSM-V
      - ICD-10
      - Any other term wielded by particular study
    - Aberrant behaviour
      - Medical shopping
      - Fulfilling early prescription
      - Illegal market
    - Chronicity
      - Long term opioid user ≥ 90 days

3.3 Data Management

For each research question the following data were extracted manually by two independent groups of two reviewers: the characteristics of the study, determinants of study population and outcome. The following characteristics of the study were extracted: title, year of publication, country of origin, study duration, study design and definition of outcome. The determinants of study population were defined as mean dose (MME), length of use (days), mean age (years), gender, presence of back pain, psychiatric comorbidities, substance abuse and education or employment level.

For both research questions the subsequent outcome data were extracted. The first research question made a distinction between number of patients per opioid, and the events of hospital admission, major medical effect, death, overdose, respiratory depression and/or all-cause mortality.

The studies were here subdivided through type of study. For the second objective the number of patients per opioid and data of misuse, abuse, aberrant behaviour and/or chronic use were retained.

3.4 Study risk of bias assessment

The Newcastle Ottawa Scale (NOS) was applied in order to study the quality of the included literature. A star was rewarded for each item that matched the corresponding assessment within the selection, comparability and outcome categories **(See appendix table 3).** In order to assess the representativeness in the selection category a truly representative of the average population was described as an opioid naïve patient wherefore opioids are prescribed for analgesic use only. People undergoing surgery were determined as a selected group of users. To assess the comparability in the quality assessment for cohort studies the following factors were determined: age and gender for the first above mentioned research question and a history of drug and or alcohol abuse and gender for the second research question. The follow-up for outcomes to occur was considered long enough as a follow-up of minimum ninety days according to our definition of chronic use. The adequacy of follow-up was accepted as a maximum loss of follow-up of maximum twenty percent.[19] A score chart was made to define the quality of the individual studies. This was based on consensus as no standardised chart for interpreting risk of bias (ROB) was found. If the individual study was given zero to three stars it was considered high ROB. Four to six stars and seven to nine stars were perceived as respectively intermediate and low ROB.

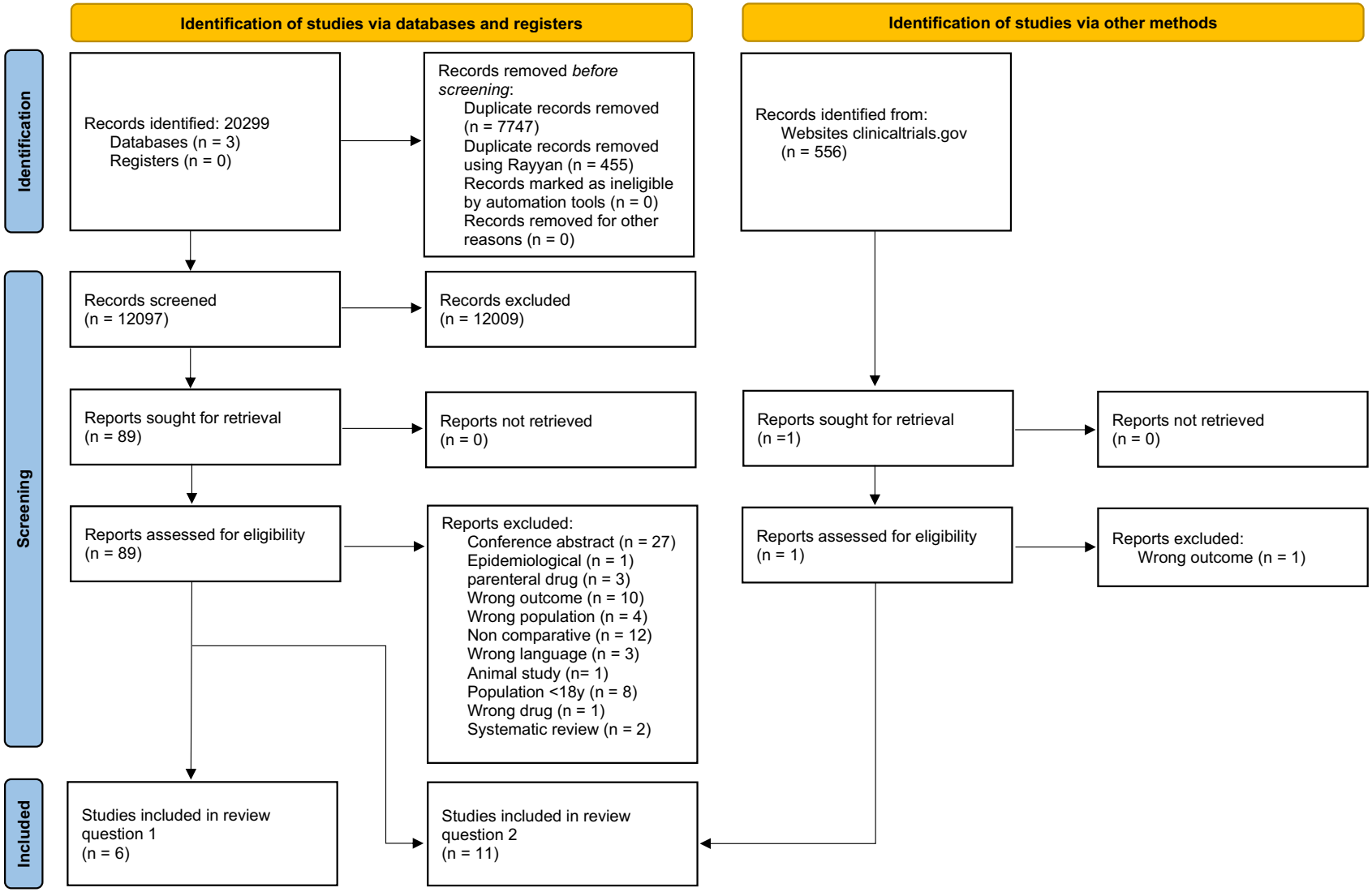
3.5 Data synthesis

The extracted data was subdivided in the result section and figures for both research questions to make the results more comparable. The subdivision for the first objective was displayed based on whether the data was derived from healthcare databases or whether it was derived from structured interviews and/or reported serious adverse effects. For the second objective the result section was displayed per outcome that was reported in the study. The wide variety of the results was noted while extracting the data. A descriptive analysis was chosen instead of statistical analysis because of excessive heterogeneity. The number of studies per outcome was specified and the results were registered per study. If possible, the significant results were reported. The number of studies with a trend favouring tramadol in comparison to the other opioids were described.

4 RESULTS

In June 2020 the databases were searched and 17854 articles were identified. End of December 2021 a new search was completed which resulted in 2445 additional articles. A total of 20299 articles were narrowed down to 12552 after omitting duplicates with Endnote. 455 remaining duplicates were additionally erased manually. 12097 articles remained to be screened based on title and abstract. 89 articles were sought for full literature review. 18 articles for research question one and 71 articles for research question 2. **(See figure 1)**

figure 1. Prisma flow diagram



5 RESULTS: serious adverse events with tramadol use

5.1 Study selection

For the first review question 18 articles were sought and assessed for their eligibility. Of these, 12 were excluded because they did not meet the inclusion criteria or no data could be retrieved. Seven were excluded because they were conference abstracts from which no useful data could be retrieved. One was excluded because it used parenteral IV drugs. Another was excluded because it was an epidemiological study. Three were excluded because of the wrong outcome. Six articles were preserved and included in this review.

5.2 Study characteristics

All included articles were published after 2015, three of which were published in 2021.The mean duration of study was 8.6 years. In none of the articles, the mean dose of the opioid used was available. Length of opioid use was registered in half of the studies for which the registered use varied between 30 and 180 days.

A wide variety of opioids were used in the included articles. The opioids mentioned were tramadol, tapentadol, hydrocodone, codeine, oxycodone, oxycodone-naloxone, oxymorphone, propoxyphene, morphine, methadone, buprenorphine, hydromorphone and fentanyl. Two studies compared tramadol only with one other opioid.[20, 21] One compared tramadol only with tapentadol and one compared only with codeine. One compared tramadol not with individual opioids but only with opioid groups in which weak opioids like codeine were in the same group as stronger opioids.[22]

5.2.1 Characteristics by study design

All studies were retrospective cohort studies using database data, no relevant clinical trials were found. Three studies were based on data from healthcare databases and the other three were based on serious adverse effects reported directly to healthcare professionals. The latter were reported either to poison control centers (PCC) or an emergency department. We decided to group the included studies in table 1.2 and 1.3 with a subdivision to make our results easier to compare.

Direct report to healthcare professional

In three studies, serious adverse effects were reported directly to a healthcare professional. **(See table 1.2 and 1.3, upper half)** Two used the same database of calls to US PCC's.[20, 23] Patients and healthcare professionals can contact PCC's by phone with questions regarding poisonings. PCC specialists then give advice and systematically register characteristics of each case which are entered in a database. There is no physical contact with the patient and the PCC specialist.
The third study used medical records of emergency department presentations in a hospital in Australia. Supply data of pharmaceutical opioids and the emergency department rates were used by Lam et al. to calculate the supply adjusted rates of overdose per 100 000mg oral morphine equivalents (OME) per opioid per year.[24] One study presented results as supply adjusted rates per 100 000g drug dispensed nationwide.[23]

Healthcare database

Healthcare databases were used in tree studies to investigate adverse events in opioids. **(See table 1.2 and 1.3, lower half)** Data from Medicare, an insurance plan for older adults, aged 65+ in the USA, were used by two studies. One used data from 50 US states[22] the other used Medicare data from only two states.[25] A database that includes information from 700 practices of general practitioners in the UK was used by a third study.[21] In these studies patients did not have direct contact with researchers or healthcare professionals. The researchers obtained the data indirectly by analysing statistical health data, recorded in these databases.

5.3 Risk of bias characteristics

Four studies were scored to have a low risk of bias[21, 22, 24, 25] and two were scored with a high risk of bias.[20, 23] The individual scores on the Newcastle-Ottawa scale are presented in **table 3 in the appendix.**

5.4 Synthesis of results

5.4.1 Serious adverse events

Death was registered in four studies.[20, 21, 23, 25] Of the opioids studied, overall less than 1% resulted in death. Across studies the rates of death were in the same range in terms of percentage and varied between 0.1% and 1.5% for other opioids compared to 0.1% to 0.3% for tramadol. **(See appendix table 1.4 for absolute numbers and percentages)**

Hospital admission was reported by four studies.[22-25] In one study hospitalisations were not a direct result of opioid use but rather a sum of multiple emergency room visits, cardiovascular disease hospitalisations, injurious falls/hip fracture, pneumonia, respiratory distress and serotonin syndrome. [22] Rates of mean hospitalisation varied widely across studies, from 3.5% to 96%. **(See appendix table 1.4)** Rates for individual opioids ranged between 3.1% and 98.3%. The range for tramadol was between 3.6 and 93.6%. If we compared tramadol with other opioids within individual studies, it was neither in the high nor in the low range of hospitalisation rates. In two studies, tramadol was slightly above the mean rate, in two others it was slightly below, in all cases never deviating more than 3.7% from the average rate.

Data for overdose were found in two studies. In one study we used a substitute parameter: the sum of hospital admission, death and major medical effect (defined as serious adverse event in the original article).[23] In this study tramadol was responsible for the second to last rate namely 0.34 overdoses per 100 000g drug dispensed. For the second study all emergency department visits for opioids were classified as overdoses. Here, tramadol was responsible for the third highest rate of 0.015 overdoses per 100 000mg OME.

For respiratory depression, only one study made a direct comparison between tramadol and another opioid.[20] This study registered adverse events for tramadol and tapentadol through calls to PCC's. Significantly less respiratory depression was registered by these PCC's in tramadol (1.6%) than tapentadol (8.8%) (RR 5.56, P<0.001)

5.4.2 Determinants

More women were presenting with serious adverse events after opioid use except in one study.[23] For our determinants of interest chronic back pain, abuse and psychiatric comorbidity almost no data were obtained. Only one study discussed chronic back pain, its prevalence was nearly identical for all opioids (ranging between 19.4% and 22.6%). [25] Only two studies partly discussed psychiatric comorbidity (anxiety and depression) for which the prevalence was similar between tramadol and other opioids.[21, 22] However there was a more than twofold difference in the prevalence of depression between the two studies. Substance abuse (alcohol related disorders) has only been mentioned by one, similar rates were found between tramadol (6.4%) and codeine (5.8%).[21] No data for the determinants mean dose, education or employment level were found.

table 1.1 study characteristics of included studies regarding serious adverse events of tramadol vs. other opioids

author	title	year	country	study duration
Tsutaoka	Comparative Toxicity of Tapentadol and Tramadol Utilizing Data Reported to the National Poison Data System	2015	USA	07/2009 - 12/2011
Murphy	Comparative rates of mortality and serious adverse effects among commonly prescribed opioid analgesics	2015	USA	01/2010 - 12/2016
Lam	Pharmaceutical opioid poisonings in Victoria, Australia: Rates and characteristics of a decade of emergency	2021	Australia	07/2009 - 06/2019
Solomon	The comparative safety of opioids for nonmalignant pain in older adults	2018	USA	01/1996 - 12/2005
Ou	Tramadol versus codeine and the short-term risk odf cardiovascular events in patients with non-cancer pain: a population-based cohort study	2021	Canada	04/1998 - 03/2017
Musich	Safety events associated with tramadol use among older adults with osteoarthritis	2021	USA	01/2016 - 03/2019

table 1.2 patient characteristics of included studies regarding serious adverse events of tramadol vs. other opioids

author	opioid	no. patients (%)	mean age (years)	male	female	unknown gender	length of use (days)	chronic backpain	psychiatric comorbidity	substance abuse
Tsutaoka										
	Tramadol	8 566 (97.5%)	27.4 ± 19.9	3 731 (43.5%)	4 827 (56.4%)	8 (0.1%)	NA	NA	NA	NA
	Tapentadol	217 (2.5%)	37.6 ± 21.3	84 (38.7%)	133 (61.2%)	0	NA	NA	NA	NA
	total	**8 783**		**3 815 (43.4%)**	**4 960 (56.5%)**	**8 (0.1%)**				
Murphy		*								
	Hydrocodone	7 872 (40.4%)	NA	NA	NA	NA	NA	NA	NA	NA
	Oxycodone	7 121 (36.5%)	NA	NA	NA	NA	NA	NA	NA	NA
	Tramadol	3 280 (16.8%)	NA	NA	NA	NA	NA	NA	NA	NA
	Morphine	1 600 (8.2%)	NA	NA	NA	NA	NA	NA	NA	NA
	Hydromporphone	667 (3.4%)	NA	NA	NA	NA	NA	NA	NA	NA
	Oxymorphone	613 (3.1%)	NA	NA	NA	NA	NA	NA	NA	NA
	Tapentadol	97 (0.5%)	NA	NA	NA	NA	NA	NA	NA	NA
	total	**19 480 (108.9%)**	**20-59 (78.1%)**	**10 234 (52.6%)**	**9 241 (47.4%)**	**5 (0.02%)**				
Lam		‡	†							
	Codeïne	2 008 (37.2%)	NA	572 (28.5%)	1 436 (71.5%)	NA	NA	NA	NA	NA
	Oxycodone	1 437 (26.6%)	NA	553 (38.5%)	883 (61.5%)	NA	NA	NA	NA	NA
	Tramadol	542 (10%)	NA	200 (36.9%)	342 (63.1%)	NA	NA	NA	NA	NA
	Morphine	201 (3.7%)	NA	107 (53.2%)	94 (46.8%)	NA	NA	NA	NA	NA
	Oxycodone-Naloxone	146 (2.7%)	NA	59 (40.4%)	87 (59.6%)	NA	NA	NA	NA	NA
	Methadone	580 (10.7%)	NA	350 (60.3%)	230 (39.7%)	NA	NA	NA	NA	NA
	Buprenorfine	90 (1.7%)	NA	54 (60%)	36 (40%)	NA	NA	NA	NA	NA
	Tapentadol	36 (1.2%)	NA	13 (36.1%)	23 (63.9%)	NA	NA	NA	NA	NA
	Fentanyl	71 (1.3%)	NA	41 (57.5%)	30 (42.3%)	NA	NA	NA	NA	NA
	total	**5 403 (95.1%)**		**2 056 (38.1%)**	**3 347 (62%)**					
Solomon										
	Hydrocodone	6 275 (20%)	78 ± 7	1 233 (19.6%)	5 042 (80.4%)	NA	180	1 253 (20%)	NA	NA
	Codeïne	6 275 (20%)	79 ± 7	1 218 (19.4%)	5 057 (80.6%)	NA	180	1 320 (21%)	NA	NA
	Oxycodone	6 275 (20%)	78 ± 7	1 614 (25.7%)	4 661 (74.3%)	NA	180	1 216 (19.4%)	NA	NA
	Propoxyfene	6 275 (20%)	79 ± 7	1 003 (16%)	5 272 (84%)	NA	180	1 269 (20.2%)	NA	NA
	Tramadol	6 275 (20%)	79 ± 7	926 (14.8%)	5 349 (85.2%)	NA	180	1 421 (22.6%)	NA	NA
	total	**31 375**		**5 994 (19.1%)**	**25 381 (80.9%)**			**6 479 (20.7%)**		
Ou					§				*anxiety + depression*	*alcohol related disorders*
	Tramadol	123 394 (11.9%)	54.4 ± 17.7	53 679 (43.5%)	69 715 (56.5%)	NA	30	NA	16 264 + 37 254 = 53 518 (43.4%)	7 921 (6.4%)
	Codeïne	914 333 (88.1%)	52.4 ± 19	386 232 (42.2%)	528 101 (57.8%)	NA	30	NA	111 642 + 241 855 = 353 497 (38.7%)	52 985 (5.8%)
	total	**1 037 727**		**439 911 (42.4%)**	**597 816 (57.6%)**				**127 906 + 279 109 = 407 015 (39.2%)**	**60 906 (5.9%)**
Musich		*ƒ*		ø	ø				*depression*	
	Tramadol (new users)	18 824 (24.2%)	77	5 591 (29.7%)	13 233 (70.3%)	NA	min 31	NA	2 184 (11.6%)	NA
	Other opioids (new)	18 661 (24.1%)	76.8	5 617 (30.1%)	13 063 (70%)	NA	min 31	NA	2 127 (11.4%)	NA
	Tramadol (continuing users)	7 075 (9.1%)	77	1 981 (28%)	5 094 (72%)	NA	min 31	NA	1 005 (14.2%)	NA
	Other opioids (continuing)	7 238 (9.3%)	77.1	1 990 (27.5%)	5 248 (72.5%)	NA	min 31	NA	1 071 (14.8%)	NA
	total	**51 798**		**15 179 (29.3%)**	**36 628 (70.7%)**				**6 387 (12.3%)**	

NA = not available

mean dose was not available in any article and was therfore excluded from this table.

* exposures could involve more than one substance (ref Murphy)

† age group ranges

‡ multiple opioids were registered but not included in this table therefore the sum does not add up to 100%

§ calculated numbers 1-male gender

ƒ patient percentages do not add up to 100% because of exclusion of non-opioid users (present in original study)

ø absolute numbers are calculated

table 1.3 outcomes of included studies regarding serious adverse events of tramadol vs. other opioids

author	opioid	no. of patients	death	hospital admission	overdose	respiratory depression
Tsutaoka						
	Tramadol	8 566 (97.5%)	10 (0.1%)	NA	NA	135 (1.6%)
	Tapentadol	217 (2.5%)	1 (0.5%)	NA	NA	19 (8.8%)
	total	**8 783**	**11 (0.1%)**			**154 (1.8%)**
Murphy		*	†	†	†	
	Hydrocodone	7 872 (40.4%)	0.02	1.9	1.93	NA
	Oxycodone	7 121 (36.5%)	0.01	1.66	1.74	NA
	Tramadol	3 280 (16.8%)	< 0.01	0.32	0.34	NA
	Morphine	1 600 (8.2%)	0.01	1.01	1.04	NA
	Hydromorphone	667 (3.4%)	0.02	7.67	8.02	NA
	Oxymorphone	613 (3.1%)	0.08	4.98	5.51	NA
	Tapentadol	97 (0.5%)	0	0.26	0.27	NA
	total	**19 480 (108.9%)**				
Lam		§			‡	
	Codeïne	2 008 (37.2%)	NA	935 (46.6%)	0.076	NA
	Oxycodone	1 437 (26.6%)	NA	657 (45.8%)	0.029	NA
	Tramadol	542 (10%)	NA	284 (52.4%)	0.015	NA
	Morphine	201 (3.7%)	NA	112 (55.7%)	0.010	NA
	Oxycodone-Naloxone	146 (2.7%)	NA	70 (48%)	0.008	NA
	Methadone	580 (10.7%)	NA	327 (56.4%)	0.007	NA
	Buprenorfine	90 (1.7%)	NA	43 (47.8%)	0.006	NA
	Tapentadol	36 (1.2%)	NA	21 (58.3%)	0.004	NA
	Fentanyl	71 (1.3%)	NA	28 (39.4%)	0.003	NA
	total	**5 403 (95.1%)**		**2 629 (48.7%)**		
Solomon						
	Hydrocodone	6 275 (20%)	9 (0.1%)	206 (3.3%)	NA	NA
	Codeïne	6 275 (20%)	24 (0.4%)	207 (3.3%)	NA	NA
	Oxycodone	6 275 (20%)	21 (0.3%)	192 (3.1%)	NA	NA
	Propoxyfene	6 275 (20%)	20 (0.3%)	275 (4.4%)	NA	NA
	Tramadol	6 275 (20%)	19 (0.3%)	229 (3.6%)	NA	NA
	total	**31 375**	**93 (0.3%)**	**1 109 (3.5%)**		
Ou			∂			
	Tramadol	123 394 (11.9%)	248 (0.2%)	NA	NA	NA
	Codeïne	914 333 (88.1%)	1 439 (0.2%)	NA	NA	NA
	total	**1 037 727**	**1 687 (0.2%)**			
Musich		ƒ		ø		
	Tramadol (new users)	18 824 (24.2%)	NA	3 106 (16.5%)	NA	NA
	Other opioids (new)	18 661 (24.1%)	NA	3 527 (18.9%)	NA	NA
	Tramadol (continuing users)	7 075 (9.1%)	NA	1 365 (19.3%)	NA	NA
	Other opioids (continuing)	7 238 (9.3%)	NA	1 744 (24.1%)	NA	NA
	total	**51 798**		**9 742 (18.8%)**		

NA = not available

* total value over 100% because exposures could involve more than one substance (ref Murphy)

† supply adjusted rate per 100 000g dispensed

‡ supply adjusted rate per 100 000mg OME per year (2009-19)

§ patient percentages do not add up to 100% because "multiple opioids" were registered but not included in this table

∂ cardiovascular death

ƒ patient percentages do not add up to 100% because of exclusion of non-opioid users (present in original study)

ø absolute numbers are calculated

6 DISCUSSION: serious adverse events with tramadol use

6.1 Summary of results

The overall death rate for analgesic opioid use was found to be low throughout all included studies. Compared to other opioids, this remained the case for tramadol. Only half of the studies have reported death directly due to opioid use.[20, 23, 25] In these studies, the number of deaths were relatively small to make a confident statement. Nevertheless, tramadol was never in the high end of death rates relative to other opioids.
One study that used a healthcare database had a much larger patient sample.[21] More than one million tramadol and codeine users were observed (versus 19 480 patients for the second largest sample), although this study only looked into cardiovascular death (not one of our major outcomes) for which no difference could be found between tramadol and codeine.[21]The same conclusion was found by Solomon et al. if opioid use was restricted to 30 days.[25] However they found an increased risk of cardiovascular events for codeine after use up to 180 days.
The low death rate seems to be confirmed by a review article by Nakhaee et al. who report fatal tramadol intoxications to be uncommon.[26] Fatal tramadol intoxications however seem to rise when there are co-ingestants, especially with the use of central nervous system depressants (benzodiazepines and alcohol).[26]

Respiratory depression is stated as one of the main clinical manifestations of opioid overdose next to stupor and miosis.[27] For this reason it is surprising that we only found one study that made a direct comparison between tramadol and tapentadol for the presence of this clinical symptom.[20] This study found a significantly lower rate of respiratory depression for tramadol versus tapentadol. However in the same study a significantly higher rate of seizures was reported for tramadol (14.6%) compared with tapentadol (1.8%) (RR 7.94, P<0.001).[20] No further conclusion could be drawn about the rate of respiratory depression of tramadol compared to other opioids.

Tramadol hospitalisations did not stand out next to other opioids, surpassing the mean in individual studies in two instances[24, 25], and remaining below in two others.[22, 23] Nevertheless, the differences in study design made it overall difficult to compare the results of the articles, especially regarding hospital admission. The mean rates varied from 3.5% to 96%. The likely explanation is the different setup, as explained below.
In the article of Murphy et al. where the highest hospitalisations were noted in absolute numbers **(see appendix table 1.4)** patients or their healthcare professionals take up contact by phone through PCC's.[23] The experts in these PCC's can give telephone advice but they can't perform a clinical examination. There was also a high selection of more serious cases where opioid use resulted in death, major medical effect or hospitalisation, as opposed to the article of Tsutaoka et al. where also less serious adverse effects were included and PCC calls were categorised as mild or severe.[20] Both the need of clinical examination and the selection of serious cases most likely explains the high hospitalisation rates in the study by Murphy et al. compared to other studies.[23]

Lam et al. presented a mean hospitalisation rate of 48.7 %.[24] Here patients were identified through emergency department visits where an emergency physician clinically evaluated which cases were

serious enough for hospitalisation, hence the lower numbers.
The study with the lowest reports of hospitalisation by Solomon et al. took on a more observatory approach by registering the number of hospitalisations up to 30 days after a pharmacy dispensed an opioid to one of the subjects, resulting in a significantly lower hospitalisation rate.[25] This can be explained because in the first two studies by Murphy et al. and Tsutaoka et al., patients were recruited from those who already presented with side effects where in the latter by Lam et al. and Solomon et al. patients were recruited from all members of an insurance program who were prescribed opioids.[20, 23-25] Further conclusions should thus be drawn with utmost precaution when comparing these articles.

A different methodological approach throughout our included studies also made it impossible to compare other outcomes such as overdose, observed in the articles by Murphy et al. and Lam et al.[23, 24] These articles presented overdose as supply adjusted rates rather than percentages of patients. In the first article by Lam et al., set in Australia, they presented the outcome as a rate per 100 000mg OME.[24] The numbers of overdoses were set out against the mass of opioids dispensed and they also corrected with a factor for opioid potency. It is peculiar that presented this way, codeine has the highest rate of overdoses before oxycodone and tramadol, despite being one of the least potent drugs in the study. The study also set out this rate as a function of time, and noticed that the rate of overdoses for codeine dropped the moment codeine was removed in Australia as an over the counter drug (the last two recorded years), suggesting that access to a drug plays a major role in the prevalence of overdose. Codeine and oxycodone were the two most used opioids in Australia and presented with the most harm.[24]
In the second article by Murphy et al., set in the USA, the outcome was presented as a rate per 100 000 g drug dispensed. [23] They showed that the rate of serious adverse events, presented this way, is a linear function of opioid potency expressed as Morphine Milligram Equivalents (MME). They noted however that despite being the least potent drug in the study with the second to last rate of overdoses, tramadol accounted for the third most serious adverse events in absolute numbers. They hypothesized that this could possibly be explained by serotonin and norepinephrine reuptake inhibition activity. If we keep the conclusion of Lam et al. in mind, another factor could be the fact that tramadol had the third highest number of users in this study and that their widespread use could have resulted in higher rates of adverse events.[23]
Without evidence for this statement, it could be hypothesised that easy access and high prescription rates for tramadol could also account for higher overdose rates. This is at least something to keep in mind while prescribing tramadol given its increasing popularity in a lot of countries.

We noticed that the majority of patients presenting with serious adverse events in the included studies were women. We did not immediately find an explanation for this difference. A retrospective cohort study reported women to have a significantly higher chance of having adverse reactions for tramadol and oxycodone which confirmed our results.[28] However the side effects reported were not serious. A possible explanation is a different interplay regarding CYP2D6 phenotypes and sex, as rapid and ultra-rapid metabolizers experienced significantly more adverse events in women but not in men.[29]
The consumption of opioids might also be region specific. All studies included in our systematic review were set in Western countries. As opposed to the high rates of women presenting with overdoses, a cross-sectional study set in Iran showed 75.6% of patients presenting with tramadol

intoxication being male.[30] In a study set in Nordic countries (Denmark, Norway, Sweden), more tramadol users were women.[31] A review by Goetz et al. showed, just as our own included articles by Musich et al. and Ou et al., that opioids were more likely to be prescribed for women.[21, 22, 32] These three studies were all set in Western countries. Cultural factors might thus also play a role in the use and prescription of tramadol and opioids in general.

In summary tramadol use does not clearly result in more or less cases of death, hospitalisation, overdose or respiratory depression than other opioids. Respiratory depression was found more in tramadol than in tapentadol but we did not find studies comparing with other opioids for this outcome.[20] Tramadol did not have a high rate of overdoses in terms of percentages. However when correcting for opioid strength with OME, we saw that tramadol had the third highest rate of overdoses in one study.[24] Cultural factors and sex could play a role in the occurrence of serious adverse events, as well as the availability of the individual opioid.[24, 29, 30] These are factors that should be considered for future research.

6.2 Comparison of results to other studies

We did not find existing reviews comparing the safety of oral tramadol directly to other opioids. We found other reviews regarding the safety of tramadol, however these reviews compared tramadol not with other opioids but only with placebo or different doses of tramadol[33-37], administered for a short period of time or single dose only.[33,36-38] Some of these reviews also included intravenously administered tramadol which was out of the scope of our own systematic review.[34, 39] Also none of these reviews focused on serious adverse events.
This systematic review charts for the first time the existing studies comparing tramadol directly to other opioids. We only found database studies but no clinical trials answering our question. It draws attention to this void in our knowledge of the exact prevalence of serious adverse events in tramadol, and whether they are in fact more or less frequent.
It is surprising that for an opioid so widely used, and marketed as being less dangerous than other opioids[40], there is no hard evidence to support this claim. We see however that there is an increasing interest in the subject tramadol, as for Medline 3586 articles were published for our search term between January 2012 and 14 December 2021 on a total of 6177 published articles. In other words, 58% of all Medline articles regarding tramadol were published the last 10 years, with the oldest study used in this systematic review published in 2015.

6.3 Strengths and limitations

For this systematic review we screened 12097 individual records. We repeated our search five months before publication and checked for ongoing trials to keep our results up to date. We deliberately kept our search term very broad to not miss any articles of interest. We contacted authors of conference abstracts for which we did not find a full text with data. Despite this approach, we only found 6 articles of interest for our review question regarding serious side-effects of tramadol compared directly with other opioids. To our knowledge this is the first systematic review that attempts to answer this exact review question.
As we mentioned, outcomes were defined and measured very differently throughout all included studies. For example, one study only included cardiovascular death, while other studies investigated

death directly caused by opioid use. This made it impossible to directly compare these articles, nor conduct statistical analysis.

Ingestion of drugs is never confirmed in any of the studies. For three studies, ingestion is supposed on prescriptions filled, amount of dispensed defined daily dosages or intention to treat on grounds of prescriptions written by general practitioners.[21, 22, 25] For two other studies, there was only contact with the patient or healthcare professional by phone.[20, 23] For the final study ingestion was not controlled in the blood, even though there was contact between the patient and an emergency doctor.[24]
Mean dose was unavailable in all studies. Length of opioid use was unknown or unclear for all included articles. Where follow-up is mentioned, ingestion during this period is not confirmed. In two articles there are possible multiple ingestions of opioids which also makes interpretation less reliable.[22, 23]

In choosing to compare tramadol with other opioids in regards to our major outcomes, we did not include any studies comparing to placebo, limiting the amount of information acquired. We limited our outcomes to only four major outcomes however these are not the only possible serious adverse effects. Other adverse effects that we did not look into were among others seizures, fractures and coma. We tried to include patient determinants to detect their possible influence on the outcome, but did not find a clear relation between determinants and a major outcome. On the other hand, our number of determinants were limited, thus it is possible that we missed important existing determinants such as race, medication use or socio-economic status.

6.4 Future recommendations

Our research shows a clear need for further studies that compare tramadol directly to other opioids. To get the most reliable data, it would be ideal that double blinded randomized clinical trials would be conducted. However this would probably pose great practical and ethical issues. Randomly allocating patients to a stronger or weaker opioid or to a higher or lower dose would risk that some patients would not receive the right dose for their level of pain. For serious adverse events to occur, opioid users should also be followed for a longer period, while in practice patients should receive the lowest dose for the shortest amount of time.
However, we believe that at least non-randomized clinical trials should be an option and that patients under single opioids could be compared regarding adverse effects after correcting for different doses and determinants. The doses and length of use should be accurately recorded throughout studies which in present studies was not the case. Registering determinants is important for future studies to detect if other factors play a role in the occurrence of serious adverse events. Apart from the determinants used in this review we suggest socio-economic status, indication of opioid and intent (pain relief versus self-harm), BMI, smoking, (chronic) medication use and comorbidities: diabetes, dyslipidaemia, hypertension, chronic kidney disease, cerebrovascular disease, coronary artery disease, COPD, heart failure, liver cirrhosis, sleep apnoea, rheumatoid arthritis, myocardial infarction, and thrombo-embolism.

7 RESULTS: abuse, misuse, aberrant behaviour and chronic use of tramadol

7.1 Study selection

For the second objective 52 articles were assessed for retrieval after the first search in 2020. After the second screening in December 2021 another 19 articles were added. When summarized, out of these 71 articles were 32 conference abstracts of which no full text and/or later publication could be retrieved. Two conference abstracts were excluded based on full-text review and its inclusion of children under 18 years and based on wrong outcome. A total of 42 articles were assessed in full text of which 11 articles were retained. Altogether 31 articles were excluded because of not meeting the inclusion criteria **(See figure 1).**

7.2 Study characteristics

The vast majority of articles were published after 2017, except for two articles that were published in 2006[41] and 2014.[42] Four studies were obtained from the US[5, 42-44], two from Korea[45, 46], and then one each from Canada[47], Finland[48], the UK[49] and Saudi Arabia.[50] One article didn't state the country of origin[41]. The study designs were mostly retrospective cohort studies (9 out of 11) as listed in **table 2.1**. All but two studies[42, 50] had study populations of more than 1000 participants. The percentage of tramadol users in all studies never exceeded 50%. Of these tramadol users, the mean ages varied greatly, ranging from 21 years up to 79 years, and the majority were female. The study duration was overall greater than one year or more, except for Dabbagh et al.[50] where the duration was four months. The two Korean studies even had a study duration of 13 years in total.[45, 46]
The other opioids to which tramadol was compared varied greatly, but the most frequent comparison was made with hydrocodone, oxycodone, codeine, morphine and fentanyl. The mean dose of tramadol was in most articles often not stated, except for one article: 150 MME median fill.[5] In Clarke et al. OME's were calculated to allow for comparison for each prescription based on drug type and strength, but no specific numbers were stated further on in the article.[47] The length of use was not stated in six out of 11 articles. In the five remaining articles, the length of use was at least 90 days. **(See table 2.2)**

Determinants were taken into account such as back pain, psychiatric comorbidities and previous substance abuse. Psychiatric comorbidities were specified in four articles: in one article 28,7% of the total study population were diagnosed with depression and 11,4% with bipolar disorder.[42] Mental illness was present in 11,9% of the total study population in Thornton. In Cooper et al., mental health diagnoses in general were present in 18,6% of patients without an opioid use disorder and in 66% of patients who were diagnosed with an opioid use disorder.[49] The final article where psychiatric comorbidities were taken into account described mental health as a type of opioid-related comorbidities and had a percentage of 15,9% of all surgical cases.[44] Previous substance abuse was generally linked to previous drug abuse or previous alcohol abuse.

The abuse potential of tramadol was subdivided in four categories with a wide variety of definitions for each category:

- **Misuse**: defined as the non medical use of a substance[48] or prevalence of lifetime, past-month, and past-year misuse of any prescription and over the counter (OTC) drug.[50]

- **Abuse**: defined as the prevalence of tramadol abuse [41] the prevalence of opioid use disorders.[49]

- **Aberrant behaviour**: defined as associations of select predefined potentially aberrant drug taking behaviours (pADTB) and opioids.[42]

- **Chronic use**: Thiels et al. uses three different definitions: Additional opioid use after surgery, persistent opioid use after surgery and the CONSORT definition of long term opioid therapy. [5]Clarke et al.defined prolonged use as a prescription filled within 12 months postoperatively.[47] In Thornton et al. transitioning to chronic opioid therapy was defined as having at least a 90-day supply of opioids during the follow-up period which was 120 days.[43] in Cha et al. and Yoo et al., the sustained use of tramadol was defined as a use ranging from three months to one year post-operatively.[45, 46] In Wackerbarth et al. chronic use was defined as persistent usage of opioid medications after a variety of urologic surgeries.[44]

7.3 Risk of bias

Dabbagh et al. was scored a total of zero stars, as assessed by the NOS scale. **(See appendix table 3)**[50] One article was assigned a total of five stars, being an intermediate ROB[42], as well as two other articles with a total score of six stars.[45, 46] The remaining seven articles all scored seven stars or more. The risk of bias in the majority of the articles was due to bias in measurement of the outcome.

When overlooking the NOS, all but one had a good ascertainment of exposure.[50] In the latter data was retrieved by a structured questionnaire, but no interview. In another article, data was collected via structured interviews and questionnaires.[41] For the remaining articles, data was collected using different databases as listed below.

7.3.1 Healthcare databases

Databases were used by nine different studies. The two articles originating from Korea used the Korean national Health insurance service sample cohort (NHIS-Sample)[45] as well as the senior cohort (NHIS-Senior).[46] In the Finnish article, data was extracted from the National Post Mortem Toxicology Database.[48] In one study, there was a linkage from different databases: the Canadian institute For Health Information (CIHI) captured hospital and same-day surgery services, physician billing records came from the Ontario Health Insurance Plan (OHIP) Database, dispensed prescriptions for opioids and other monitored drugs were recorded in the Narcotics Monitoring System (NMS), and lastly additional patient and physician characteristics were obtained from the Registered Persons Database and the ICES Physician database, respectively.[47] In Cooper et al., data was obtained from the UK

Clinical Practice Research datalink (CPRD).[49] The four American studies used four different databases: prescription records were collected from the Electronic Health Records from the Belleville Family Health Center (BFHC)[42], Thiels et al. acquired claims data from the Optumlabs Data Warehouse (Optumlabs)[5] whereas Thornton et al. collected adjudicated claims from a database owned by IQVIA information services[43], and lastly in Wackerbarth et al., the Truven Health Marketscan Database (THMD) was used.[44]

7.4 Synthesis of results

The different outcomes for our second review question are presented **in table 2.3**. The outcome misuse was reported by two articles. In Haukka et al., three opioids were found in the postmortem toxicology in the study (oxycodone, fentanyl and tramadol).[48] Tramadol was one of the most prevalent non-medical findings when compared to the other opioids, about 5.6%. In Dabbagh et al., estimates were higher for overall prescription drug misuse than those for OTC drugs.[50]Lifetime prevalence for prescription drug misuse for tramadol and other opioids was 62.24%, past year prevalence was 52.60%, and past month prevalence was 34.68% in comparison to 29.09%, 22.35% and 11.95% respectively for OTC codeine. The most frequently misused drugs were tramadol (23.87% in Non-Health College and 22.90% in Health College), diphenhydramine (13.51% and 8.42% respect) and acetaminophen (9.91% and 9.09% respect). The percentages of the other opioids were 5.86% and 3.03% for prescription codeine, 5.86% and 3.70% for fentanyl, morphine and oxycodone combined. The most common reason for misuse was pain relief. Thus, tramadol was described in both articles as more contributing for misuse in comparison with other opioids.

Data for abuse was found in two articles. In Adams et al. the prevalence of abuse was stated as significantly less for tramadol than for hydrocodone (2.7% vs 4.9%, P <0.01), over a 12-month period.[41] In Cooper et al. the prevalence of opioid use disorders identified by Read codes was low at 0.05% and there was no obvious change in the incidence of newly diagnosed opioid use disorders when subdivided by opioid drug.[49] The most frequently first prescribed drug was codeine (40.6%), whereas tramadol was prescribed in 15.9% of the cases. The 5-year period prevalence among diagnosed patients for abuse was highest for oxycodone, and tramadol was second last. **(See table 2.3)** In conclusion, in both articles the abuse potential of tramadol is stated as lower compared to the other opioids.

Concerning aberrant behaviour, it was registered by one article.[42] The most commonly found pADTB was multiple pharmacy use and prescribing by multiple physicians. Patients who were prescribed tramadol had significantly reduced odds of demonstrating one or more problem behaviours compared to the other opioids. **(See table 2.3)** Prescriptions for fentanyl, oxycodone, or hydrocodone were associated with higher numbers of pADTBs, respectively 1.4, 0.6, 0.5 pADTBs on average.

And lastly, chronicity was stated in six articles. In Thiels et al., patients with a prescription for tramadol were overall at higher adjusted risk of chronic opioid use for the 3 different definitions wielded in the article. **(See table 2.3)**[5] In Thornton et al. 13 out of 1000 patients with an initial

prescription for opioids transitioned to chronic opioid therapy (incident cases).[43] 4.2% of tramadol prescriptions transitioned into chronic opioid use in comparison to 0.5% codeine, 1% hydrocodone, 1.1% oxycodone and 7.1% all other opioids. In Clarke et al. it was stated that 1% of a total study population of 90,362 - who were not on opioids prior to surgery - received an opioid prescription one year after surgery.[47] Tramadol was found to be one of the prescribed opioids (11%), although codeine (49%) and oxycodone (25%) were more frequently prescribed, hydromorphone (11%) and morphine (2.8%) were the same amount or less prescribed. In Cha et al. the numbers of sustained tramadol use after surgery were 48,71% compared to 42,7% of other strong opioids.[45] In Yoo et al. the numbers of sustained tramadol were 43,43% compared to 12.1% of other strong opioids.[46] The trends for tramadol sustained use were described as similar to other opioids for both articles. These findings were not statistically analyzed. Discharge with tramadol was associated with 23% higher odds (OR 1.23, 95% CI 1.13-1.35) of persistent usage after surgery compared to other short acting opioids in Wackerbarth et al.[44] Overall, tramadol was found to comprise a greater risk of evolving into chronic use compared to other opioids in five of the six articles. As stated above, two of these articles were not statistically analysed.

table 2.1 study characteristics of included studies regarding abuse potential of tramadol vs. other opioids

author	title	year	country	study duration	study type
Adams	A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain	2006	NA	12 month follow up	Prospective randomized comparative
Cha	Effect of Opioids on All-cause Mortality and Opioid Addiction in Total Hip Arthroplasty: a Korea Nationwide Cohort Study	2021	Korea	2002-2015	Retrospective cohort study
Clarke	Opioid use after outpatient elective general surgery: quantifying the burden of persistent use	2021	Canada	2013-2016	Retrospective cohort study
Cooper	Prevalence and Incidence Trends for Diagnosed Prescription Opioid Use Disorders in the United Kingdom	2017	United Kingdom	2008-2012	Retrospective cohort study
Dabbagh	Prescription and over the counter drug misuse among female students at Saudi University	2020	Saudi Arabia	2019 (January-April)	Cross sectional study
Haukka	Non-medical use of psychoactive prescription drugs is associated with fatal poisoning	2018	Finland	2011-2013	Retrospective cohort study
Lewis	Patient aberrant drug taking behaviors in a large family medicine residency program: a retrospective chart review of screening practices, incidence, and predictors	2014	United States	2007-2009	Retrospective chart review
Thiels	Chronic use of tramadol after acute pain episode: cohort study	2019	United States	2009-2018	Retrospective analysis of claims data
Thornton	Predictors of Transitioning to Incident Chronic Opioid Therapy Among Working-Age Adults in the United States	2018	United States	2007-2015	Retrospective cohort study
Wackerbarth	Persistent Opioid Usage After Urologic Intervention and the Impact of Tramadol	2021	United States	2014-2017	Retrospective cohort study
Yoo	Effect of Opioids on All-cause Mortality and Sustained Opioid Use in Elderly Patients with Hip Fracture: a Korea Nationwide Cohort Study	2021	Korea	2002-2015	Retrospective cohort study

table 2.2 patient characteristics of included studies regarding abuse potential of tramadol vs. other opioids

author	opioid	no. patients (%)	mean dose	mean age (years)	male	female	length of use (days)	backpain (%)	psychiatric comorbidities (%)	substance abuse
Adams										
	Tramadol alone	1 475 (12.99%)	NA	NA	431 (29.2%)	1 044 (70.8%)	210	235 (15.9%)	NA	NA
	Hydrocodon + Tramadol	4 321 (38.06%)	NA	NA	1 460 (33.8%)	2 861 (66.2%)	196	920 (21.3%)	NA	NA
	NSAID + Tramadol	5 556 (48.94%)	NA	NA	1 717 (30.9%)	3 839 (69.1%)	217	733 (13.2%)	NA	NA
	total	**11 352**		**36**	**3 608 (31.8%)**	**7 744 (68.2%)**		**1 888 (16.6%)**		
Cha		*current user*								
	Tramadol	884 (78.86%)	NA	NA	NA	NA	NA	NA	NA	NA
	Strong opioids	853 (76.09%)	NA	NA	NA	NA	NA	NA	NA	NA
	total	**1 737**		**> 70**	**420 (47.51%)***	**701 (62.5%)***				
Clarke		*prescribed the day of surgery*								
	Tramadol	10 386 (18%)	NA	NA	NA	NA	NA	NA	NA	NA
	Codeine	23 657 (41%)	NA	NA	NA	NA	NA	NA	NA	NA
	Oxycodone	17 887 (31%)	NA	NA	NA	NA	NA	NA	NA	NA
	Hydromorphone	5 193 (9%)	NA	NA	NA	NA	NA	NA	NA	NA
	Morphine	577 (1%)	NA	NA	NA	NA	NA	NA	NA	NA
	total	**57 717**		**53**	**47 873 (53%)***	**42 453 (47%)***				
Cooper	*first prescribed*						*mean duration of opioid exposure*		*mental health diagnoses*	
	Tramadol	246 499 (15.9%)	NA	NA	NA	NA	NA	NA		NA
	Codeine	629 425 (40.6%)	NA	NA	NA	NA	NA	NA		NA
	Dihydrocodeine	496 098 (32%)	NA	NA	NA	NA	NA	NA		NA
	Buprenorphine	69 764 (4.5%)	NA	NA	NA	NA	NA	NA		NA
	Morphine	66 663 (4.3%)	NA	NA	NA	NA	NA	NA		NA
	Oxycodone	38 758 (2.5%)	NA	NA	NA	NA	NA	NA		NA
	Fentanyl	23 254 (1.5%)	NA	NA	NA	NA	NA	NA		NA
	Metanizol	NA	NA	NA	NA	NA	NA	NA		NA
	Diamorphine	NA	NA	NA	NA	NA	NA	NA		NA
	Dipipanone	NA	NA	NA	NA	NA	NA	NA		NA
	Hydromorphone	NA	NA	NA	NA	NA	NA	NA		NA
	Methadone	NA	NA	NA	NA	NA	NA	NA		NA
	Papaveretum	NA	NA	NA	NA	NA	NA	NA		NA
	Pentazocine	NA	NA	NA	NA	NA	NA	NA		NA
	Pethidine	NA	NA	NA	NA	NA	NA	NA		NA
	Tapentadol	NA	NA	NA	NA	NA	NA	NA		NA
	total	**1 550 307**		**38.6**	**636 289 (41%)**	**914 018 (59%)**	**171.5**		**288 815 (18.6%)**	
Dabbagh										
	Tramadol	121 (23.3%)	NA	NA	NA	NA	NA	NA	NA	NA
	Codeine	37 (7%)	NA	NA	NA	NA	NA	NA	NA	NA
	Other opioids (fentanyl, morphine, oxyco	24 (4.6%)	NA	NA	NA	NA	NA	NA	NA	NA
	total	**182**		**21**		**519 (100%)**				
Haukka	*positive toxicology postmortem*									
	Tramadol	447 (15%)	NA	52y	343 (76.7%)	104 (23.3%)	NA	NA	NA	NA
	Oxycodone	199 (6.69%)	NA	55y	131 (65.8%)	68 (34.2%)	NA	NA	NA	NA
	Fentanyl	79 (2.66%)	NA	55y	57 (72.2%)	22 (27.8%)	NA	NA	NA	NA
	total	**725**		**54**	**531 (73.2%)**	**194 (26.8%)**				

Lewis		*n° of prescriptions*							*depression diagnosis + bipolar disorder*	
	Tramadol	50 (13.2%)	NA	NA	NA	NA	NA	NA		NA
	Hydrocodon	130 (34.2%)	NA	NA	NA	NA	NA	NA		NA
	Oxycodone	58 (15.3%)	NA	NA	NA	NA	NA	NA		NA
	Codeine	36 (9.5%)	NA	NA	NA	NA	NA	NA		NA
	Fentanyl	28 (7.4%)	NA	NA	NA	NA	NA	NA		NA
	Morphine	26 (6.8%)	NA	NA	NA	NA	NA	NA		NA
	Propoxyphene	25 (6.6%)	NA	NA	NA	NA	NA	NA		NA
	Methadon	20 (5.3%)	NA	NA	NA	NA	NA	NA		NA
	Hydromorphone	7 (1.8%)	NA	NA	NA	NA	NA	NA		NA
	Total	**380**		**47.4**	**74 (36.6%)***	**128 (63.4%)***	**365**		**58 (28.78%) + 23 (11.4%)***	
Thiels										
	Tramadol	13 519 (3%)	150 MME	NA	5 130 (37.9%)	8 389 (62%)	NA	NA	NA	NA
	Short acting opioids other than tramadol	333 289 (74.9%)	NA	NA	174 368 (52.3%)	158 921 (47.7%)	NA	NA	NA	NA
	Tramadol + other short acting opioids	5 457 (1.2%)	NA	NA	2 543 (46.6%)	2 914 (53.4%)	NA	NA	NA	NA
	Any long acting opioid	5 619 (1.3%)	NA	NA	3 244 (57.7%)	2 375 (42.3%)	NA	NA	NA	NA
	Total	**357 884**			**185 285 (51.8%)**	**172 599 (48.2%)**	**90**			
Thornton									*mental illness*	
	Tramadol	48 450 (9.9%)	NA	NA	NA	NA	NA	NA		NA
	Hydrocodone	300 008 (61%)	NA	NA	NA	NA	NA	NA		NA
	Oxycodone	94 822 (19.3%)	NA	NA	NA	NA	NA	NA		NA
	Codeine	44 588 (9.1%)	NA	NA	NA	NA	NA	NA		NA
	All other opioids	3 574 (0.7%)	NA	NA	NA	NA	NA	NA		NA
	Total	**491 442**		**>45**	**233 393 (47.5%)**	**258 049 (52.5%)**	**90**		**58 356 (11.9%)**	
Wackerbarth									*mental health*	
	Tramadol (Class IV)	3 875 (3.3%)	NA	NA	NA	NA	NA	NA		NA
	Class II	7 009 (6%)	NA	NA	NA	NA	NA	NA		NA
	Class III	104 803 (90.6%)	NA	NA	NA	NA	NA	NA		NA
	Total	**115 687**		**47**	**72 147 (62.4%)**	**43 540 (37.6%)**			**18 338 (15.9%)**	
Yoo		*current user*								
	Tramadol	9 767 (75.55%)	NA	NA	NA	NA	NA	NA	NA	NA
	Strong opioids	1 700 (13.15%)	NA	NA	NA	NA	NA	NA	NA	NA
	Total	**11 467**		**75-79**	**2 613 (20.2%)***	**10 314 (79.8%)***				

NA = not available

* Calculation based on the total study population

table 2.3 outcomes of included studies regarding abuse potential of tramadol vs. other opioids

author	opioid	non medical use	prevalence of misuse		
Dabbagh			*lifetime misuse*	*past-month misuse*	*past-year misuse*
	Prescription Tramadol and other opioids	NA	323 (62.24%)	180 (34.68%)	273 (52.6%)
	Codeine OTC	NA	151 (29.09%)	62 (11.95%)	116 (22.35%)
Haukka		*n + Prevalence (95% CI)*			
	Tramadol	167 + (0.374 (0.329-0.420))	NA	NA	NA
	Oxycodone	101 + (0.508 (0.436-0.579))	NA	NA	NA
	Fentanyl	44 + (0.557 (0.441-0.669))	NA	NA	NA

NA = not available

author	opioid	prevalence of abuse
Adams§		
	Tramadol	2.7%°
	Hydrocodon	4.9%°
Cooper*		*prevalence (95% CI)*
	Tramadol	4.32 (3.69-5.03)
	Oxycodone	14.29 (10.06-19.69)
	Fentanyl	8.26 (5.49-11.93)
	Buprenorphine	7.98 (5.80-10.71)
	Morphine	6.94 (5.37-8.83)
	Dihydrocodeïne	6.76 (5.95-7.64)
	Codeïne	2.56 (2.29-2.87)

§ prevalence = relative abuse of an opioid. Percentages based upon total population exposed to medication

° percentages based upon total population exposed to medication

* prevalence = 5 y period prevalence (per 10,000 patients exposed) among diagnosed patients (n = 715)

for Cooper et al., results were not presented for specific opioid drugs with <5 patients diagnosed with an opioid use disorder

author	opioid	pADTB§ (OR)	pADTB (B)°
Lewis		*Prevalence (95% CI)*	
	Tramadol	0.16 (0.06-0.38) p<0.001	
	Methadone	0.26 (0.08-0.94) p=0.02	
	Fentanyl		1.4 (p<0.001)
	Oxycodone		0.6 (p=0.004)
	Hydrocodone		0.5 (p=0.02)

§ predefined, potentially aberrant drug-taking behaviors

° unstandardized regression coefficient

multiple logistic regression was used to predict pADTBS (0= none, 1= one or more). In this table = adjusted results of 2 significant predictors

author	opioid	transition to chronic therapy	persistent/prolonged/sustained use		
Cha§					
	Tramadol	NA	546 (48.71%)		
	Strong opioids	NA	479 (42.73%)		
Clarke			*opioid prescription 1y after surgery*		
	Tramadol	NA	9 936 (11%)		
	Codeine	NA	44 260 (49%)		
	Oxycodone	NA	22 582 (25%)		
	Hydromorphone	NA	9 936 (11%)		
	Morphine	NA	2 529 (2.8%)		
Thiels			*additional use ARR (95% CI)*	*persistent use ARR (95% CI)*	*CONSORT definition ARR (95% CI)*
	Tramadol only	NA	1.06 (1.00-1.13) ; p=0.049	1.47 (1.25-1.69) ; p<0.001	1.41 (1.08-1.75) ; p=0.013
	Tramadol + short acting	NA	1.05 (0.96-1.14) ; p=0.261	1.04 (0.86-1.21) ; p=0.685	1.40 (1.05-1.74) ; p=0.022
	Any long acting	NA	0.95 (0.87-1.03) ; p=0.218	1.18 (1.02-1.35) ; p=0.029	1.69 (1.36-2.02) ; p<0.001
Thornton					
	Tramadol	2 039 (4.2%)	NA	NA	NA
	Codeine	201 (0.5%)	NA	NA	NA
	Hydrocodone	3 023 (1%)	NA	NA	NA
	Oxycodone	1 039 (1.1%)	NA	NA	NA
	All other opioids	254 (7.1%)	NA	NA	NA
Wackerbarth					
	Tramadol (Class IV)	NA	687 (17.7%)		
	Class III	NA	903 (12.9%)		
	Class II	NA	15 514 (14.8%)		
Yoo					
	Tramadol	NA	5 614 (43.43%)		
	Strong opioids	NA	1 558 (12.05%)		

§ Past tramadol and strong opioid use in current users increased the risk of sustained use of tramadol and strong opioids 1.45 fold (aRR; 95% CI, 1.12-1.87; P= 0.004) and 1.65- fold (aRR; 95% CI, 1.43-1.91; P< 0.001) respectively, compared to past non-users

8 DISCUSSION: abuse, misuse, aberrant behaviour and chronic use of tramadol

8.1 Summary of results

Tramadol is generally considered to be safer than other opioids due to its unique low affinity for the mu-opioid receptor and is therefore worldwide one of the most prescribed opioids.[3, 5] More specifically in Belgium there is a tendency of growth towards prescription and obtaining of these drugs illegally.[11] However there is a shortage of data to support the safety and lower risk of chronic use of tramadol.[5]

In This systematic review an attempt was made to provide an overview of the existing literature regarding tramadol and its position compared to opioids with a focus on the safety profile, abuse, misuse, aberrant behaviour and the risk of prolonged use.

Regarding the second objective: "abuse, misuse, aberrant behaviour and chronic use" there was an inconsistency found regarding the objectives misuse and chronicity with respect to what is considered to be known in the aforementioned literature. For both the risk of misuse and the risk of transitioning from acute to chronic use, tramadol was found to comprise a greater risk compared to other opioids.[5, 43-46, 48, 50]

In Haukka et al. the result is stated as tramadol favoring non-medical findings in postmortem toxicology.[48] However, after a close reading of the figures and taking the proportion of non-medical use in relation to the toxicology of fatal poisonings into account, this is more pronounced for oxycodone and fentanyl compared with tramadol. Thus if there is an abuse of the previously named drugs there is a higher risk of wrong dosage and therefore a higher risk of fatal poisoning. Another limitation of this study is that there is a possible bias in selection outcome due to not having information of the actual intake of the drugs after having received reimbursement. In Dabbagh et al. the preferred drug of choice for misuse is tramadol.[50] This can be explained by the high accessibility in Saudi Arabia as it is commonly prescribed as a treatment for post-operative pain.[51, 52] This article also scored poorly on the NOS scale illustrating possible risk of bias related to these data.[50] In this article, the study population was limited to the female population of a certain age category, which contributes to a risk of selection bias. Additionally, a shorter study duration and a smaller study population was used compared to the other articles.

Concerning chronicity there was an important risk of prolonged use after prescription of tramadol in comparison to other opioids. In Thiels et al. there is a difference noted when comparing the three definitions of prolonged use.[5] If the less stringent definition: "additional opioid use after surgery" is used (at least one opioid fill in the 90-180 days after surgery) the risk of chronicity becomes much higher. This aligns more with the before-published risk.[53] Interpretation of these results is affected by the wide variety of chronicity in the different articles. By using a cut off of a usage of more or equal to 90 days an attempt was made to minimize the variability of these definitions. By using a less stringent definition there might be an overestimation of the prolonged use. There is also a lack of uniformity for the definitions abuse, misuse and aberrant behaviour. Therefore it is possible that our results are not consistent.

Tramadol, when compared to other opioids, was less likely to result in aberrant behaviour and abuse which aligns with the expectation of its safety. However, only one article was found that used the definition of aberrant behaviour.[42] Consequently, it is not possible to draw a conclusion for this particular objective in our systematic review. In Adams et al.[41] and Cooper et al.[49] the hypothesis of the lower rate of tramadol abuse is followed. A potential limitation of selection of Adams et al. is the utilization of a questionnaire instead of using secure records whereby the abuse rate for all opioids may have been underestimated.[41] On the other hand, in Cooper et al. the used database assumes that problematic opioid use is coded by physicians systematically and therefore suggests alternative data sources for further research to decrease the possible underestimation of abuse diagnosis.[49]
It was not possible to make a statistical statement concerning the determinants that enhance the abuse risk for tramadol since only a limited number of articles stratified the characteristics per opioid. This would be very interesting to take into account for further investigation in the future as this is important for the prescribing behaviour of general practitioners (GP) and/or specialists. In the daily practice of a general practitioner, other opioids aside from tramadol are not as frequently prescribed. A GP should be very aware of the risks of non-medical use of tramadol. In Cooper et al. it is stated that the most commonly first-prescribed opioid regardless of their potency tends to be more frequently associated with an opioid use disorder.[49] There was also a greater risk of transitioning to chronic use for tramadol, and even if the majority of opioids are prescribed after surgery, it is still a responsibility of the GP to guide the patient, and to provide him/her with the right information concerning risks of further prescribing tramadol. If the GP would be more aware of the risk factors, there could be more careful monitoring of the prescription pattern and in particular for the patients prone to substance abuse.

8.2 Strengths and limitations

This systematic review had several strengths. Firstly, most of the included articles used data from national databases allowing them to represent the average population in the community. One point of criticism is that therefore there is a possible underestimation of our results as there is a lack of a potentially more susceptible population e.g. people who live in poverty and can't afford insurance and therefore aren't included in the used insurance databases. Nonetheless this is only speculation as no statements could be made for the determinants as mentioned above. Another potential criticism is that by using databases there is no information of the actual intake of the prescribed medication and wrong assumptions can be made. Secondly, because of the large study population in the majority of the studies it is unlikely to over-or underestimate the results. Thirdly, to minimize the bias in the selection process this review was a double-blind review in the selection of articles and data management. The greatest limitation of our review is the lack of uniformity of the definition and presentation of results. Therefore a statistical analysis of the results was not possible making it difficult to draw conclusions of descriptive results. There was a shortage of studies that specifically compared tramadol to other opioids to depict the abuse potential in our search. This would be interesting for further investigation in the future whereby a statistical comparison can be made.

9 Conclusion

Serious adverse events did not seem to occur more in tramadol compared to other opioids. However we could not conclude that they occur less. Women might be more susceptible to serious adverse events. Cultural differences and/or different metabolization due to different genotypes could play a role. Furthermore our results suggest that the overall perception of the low abuse potential of tramadol should be reconsidered, although results vary and it is difficult to get a clear picture. This also applies for the determinants that make the patients susceptible for abuse. Further comparative clinical studies and statistical research with more uniform data should be conducted to assess the safety profile and abuse potential of tramadol. Especially a more homogeneous definition of misuse, abuse, aberrant behaviour and chronicity is required. In this way a clinical guideline could be achieved for the general practitioner (GP) in the future.

10 Acknowledgements

We would like to dedicate this systematic review to Cathy Matheï who has been the inspiration and drive for this work. Cathy sadly passed away during the process and will gravely be missed by family and colleagues alike.

We thank Kristel Paque PhD and Eline Vancoppenolle of KU Leuven libraries 2Bergen for technical support and advise, Bert Vaes MD, PhD for his expertise on risk of bias study.

11 Conflict of interest & funding

We declare no conflict of interest. No funding has been received for the writing of this review.

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13 Appendix

13.1 Full search strategy

Medline through Pubmed advanced search:

- tramadol[tiab] OR "Tramadol"[Mesh] OR tramundin[tiab] OR K-315[tiab] OR K315[tiab]

Embase advanced search:

- tramadol:ab,ti OR tramundin:ab,ti OR 'k 315':ab,ti OR k315:ab,ti

Cochrane Database of Systematic Reviews + Cochrane Central Register of Controlled Trials:

- tramadol in Title Abstract Keyword OR tramundin in Title Abstract Keyword OR K-315 in Title Abstract Keyword OR K315 in Title Abstract Keyword

Clinical Trials.gov:

- search term 'tramadol' (filter adults (18-64) and older adults (65+)

13.2 Expanded outcomes: serious adverse events

table 1.4 shows expanded outcomes of included studies regarding serious adverse events of tramadol vs. other opioids. This is an expanded version of **table 1.3** with inclusion of 'all-cause mortality' and 'major medical effect' as outcomes as well as all outcomes presented in absolute numbers and percentages instead of those with supply adjusted rates.

13.3 Risk of bias assessment using Newcastle-Ottawa scale

See **table 3.**

13.4 Favourable advice ethical committee

See **figure 2.**

table 1.4 expanded outcomes of included studies regarding serious adverse events of tramadol vs. other opioids

author	opioid	no. of patients	death	hospital admission	overdose	respiratory depression	all cause mortality	major medical effect
Tsutaoka								*coma + seizures*
	Tramadol	8 566 (97.5%)	10 (0.1%)	NA	NA	135 (1.6%)	NA	114 (1.3%) + 1 249 (14.6%)
	Tapentadol	217 (2.5%)	1 (0.5%)	NA	NA	19 (8.8%)	NA	12 (5.5%) + 4 (1.8%)
	total	**8 783**	**11 (0.1%)**			**154 (1.8%)**		**126 (1.4%) + 1 253 (14.2%)**
Murphy		*			*hospital admission + death + major medical effect* *			*life threatening symptoms, significant residual disabilty*
	Hydrocodone	7 872 (40.4%)	72 (0.9%)	7 736 (98.3%)	7 872 (40.4%)	NA	NA	951 (12.1%)
	Oxycodone	7 121 (36.5%)	57 (0.8%)	6 801 (95.5%)	7 121 (36.5%)	NA	NA	1 154 (16.2%)
	Tramadol	3 280 (16.8%)	7 (0.2%)	3 070 (93.6%)	3 280 (16.8%)	NA	NA	526 (16%)
	Morphine	1 600 (8.2%)	14 (0.9%)	1 547 (96.7%)	1 600 (8.2%)	NA	NA	316 (19.8%)
	Hydromorphone	667 (3.4%)	2 (0.3%)	638 (95.7%)	667 (3.4%)	NA	NA	106 (15.9%)
	Oxymorphone	613 (3.1%)	9 (1.5%)	554 (90%)	613 (3.1%)	NA	NA	184 (30%)
	Tapentadol	97 (0.5%)	0	93 (95.9%)	97 (0.5%)	NA	NA	14 (14.4%)
	total	**19 480 (108.9%)**	**148 (0.8%)**	**18 713 (96%)**	**19 480 (108.9%)**			**2 955 (15.2%)**
Lam		§			‡			
	Codeïne	2 008 (37.2%)	NA	935 (46.6%)	2 008 (37.2%)	NA	NA	NA
	Oxycodone	1 437 (26.6%)	NA	657 (45.8%)	1 437 (26.6%)	NA	NA	NA
	Tramadol	542 (10%)	NA	284 (52.4%)	542 (10%)	NA	NA	NA
	Morphine	201 (3.7%)	NA	112 (55.7%)	201 (3.7%)	NA	NA	NA
	Oxycodone-Naloxone	146 (2.7%)	NA	70 (48%)	146 (2.7%)	NA	NA	NA
	Methadone	580 (10.7%)	NA	327 (56.4%)	580 (10.7%)	NA	NA	NA
	Buprenorfine	90 (1.7%)	NA	43 (47.8%)	90 (1.7%)	NA	NA	NA
	Tapentadol	36 (1.2%)	NA	21 (58.3%)	36 (1.2%)	NA	NA	NA
	Fentanyl	71 (1.3%)	NA	28 (39.4%)	71 (1.3%)	NA	NA	NA
	total	**5 403 (95.1%)**		**2 629 (48.7%)**	**5 403 (95.1%)**			
Solomon			*hospitalised death (excl. all cause)*	*hospitalised safety event + hospitalised deaths*				*CVD + fracture + GI*
	Hydrocodone	6 275 (20%)	9 (0.1%)	206 (3.3%)	NA	NA	32 (0.5%)	431 (6.9%)
	Codeïne	6 275 (20%)	24 (0.4%)	207 (3.3%)	NA	NA	57 (0.9%)	373 (5.9%)
	Oxycodone	6 275 (20%)	21 (0.3%)	192 (3.1%)	NA	NA	60 (1%)	388 (6.2%)
	Propoxyfene	6 275 (20%)	20 (0.3%)	275 (4.4%)	NA	NA	49 (0.8%)	443 (7.1%)
	Tramadol	6 275 (20%)	19 (0.3%)	229(3.6%)	NA	NA	46 (0.7%)	274 (4.4%)
	total	**31 375**	**93 (0.3%)**	**1 109 (3.5%)**			**244 (0.8%)**	**1 909 (6.1%)**
Ou			*cardiovascular death*					
	Tramadol	123 394 (11.9%)	248 (0.2%)	NA	NA	NA	496 (0.4%)	NA
	Codeïne	914 333 (88.1%)	1 439 (0.2%)	NA	NA	NA	2 985 (0.3%)	NA
	total	**1 037 727**	**1 687 (0.2%)**				**3 481 (0.3%)**	
Musich		*ƒ*		*ø*			*ƒ*	
	Tramadol (new users)	18 824 (24.2%)	NA	3 106 (16.5%)	NA	NA	1 299 (6.9%)	NA
	Other opioids (new)	18 661 (24.1%)	NA	3 527 (18.9%)	NA	NA	1 250 (6.7%)	NA
	Tramadol (continuing users)	7 075 (9.1%)	NA	1 365 (19.3%)	NA	NA	566 (8%)	NA
	Other opioids (continuing)	7 238 (9.3%)	NA	1 744 (24.1%)	NA	NA	717 (9.9%)	NA
	total	**51 798**		**9 742 (18.8%)**			**3 832 (7.4%)**	

NA = not available

outcomes presented as absolute numbers and percentages instead of supply adjusted rates

* total value over 100% because exposures could involve more than one substance (ref Murphy)

‡ absolute numbers of overdose equal total ER presentations

§ patient percentages do not add up to 100% because "multiple opioids" were registered but not included in this table

ƒ patient percentages do not add up to 100% because of exclusion of non-opioid users (present in original study)

ø absolute numbers are calculated

table 3. Risk of bias assessment tramadol serious adverse events and abuse potential (systematic review): Newcastle-Ottawa scale

	Score Total	Selection				Comparability		Outcome		
		Representativeness of exposed cohort	*Selection of non-exposed cohort*	*Ascertainment of exposure*	*Demonstration that outcome of interest was not present at start of study*	*Adjustment for the most imortant risk factors*	*Adjustment for other risk factors*	*Assessment of outcome*	*Follow-up length*	*Adequacy of follow-up*
Tsutaoka	2/0/1	*	*	/	/	/	/	/	*	/
Murphy	2/0/1	*	*	/	/	/	/	/	*	/
Lam	3/2/2	*	*	*	/	*	*	*	*	/
Solomon	3/2/3	*	*	*	/	*	*	*	*	*
Ou	3/2/3	*	*	*	/	*	*	*	*	*
Musich	3/2/3	*	*	*	/	*	*	*	*	*
Adams	3/2/2	/	*	*	*	*	*	/	*	*
Thiels	3/1/3	/	*	*	*	/	*	*	*	*
Haukka	2/2/3	/	*	*	/	*	*	*	*	*
Lewis	2/0/3	/	*	*	/	/	/	*	*	*
Thornton	4/2/2	*	*	*	*	*	*	*	*	/
Cooper	4/2/2	*	*	*	*	*	*	*	*	/
Clarke	3/1/3	/	*	*	*	/	*	*	*	*
Dabbagh	0/0/0	/	/	/	/	/	/	/	/	/
Cha	2/1/3	/	*	*	/	/	*	*	*	*
Yoo	2/1/3	/	*	*	/	/	*	*	*	*
Wackerbarth	3/2/3	/	*	*	/	/	*	*	*	*

figure 2. Favourable advice ethical committee: tramadol serious adverse events and abuse potential (systematic review)

Van: KU Leuven - SCONE <no-reply@gbiomed.kuleuven.be>
Verzonden: vrijdag 27 november 2020 18:17
Aan: Louise Magnus
Onderwerp: Goedkeuring: masterproef ""Safety and abuse potential of oral analgesic tramadol: a systematic review"" (MP017120)

KU LEUVEN

SCONE - Het platform voor stages en masterproeven

Geachte professor,
Beste student,

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.
Veel succes!

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Do you have questions? Check out the extensive documentation on SCONE.

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Persoonlijk Reflectieverslag kandidaten

Dries Vergauwen

Eind 2019 startten Lukas Hermans en ikzelf met onze thesis. We kozen een onderwerp dat we terugvonden in de lijst aangeboden door het ICHO. Een literatuuronderzoek en systematische review over tramadol, een zwak opioïd dat enorm veel wordt voorgeschreven maar waarvan de potentiële gevaren onderbelicht waren, leek ons wel interessant. We stuurden samen een mailtje naar professor Cathy Matheï en al snel werd zij ook officieel toegewezen als promotor. Omdat prof. Matheï de vraag wou opsplitsen in het gevaar voor ernstige nevenwerkingen én het verslavingspotentieel van tramadol, werden er nog twee studenten aan onze onderzoeksvraag toegevoegd. Ine Frederickx en Louise Magnus vervolledigden ons team en namen de laatste vraag voor hun rekening.
We spraken al snel af met onze promotor en ook apart onder de vier studenten om het kader en methodologie van onze thesis uit te denken. Spijtig genoeg hebben we daarna nooit meer met vier fysiek kunnen afspreken omwille van de corona maatregelen. Het samenwerken en afstemmen werd hierdoor enorm lastig. We hebben naar nieuwe manieren moeten zoeken om met elkaar in contact te blijven en te overleggen. Regelmatig werd er een vergadering ingepland via videobellen voor officieel overleg en de grote lijnen van ons werk te bespreken. Daarnaast maakten we een overlegplatform aan om kleine, dringendere zaken, vragen, updates en bestanden met elkaar te delen.
We beslisten ook om een online opslagplaats te gebruiken zodat iedereen altijd vanop afstand aan de bestanden kon. Zo kon ieder van ons heel gemakkelijk overal en altijd verder werken aan de thesis: thuis, op het werk, maar even goed onderweg of op verplaatsing. We konden ook ‘in real-time’ de aanpassingen van onze medestudenten volgen, wat de kans op fouten of dubbel werk verminderde. Desondanks is het ons een aantal keer overkomen dat we tijdens bepaalde processen opnieuw moesten beginnen omdat er niet voldoende was afgestemd over de rolverdeling of op welke manier we een bepaalde taak gingen aanpakken. Omdat ik merkte dat dit tot frustraties leidde omwille van verloren werkuren, deed ik het voorstel om een gedeelde takenlijst te maken waar iedereen de verantwoordelijke en de voortgang van elke taak kon zien. Dit leidde duidelijk tot een efficiëntere samenwerking.

Nadat we samen onze methodologie en het kader voor onze systematic review hadden uitgetekend, nam ik het initiatief om in de drie databases Embase, Medline en Cochrane onze zoekopdracht uit te voeren en alle citaten te exporteren naar een bestand dat we konden inladen in een reference manager. Ik zocht uit op welke manier we de meer dan 10.000 artikels konden verdelen over twee groepen van twee onderzoekers en deze geblindeerd screenen via de website Rayyan.ai. Ik kreeg hulp van Ine en Louise om de duizenden dubbele artikels te verwijderen.

In het voorjaar van 2021 kregen we het onverwachte nieuws dat onze promotor, professor Cathy Matheï langdurig afwezig zou zijn. Onze thesis zou verder begeleid worden door Trudy bekkering PhD en Professor Bert Aertgeerts. Na een periode van zoeken en terug op elkaar afstemmen gingen we terug verder met de volgende fases van ons onderzoek. We hadden het geluk dat Trudy met haar expertise de systematiek van ons werk bewaakte en steeds snel bereikbaar was. Prof. Aertgeerts hielp met zijn klinische blik en als ervaren auteur om moeilijke inhoudelijke beslissingen te nemen. Slechts een half jaar later kregen we echter de volgende ernstige klap te verwerken wanneer het

enorm droevige nieuws ons bereikte van het overlijden van Professor Cathy Matheï. We waren alle vier hier enorm door aangedaan, te meer omdat het overlijden van deze enthousiaste vrouw/moeder/huisarts/onderzoekster voor ons als een complete verrassing kwam. Het overlijden van Cathy is een enorm verlies voor familie, vrienden, collega's, patiënten en de academische wereld.

Naarmate we meer zicht kregen op onze resultaten en studies die geïncludeerd werden, merkten Lukas en ik dat het lastiger werd om vanop afstand gezamenlijk aan de thesis te werken. We spraken frequent fysiek met elkaar af om samen aan de thesis te werken. Deze bijeenkomsten verliepen altijd heel vlot en aangenaam. Onze samenwerking zorgde ervoor dat onze thesis schrijven minder als een opgave aanvoelde en we vaak zelfs al uitkeken naar ons volgende overleg. We maakten ieder overleg een eerlijke taakverdeling en afspraken voor een volgende bijeenkomst. De thesis vorderde hierdoor rustig maar gestaag. Lukas respecteerde altijd de onderling gemaakte afspraken en deadlines. Hoe dichter de deadline naderde, moesten we opnieuw nauwer samenwerken met Ine en Louise om alles af te stemmen en één mooi geheel te vormen. Het was heel aangenaam om te merken dat iedereen zijn taak serieus nam en zijn bijdrage leverde voor het eindresultaat. Zo nam bijvoorbeeld Lukas de layout van het artikel en de tabellen voor zijn rekening, verzorgde Ine voor het grootste deel de methodologie, beheerde Louise de bibliografie en de referenties in het artikel. Zelf gaf ik een aanzienlijk deel van de aanzet voor de tekst van de resultaten en onderzoeksvraag, die ik dan raffineerde met Lukas. Ik nam ook regelmatig een leidersrol op om de richting van de thesis uit te zetten en overleg in te plannen. Ik was wel heel opgelucht dat ook de andere leden met initiatief kwamen wanneer ikzelf wat minder tijd of ideeën had.

Ons eindwerk werpt licht op de hypothese dat tramadol een veilig en niet-verslavend opioïd is. Een stelling die in onze eigen ervaring in de huisartsenpraktijk als een vaststaand feit wordt beschouwd. Dit vertaald zich in de koploperpositie die België wereldwijd inneemt wat betreft opioïdengebruik. Na het uitvoerig screenen van databases en lezen van honderden abstracten kunnen we echt wel besluiten dat deze aanname gebaseerd is op te weinig kwalitatieve data en dat rechtstreeks klinisch, vergelijkend onderzoek naar ernstige bijwerkingen tussen tramadol en andere opioïden nooit uitgevoerd is. De ernstige bijwerkingen en verslavingen zijn echter niet onbestaand. Toekomstig onderzoek zou zich dan ook moeten focussen op kwalitatieve klinisch vergelijkende studies. Hopelijk groeit niet alleen bij ons maar ook bij andere zorgverleners in België en bij uitbreiding wereldwijd het besef dat een opoïdenvoorschrift, ook niet voor tramadol, nooit zonder gevaren is. De toenemende interesse in het onderwerp geeft ons alvast goede hoop

Lukas Hermans

Eind 2019, aan de start van onze opleiding, besloot ik om van mijn eindwerk een gezamenlijk project te maken. Tijdens mijn jaren als student heb ik mij mezelf de neiging ontdekt om te flirten met deadlines, waardoor het me een goed idee leek dit opleidingsonderdeel te delen met Dries (Vergauwen), één van mijn beste vrienden (zowel binnen als buiten de opleiding) om samen dezelfde last te dragen. Aanvankelijk vreesde ik dat dit onze vriendschap mogelijk op de proef zou kunnen stellen, je weet namelijk nooit hoe zo'n project verloopt en welke obstakels we zouden tegenkomen. Anderzijds wist ik dat we deze problemen samen beter zouden kunnen trotseren en dat ik algemeen meer gemotiveerd zou zijn voor dit werk aangezien ik hem niet zou willen teleurstellen. We besloten er samen voor te gaan en na een blik te werpen op de thema's in de voorbeeld-lijst, kozen we voor een systematisch literatuuronderzoek. Ons oog viel op tramadol als onderwerp omdat dit een goed

afgelijnd subject was en we beiden interesse toonden voor de huidige opioïdencrisis in de VS. We contacteerden prof. Cathy Matheï, en tot onze verbazing kregen we te horen dat Ine (Frederickx) en Louise (Magnus) ons zouden vervoegen en we een groep met vier zouden vormen. Dit was iets waar ik me initieel wat onwennig over voelde, gezien we ons als duo hadden opgegeven.

Het klikte echter meteen goed met beide dames, en na enkele gesprekken met prof. Mathei hadden we samen een goed omschreven onderzoeks-domein en besloten we twee onderzoeksvragen te formuleren, die we zouden verdelen onder beide duo's. We concretiseerden samen met haar onze in- en exclusiecriteria alsook de zoekstrategie en konden aan de slag. Tijdens onze eigenlijke literatuurstudie kon het werk niet meer evenwichtig verdeeld worden; we splitsten de (meer dan 10 000) artikels in twee groepen die we per twee dubbel geblindeerd zouden doornemen, iet waar ik persoonlijk ongeveer 30 uur mee bezig ben geweest. Vervolgens werden onze resultaten vergeleken en zouden we in groep de finale selectie van studies bekomen. Vanaf nu zou het grootste deel van ons proces in twee groepen verlopen, om uiteindelijk voor de afwerking opnieuw nauwer met vier samen te werken. Het is voor ons dan ook moeilijk om te oordelen over de samenwerking met/tussen Ine en Louise, gezien beide groepen in de praktijk hun eigen afzonderlijke systematic review zouden schrijven, met afzonderlijke resultatensectie en discussie. Ikzelf nam de inleiding voor m'n rekening, en Ine zou zich toespitsen op de (gezamelijke) methodologie.

Ik en Dries verdeelden de taken evenwichtig; Dries nam meer een leidinggevende rol en focuste zich op 'the bigger picture', terwijl ik eerder bijschaafde en me toespitste op de figuren/tabellen, de schrijfstijl en de gedetailleerde afwerking. We zagen elkaar naarmate we dichter bij de eindmeet kwamen steeds frequenter. We legden onze agenda's samen en zorgden ervoor dat we wekelijks een vaste dag afspraken om in dezelfde ruimte te kunnen werken, iets wat er aangenaam verliep en waar we uiteindelijk zelfs naar uitkeken. We raakten steeds beter op elkaar ingespeeld en niets zou ons uit ons lood kunnen slaan…

Zomer 2021 kregen we na een lange afwezigheid het nieuws te horen dat onze promotor Cathy Matheï was overleden na haar strijd tegen kanker. Dit kwam als een enorme klap bij ons allen. Haar passie en drive als huisarts, academica en moeder inspireerde ons om dit werk als eerbetoon aan haar op te dragen. We kregen prof. Dr. Bert Aertgeerts en Trudy Bekkering (PhD) als nieuwe promotoren, een niet evidente opgave voor zowel ons als hen gezien we inmiddels al een eind gevorderd waren en we onszelf tot dan zeer goed op prof. Matheï's visie afgestemd hadden.

Gelukkig is deze samenwerking erg vlot verlopen, en konden we rekenen op de grondigheid en beschikbaarheid van Trudy alsook de medische expertise van prof. Aertgeerts om ons door deze moeilijke periode te loodsen. We troosten ons met de hoop dat Cathy trots zou kunnen zijn op ons eindproduct, dat zonder haar nooit tot stand zou kunnen gekomen zijn.

De laatste weken voor de deadline verliepen gestructureerd. De steilste helling was reeds beklommen, en het zou nu een kwestie van focus en doorzetting worden. We overlegden als groep geregeld om de laatste taken te verdelen: Ine schreef het abstract, Louise zou de referenties managen, Dries schetste met achtergrond-artikels het nodige referentiekader en ikzelf voegde beide delen en bijlages voor het eerst tot één geheel. Iedereen respecteerde steeds de nodige deadlines, en naar mijn mening hebben we elkaar als groep mooi gebalanceerd.

Gezien het aandeel dat België aanneemt in de globale opioïdegebruik, hebben we met dit werk getracht de veronderstelling dat tramadol in vergelijking met andere opioiden veiliger en minder verslavend zou zijn te onderzoeken. Na een uitvoerig literatuuronderzoek kunnen we concluderen dat hiervoor te weinig evidentie bestaat en dat vergelijkende klinische studies nodig zijn om de ernstige bijwerkingen en het verslavingspotentieel van tramadol te bestuderen. We hopen dat huitsartsen en andere zorgverleners zich bewust blijven van de risico's die het voorschrijven van opioïden met zich meebrengen, zodat het gebruikt van deze middelen op een wetenschappelijk verantwoorde manier kan gebeuren.

Ine Frederickx

Geachte lezer,

Ik zou u graag even willen meenemen in het schrijfproces en ook in de moeilijkheden die gepaard gingen met het uitwerken van een thesis als huisarts in opleiding (HAIO).
In 2019 werd dit project opgestart op basis van een suggestielijst van het ICHO, waarbij een literatuuronderzoek over 'het voorschrijfgedrag van Tramadol' mij erg boeiend leek. Ik was aanvankelijk van plan om dit werk uit te voeren met een goede vriendin, Louise Magnus. Na het aanschrijven van onze mogelijke promotor, professor Cathy Matheï, kregen we al snel een mail terug voor een eerste contactmoment. We waren echter zeer verrast toen bleek dat er - toen nog twee onbekende - medestudenten zich eveneens aangemeld hadden voor dit eerste gesprek: Lukas Hermans en Dries Vergauwen.
Maar al gauw bleek dit gelukkig voor weinig problemen te zorgen. We kwamen overeen om met zijn vieren 1) een gemeenschappelijke onderzoeksvraag en 2) een protocol gebaseerd op de Prisma Guidelines uit te werken, waarna onze wegen zich gedeeltelijk zouden scheiden door het uitwerken van deze twee items per twee. Met goede moed startten we eraan in een gezellig cafeetje in het Leuvense. Ik zie ons daar nog zitten met onze notablokken op onze knieën rond een veel te kleine tafel voor vier personen. Toch was het al snel duidelijk dat we dezelfde visie en motivatie deelden omtrent dit proefwerk dat ons de komende drie jaar zou verbinden.

Helaas word je in het eerste jaar als HAIO al snel overladen met werk: seminaries en lessen volgden elkaar in een snel tempo op. Je moet ook wennen aan een nieuwe praktijk, nieuwe werkomstandigheden, alsook van wacht zijn op weekavonden en gedurende het weekend. In het eerste jaar was het dus af en toe zoeken naar tijd om even samen te komen. In het tweede jaar bleek dit nog minder evident te zijn, gezien we toen een ziekenhuisstage liepen waarbij we allen een zo mogelijk nog meer verschillend uurrooster hadden. En toen kwam daar ook nog de uitbraak van corona bij, die een vlotte samenwerking nog moeilijker dan gepland deed verlopen.
We moesten dus op zoek gaan naar nieuwe manieren om met elkaar te overleggen en zodoende begonnen we gebruik te maken van digitale communicatie. We overlegden regelmatig via Zoom-sessies en we gebruikten een gemeenschappelijk online platform. Ondanks onze goede bedoelingen en motivatie gebeurden er toch al wel eens misverstanden, zoals bv. een taakverdeling die niet duidelijk genoeg was afgesproken, waardoor er al eens een taak langdurig bleef liggen, ofwel werd er juist onnodig dubbel werk geleverd. We leerden echter uit onze fouten en er werd een logboek gecreëerd waarin we een taakverdeling konden voorzien, wat tot een efficiëntere samenwerking leidde. Uiteindelijk heb ik toch het gevoel dat de planning altijd in samenspraak met iedereen werd

opgesteld, zodat er een eerlijke taakverdeling uit voortgevloeid is.
In het midden van onze thesiswerken werden we - omwille van de langdurige afwezigheid van onze promotor professor Cathy Matheï - toegewezen aan een nieuwe promotor, professor Bert Aertgeerts, alsook een co-promotor, mevr. Trudy Bekkering. Trudy is dank zij haar enorme inzet een enorme rots in de branding gebleken, maar daarnaast konden we tijdens het gemeenschappelijk overleg ook steeds op het deskundig advies van professor Aertgeerts rekenen. Na een tijdje kregen we spijtig genoeg het droevige nieuws te horen dat Cathy overleden was. Dit kwam aan als een enorme klap voor ons. We hopen dat ons eindwerk dan ook als een klein eerbetoon aan haar mag beschouwd worden, gezien dit zonder haar nooit tot stand zou gekomen zijn. Onze gedachten gaan nog steeds uit naar haar, haar familie en collega's.

Om onze thesis tot een goed einde te brengen zijn we tijdens het werkproces zo methodisch mogelijk tewerk gegaan. Zoals eerder gezegd verliep de taakverdeling in het begin gemeenschappelijk. We hebben eerst samen een zoekstrategie en een protocol uitgewerkt waarna Dries, de IT 'er van dienst, ervoor zorgde dat we onze citaten in Endnote - een reference management Tool - konden verdelen. Ikzelf zocht uit hoe we het merendeel van de duplicaten via deze tool konden verwijderen, zodat we dit niet meer handmatig moesten doen. Uiteindelijk eindigden we net onder de 20.000 artikels, die we eerlijk verdeelden per groep en verder dubbel blind zouden nagaan op basis van titel en/of abstract. Dit bleek een erg intensieve taak voor mij te zijn, waar ettelijke uren zijn ingekropen omdat ik zeker geen belangrijke artikels wou missen en moeilijk op titel durfde weg te selecteren. Bij de tweede zoekopdracht waarbij er nog eens 1.000 artikels zijn bijgekomen kende ik de materie al beter en ging het duidelijk al veel vlotter. Na het verdelen van de resterende artikels werd ons werk dan meer opgedeeld per twee groepen (Louise en ik enerzijds, Lukas en Dries anderzijds).
Louise en ik communiceerden eveneens voornamelijk online, hetgeen soms alweer tot wat vertraging leidde. Daarom heb ik nadien voorgesteld om meer fysiek af te spreken, waarbij we telkens een deadline voor onszelf vastlegden tot de volgende bijeenkomst. Zo kwamen we tot een vlottere samenwerking en ook de deadlines werden van beide kanten beter gerespecteerd. Het schrijfwerk werd onderling verdeeld, waarbij ik zelf het abstract, de methodologie, de discussie voor onderzoeksvraag twee en de algemene conclusie voor mijn rekening nam. Louise heeft voornamelijk de resultatensectie van onze onderzoeksvraag uitgewerkt, in combinatie met het - niet te onderschatten werk - om deze resultaten in een duidelijke tabel te presenteren. Ook de referenties werden door haar in orde gebracht op het einde van onze werken.
Lukas nam de inleiding voor het gemeenschappelijke deel voor zijn rekening. De uitgewerkte teksten werden bovendien ook altijd nagekeken door Lukas en Dries waarna de nodige aanpassingen volgden, zodat we zeker kunnen spreken van een gemeenschappelijk uitgewerkt groepswerk.

Onze literatuurstudie probeert een antwoord te geven op de vraag of de ernstige nevenwerkingen en het verslavingspotentieel van Tramadol niet onderschat worden. Na het beschrijven van ons literatuuronderzoek kunnen we een duidelijk antwoord echter nog niet voldoende staven, temeer omdat ons werk uiteindelijk een beschrijvende analyse betreft, waarbij we onze resultaten niet statistisch hebben kunnen toetsen. Dit wijten we vooral aan het gebrek aan vergelijkende klinische studies. We kunnen enkel stellen dat er te weinig bewijs is om lichtzinnig om te gaan met het voorschrijven van Tramadol, maar als huisartsen van de toekomst hopen we evenwel dat er meer bewustzijn komt omtrent de zeker niet onbestaande nevenwerkingen van dit geneesmiddel. We hopen van harte dat we met onze thesis hierbij al een eerste stap in de juiste richting hebben gezet.

Louise Magnus

Toen wij aan het begin van onze HAIO carrière een onderwerp voor onze masterthesis moesten kiezen, viel mijn oog meteen op het onderwerp tramadol. Het was tijdens mijn stages een opioid dat immens veel voorgeschreven werd, en het leek me als toekomstige huisarts een verrijking om hier verder in ondergedompeld te worden. Ik sprak een van mijn goede vriendinnen en collega HAIO, Ine Frederickx aan met de vraag of ze dit eventueel samen wou aanpakken. Zij was ook geboeid door dit onderwerp en zo meldden wij ons gezamenlijk aan om onderdeel uit te maken van het 'Tramadol-team'. We werden onder supervisie van Catharina Mathei gekoppeld aan ons mede duo : Dries Vergauwen en Lukas Hermans. Tijdens een eerste kennismaking met Cathy werd duidelijk dat het om een literatuuronderzoek ging, waarbij zij het interessant vond om onze onderzoeksvraag zowel over de mogelijke ernstige nevenwerkingen van tramadol te laten gaan, als over het mogelijk misbruik. Zo gezegd, zo gedaan. Dries en Lukas zouden het onderwerp nevenwerkingen aannemen, Ine en ik namen het misbruik voor onze rekening.

Initieel hebben we reeds met z'n vieren erna afgesproken om een planning op te stellen, en een tijdlijn vast te leggen. We maakten een groepsgesprek aan op Messenger, en een Google Drive document om onze voortgang vast te leggen. Zoals ieder wel weet, werd er maart 2020 roet in het eten gestrooid, om live met elkaar samen te komen. Vanaf dan waren Zoom meetings het voornaamste kanaal om met elkaar in contact te komen. Dit is natuurlijk iets stroever verlopen dan wanneer we een vaste afspraak zouden hebben gehad, waarbij we elk bijvoorbeeld 3 uur van onze tijd zouden uittrekken om aan onze paper te werken. Soms zorgde dit dan ook voor miscommunicatie, waardoor we een aantal keer wat dubbel werk hebben gedaan. Het voordeel is natuurlijk wel dat een meer frequente korte meetings konden plaatsvinden, waardoor we kort konden opvolgen wat de ander deed.

De methodologie, PICO en zoekstrategie heeft even geduurd om uit te werken, maar daarna konden we onze zoekopdracht uitvoeren in de verschillende databases, en kwamen we uit op zo'n 'kleine' 10.000 artikels. Dries heeft deze zoekopdracht uitgevoerd en heeft deze artikels via Rayyan in 2 gesplitst. Zo had elk duo ongeveer 5000 artikels, die we geblindeerd van elkaar moesten screenen. Ine en ik hadden elk zo onze eigen strategie. Ik probeerde een eerste grote exclusie uit te voeren door als trefwoorden onze exclusiecriteria in te voeren. Dit zorgde voor een snelle selectie, maar toch duurde het een aantal maanden eer we door dit huzarenstukje waren.

In de zomer van 2020 legde Lukas zich voornamelijk toe op de inleiding, die we toen naar Cathy doorstuurden voor feedback, waarvan we snel groen licht kregen. Wij gingen verder met het screenen van de gevonden artikels. Echter in februari 2021 kregen wij te horen dat Cathy voor een langere tijd afwezig zou zijn, waardoor we een nieuwe promotor : Prof. Dr. Bert Aertgeerts, en copromotor Trudy Bekkering, PhD toegewezen kregen. Meteen werden nieuwe afspraken gemaakt met prof Aertgeerts en Trudy via Zoom, en de uitleg over het concept werd duidelijk gemaakt. Helaas kregen wij enkele maanden later te horen dat Cathy overleden was, wat bij ons allen zeer hard aankwam. Hierdoor denk ik dat we wel alle vier een extra boost hebben gekregen om er voor haar iets moois van te maken.

Begin 2021 waren er na verloop van tijd wel wat meer mogelijkheden om samen te komen. Ine en ik hebben dan ook samen gezeten wanneer wij onze artikels op basis van abstract hadden

geselecteerd. De blindering werd uitgezet, en de mogelijke conflicten werden zo duidelijk. Door zeer grondig over deze conflicten te gaan, zijn we uiteindelijk op onze selectie van full texts gekomen, die we dan evenwichtig hebben verdeeld, en in een excel bestand gegoten. De samenwerking met Ine verliep zeer vlot. Ine is een zeer leidinggevend persoon, waardoor ik misschien iets meer op mijn lauweren gerust heb dan dat ik zou willen. Zij is zeer consciëntieus, en nam vaak de aanzet. Wat mij betreft, heeft zij een zeer centrale rol gespeeld in het tot stand komen van de paper!

Nadat Dries en Lukas een tweede search hebben uitgevoerd, hebben we het proces nog eens opnieuw overlopen, en zijn Ine en ik na het analyseren van de volledige artikels meer en meer samengekomen. We merkten ook dat deze manier veel vlotter voor ons ging, en ik merkte dat ik dan ook veel meer gedaan kreeg. Ine wierp zich op om de methodologie te ontwikkelen, de jongens hielden zich bezig met de PRISMA flowchart, en ik probeerde onze resultaten uit te schrijven en ook om te zetten naar verscheidene tabellen. Ine startte hierna met onze discussie. Tijdens onze live meetings was het veel makkelijker om onze twijfels en bezorgdheden aan elkaar te uiten, die dan gezamenlijk en zonder misverstanden konden uitgeklaard worden.

Met z'n vieren stuurden we de laatste dagen vaak onze resultaten en discussie door naar elkaar, om uiteindelijk ook tot een gezamenlijke conclusie te komen. Op basis van een bijna afgewerkt product maakte ik ook een bibliografie in Endnote en konden de referenties toegevoegd worden.

Onze studie belicht nogmaals de gevaren van tramadol, die niet altijd zichtbaar zijn aan de oppervlakte, maar die hopelijk voor huisartsen een soort samenvatting kan zijn van de beschikbare literatuur. Ik denk dat we als team de gebruikelijke ups en downs hebben gekend, maar dat we achteraf gezien wel een product hebben gemaakt waar we trots op kunnen zijn om in te dienen, zeker met prof Mathei in onze gedachten!