The Influence of Chronic Opioid Use on Social Relations: A Scoping Review

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Table of content

1. Abstract 5
2. Background 5
3. Methods 7
   3.1 Design 7
   3.2 Data collection 7
   3.3 In- and exclusion criteria 8
   3.4 Data analysis 8
4. Results 8
   4.1 Study methodology 9
   4.2 Study location 9
   4.3 Patient population 9
   4.4 Definition, indication, and specification of (chronic) opioid use 10
      4.4.1 Definition of chronic opioid use 10
      4.4.2 Indication of chronic opioid use 10
      4.4.3 Specification of opioid use 10
   4.5 Definition of social relations 11
   4.6 Association chronic opioid use and social relations 12
5. Discussion 13
   5.1 Association Chronic Opioid Use and Social Relations 13
   5.2 Bidirectionality 13
   5.3 Heterogeneity in definitions of outcome terms 14
   5.4 Strengths 15
   5.5 Limitations 16
   5.6 Clinical implications 17
   5.7 Future research 18
   5.8 Conclusion 18
6. Kritische zelfreflectie 19
   Alexander Berghmans 19
   Clara Merckx 19
   Etienne Gombert 21
7. REFERENCES 22
8. ADDENDA 26
   Figure 1: Prisma flowchart 26

Appendix 1 (protocol): 27
Appendix 2: MINDMAP bidirectionality 32
Appendix 3: search string 33
Ethical commission 35
Table 1 36
Table 2 37

The Influence of Chronic Opioid Use on Social Relations: A Scoping Review.

1. Abstract

Background: The opioid epidemic is a well-known concern in the world. Chronic use of opioids can influence different aspects of a person's daily life. The purpose of this review is to give an overview of what is known about the influence of chronic opioid use on social relations.

Methods: This scoping review was conducted by 3 researchers. Screening the literature was done using the following databases: PubMed, Cochrane Library, Web of Science, and Embase. A search string with the concepts "opioid use" and "social relationship" was used. Articles were in- or excluded based on strict in- and exclusion criteria. The official steps of the PRISMA protocol for scoping reviews were followed. The included articles were analyzed and recorded in a data charting table.

Results: The title and abstracts of 5804 articles were screened. After a full-text analysis of 38 articles, 9 articles were included. Several studies did not provide a specific definition of chronic opioid use. The indication for opioid use varied across the studies as well as the used definition of "social relations". The articles show us a possible bidirectional link between chronic opioid use and social relations.

Conclusion: This scoping review elicits certain gaps in the current existing literature concerning the influence of chronic opioid use on social relations. To demonstrate any causal relation between opioid use and social relations, additional research is needed with a prospective and longitudinal study design. The lack and necessity of a consensus concerning the definitions of used terms like "chronic opioid use" and "social relations" to draw general conclusions about this subject, is also exposed. Understanding the impact of long-term opioid use on social functioning is crucial. The prescription of opioids for patients who have a smaller social network or who live in social isolation should be delivered with extra caution. When physicians prescribe long-term opioids, close monitoring of these patients is in order. Nevertheless, as this needs further investigation, this scoping review might be a starting point for any future research in this research domain.

2. Background

In humans, endogenous opioids are involved in addiction, sexual behavior, mental disease, mood, learning, and memory, as well as digestion, breathing, appetite, stress, and immunity. (1) Endogenous opioids play a role in the development of social bonds in animals, which is essential for the survival of the species. Additionally, social interaction raises endogenous opioid levels. In the development and maintenance of social interactions, the endogenous opioid system is essential. The BOTSA theory (brain opioid theory of social attachment) is based on the acknowledged resemblance between opioid dependence and dependence on a social connection. It claims that endogenous

opioids are essential for human social connection. (2, 3) According to BOTSA, opioids influence how people feel emotionally in close relationships and how they act or feel in ways that can encourage them to bond more profoundly. (4)

Science has previously made clear that social connections and a social network are crucial to a person's function in society. Humans are social beings and social relationships are essential to our overall well-being and happiness. Years of observational study demonstrate a bidirectional causal relationship between social connections, relationships and good health. (5) While having a strong social network is essential for maintaining mental health. If you're not fortunate enough to have one, it can result in a socially isolated life. Social isolation causes physical as well as psychological harm. The definitions of social isolation in the literature vary widely. (6, 7) .avaleta et al. defined it in their review as "the inadequate quality and quantity of social relations with other people at the different levels where human interaction takes place (individual, group, community and the larger social environment)." (8)

In the research of Waltona et al (2003), social factors are also discussed as potential predictors of drug use following abstinence. Minority status and lower income levels were reliable indicators of drug usage. Additionally, a protective factor against drug use after abstinence was being married. Previous research has shown that among male drug users who are married, recovery from addiction is more successful. (9) Furthermore, according to Vyas et al., older persons who are lonely tend to take higher amounts of opioids and benzodiazepines on a daily basis. (10)

According to the studies mentioned above, people without social networks are more likely to use drugs or opioids, and have higher risk of relapse after abstaining from drugs. What about the inverse relationship, though? Is there a correlation between long-term opioid use and social isolation? Does long-term opioid use increase social isolation?

Studies have shown that the exogenous ingestion of opioids prevents social interactions with conspecifics. According to Carlyle et al., opioid users have altered social functioning. (11) It has been demonstrated that opioids reduce separation anxiety in rodents.(12)Because chronic opioid abuse makes it harder to fit in with a social group, it has a detrimental effect on a person's psychological and neurological health. It has been demonstrated that opioids reduce separation anxiety in rodents.(12) Because chronic opioid abuse makes it harder to fit in with a social group, it has a detrimental effect on a person's psychological and neurological health. There is a correlation between the increase in opioid use and increasing social isolation. (3) According to Vina et al, opioid analgesic users were more likely than non-users to experience moderate to severe depressive symptoms and less social support. (13) According to scientific research, individuals who use opioids are more likely than those who use other drugs to have unstable social networks, unstable jobs, and poorer levels of education. So, compared to those who take other drugs, opioid users are more likely to feel socially isolated. (14) The use of opioid analgesics was independently linked to a higher level of depression than use of other oral analgesics.(13) Exogenous opioid consumption over an extended period of time is harmful to socialization, healthy behavior, and coping mechanisms for life's challenges including social rejection. (15)

The definition of chronic opioid use has clearly changed in recent years in the literature, going from 120 days to 90 days. (16) In other words, the threshold for chronic opioid consumption was lowered.

With an increase in opioid overdose deaths, the opioid epidemic is a well-known concern in the US. The rise in opioid use is an important issue, not just in the US but also in Europe. Five opioids (tramadol, tilidine, oxycodone, fentanyl, and piritramide) that makeup around 80% of all opioids that are reimbursable in Belgium were examined by the National Institute for Health and Disability Insurance (RIZIV). The number of patients who took at least one of these five opioids increased by 88% between 2006 and 2017. This is equivalent to 1,104,485 insured people, or almost 10% of all Belgians. (17) Given the significant social impact of opioids, it is important to learn more about how long-term opioid use may disrupt social functioning. The purpose of this review is to give an overview of what is known about the influence of chronic opioid use on social relations.

3. Methods

3.1 Design

The design of this qualitative study is a scoping review, which aims to identify and analyze available evidence. Furthermore, it helps to identify existing knowledge gaps. (18) This review followed a predetermined procedure that can be found in the protocol. *(Appendix 1)*

3.2 Data collection

A literature search was conducted by 3 researchers. The following databases were used: PubMed, Cochrane Library, Web of Science, and Embase. A search string with the concepts “opioid use” and “social relationship” was used to get an overview of what we do and do not know about the research question. By reading the published articles, we obtained a feeling for the existing literature and could refine our search terms to obtain as many articles as possible. First, we screened the hits we obtained with a draft version of our search string, by including articles for background information based on title and abstract. This way we got a selection of studies to help us build a more accurate search string.

Before starting the search for our review, the search strings were verified by an expert in the matter of the KU Leuven library. The search strings were modified in response to the input, and then were applied to the databases. The final search strings that were used can be found in the appendix section. *(Appendix 3)* The results of this first search were collected in the EndNote library software program to screen for and immediately delete any doubles in the collection.

As the design of the study is a scoping review, an additional search was conducted to check for any grey literature. For this mainly the following sources were used: Grey lit, Mednar and Grey Matters. More specifically the next search terms were used: “chronic opioid use” and “social relations”. During the search process, every researcher paid attention to any useful and interesting article by snowballing in the lists of references. For snowballing, we started with the included articles. The methods of backward (we looked at the articles in the reference list of our articles) and forward snowballing (identifying publications that cited our original included articles) were conducted. (19)

To make the final selection, every researcher screened 2/3 of the articles. Using this method, every article was checked by at least 2 researchers. All the resulting articles were collected on Rayyan.ai

for a profound screening. The conflicting results were collectively discussed to obtain a consensus. Finally, the resulting articles were included for the next and final step of the search: an analysis of the full text. The predetermined in- and exclusion criteria discussed below were used to check the eligibility, as well as a collective discussion to decide on any conflicting screening results.

The Prisma Flow chart is used to schematically show the results of the screening process (fig 1).

3.3 In- and exclusion criteria

For defining specific inclusion and exclusion criteria, the set-up was to include articles that made it possible to withdraw conclusions as much generalizable as possible. For example, residents, hospitalized and palliative patients were excluded because many social cofactors would influence the outcome. Only persons older than 18 years were included, as adolescents and children are a specific type of patients with specific cofactors in their social relationships.

The following in- and exclusion criteria were applied. Inclusion criteria: adults (>18 years old), prescribed pharmaceutical opioid use, chronic opioid use (>/= 3 months), social relations. Exclusion criteria: Residents, palliative patients, and hospitalized patients; Illegal opioid (ab)use (heroin) or substitution therapy in the form of, for example, methadone.

3.4 Data analysis

All the included articles were analyzed to obtain useful data and outcomes. The data extraction was done using the program Excel to create an extensive data charting table. As mentioned in the study protocol, the information was systematically recorded as follows:

- Title, author(s), year of publication, and study location
- Study type & methodology
- Study population (age, sample size)
- Indication of opioid use, type and dose of opioids used, duration of opioid use
- Outcome measures
- Definition of 'social relations'/ setting of living
- Conclusion(s) of the author(s)
- Gaps/inspiration for future research

Together, these data formed the basis of analysis and discussion in this scoping review.

4. Results

In total, the literature search, conducted on the 5th of July 2022, yielded 7737 articles. After removing the duplicates with Endnote 6348 studies remained. After uploading the articles in Rayyan, 544 remaining duplicates were also removed. As such 5804 articles were screened, based on title and abstract. This screening resulted in the selection of 24 articles. After full-text analysis, 9 articles were included. None of the articles from the grey literature databases or the snowballing process were eligible. The results of the screening process are shown in the Prisma flowchart *(fig. 1)* Next, we will provide an overview of the key components and most relevant findings from the selected

articles. Any further details about the studies can be found in the data extraction table *(Tables 1 and 2).*

4.1 Study methodology

Four of the articles are cross-sectional analyses, in which data is collected from subjects at one particular point in time. (10, 13, 20, 21) The other study designs are and include a retrospective cohort, a longitudinal study, two narrative reviews, and one descriptive study. (14, 22, 23, 24, 25)

In four studies, participants had to complete questionnaires. (10, 13, 20, 23) Vyas et al. administered their questionnaire using telephone interviews with the study subjects. Soin et al. conducted the Short Form -36 (ware, 36), which is a short-form health survey that assesses physical, mental, and reported health transition to produce a profile of functional health and well-being scores. (23) Two studies by Yang et al. used data from Medicare datasets. (21, 25) Medicare is a federal healthcare program for senior individuals in the United States (65 and older) who paid Medicare taxes while they were employed. *Conversations about opioids* is a qualitative study by Dassieu et al. that drew data from interviews conducted via telephone calls. (22)

4.2 Study location

All studies were conducted in the northern part of the American continent. While the studies of Dassieu et al. and Vyas et al. are both conducted in Canada with datasets and results derived from Canadian study populations (10, 22), the other 7 researches are conducted in the United States. Furthermore, Dassieu et al. collected all the data in 2 provinces of Canada, more specifically Quebec and British Columbia. In contrast, other studies used nationwide databases for the selection of the study population and/or the data extraction. Day et al. and Vyas et al. are two examples of research where a nationwide database is used. Respectively pooled data from the National Survey on Drug Use and Health (NSDUH) of 2015-2017 (26, 27, 28) and data from the 'Healthy Aging' study of the Canadian Community Health Survey (CCHS) of 2008 are used for these 2 articles. (29)

4.3 Patient population

Sample size varied significantly between studies, with four studies having a large sample size (ranging from 3079 (21) to 9 249 288 (25)). The remaining five studies had smaller sample sizes, ranging from 22 respondents (22) to 360 participants. (13)

The age of the research population ranges widely. Two articles have a population ranging from 20 to 70 (22) and from 20 to 87 years. (23) Two of the included studies (21, 25) Two studies included patients of 50 years old. (13, 20) This cutoff was set in the article of Day et al. because the older population are more likely to be prescribed opioids with abuse potential. Approximately 25% of elderly are using psychoactive medication. (30) In the last four studies mentioned, it was not specified what the upper age limit of the study subjects was.

Four of the articles are representative of the population. (10, 20, 21, 25) The study of Vina et al. can't be extrapolated to the general population because they only included patients with knee

osteoarthritis. (13) In the other articles either authors didn't specify a population (14, 23, 24) or the sample size was too small to generalize to the general population. (22)

There is a distinction in the participants' gender in five of the included papers. (10, 13, 20, 22, 23) Four of these studies have a higher proportion of women. 12 women and 10 men took part in the interview study of Dassieu et al. Women are also slightly more numerically represented in the Day et al. study, with 14281 female participants compared to 12041 male participants. 39 women and 28 males participated in the study by Soin et al. Likewise, there are more women than men in the study of Vyas et al. Only in the research of Vina et al. of patients with knee osteoarthritis was a higher participation rate for men observed. The participants' gender is not mentioned in the other articles.

4.4 Definition, indication, and specification of (chronic) opioid use

4.4.1 Definition of chronic opioid use

Neither Christie et al. nor Dassieu et al. or Vina et al. provides a specific definition of chronic opioid use. (13, 14, 22) Day et al. describe chronic opioid use as "past-year opioid misuse". (20) Soin et al. interviews subjects 6-36 months after institution of opioid therapy. (23) In his narrative review, Sullivan defines chronic opioid use as use of these analgesics for more than 90 days. (24) The definition of chronic use in the study by Vyas et al. was one month (10), while Yang et al. use patients with an OUD status in the health insurance database (Medicare). (21, 25) The requirements under which patients are given this OUD status are explained below.

4.4.2 Indication of chronic opioid use

In two studies the indication of opioid use is only described as having pain for 3 months or more. (22, 24) In one study they used having nonmalignant pain for more than 6 months as an indication for opioid use. (23) The indication of opioid use was for "chronic or potentially disabling diseases" in both studies conducted by Yang et al. (21, 25) Vina et al. dealt specifically with patients with knee osteoarthritis. (13)

4.4.3 Specification of opioid use

Day et al. assessed opioid drug use by asking participants to report the use of a drug in question in any way a doctor did not direct them to use it (opioids, benzodiazepines). This includes:
1) use without a prescription,
2) use in a greater amount, more often or longer than prescribed
3) use in any other way a doctor did not direct them to take it. (20) Vina et al. used a dichotomous variable indicating use or no use of osteoarthritis medication of interest (NAIDS, COX 2 inhibitors and opioids). For this study, patients were grouped into three categories of analgesic use: oral opioids (with or without other oral analgesic treatments), oral non-opioid analgesics, and no oral analgesic use. Dosage, frequency, and quantity are not specified. (13) Vyas et al. investigated three medication groups: 1) opioids, 2) benzodiazepines or 3) non-opioid analgesics. For each group, participants were classified as 'non-users' (did not take the medication in the past month), 'occasional users' (took the

medication in the last month, but not daily) and 'daily users' (daily use of medication in the past month). (10) An exact formulation of dosage, frequency or quantity is not specified in any of these three articles.

Yang et al. utilized three sub-indicators to define opioid use disorder: 1) Diagnosis and procedure basis for opioid use disorder, 2) Opioid-related hospitalization or emergency department visits, and 3) Use of medications for opioid use disorder. When any of the three criteria were met, the beneficiary was defined as having opioid use disorder. (21, 25) Vina et al. used a dichotomous variable indicating use or no use of osteoarthritis medication of interest (NAIDS, COX 2 inhibitors and opioids). For this study, patients were grouped into three categories of analgesic use: oral opioids (with or without other oral analgesic treatments), oral non-opioid analgesics, and no oral analgesic use. Dosage, frequency and quantity are not specified. (13) Vyas et al. investigated three medication groups: 1) opioids, 2) benzodiazepines or 3) non-opioid analgesics. For each group, participants were classified as 'non-users' (did not take the medication in the past month), 'occasional users' (took the medication in the last month, but not daily) and 'daily users' (daily use of medication in the past month). (10) An exact formulation of dosage, frequency or quantity is not specified in any of these three articles.

4.5 Definition of social relations

Different aspects and definitions of the concept "social relations" are used in the selected articles. Four studies used the parameter social isolation. For example, Christie et al. focuses specifically on the social isolation concept, seen as having no or limited social relationships or having social relationships of poor quality. (14) The concept of "social isolation" is described by Day et al. with different social proxy variables (marital status, living alone or not, attending religious services or not). (20) Yang et al. focused on the role of county-level social isolation. County-level social isolation was specified as the experience of social disconnectedness or low social interactions and connections. Also, in this article, the "social isolation index" was used, which was generated by averaging the following standardized variables: percentage of older households (aged 65+) who live alone, percentage of older adults living in poverty, and percent of older adults living with a disability. In here higher values indicate higher levels of social isolation. This index aimed to assess exposure to marginalized populations, under the premise that exposure to such populations places one at risk for social isolation. (21, 25, 31)

On the other hand, Dassieu et al. focuses more on the interaction aspect of social relationships. More specifically they assessed the worries of patients with chronic pain using opioids, and their families, prejudices, stigma and discrimination these patients may experience and how these people are handling this stigma. (22)

Another definition of social relations is used by Soin et al. As outcome measures different terms were used, concerning physical and mental health. One of these parameters is 'social functioning', as defined in the Short Form 36 health survey. (23, 32) Here social functioning was scored based on how someone can or can't perform his/her social activities, and how much these social activities are interfered by his/her emotional or physical problems.

Vina et al. investigated the parameter of social support and the presence of depressive symptoms. The 'social support' of subjects was calculated with a score generated through a 4-item scale that represents four dimensions: emotional/informational, tangible, affectionate, and positive social interaction. (13, 33)

Different from the other included articles, Vyas et al. used the term 'loneliness' as parameter to represent "social relations". To assess loneliness the Los Angeles Loneliness Scale of the University of California is used. The medication use was assessed through a self-report method. (10)

Nevertheless, not every article gives a detailed definition of "social relations". For example, Sullivan et al. uses the terms social and emotional functioning without giving an exact definition of these terms. (24)

4.6 Association chronic opioid use and social relations

Every included article has its specific outcome parameters concerning 'opioid use' and 'social relations'. The results of investigating the association between these parameters are shown below:

Dassieu et al. described that the participants' social interactions were more frequently characterized by stigma and misconceptions of opioids. This might result in a decline in their personal and professional relations. (22)

Christie et al. explained a possible bidirectional link between opioid use and social isolation in a narrative review. (14) The other narrative review by Sullivan et al. provided a brief insight in the link between chronic opioid use and stated that it can impair social and emotional functioning. (24)

Day et al. shows a significant association between marital status as a social-isolation proxy-variable and combined opioid and benzodiazepine use. This association was significant between being unmarried and the combined use of opioid and benzodiazepines, but not for opioid use alone. (20)

Yang et al researched county-level social isolation and the association with opioid use disorder (OUD). A significant association was found between high levels of social isolation and a higher risk of OUD, at least when it came to non-Hispanic white people. (25) The second included article of Yang et al. showed that the relation between social isolation and OUD is significant regardless of the metropolitan status. (21)

The questionnaire conducted by Soin et al. showed a small but statistically significant self-reported increase in social functioning after at least 6 months of opioid use in patients with chronic nonmalignant paint. (23)

Vina et al. investigated the link between social and psychological factors and the use of opioids. The results showed that opioid users had lower social support and also had a higher risk of having severe depressive symptoms. However, after adjusting these results to a few sociodemographic covariates, these findings were no longer significant. (13)

The association between loneliness in older adults and medication use, under which opioids, was investigated by Vyas et al. Older adults with a higher level of loneliness appeared to use higher daily doses of opioids. (10, 34, 35)

5. Discussion

In this study we aimed to identify the influence of opioid use on social relationships. As such the initial purpose was to investigate a unidirectional relationship between chronic opioid use and social relations. However, in the current literature not many articles answering this research question could be found.

5.1 Association Chronic Opioid Use and Social Relations

As described in the results, in 8 out of 9 articles the likelihood of consuming chronic opioids is - whether significant or not - associated with having a poor social network, although it should be noted that this link may be bidirectional. There is a connection between social interactions and opioid usage, depending on how they are specifically defined. For instance, we observe a lower risk of opioid use disorder when a social relationship indicator is positive, such as social support or social stability. The risk of opioid use disorder will rise with a negative description of social relationships, such as social isolation. For example, the articles with 'loneliness' (10) or social isolation (14, 20, 21, 25) showed a possible link with a higher use of opioids. Whereas the articles with terms like 'social support' (13) or 'social functioning' (24) showed an inverse association with opioid use.

Only one of the included articles shows an increase in the 'social relations' outcome measure when opioid use was compared with no opioid use. Soin et al. found a significant increase in social functioning, after at least 6 months of opioid therapy. (23) However, there are several aspects that must be taken into account before conclusions could be drawn. For example, this study had a retrospective patient selection and there is also a risk for bias because of the wide variation in follow-up times. Besides this, the patient population was heterogeneous. Dr. Soin reported also that he was a recipient of a research fellowship from Alpharma which poses a conflict of interest.

5.2 Bidirectionality

Most of the articles, matching our in- and exclusion criteria, were studies investigating the relationship between 'social relations' outcome measures and opioid use, the other way around. Nevertheless, these articles were perceived to be useful for this scoping review because of a possible bidirectional relationship between the two research terms. The bidirectionality of the association was first mentioned in the BOTSA theory. (1) For this review, the most interesting aspect of the theory is the hypothesis that endogenous opioids are essential for human social connection. (2, 3) According to BOTSA, opioids influence how people feel emotionally in close relationships and how they act or feel in ways that can encourage them to bond more profoundly. (4)

As previously stated, there is overlap in the brain regions used in opioid use disorder, pain and social-emotional functioning. (7) There exists a link between social isolation and opioid use. Acute opioid use will lead to a pharmacologically-induced sense of social connection. This in turn gives a decreased motivation to experience physical social connection. As a consequence, there is an increased perception and experience of social isolation which may lead to more acute opioid use.

(14) Acute opioid use has been demonstrated to reduce pain in physical and emotional dimensions when used in an acute setting. As Christie states in her narrative review, this immediate opioid effect might eventually result in chronic use and increased social isolation, creating a vicious cycle. The endogenous opioid system could be an explanation and a mechanistic basis for a possible bidirectional link between social isolation and opioid use disorder. (14) For the use of illegal opioids, like heroin and cocaine, this bidirectional link has already been demonstrated. (36) This might also be the case for prescribed legal opioid use, but there is a gap in the existing literature when it comes to the effects on social relations of prescribed legal opioids.

As was stated above, it is not possible to establish a clear unidirectional link between our research terms. The bidirectionality of the outcome terms is highlighted in the papers, which will be further discussed below. For example, the findings of Vyas et al. and Day et al (table 2) might be biased by reverse causality (10, 20), a two-way causal relationship, due to its cross-sectional methodology. In addition, Yang et al reports the possibility of reverse causality in their limitations. (25)

Sturgeon et al. also suggested a bidirectional link between emotional distress and chronic pain. (37) The included paper of Vina et al. showed that having depressive symptoms is associated with higher use of oral opioids in knee osteoarthritis patients. (13) Conversely another retrospective cohort study Scherrer et al. demonstrated that opioid users have a higher risk of developing depressive symptoms. (38) Again, any causality could not be concluded due to the non-prospective study design. Nevertheless, all these findings indicate a possible bidirectional link between depressive symptoms and opioid use. Taking all this into account and considering that depressive mood disorder will affect any person's social functioning and social relations as such, this may indicate a bidirectional link between social relations and chronic opioid use.

Important to notice is that chronic pain as such can lead to social isolation, as individuals may avoid activities or social events due to pain. Social isolation can exacerbate chronic pain, as it can lead to decreased physical activity and a lack of social support. The relationship between chronic pain and social isolation is bidirectional, meaning that chronic pain can lead to social isolation, and social isolation can worsen chronic pain. A review by Duenas et al. documented that individuals with chronic pain are more likely to report feelings of loneliness and social isolation, and may have smaller social networks. (39) This makes it challenging to measure the exact effect of opioid use for chronic pain on the social relations of patients, without overestimating it because of the additional effects of the factor chronic pain itself.

An overview of all the bidirectional links can be found in the appendix section. (appendix 2)

5.3 Heterogeneity in definitions of outcome terms

According to the results, a certain heterogeneity can be seen when it comes to the used definition of ‘social relations’ in the included articles. It makes it necessary to interpret all the results with a certain restraint if we want to draw general conclusions. A few articles use the same general term to describe the outcome measure of social relations. For example, Day et al. and Yang et al. talk about specifically ‘social isolation’. (20, 21, 25) Nevertheless, it's important to notice that they use a

different definition of social isolation (table 1). Yang et al. specifically defines “social isolation” as deprivation of social connectedness, lack of contact or sustained interaction with individuals of institutions. (21) In the literature there is no international consensus about how exactly to measure parameters as for example social isolation. It’s important to pay attention to this, because this can have a significant influence on interpreting study’s results.

Another definition to describe ‘social relations’ is the parameter loneliness. Vyas et al. used the Los Angeles Loneliness Scale of the University of California to assess levels of loneliness and found an association between higher levels of loneliness and daily use of opioids. (10) In contrast to these results, the cross-sectional study of Day et al. could not find a significant association between living alone and the misuse of prescribed opioids. (20) On the other hand, a study from 2015 conducted in Germany, found that lonely older adults were more likely to use opioids and benzodiazepines. (40) The available literature consists of contradictory studies and results when it comes to the link between loneliness and opioid use. Hence it is difficult to demonstrate a clear relationship between loneliness and opioid use in this scoping review.

Vina et al. used the parameters “social support” and “depressive symptoms”. An independent association was found between moderate to severe depressive symptoms and oral opioid use in patients with knee osteoarthritis. (13) More important for this review, they also found that opioid users had lower social support in comparison with non-medication users. These findings of Vina et al. are somehow in line with Rosemann et al. who stated in 2007 that living alone was the strongest predictor to an increase in general practitioner visits for osteoarthritis patients in Germany. (41) As Vina et al states, social support may be a factor that mitigates the experienced severity of a disease like osteoarthritis. Moreover, lower social support may lead to an increase in general practitioner visits, and consequently. (13) Other studies also suggested that higher levels of social support were also linked with lower needs for specific health care like for example mental health care (42), as well as it is linked with better physical and mental functioning. (43) However after adjusting to certain socio demographic factors, the findings concerning depressive symptoms and social support when it comes to opioid use, were no longer statistically significant. Hence other factors may be of more influence on whether or not patients with knee osteoarthritis will use opioids or not.

Similar as for “social relations”, no homogeneity can be assured when it comes to the definition of opioid use in the included articles. The specific indications for the use of opioids are not described in detail in every article. In most cases, it is stated that it is used for chronic pain lasting more than 3 months. (table 2) The description of opioid use in the articles we reviewed showed significant variability, as demonstrated in table 2. Given this lack of a clear definition of opioid use, it is challenging to arrive at general conclusions based on the differences in the studies.

5.4 Strengths

The strengths of this scoping review manifest themselves primarily in the methodology. Publications were included via a blinded selection process by three researchers to prevent researcher bias. This guarantees the most unbiased method of article selection. Further, it is important to highlight that

the official steps of the PRISMA protocol for scoping reviews were followed. (18) Thanks to this scoping review, the gaps in the literature concerning this specific topic were identified.

5.5 Limitations

This scoping review has some noteworthy limitations. The first is that there aren't many studies involved. This makes drawing a general conclusion extrapolated to the population a challenge. In addition, the included studies are quite heterogeneous in terms of both quality and design. For example, this scoping review contains two narrative reviews. Because of the authors' hypothetical point of view in these reviews, it is impossible to draw a conclusion from these articles. Further, the selected articles also contain four cross-sectional studies, from which it is known that it is challenging to infer causal relationships. (44) We included one longitudinal study, which can be good for showing causal relations, but in this specific article, the association between chronic opioid use and social interactions that they show, reverse causality may take place. Also, there is no randomized controlled trial among the articles, which would provide the highest level of scientific evidence. (45) Because of the design of the research there are no control groups to compare the findings. Additionally, there were no other reviews that met our inclusion criteria, so we cannot compare our own methodology and results with the results of a review.

It is difficult to extrapolate the findings from the included articles to the general public. Firstly, because of the location of the studies. The study by Dassieu et al. takes place in two Canadian provinces (22), all other included studies in North America. As a result, extrapolating outcome data to populations with different epidemiological data is challenging.
Second, it can be challenging to incorporate the findings of the research in one conclusion because some research had relatively small study populations. (13, 22, 23) Due to the small sample size, it may be challenging to identify whether a specific result is a significant finding. Sometimes a type II error may also occur, in which the null hypothesis is wrongly accepted and no difference between the research groups is reported. Small studies can frequently overestimate the degree of associations or yield false-positive results, which is a limitation of small sample sizes. (46) Third, a wide variation of inclusion and exclusion criteria was seen between the included research. For example, the population investigated in the different studies covers a wide range of ages. Patients as young as 20 years old are included in the study by Dassieu et al.(22), whereas Yang et al. for instance, exclusively look at older adults over 65. (21, 25) While there are significant differences between the social interactions of 20-year-olds and the elderly population (47), this may have an impact on the findings of the studies. Age-related distinctions between a younger population and elderly also exist besides social interactions, such as physical traits or different values and norms regarding medication use. Due to changes in their phases of life, such as retiring or age-related losses, along with decreasing health and increasing mobility impairments, older persons generally have smaller social networks than younger individuals. (47)

Moreover, the included studies often have a slightly higher percentage of women than men. (10, 20, 22, 23) In other articles there was no specification of gender mentioned. There can be variations between how men and women engage socially. For example, a study conducted by Friebel et al. where they observed participants playing a trust game, it was shown that when interacting with

people they had previously played with, women are more stable and less flexible than men. (48) With a higher participation rate of women in a considerable number of articles, this could potentially result in gender bias in the conclusions of four of the included articles.

The fact that not all of the included studies are representative is also necessary to mention. The article by Vina et al. focuses on patients with knee osteoarthritis. (13) Their results cannot be extrapolated to the general population, as it is possible that people with knee osteoarthritis are limited in certain activities that people with other types of pain are not. Similar to the investigations by Yang et al., the study by Vyas et al. is representative for the older population. Hence, we cannot assume that long-term opioid usage in a younger population will result in the same outcomes.

Furthermore, different forms of bias are likely to occur in the studies we discuss. For example, in the study by Vyas et al. where a question was asked to participants over the telephone, reporting bias potentially occurred. (10) One possible form of reporting bias, for example, could be social desirability bias. This is the tendency of participants to give answers that they believe are socially desirable. (49, 50) Stigma surrounding opioids may lead people to downplay their use. (50) Despite this possible bias, self-reporting methods of medication behavior seem to have a good concordance with non-self-reporting methods. (51) This type of bias may also have occurred in the study by Dassieu et al, where interviews were conducted over the telephone. However, other included articles also used data via questionnaires. (13, 20, 23) Here it is feasible that recall bias occurred. This is a form of information bias. When participants have to answer questions around things that happened in the past, they may remember things differently. (52) As mentioned earlier, we included four cross-sectional analyses. For cross-sectional studies, a sample of participants often must be recruited from a sizable and diverse study population. They are therefore susceptible to sampling bias.(44) It is also noteworthy that the studies included in the present review have not gone through any systematic risk of bias analysis.

5.6 Clinical implications

This scoping review raises a number of clinical implications. As we discussed earlier, it is difficult to describe a unidirectional association between chronic opioid use and its impact on social relationships. In the literature mostly bidirectional associations are seen between these two parameters. This implies that it is always important for clinicians to consider both aspects (chronic opioid use and social relationships). For example, by encouraging patients with known long-term opioid use to broaden their social network.

In addition, causality could not be demonstrated between chronic opioid use and social relations. Ideally longitudinal prospective study design should be used to make conclusions about causality. Nevertheless, this will be difficult to realize due to ethical and moral considerations. Randomizing a study group to take chronic opioids and evaluate how this has an impact on the social relations of this group and compare this with a control group, is obviously a methodology that would raise ethical questions.

On the other hand, it is also important that when clinicians decide to prescribe opioids, that they evaluate the social network of the patient in question beforehand. The Prescription of opioids for patients who have a smaller social network or who live in social isolation should be delivered with extra caution. It is crucial to identify and acknowledge loneliness in time. When physicians prescribe long-term opioids, close monitoring of these patients is in order. Not only physical follow-up of these patients and monitoring of their symptoms, but also psychosocial consultations in which their social well-being is checked. Knowing that elderly patients are more vulnerable to be socially isolated, it is important to avoid unnecessary exposure to opioids in older persons. (20)

5.7 Future research

To understand the causal mechanisms behind the association between social isolation and chronic prescribed opioid use, future research should incorporate more longitudinal prospective research methods, preferably with large study samples. This scoping review also highlighted the importance of a common comprehension of what defines social isolation. In addition, a precise definition of chronic opioid use, such as a detailed description of the different type, duration, frequency and dosage of opioid use, as well as the indication of use, should be incorporated in the methodology of the study. Given the risks associated with their use, managing psychotropic medicines should be a part of future interventions to avoid risks of social isolation. The overall results highlight the necessity for paying attention to mental health difficulties in the management of individuals with chronic pain, even though more, etc. research using long term data is required.

5.8 Conclusion

This scoping review elicits certain gaps in the current existing literature concerning the influence of chronic opioid use on social relations. To demonstrate any causal relation between opioid use and social relations, additional research is needed with a prospective and longitudinal study design. The lack and necessity of a consensus concerning the definitions of used terms like “chronic opioid use” and “social relations” to draw general conclusions about this subject, is also exposed. Understanding the impact of long-term opioid use on social functioning is crucial. The prescription of opioids for patients who have a smaller social network or who live in social isolation should be delivered with extra caution. When physicians prescribe long-term opioids, close monitoring of these patients is in order. Nevertheless, as this needs further investigation, this scoping review might be a starting point for any future research in this research domain.

6. Kritische zelfreflectie

Alexander Berghmans

Als lid van een groepswerk met 3 personen die samenwerking aan een universitaire thesis heb ik veel waardevolle inzichten opgedaan. Ons onderwerp is uiteindelijk 'The Influence of Chronic Opioid Use on Social Relations: A Scoping Review' geworden. We hebben gedurende 3 jaar samengewerkt om een onderzoeksvraag te ontwikkelen aan de hand van een korte literatuuronderzoek. Vervolgens een methodologie uit te werken met een uitgebreide zoekstrategie samen met de bibliothecaris. Nadien alles gegevens en artikels te verzamelen om deze vervolgens te analyseren en de thesis te maken.

Het topic opiaat gebruik is een topic dat mij erg interesseert. Ikzelf heb ook veel interesse in het meer 'sociale' aspect van de geneeskunde. Deze brede toepassing in de geneeskunde is wat voor mij de huisartsgeneeskunde ook zo aantrekkelijk en interessant maakt. Dus voor mij was dit onderwerp heel tof en leerrijk.

Een belangrijke uitdaging aan een groepswerk was dat we als groep ook werden geconfronteerd met onze verschillende (vaak drukke) agenda's om samen te komen. Ook werden er regelmatig meetings georganiseerd met onze promotor en copromotor om tijdig feedback te krijgen om zeker te zijn dat onze gedachtegang de juiste weg opging. We probeerden gedurende 3 jaar met relatieve regelmaat samen te komen om dan samen een hele of halve dag te werken aan onze thesis, deze methode werkte voor ons het beste. We moesten steeds ook duidelijk onze rollen stellen en wie wat deed. Na elke samenkomst stelde we een duidelijk plan op voor de toekomst. Taken werden eerlijk verdeeld en moesten worden afgehandeld tegen onze volgende meeting. Het was niet altijd even gemakkelijk om alle verschillende ideeën en perspectieven samen te zetten en tot een gemeenschappelijke beslissing te komen. Dit vereiste goede communicatie en luistervaardigheden. Evenals de bereidheid om compromissen te sluiten en onze aanpak waar nodig aan te passen.

Al met al heb ik het gevoel dat deze thesis een waardevolle leerervaring was die me hielp belangrijke vaardigheden te ontwikkelen op het gebied van teamwerk, communicatie en kritisch denken. Dit zijn mijn inziens zeker belangrijke kwaliteiten die als arts ook belangrijk zijn. Groepswerk helpt je dingen vanuit het perspectief van anderen te bekijken. Als je de taak alleen hebt uitgevoerd, heb je misschien niet aan sommige ideeën gedacht die je teamleden aan het project hebben bijgedragen. Ik kreeg meer waardering voor de complexiteit van academisch onderzoek en het belang van samenwerking om betekenisvolle resultaten te bereiken. Hoewel er onderweg zeker uitdagingen waren, ben ik trots op het eindproduct dat we hebben geproduceerd. Ik kijk ernaar uit om deze vaardigheden toe te passen in mijn toekomstige academische en professionele omgevingen.

Clara Merckx

Het verloop van het schrijven van deze thesis ging zeer vlot. Ik werkte hiervoor samen met Etienne Gombert en Alexander Berghmans, en de communicatie alsook de samenwerking verliepen goed. Het lukte telkens goed om af te spreken en de taken eerlijk te verdelen. Ieder van ons had duidelijk

zijn sterke punten in de samenwerking, waardoor deze extra vlot kon verlopen. Ieder van ons heeft evenveel aandeel in het schrijven van deze thesis. Ik ben voorstander van samenwerken in een groepje, omdat dat zorgt voor verschillende inzichten en sterke punten die dan samen kunnen gelegd worden tot een groot geheel. Ik denk wel dat drie of vier personen zeker een maximum aantal thesispartners is voor een ideale samenwerking.

In het begin kreeg ik soms het gevoel dat ons werk niet voldoende vooruitging. Dit voornamelijk omwille van het feit dat het moeilijk was om onze zoekstring voor de databases op punt te stellen. Dit heeft een tijdje aangesleept omdat het vaak niet helemaal juist lukte en we heel afhankelijk waren van feedback hierrond. Zodra we onze zoekstring op punt hadden, konden we overgaan naar de dataverzameling en screening, en hadden we meteen een duidelijker plan, alsook een duidelijke verdeling van de taken. Vanaf dan is het heel vlot gegaan, en maakten we regelmatig gebruik van onze dinsdagen voor de les of seminarie om met elkaar af te spreken.

Het thema van de thesis zelf lag ons in het begin een beetje moeilijk. We konden voorkeuren geven voor onderwerpen, maar kregen uiteindelijk een onderwerp toegewezen dat niet meteen onze eerste keuze was. In principe was dat geen probleem, maar ik merkte in het begin dat ik het soms wel moeilijk vond dat er nog niet zoveel literatuur rond ons onderwerp bestond. Dat maakte mij/ons in het begin wat onzeker over bijvoorbeeld het schrijven van de inleiding en achtergrond. We hadden na het ingeven van onze zoekstring ongeveer 6000 hits, en na een screening om te kijken welke artikels aan onze inclusiecriteria voldeden, hielden we er nog maar 9 over. Het was dus zeer moeilijk om literatuur te vinden die voldeed aan onze zoekcriteria. Met onze thesis kunnen we dus duidelijk de hiaten in dit onderzoeksgebied aanwijzen. Wel gaf de thesis mij meer inzichten en achtergrondkennis rond opioïden, en dankzij de bestaande literatuur leerde ik opnieuw een aantal valkuilen kennen rond langdurig gebruik van opiaten. Verder leerde ik ook meer over de opioïdencrisis en zijn gevolgen ervan.

Ik leerde dankzij deze thesis (welke intussen tevens mijn derde thesis is omwille van een extra master in Sportgeneeskunde) om opnieuw vlotter gebruik te maken van de verschillende databanken voorhanden, om daarnaast ook in de grijze literatuur te duiken en hoe je dit best kan doen. We leerden gebruik te maken van EndNote en Rayyan, programma's waar ik voordien nog niet mee had gewerkt. We schreven deze thesis in het Engels, wat ook weer een goede oefening was voor mijn wetenschappelijk Engels.

In conclusie kan ik dus stellen dat het verloop van de thesis naar behoren is gegaan, dat ik weer heel wat heb bijgeleerd rond dit onderwerp maar ook rond wetenschappelijk schrijven en dat de samenwerking tussen ons drie vlot verlopen is.

Etienne Gombert

Het doel van deze thesis was om een weergave te maken van de huidig beschikbare literatuur omtrent de invloed van chronisch opioiden gebruik op het sociale leven van patiënten en meer bepaald op hun sociale relaties. Chronisch opioïden gebruik is een wijdverspreid fenomeen waar je als huisarts in opleiding regelmatig mee geconfronteerd wordt bij patiënten. De directe effecten en mogelijke bijwerkingen van opioïden zijn goed bekend, doch leek het mij zeer interessant om de minder directe gevolgen van opioïdengebruik op de langere termijn even on der de loep te nemen. Dit thesisonderwerp bood mij de kans om een uitgebreide literatuurstudie te doen betreffende de invloed van deze medicatie op mensen hun sociale relaties.

Samen met 2 jaargenoten heb ik mij verdiept en zijn wij op een nauwkeurige en gestructureerde manier te werk gegaan. Door met 3 aan deze thesis te werken, konden we, na het selecteren van de databases en het opstellen van de juiste zoekstrings, alle artikels door minstens 2 personen laten screenen. Vooraf bepaalde in- en exclusiecriteria werden gebruikt om artikels al dan niet te includeren. Het laten screenen van alle artikels door minstens 2 personen, verkleinde de kans op het missen van interessante literatuur voor deze thesis. Het hele zoekproces en de gebruikte methodes werden bovendien goed gedocumenteerd. Het maken van goede afspraken, een goede taakverdeling en het vooropstellen van tussentijdse deadlines d.m.v. een tijdslijn, zorgden er allemaal voor dat de samenwerking tussen iedereen vlot en efficiënt kon verlopen. Bovendien is het mijns inziens ook een meerwaarde om met meerdere personen aan een scoping review te werken. Iedereen heeft immers zijn eigen specifieke bijdrage en kijk op de zaken. De specifieke insteek van elke onderzoeker afzonderlijk en het afstemmen ervan op die van de medeonderzoekers, heeft uiteindelijk geleid tot de eindversie van deze thesis. We mogen terugblikken op een goed georganiseerde en vlotte samenwerking.

De belangrijkste bevinding van deze thesis, is het huidige gebrek aan bestaande literatuur betreffende de invloed van chronisch opioïdengebruik op sociale relaties. Bijgevolg is het ook onmogelijk om een eenduidige conclusie te trekken wat betreft een mogelijke causaliteit tussen het gebruik van opioïden en de sociale relaties van mensen. Voor onderzoekers binnen dit vakdomein zal het dan ook zaak zijn om naar de toekomst toe idealiter prospectief en longitudinaal onderzoek op te zetten. Ondanks het gebrek aan literatuur, zijn er wel sterke aanwijzingen voor verschillende bidirectionele verbanden tussen het gebruik van opioïden, sociale relaties, chronische pijn,… Dit neem ik als huisarts zeker mee naar de toekomst, wanneer het gaat over het voorschrijven van opioïden i.k.v. bijvoorbeeld chronische pijn. Sociale relaties van patiënten en het chronische gebruiken van opioïden zijn van invloed op mekaar. Bij het voorschrijven van dit soort medicatie is het dan ook belangrijk om het breder te plaatje van de patiënt niet uit het oog te verliezen en aandacht te blijven hebben voor zaken zoals sociaal functioneren en de sociale relaties van de patiënt. Zaken zoals een kleine sociaal netwerk en een hogere mate van sociale isolatie moeten de drempel om opioïden voor te schrijven voor chronisch gebruik verhogen, alsook is het nauwlettend opvolgen en monitoren van deze patiënten noodzakelijk. Dit allemaal met als doel om onoordeelkundig en overdreven gebruik van opioïden te vermijden. Enkel op deze manier kunnen mogelijke nadelige lange termijneffecten van chronisch opioïdengebruik, tot een minimum beperkt worden.

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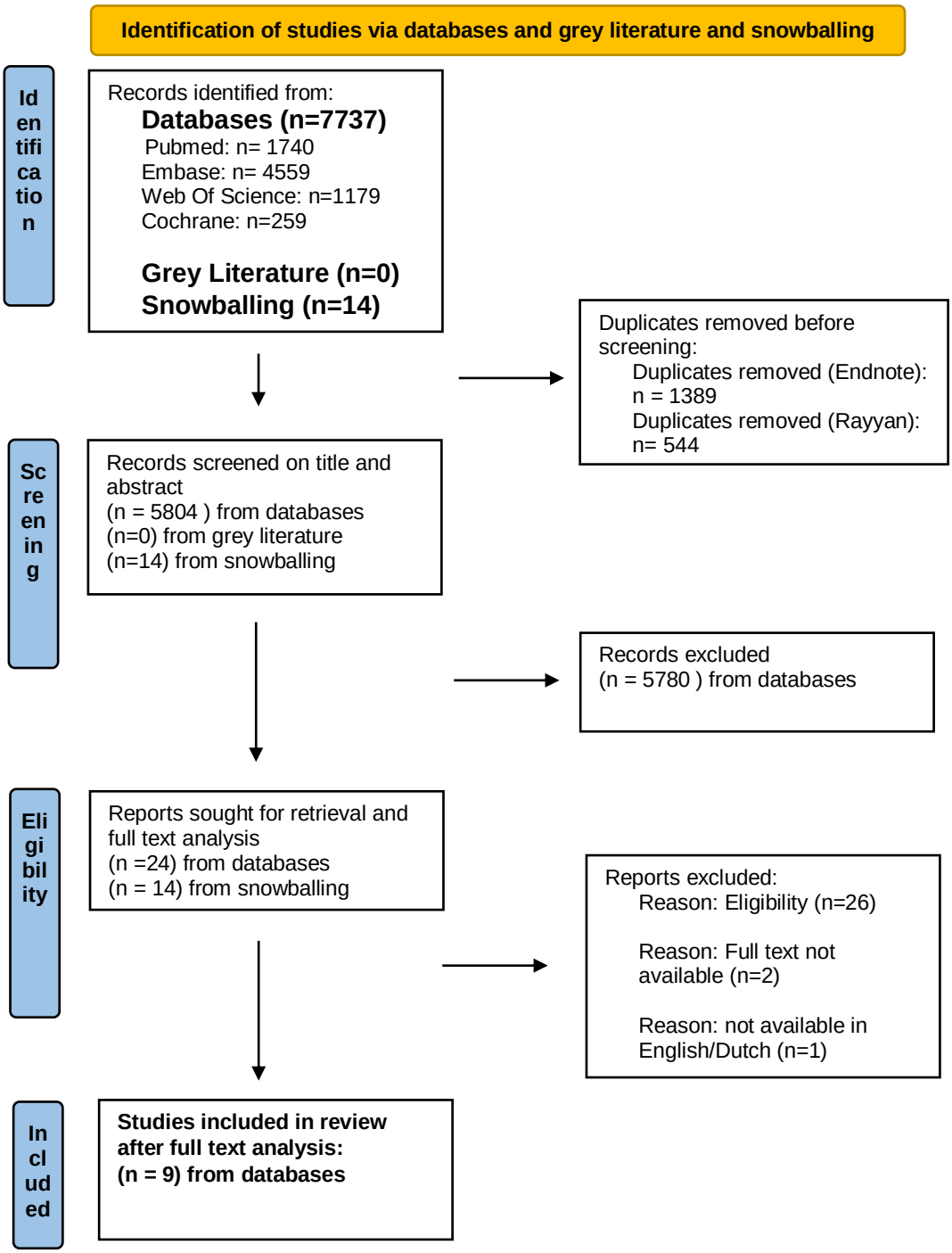
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8. ADDENDA

Figure 1: Prisma flowchart



Appendix 1 (protocol):

Background:

The opioid crisis is a known problem in the US, with a rising number of deaths due to opioid overdose. Not only in the US but also in Europe this is a major issue. In Belgium, the National Institute for Health and Disability Insurance (RIZIV) analyzed the use of five opioids (tramadol, tilidine, oxycodone, fentanyl, piritramide) that account for about 80% of the total use of all reimbursable opioids. Between 2006 and 2017, the number of patients who used at least one of these five opioids increased by 88%. This corresponds to 1,104,485 insured persons, or about 10% of all Belgians. (1).

The importance of social relationships and having a social network to function in society is already highlighted by science. Humans are social animals and social relationships are important for overall health and happiness. Social isolation hurts not only psychologically, but physically as well. (2,3) Years of observational research shows a causal link between social relationships and good health. (4)

A study conducted by Wasserman et al (2001) looked at different forms of social support in abstinence from opioids and cocaine. It was shown that among participants who received primarily abstinence-specific general support, defined as fewer cocaine users in their immediate environment, were more likely to be abstinent in follow-up. Opiate abstinence was not found to be associated with the forms of social support discussed in the article. (5)

Research by Waltona et al (2003) discusses a number of social factors that may predict drug use after abstinence. Being involved in activities where individuals come into contact with substance use predicted alcohol and drug use. Lower income and minority status were also good predictors of drug use. Minorities in the study often lived in urban neighborhoods, which were described as stressful environments. In addition, being married was a protective factor for drug use after abstinence. Previous studies showed that being married provides more positive outcomes after addiction treatment for male drug users.(6)

In humans, endogenous opioids play a role in forms of reward, addiction, sexual activity, mental illness, mood, learning and memory, digestion, respiration, appetite, stress, immunity, ...(7) In mammals, endogenous opioids are also important for creating social relationships, something that is crucial for the survival of this species. Furthermore, social behavior causes an increase in endogenous opioids. The endogenous opioid system plays a crucial role in the formation and maintenance of social relationships. The BOTSA theory (brain opioid theory of social attachment) states that endogenous opioids are the important missing association between primate and human attachment. The theory is based on the recognized similarity between dependence on a love relationship and dependence on opioids. It states that human social attachment is dependent on endogenous opioids. (8,9)

The exogenous ingestion of opioids, however, prevents social interactions with conspecifics. In rodents, opioids have been shown to reduce separation anxiety. (10) Chronic opioid ingestion negatively impacts an individual's psychological and neurological well-being because of a decreased ability to be part of a social group. There is a correlation between the increase in opioid use and increasing social isolation. (9) Scientific evidence shows that individuals who use opioids have a greater risk of an unstable social network and employment and lower education levels compared to those who use other substances. So, people who use opioids are more likely to have feelings of social isolation than people who use other drugs. (11) Chronic ingestion of exogenous opioids is detrimental to healthy behavior, socialization, and way of dealing with situations that are part of life, like for example social rejection. In overdose, the harm is not limited to the individual taking the

opioids, but extends to families, communities, and society. (12) In our exploratory literature research we see a clear trend in the definition of chronic opioid intake in articles of recent years, with a shift from 120 days to 90 days. (15) In other words, the cut-off value to speak of chronic opioid intake is currently set earlier.

The findings of our brief literature review show that - despite relatively little research on the impact of opioid use on social isolation - there is clear evidence that people who take opioids chronically are at greater risk of social isolation. There are certainly benefits of opioids in the right medical circumstances and situations, for example in the treatment of cancer-related pain. Hence, more research on social consequences and certainly important in the clinical setting is necessary, to better inform prescribing behaviors of health care providers.

A strict formulation of the outcome measure "social relationships" was not found in literature. Even though the literature related to our research question is relatively limited, an initial exploratory search shows that the concept of "social relationships" is described very vaguely and broadly. This can range from personal or professional interpersonal relationships to things like empathy and emotional attachment. In order to keep the risk of missing valuable literature as low as possible, it was therefore decided to formulate our outcome measure broadly in the search strategy.

In terms of social outcome, we chose social isolation. There are a lot of definitions for social isolation in the literature. Zavaleta et al. concluded a general definition of social isolation in their review as "the inadequate quality and quantity of social relations with other people at the different levels where human interaction takes place (individual, group, community and the larger social environment)." In this review, a few definitions of social isolation in the literature are discussed. (13)

We chose to write a scoping review because our research question is quite broadly defined. A scoping review allows us to create an overview of the available literature. This way we can perform research very broadly and involve different types of literature and knowledge. Our purpose is to identify knowledge gaps in the available literature.

PROTOCOL

Stage 1: identifying the research question

First, the research question was defined very broadly. The first rough research subject was "the influence of chronic opioid use on social relations". The patients of our interest are adults, the intervention in our research will be "chronic opioid use". After a broad screening through the literature, the following research question was selected: "**What is the influence of chronic opioid use and social isolation on each other in non- hospitalized, non-resident and non-palliative adults?"**

Stage 2: identifying relevant studies

A search string with the concepts "opioid use" and "social relationship" was used to get an overview of what we do and do not know about this research question (addendum). By reading the published articles, we could refine our search terms to obtain as many articles as possible about the subject. First, we screened the hits we obtained with a draft version of our search string, by including articles for background information based on title and abstract. This way we got a selection of studies to help us build a more accurate search string.

Relevant literature was searched in the following **databases**: Pubmed, Web of Science, Embase and Cochrane Library. For the final selection for this scoping review, supplementary articles will be included through the process of **snowballing**, as well as grey literature that corresponds with the in- and exclusion criteria. For snowballing, we will first start with a set of articles that match our in- and exclusion criteria. Then there are two options. Backward snowballing (we look at the articles in the reference list of our articles) or forward snowballing (we look at the studies that cited our articles). The **grey literature** will be searched on sites of governmental and non-governmental organisations that are focused on opioid users and their social network as well as on search engines like Google.com. To search and obtain useful grey literature also some websearch engines specific for grey literature will be used, as for example Mednar.com and Greylit.org.

Stage 3: study selection

Inclusion and exclusion criteria have been formulated in advance for selecting articles for the scoping review. **Concerning the patient population**, the following inclusion criteria apply:

- adults (>18 years old)
- prescribed pharmaceutical opioid use
- chronic opioid use (>/= 3 months)
- Social isolation defined as "the inadequate quality and quantity of social relations with other people at the different levels where human interaction takes place (individual, group, community and the larger social environment)"

Several clear exclusion criteria have also been drawn up:

- Residents, palliative patients and hospitalized patients
- Illegal opioid (ab)use (heroin) or substitution therapy in the form of, for example, methadone

After collecting the references, duplicates will be removed and the remaining articles will be screened by using the software program “Rayyan qcri” (14). Each article will be screened by two researchers independently from each other. First, screening will be done based on title and abstract. Next, full texts of the included articles will be reviewed. Discrepancies in the review process will be discussed with the third reviewer, and if necessary the promotor and co-promotor of the thesis.

Stage 4: charting the data and quality appraisal

Data charting will be done using the program Excel to create an extensive data table. The information will be systematically recorded as follows:

- Author(s), year of publication and study location
- Study type & methodology
- Study population (age, indication of opioid use, setting of living, sample size)
- Type and dose of opioids used
- Duration of opioid use
- Outcome measures
- Definition of ‘social isolations’
- Capture results
- Conclusion(s) of the author(s)
- Gaps/inspiration for future research

Together, these data will form the basis of our analysis.

Stage 5: collecting, summarizing and reporting the results

In the last step, all the included results will be summarized and reported. As described earlier, an extensive summary table will be used to report all the characteristics and outcome measures of the included studies. This way we will also be able to compare similar outcomes from different articles. Our results will be written down in a narrative synthesis.

All the conclusions of the included articles will be analyzed, in order to draw a general conclusion and state hypotheses as adequate as possible. The final goal of this scoping review is to give a wide overview of the existing literature concerning this subject. The review should serve as a reliable guideline for future research about the effect of chronic opioid use on social relationships.

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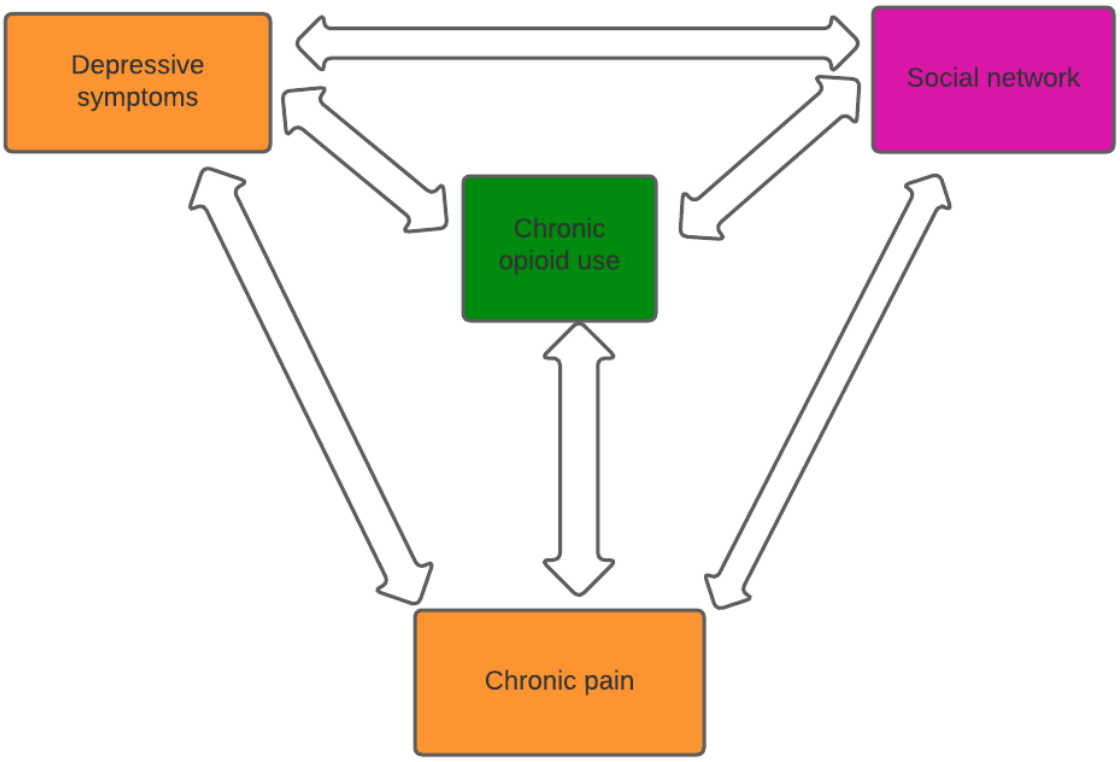
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Appendix 2: MINDMAP bidirectionality



Appendix 3: search string

PUBMED

("Analgesics, Opioid"[Mesh] OR "Opioid Epidemic"[Mesh] OR "Opioid-Related Disorders"[Mesh:NoExp] OR "Morphine Dependence"[Mesh] OR "Opiate Overdose"[Mesh] OR "Opium Dependence"[Mesh] OR "Opiate Alkaloids"[Mesh] OR "Analgesics, Opioid" [Pharmacological Action] OR "Oxycodone"[Mesh] OR "Codeine"[Mesh] OR "Hydrocodone"[Mesh] OR "Morphine"[Mesh] OR "Hydromorphone"[Mesh] OR "Fentanyl"[Mesh] OR "Methadone"[Mesh] OR "Oxymorphone"[Mesh] OR "Meperidine"[Mesh] OR "Tramadol"[Mesh] OR "carfentanil" [Supplementary Concept] OR "Buprenorphine"[Mesh] OR "Opioid*"[tiab] OR "opiate*" [tiab] OR "Oxycodone" [tiab] OR "Hydrocodone" [tiab] OR "Morphine" [tiab] OR "Hydromorphone" [tiab] OR "Fentanyl" [tiab] OR "Codeine" [tiab] OR "Methadone" [tiab] OR "Oxymorphone Hydrochloride" [tiab] OR "Meperidine" [tiab] OR "Tramadol" [tiab] OR "Carfentanil" [tiab] OR "Buprenorphine" [tiab])

("Social Desirability"[Mesh] OR "Social Inclusion"[Mesh] OR "Social Isolation"[Mesh] OR "Social Marginalization"[Mesh] OR "Social Skills"[Mesh] OR "Social Stigma"[Mesh] OR "Social Integration"[Mesh] OR "Social Interaction"[Mesh] OR "Social Support"[Mesh] OR "Social Vulnerability"[Mesh] OR "Social Isolation"[tiab] OR "Social exclusion*"[tiab] OR "social inclusion"[tiab] OR "Loneliness"[tiab] OR "social deprivation"[tiab] OR "social stigma"[tiab] OR "social support"[tiab] OR "social interaction"[tiab] OR "social integration"[tiab] OR "Social Network"[tiab] OR "Social Adjustment"[tiab] OR "social behav*"[tiab] OR "Social Cohesion"[tiab] OR "Social Skills"[tiab] OR "Social Marginalization"[tiab] OR "Social Environment"[tiab] OR "Social Desirability"[tiab] OR "Social Vulnerability"[tiab])

EMBASE

('opiate agonist'/exp OR 'opiate addiction'/exp OR 'morphine addiction'/exp OR 'opiate overdose'/exp OR 'oxycodone'/exp OR 'hydrocodone'/exp OR 'morphine'/exp OR 'naltrexone'/exp OR 'hydromorphone'/exp OR 'fentanyl'/exp OR 'codeine'/exp OR 'methadone'/exp OR 'oxymorphone'/exp OR 'pethidine'/exp OR 'tramadol'/exp OR 'carfentanil'/exp OR 'buprenorphine'/exp OR 'Opioid*':ti,ab,kw OR 'opiate*':ti,ab,kw OR 'Oxycodone':ti,ab,kw OR 'Hydrocodone':ti,ab,kw OR 'Morphine':ti,ab,kw OR 'Morphine-Naltrexone':ti,ab,kw OR 'Hydromorphone':ti,ab,kw OR 'Fentanyl':ti,ab,kw OR 'Codeine':ti,ab,kw OR 'Methadone':ti,ab,kw OR 'Oxymorphone Hydrochloride':ti,ab,kw OR 'Meperidine':ti,ab,kw OR 'Tramadol':ti,ab,kw OR 'Carfentanil':ti,ab,kw OR 'Buprenorphine':ti,ab,kw)

('social desirability'/exp OR 'social inclusion'/exp OR 'social exclusion'/exp OR 'social isolation'/exp OR 'social competence'/exp OR 'social stigma'/exp OR 'integration'/exp OR 'social interaction'/exp OR 'social support'/exp OR 'social vulnerability'/exp OR 'Social Isolation':ti,ab,kw OR 'Social exclusion*':ti,ab,kw OR 'social inclusion':ti,ab,kw OR 'Loneliness':ti,ab,kw OR 'social deprivation':ti,ab,kw OR 'social stigma':ti,ab,kw OR 'social support':ti,ab,kw OR 'social interaction':ti,ab,kw OR 'social integration':ti,ab,kw OR 'Social Network':ti,ab,kw OR 'Social Adjustment':ti,ab,kw OR 'social behav*':ti,ab,kw OR 'Social Cohesion':ti,ab,kw OR 'Social Skills':ti,ab,kw OR 'Social Environment':ti,ab,kw OR 'Social Desirability':ti,ab,kw OR 'Social Marginalization':ti,ab,kw OR 'Social Vulnerability':ti,ab,kw)

WEB OF SCIENCE

TS=(“Opioid*” OR “opiate*” OR “Oxycodone” OR “Hydrocodone” OR “Morphine” OR “Hydromorphone” OR “Fentanyl” OR “Codeine” OR “Methadone” OR “Oxymorphone Hydrochloride” OR “Meperidine” OR “Tramadol” OR “Carfentanil” OR “Buprenorphine”)

TS=(“Social Isolation” OR “Social exclusion*” OR “social inclusion” OR “Loneliness” OR “social deprivation” OR “social stigma” OR “social support” OR “social interaction” OR “social integration” OR “Social Network” OR “Social Adjustment” OR “social behav*” OR "Social Cohesion" OR "Social Skills" OR “Social Marginalization” OR "Social Environment" OR “Social Desirability” OR "Social Vulnerability")

COCHRANE

[mh "Analgesics, Opioid"] OR [mh "Opioid Epidemic"] OR [mh "Opioid-Related Disorders"] OR [mh "Morphine Dependence"] OR [mh "Opiate Overdose"] OR [mh "Opium Dependence"] OR [mh “Opiate Alkaloids”] OR [mh "Oxycodone"] OR [mh "Hydrocodone"] OR [mh "Morphine"] OR [mh "Hydromorphone"] OR [mh "Fentanyl"] OR [mh "Methadone"] OR [mh "Oxymorphone"] OR [mh "Meperidine"] OR [mh "Tramadol"] OR [mh "Buprenorphine"] OR (“Opioid*” OR “opiate*” OR “Oxycodone” OR “Hydrocodone” OR “Morphine” OR “Hydromorphone” OR “Fentanyl” OR “Codeine” OR “Methadone” OR “Oxymorphone Hydrochloride” OR “Meperidine” OR “Tramadol” OR “Carfentanil” OR “Buprenorphine”):ti,ab,kw

[mh "Social Desirability"] OR [mh "Social Inclusion"] OR [mh "Social Isolation"] OR [mh "Social Marginalization"] OR [mh "Social Skills"] OR [mh "Social Stigma"] OR [mh "Social Integration"] OR [mh "Social Interaction"] OR [mh "Social Support"] OR [mh "Social Vulnerability"] OR (“Social Isolation” OR “Social exclusion*” OR “social inclusion” OR “Loneliness” OR “social deprivation” OR “social stigma” OR “social support” OR “social interaction” OR “social integration” OR “Social Network” OR “Social Adjustment” OR “social behav*” OR "Social Cohesion" OR "Social Skills" OR “Social Marginalization” OR "Social Environment" OR “Social Desirability” OR "Social Vulnerability"):ti,ab,kw

Ethical commission

The Influence of Chronic Opioid Use on Social Relations: A Scoping Review.

Dossiernr.:	MP018624
Masterproef:	Masterproef I HAIO, 2020 – 2023
Faculteit/opleiding:	Faculteit Geneeskunde - Master in de huisartsgeneeskunde
Studiefase:	eerste fase
Academiejaar:	2021-2022
Korte omschrijving / abstract:	The opioid crisis is a known problem in the US, with a rising number of deaths due to opioid overdose. Not only in the US but also in Europe this is a major issue. In Belgium, the National Institute for Health and Disability Insurance (RIZIV) analyzed the use of five opioids (tramadol, tilidine, oxycodone, fentanyl, piritramide) that account for about 80% of the total use of all reimbursable opioids. Between 2006 and 2017, the number of patients who used at least one of these five opioids increased by 88%. This corresponds to 1,104,485 insured persons, or about 10% of all Belgians The importance of social relationships and having a social network to function in society is already highlighted by science. Humans are social animals and social relationships are important for overall health and happiness. Social isolation hurts not only psychologically, but physically as well. Years of observational research shows a causal link between social relationships and good health. In humans, endogenous opioids play a role in forms of reward, addiction, sexual activity, mental illness, mood, learning and memory, digestion, respiration, appetite, stress, immunity, ... In mammals, endogenous opioids are also important for creating social relationships, something that is crucial for the survival of this species. Furthermore, social behaviour causes an increase in endogenous opioids. The endogenous opioid system plays a crucial role in the formation and maintenance of social relationships. The BOTSA theory (brain opioid theory of social attachment) states that endogenous opioids are the important missing association between primate and human attachment. The theory is based on the recognized similarity between dependence on a love relationship and dependence on opioids. It states that human social attachment is dependent on endogenous opioids. The exogenous ingestion of opioids, however, prevents social interactions with conspecifics. In rodents, opioids have been shown to reduce separation anxiety. Chronic opioid ingestion negatively impacts an individual's psychological and neurological well-being because of a decreased ability to be part of a social group. There is a correlation between the increase in opioid use and increasing social isolation. Scientific evidence shows that individuals who use opioids have a greater risk of an unstable social network and employment and lower education levels compared to those who use other substances. So, people who use opioids are more likely to have feelings of social isolation than people who use other drugs. Chronic ingestion of exogenous opioids is detrimental to healthy behaviour, socialization, and way of dealing with situations that are part of life, like for example social rejection. In overdose, the harm is not limited to the individual taking the opioids, but extends to families, communities, and society. The findings of our brief literature review show that - despite relatively little research on the impact of opioid use on social isolation - there is clear evidence that people who take opioids chronically are at greater risk of social isolation. There are certainly benefits of opioids in the right medical circumstances and situations, for example in the treatment of cancer-related pain. Hence, more research on social consequences and certainly important in the clinical setting is necessary, to better inform prescribing behaviours of health care providers. We chose to write a scoping review because our research question is quite broadly defined. A scoping review allows us to create an overview of the available literature without providing a summary answer to a specific research question.
Opmerkingen / praktische informatie:	/
Website:	https://pubmed.ncbi.nlm.nih.gov/
Toegepaste technieken:	Zoekstrategie via Pubmed, Cochrane, Embase, Web of Science
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Trefwoorden:	Social relations Chronic opioid use
Gewenste taal van communicatie:	nl
Promotor:	Dr Marc Van Nuland (u0040434)
Copromotor:	Mej Kristien Coteur (u0108686)
Organisatie:	KU Leuven
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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.

Table 1

Authors, year of publication	Study location	Study design	Study population, age, sample size	Definition of social relations/ setting of living
N.C. Christie; 2021	Not mentioned	Narrative review	Not defined	No/limited social relationships or few social relationships of poor quality
Dassieu L. et al. ; 2021	Canada	Descriptive research	n= 22, 12 women and 10 men age: 20-70 years	Not defined
Brendan F. Day et al. ; 2019	United States	Cross-sectional analysis	n= 26 322 non-institutionalized USA individuals age: >= 12 years	Social isolation proxy variables: lives alone, unmarried, no religious services
Soin A. et al. ; 2008	United States	Retrospective cohort	n= 67 Patients with chronic non-malignant pain; age: 20-87 years	SF-36: how someone can or can't perform his/her social activities, and how much these social activities are interfered by his/her emotional or physical problems
Sullivan M.D. et al.; 2021	United States	Narrative review	Not defined	Not defined
E.R. Vina et al.; 2018	United States	Cross-sectional analysis	n= 360 veterans with symptomatic knee osteoarthritis mean age: 64.2 years	Four dimensions of social support: emotional/informational, tangible, affectionate, and positive social interaction.
M.V. Vyas et al.; 2020	Canada	Cross-sectional analysis	n= 15 302 patients age: >65 years	Loneliness: a subjective, unwelcome feeling of a lack of or loss of companionship that occurs when there is a mismatch between the desired and the perceived quantity and quality of social relationships
Tse-Chuan Yang et al. ; 2022	United States	Longitudinal analysis	n= 9,249,288 beneficiaries age: >65years	Social isolation index average of: 1) % of older householders (ages 65+) who live alone 2) % of older adults who live in poverty 3) % of older adults who have a disability Higher values correspond to a higher rate of social isolation levels
Tse-Chuan Yang et al.; 2022	United States	Cross-sectional analysis	n=3079 counties	Social isolation: deprivation of social connectedness and lack of contact or sustained interaction with in- dividuals or institution

Table 2

Authors, year of publication	Definition of chronic opioid use	Indication of opioid use, type and dose, duration	Outcome measures	Conclusions by authors
N.C. Christie; 2021	Not defined	Not defined	Not defined	1) According to the brain opioid theory of social attachment (BOTSA) paradigm, the opioid epidemic can be seen as a social isolation and a sense of belongingness epidemic that people are attempting to combat by using opioids 2) In comparison to other drugs, prolonged opioid use in humans seems to be especially damaging to personal relationships
Dassieu L. et al. ; 2021	Prescribed chronic opioid treatment for chronic pain	Chronic pain usually lasting more than 3 to 6 months. No information about type and dosage available	- Worries and fear of patients and family - Prejudices: negative judgements, unsolicited advice, rejection and discrimination - Stigma concealment: advocacy work, stigma concealment	1) Stigma and negative representations of opioids were increasingly frequent in participants' daily social interactions. This could lead to deteriorating relationships within their personal and professional circles 2) On the interventional level, it seems essential to start more encouraging discussions about opioids and their hazards by generally destigmatizing opioid consumers in the media, public health campaigns, and healthcare settings
Brendan F. Day et al. ; 2019	Not defined	No information about indication, type and dosage available	Past-year prescription opioid/benzodiazepine misuse	Being unmarried was substantially related with increased risks of combined opiate and benzodiazepine abuse
Soin A. et al. ; 2008	6-36 months	Chronic non-malignant pain. No information about type and dosage available.	Social functioning	A slight but statistically significant improvement was seen in the Social Functioning section of the SF-36 indicating more social time and activity
Sullivan M.D. et al.; 2021	More than 90 days	Chronic pain. No information about type and dosage available.		Long-term opioid therapy that lasts months and perhaps years should be a rare occurrence because it does not treat chronic pain well, it impairs human social and emotional function, and can lead to opioid dependence or addiction
E.R. Vina et al.; 2018	Not defined	Knee osteoarthritis. No information about type and dosage available.	Three categories of analgesic use: - oral opioids (with or without other oral analgesic treatments) - oral non-opioid analgesics - no oral analgesic use.	Opioid analgesic users, compared to others, were more like to have moderate to severe depressive symptoms and lower social support. Higher level of depression was independently associated with opioid analgesic use versus no oral analgesic use.
M.V. Vyas et al.; 2020	Not defined	No information about indication, type and dosage available	Self-reported usage of three classes of medications: - Opioids (for example Codeine, Demerol, and morphine)	An association between loneliness and daily but not occasional use of opioids and benzodiazepines in older adults, suggesting that loneliness can potentiate continual use of these drugs, and that factors that lead to such an effect of loneliness require

			- Benzodiazepines (for example Ativan and Valium) - Non-opioid analgesics (for example aspirin, acetaminophen, and drugs for arthritis and inflammation)	further study
Tse-Chuan Yang et al. ; 2022	Opioid use disorder status in medical file	Physical pain. No information about type and dosage available.	Opioid use disorder status	County-level social isolation is related to the risk of opioid use disorder in non-Hispanic whites
Tse-Chuan Yang et al.; 2022	Opioid use disorder status in medical file	No information about indication, type and dosage available	- Impact of social isolation on the prevalence of opioid use disorder - Impact of residential stability on the relationship between social isolation and opioid use disorder prevalence - Evaluate any variations in these relationships between metropolitan and non-metropolitan counties.	The results show that social isolation is a significant factor for county-level OUD prevalence, regardless of metropolitan status. In addition, counties with high residential stability have low prevalence of OUD among older adults and this association is stronger in metropolitan than in non-metropolitan counties