The effect of chronic opioid use on sexuality in non-cancer patients: a scoping review

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ABSTRACT (Nederlands)

Achtergrond
Door het stijgend gebruik van opioïden zijn er meer patiënten die risico lopen om bijwerkingen te ontwikkelen zoals nausea of constipatie, maar ook seksuele dysfunctie. Er zijn meerdere studies die een relatie tussen chronisch gebruik van opioïden en opioïd-geïnduceerd androgeentekort aantonen, maar onderzoek over de gevolgen op de verschillende domeinen van seksualiteit is schaars. Hiernaast bevragen artsen zelden patiënten hun seksuele problemen.

Onderzoeksvraag
Het doel van deze scoping review is om een overzicht te geven van de invloeden van chronisch gebruik van opioïden op de verschillende aspecten van de seksualiteit.

Methode
Een uitgebreid literatuuronderzoek werd uitgevoerd in zes databases, gebruikmakend van de hoofdconcepten “opioïden” en “seksuele dysfunctie”. Aanvullend werd gericht gezocht in grijze literatuur. Studies werden gescreend en geselecteerd op basis van onze inclusiecriteria. Relevante data werd geëxtraheerd en verwerkt in een data chart.

Resultaten
17541 studies werden geïdentificeerd, waarvan 13 publicaties met in totaal 68439 patiënten geïncludeerd werden na een grondig selectieproces. De meeste studies verzamelden informatie op basis van zelfrapportage over seksueel verlangen en/of erectiele dysfunctie, maar ook over voldoening, seksuele activiteit/capaciteit, frequentie en orgasmefunctie. Drie studies gebruikte gestandaardiseerde vragenlijsten: de IIEF, FSFI en 4-item MOS seksuele problemen schaal. 11 studies vonden een correlatie tussen de aanwezigheid van seksuele dysfunctie en het chronisch gebruik van opioïden. Belangrijke beïnvloedende factoren waren leeftijd, depressie en comorbiditeiten.

Conclusie
Chronisch gebruik van opioïden heeft mogelijk negatieve effecten op alle domeinen van seksualiteit. Door de heterogeniteit van de geïncludeerde studies en meerdere beïnvloedende factoren, kan een causale relatie niet aangetoond worden. Verder onderzoek omtrent dit onderwerp is nodig.

ABSTRACT (English)

Background

Due to increased opioid use, more patients are at risk of developing side effects such as nausea or constipation, but also sexual dysfunction. Although there are multiple studies suggesting a relation between chronic opioid use and opioid-induced androgen deficiency (OPIAD), research about the consequences on all domains of sexuality remains scarce. Moreover, physicians infrequently inquire about patients' sexual problems.

Research question

Our scoping review aims to give an overview of literature about the effects of chronic opioid use on the different domains of sexuality.

Methods

A comprehensive literature search was carried out in six databases using key concepts of "opioids" and "sexual dysfunction". Additionally, a focused search in gray literature was executed. Articles were screened and selected based on our inclusion criteria. Relevant data was extracted and processed in a data chart.

Results

Of 17.541 identified articles, 13 publications were included in this study after a thorough selection process, consisting of 68.439 patients in total. Most studies gathered information through self-reported data on sexual desire and/or erectile dysfunction, but also satisfaction, sexual activity/capability, frequency and orgasmic function was described. Three studies used standardized questionnaires: IIEF, FSFI and 4-item MOS sexual problems scale. 11 studies found a correlation between the presence of sexual dysfunction and the chronic use of opioids. Important confounding factors were age, depression and comorbidities.

Conclusion

Chronic opioid use has possible negative effects on all domains of sexuality. Due to heterogeneity of articles and multiple confounding factors, a causal relation can not be determined. Further research regarding this topic is necessary.

INTRODUCTION

Opioids are a group of well-known analgesics that inhibit pain perception by binding to G protein-coupled receptors in the central and peripheral nervous system (1). Opioid use has increased dramatically over the past decades in the United States, with more than 245 million prescriptions made in 2014, testimony to an epidemic (2,3). A rising trend is also seen in Belgium where the amount of opioid users has doubled between 2006 and 2017. More than 1,2 million people received a prescription for opioids in 2017 of which more than 80% had been prescribed by their general practitioner (3). Moreover, Belgium ranks third place in Europe and fifth place worldwide when looking at daily use of opioids per million inhabitants (4).

Commonly mentioned side-effects to opioid treatment are nausea and constipation as well as the development of tolerance over time, resulting in a need for progressively higher doses and increased risk of abuse in chronic users (5,6). Additionally, patients using opioids in high doses are more at risk of using other medications such as benzodiazepines and suffer from depression (7). A lesser known adverse effect of chronic opioid use is sexual dysfunction. Although causality has yet to be established, multiple studies suggest a relation between opioid use and hormonal imbalance, also known as opioid-induced androgen deficiency (OPIAD) (8-10). The opioid induced inhibitory feedback on the hypothalamic-pituitary-gonadal (HPG) axis results in decreased testosterone production and a stimulation of testosterone denaturation (9). Coluzzi et al. reported in 2018 a prevalence of OPIAD in chronic users of up to 86% (11). Aside from sexual dysfunction, hypogonadism may also cause fatigue, depression, menstrual irregularities and loss of bone mass (9).

Despite an increase in opioid prescriptions, general practitioners infrequently inquire about patients' sexual dysfunction (12). In 2021, a web-based survey from Finland showed that while general practitioners believe to be competent in the management of sexual health issues, there are several barriers to bringing up this topic. Often reported was a shortness of time, the sexual health issues not being a priority and a lack of knowledge or experience in dealing with sexual health medicine. The minority of general practitioners said to inquire after a patient's sexual satisfaction and 87,8% of questioned general practitioners reported the need for better education on sexual medicine (13).

The reported prevalence of sexual dysfunction in the general population is approximately 15,5% in women and 25% in men with patients citing problems such as erectile dysfunction, vaginismus, loss of desire or premature ejaculation (14,15). Likewise, the Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE) study from 2008 indicated the prevalence of at least one sexual problem in a sample of U.S. women to be as high as 43,1% (16). Amongst the barriers in the detection of sexual dysfunction is also the patients' own attitudes. One of many reasons for not seeking medical care is embarrassment (17). Yet patients appear more likely to report sexual dysfunction as an adverse drug event when asked directly by a physician compared to spontaneous self-reportage (18). Sexual dysfunction entails an associated increased risk of depression, and impaired sexual health has shown to have a significant negative impact on quality of life (19-21).

Given its prevalence in the general population, general practitioners should make inquiries about possible sexual problems when prescribing medication that affects sexual function. The domains of sexual function (i.e. desire, arousal, satisfaction, orgasmic function, erectile function, lubrication and

vaginal pain) can be difficult to objectify by a physician due to their subjective nature. Sexual function is commonly evaluated in three different ways. The most common form of evaluation is self-rapportage, which is also most subject to bias. Second, a variety of questionnaires, such as the International Index of Erectile Function (IIEF) and the Female Sexual Function Index (FSFI) are used to take account of changes in the various domains of sexual functioning. However these remain subject to some bias and are not validated in every country (22). Last, serum hormone levels can be measured to attempt to objectify symptoms of sexual dysfunction. Unfortunately their contribution is limited due to poor correlation with some of the domains of sexual function, for example loss of libido in women (23).

Some systematic reviews and meta-analyses exist on the incidence of OPIAD and erectile dysfunction in men (9,24), but there is little research about the other sexual health domains in relation to chronic opioid use. In addition, many studies about opioids focus on opioid abuse or intrathecal opioid use and conclusions are therefore difficult to adopt in primary care settings, where patients frequently receive opioids for conditions such as chronic pain (24). Our scoping review aims to produce an overview of possible changes in various domains of sexuality following chronic oral or transdermal opioid use in chronic non-cancer patients.

RESEARCH METHOD

Objectives

As this scoping review aims to summarize the evidence in the existing literature, broad research questions and objectives were defined as followed:

1. To determine if chronic opioid use has effects on multiple domains of sexuality, i.e. sexual desire, erectile function, orgasmic function, satisfaction etc.
2. How these effects correlate with other factors, including but not limited to dose or duration of opioid therapy, gender differences, ..

Protocol and registration

The scoping review is registered by the ethics committee of KULeuven. The Research Ethics Committee Approval can be found in Appendix 1. The approved protocol can be found in Appendix 2.

Search strategy

We conducted a broad literature search using the concepts “opioids” and “sexuality” by examining the following electronic databases: Pubmed, Embase, Web of Science, CINAHL, Cochrane library and PsycArticle. MeSH Terms and entry terms were identified through the MeSH Tree provided by the National Library of Medicine. The identified terms were also entered as title/abstract(TIAB) terms. Additional keywords identified by a database were added to the search string of all databases. Unpublished data was captured through gray literature in the Open Grey database. There was no limitation regarding study design, year of publication or location of the study. Other relevant sources

were identified through searching reference lists using the snowball principle. A detailed overview of our search strategy is provided in Appendix 3. The search was conducted May 10, 2022 and consisted of all existing literature up to this date.

Selection and eligibility criteria

All identified articles were uploaded in Rayyan and prior to screening, duplicates and publications regarding research in animals were removed. References were managed using Mendeley. Articles were screened by two independent reviewers on title and/or abstract for relevance. Disagreement was solved by consulting a third researcher. Inclusion criteria were the use of legally prescribed opioids in sexually active, non-cancer patients for a duration of at least eight weeks. This study focuses on primary care settings, where most patients have their first contact with prescribed opioids. This work therefore includes studies which predominantly research on oral and transdermal opioid use. Studies were included if the manner of administration of the intervention drug was not specified. Publications were required to clearly define the studied aspects of sexuality. Furthermore, a free, full text had to be available in English or Dutch. Exclusion criteria comprise the therapeutic use of opioids for sexual dysfunction (i.e. tramadol use for erectile dysfunction), the presence of pre-existing sexual dysfunction prior to opioid use, important drug abuse and the use of opioid maintenance therapy for dependency. Research in cancer patients was excluded to avoid interference of chemotherapeutic side effects. If articles were based on the same sample, either the most recent publication was included, or the original study if identified by our search.

Critical appraisal

Selected studies did not undergo a critical appraisal. This is a deviation from our written protocol due to few studies that were included and the aim of this scoping review.

Data extraction

A data collection instrument was developed by the authors to extract relevant study characteristics. The extracted data included: author, journal, year of publication, country, study population, age of the studied population, study setting, the use of a control group, sexual outcome, definition of sexual outcome, opioid type/form and dose, duration of chronic use, follow-up, relevant results, possible confounding factors and gaps in knowledge. Data-charting was undertaken by two independent researchers. A random sample of three articles were used to compare extraction data and refine the data form. Extracted study characteristics were discussed between the researchers and the data form was repeatedly updated.

RESULTS

Through an extensive literature search in the aforementioned six databases on 10 May 2022 , 17.541 publications were identified. After removal of duplicates and non-human research, 10.906 articles were screened for relevance based on title and abstract. The remaining 306 relevant publications were assessed for eligibility, and 293 publications were excluded with the most common reason being the lack of a free, full text. All reasons for exclusion can be found in the flow diagram in Figure 1. Thirteen articles met the inclusion criteria and were incorporated in this scoping review. Characteristics of the included studies are summarized in Table 1.

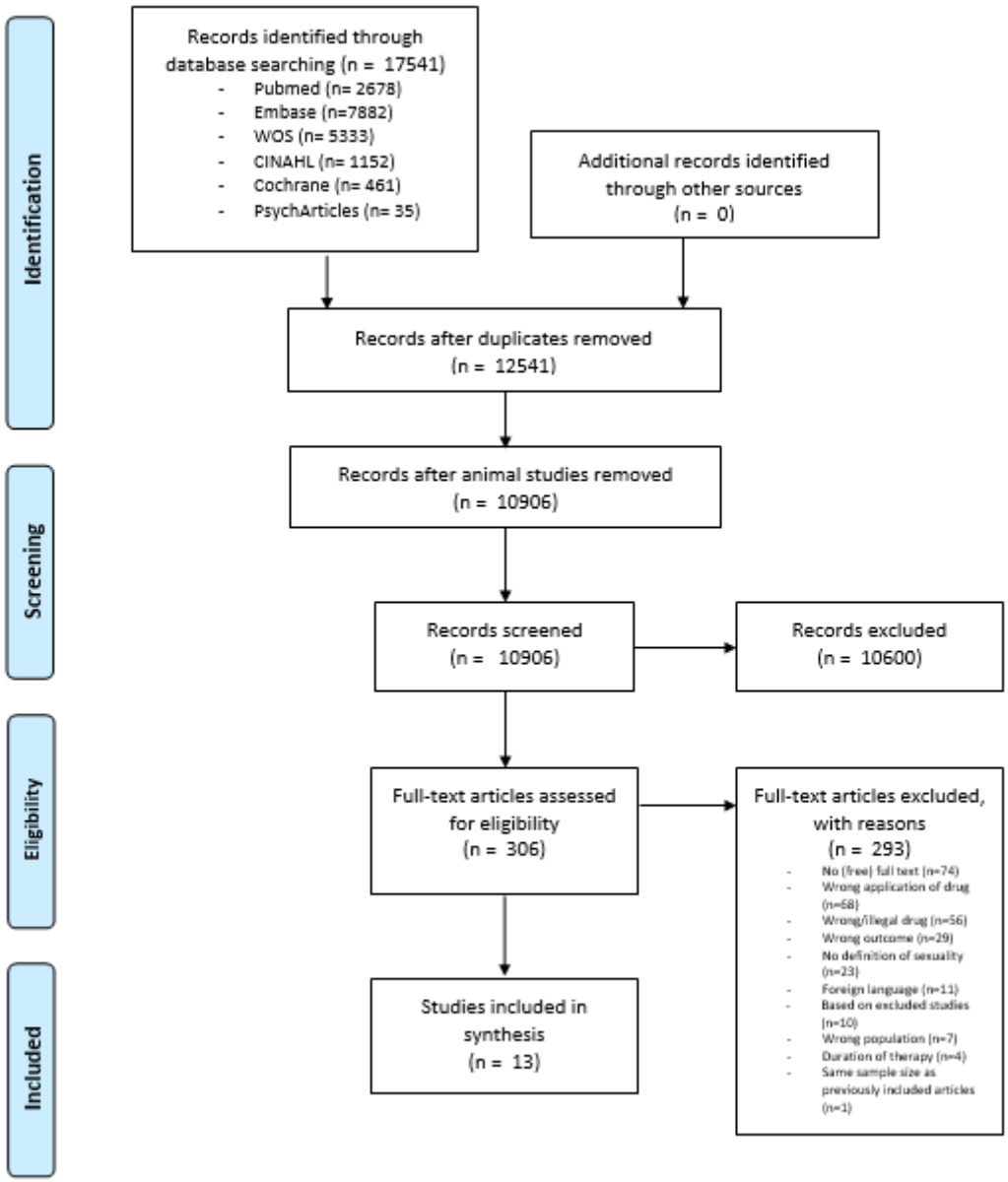


Figure 1: Flowchart of the selection procedure

Articles were published between 2010 and 2021, and consisted of nine cross-sectional studies (25-33), three prospective cohorts (34-36) and one case report (37). Four studies took place in Europe (Spain,

England, Sweden and Denmark) (25,31,32,34), four in Asia (Taiwan, Japan) (28-30, 37), three in North-America (Canada, US) (26,33,35), one in Brazil (36) and one in Australia (27).

A total of 68.439 patients were studied, of which 141 patients were controls. Most patients were identified and selected through outpatient (pain) clinics. Although chronic pain as a reason for chronic opioid use was not incorporated in our inclusion criteria, through our selection we exclusively found a population of chronic non-cancer pain patients. Most studies did not specify the type of chronic pain, but for example Deyo et al. included patients with chronic back pain (33). Three studies used database records resulting in a larger sample size (31,33,34).

Since two articles, with a total of 11.536 patients, did not provide any information on gender, we can not make a definitive statement about gender distribution (31,36). In the eleven articles where gender was mentioned, with a total of 56.884 patients, 11.951 men and 44.933 women were included. (25-30,32-35,37)

The mean age of patients in the study population varied between 42 and 59 years old. Participants in eight studies had a mean age of over 50 years old (25-27, 29-31,33,35). However, most studies used a wide age span, as evident by large standard deviations or ranges mentioned.

Five out of thirteen articles used some form of control group in their analysis, although the various control groups had different characteristics (25-27,32,36). The majority of the control groups contained chronic pain patients treated with non-opioid analgesics, but Ajo et al. (25) used a control group with opioid users without symptoms of sexual dysfunction. Three studies did not define a control group but carried out comparisons between subgroups, for example between long-term and short-term opioid use (31,33,34).

Multiple types of opioids were used and as per our inclusion criteria mostly were oral or transdermal. The studies which based opioid use behavior on the number of filled prescriptions did not specify doses nor the manner of application (33,34). The mentioned opioid treatment doses varied with substantial range differences between studies. Duration of opioid use was at least 90 days, but in most studies patients were using opioids for over a year, with durations mentioned up to 32 years (29).

Various domains of sexual dysfunction were described in the used studies. The most investigated domain was sexual desire or libido, with nine articles defining this as a primary outcome (26,28-32,34,36,37). Other explored domains were erectile dysfunction, sexual satisfaction, frequency, capability, sexual activity and orgasmic function.

Although most articles used self-reported data (26,28-32,36,37), three articles used standardized questionnaires to examine sexual function in opioid users: the International Index of Erectile Function (IIEF) (25,27), the the Female Sexual Function Index (FSFI) (25,27) and the 4-item Medical Outcome Study Sexual Scale (4-item MOS) (35). These studies did not subdivide sexual dysfunction into individual domains, but treated it as a whole. Ajo et al. and Lamprecht et al. both used the validated FSFI and IIEF questionnaires (25,27), which are the most frequently used scales to inquire about patients' sexual function. Morasco et al. used the 4-item MOS scale, comprising of 4 questions about sexual function to measure *(i)* lack of sexual interest, *(ii)* inability to relax and enjoy sex, *(iii)* difficulty

in becoming sexually aroused and *(iv)* difficulty keeping or getting an erection (for men) or difficulty having an orgasm (for women) (35).

Authors – Year country	Population / control group Age in years	Study setting	Definition of chronic use	Opioids: type, form, dose	Sexual outcomes + Definition
Ajo et al. 2016 (25) Spain	- 210 patients with SD (116 F, 94M) - 53 matched controls (27F, 26M) - Mean age 59 (+/-12)	Outpatient pain clinic	>1 year	- Multiple types - O/TD - Mean MED 40-103,9mg/d	- Multiple domains - IIEF, FSFI
Birke et al. 2018 (31) Denmark	- 11.517 individuals - Age: 54,7% 45-64, 28% 65-74, 17,3% 18-44	Data from DANCOS (database)	Min. 1 prescription/ month, min. 6/12 months	- Not mentioned	- Sexual desire, satisfaction, sexual activity, communication with healthcare providers about sexuality - Self-reported
Deyo et al. 2013 (33) US	- 11.327 men with back pain - Mean age 55,7 (+/- 11,3)	Electronic medical and pharmacy records	>120 days or >90days with >10 refills	- Not mentioned - 0->120mg	- ED - Use of medication for ED
Ho ST et al. 2021 (30) Taiwan	- 100 CNCP patients (38 F, 62M) - Mean age F 55,4 (+/-13,6), M 50,3 (+/- 9,2)	9 outpatient pain centres	Mean F 104,3 months , M 126,5 months	- Multiple types - O/TD/IM - Mean MED F 194,2mg/d, M 227,6 mg/d	- Sexual desire, function, frequency and satisfaction, hormonal tests - Self-reported
Lamprecht et al. 2018 (27) Australia	- 40 CNCP patients (15F, 25M) - 25 controls (11F,14M) - Mean age 52 (22-72)	90% patients of one outpatient pain clinic, 10% other hospitals	>6 months (1-25 year), mean duration of 4 years	- Multiple types - O/TD - MED >25mg/d, mean MED 74mg/d	- Multiple domains of sexual dysfunction (also ED), hormonal tests for HPG- and HPA-axis - IIEF, FSFI
Lin et al. 2010 (28) Taiwain	- 61 patients (36M, 25F) - Mean age 45,3 (+/- 16,6)	CNCP patients registered by the NBCD	Mean 54 months (range 6-240 months)	- Multiple types - O/TD/IM	- Sexual desire and capability - Self-reported
Lin et al. 2017 (29) Taiwan	- 210 CNCP patients (68 F, 142 M) - Mean age 50 (+/- 14,6)	Outpatient pain clinic	Mean 63,7 months (range 12-240)	- Multiple types - O/TD/IM - Mean MED 176,5mg/d	- Sexual desire, frequency, capability and satisfaction - Self-reported
Morasco et al. 2020 (35) US	- 441 patients (272F,169M) - Mean age 59 (+/- 11,2)	Two large medical centres	>90 days	- Not mentioned - Mean MED 36,2mg/d	- Sexual dysfunction - 4-item MOS sexual problems scale
Rhodin et al. 2010 (32) Sweden	- 39 CNCP patients (15M,24F) - 20 control CNCP patients without opioid (8M,12F) - Mean age 48 (32-63)	Outpatient pain clinic	> 1 year	- Multiple types - O - Mean MED M 133mg/d , F 111mg/d	- Sexual function (libido, capability, orgasmic function) - Self-reported on 4-grade scale
Richardson et al. 2018 (34) UK	- 44.260 women (22.130 each cohort) - Mean age 43 (35-49)	Data from primary care database	Min. 3 prescriptions in 90 days	- Multiple types and forms	- Libido - Codes in databases
Tabuchi et al. 2012 (37) Japan	- 1 male CNCP patient - Age 42	Hospital admission	4 months	- Fentanyl - TD - 42mg/d	- Libido, ED, hormonal tests - Self-reported
Valverde et al. 2016 (36) Brazil	- 19 CNCP patients - 19 control CNCP non-opioid patients - (also 19 CNCP patients with intrathecal opioids) - Mean age 43 (+/- 8,5)	Outpatient pain clinic	> 6 months	- Morphine - O - 60-120mg/d	- Libido, ED, hormonal tests - Self-reported
Wong et al 2011 (26) Canada	- 73 CNCP patients (47F, 26M) - 24 patients in control group (18F, 6M) - Mean age F 53 (28-83), M 55 (29-77)	Multidisciplinary pain clinic	<1 year - >5 years	- Multiple types - O/TD - MED 0->200mg/d	- Sexual desire, ED, hormonal tests - Self-reported

Table 1: Characteristics of included studies. F: female, M: male, O: oral, TD: transdermal, IM: intramuscular, SD: sexual dysfunction, ED: erectile dysfunction, MED: morphine equivalent dose

The majority of studies found chronic opioid use to have a possible negative impact on at least one of the aforementioned domains. However, both Wong et al. and Richardson et al. did not find a statistical significant association between chronic opioid use and sexual dysfunction (26,34). None of the included articles found a positive effect of chronic opioid use on sexuality. Considering the different studies focused on different domains of sexuality, the remaining results are divided in categories. A summary of the results can be found in Table 2.

Libido and sexual desire

Nine articles examined libido or sexual desire as a primary outcome (26,28-32,34,36,37). Seven articles found a correlation between loss of libido or diminished sexual desire and the chronic use of opioids (28-32,36,37). Three Taiwanese studies, with the same main authors, measured sexual desire in CNCP patients using self-reported data. In 2010, Lin et al. reported a reduced desire in 48% of patients with chronic opioid use based on self-reported data (28). In their study from 2017, with a larger sample size, a low desire was found in 69,5% of patients (29). In a recent study from 2021, Ho et al. found a low desire in 62% of patients (30). These last three studies had no control group, so there is no comparison of these incidence rates in non-opioid treated patients. While comparing long-term opioid users and CNCP patients without opioid use, Birke et al. found that long-term opioid users had significantly higher odds of reporting a low desire. This correlation was not present in short-term opioid users (31). Rhodin et al. concluded that 84% of their opioid-treated population reported sexual dysfunction, including loss of libido, compared to 32% of their control group with CNCP patients without opioid use (32). Valverde-Filho et al. also reported that men and women with chronic opioid use had significantly impaired libido, whereas more than 84% of control patients had no sexual complaints (36). The case report from Tabuchi et al. presented a patient with loss of libido after 4 months of transdermal fentanyl (37). Wong et al. found no statistical difference between prevalence of sexual desire dysfunction in opioid and non-opioid users (26). The matched cohort study of Richardson et al., which uses data of 44.260 women from a database, found no significant difference of loss of libido between short-term opioid users and long-term opioid users, while menopause and abnormal menstruation were positively correlated with long-term use (34).

Erectile function

The presence of erectile dysfunction was assessed in three studies, with a positive association with chronic opioid use found in two of the studies (26,33,37). These articles all used self-reported data. Two other articles, Ajo et al. and Lamprecht et al., also examined erectile function, but used IIEF questionnaires and their conclusions were thus covering all sexual domains (25,27). The cross-sectional study of Wong et al. found an equal incidence of erectile dysfunction in both opioid and non-opioid users (26). In a different approach, Deyo et al. used electronic medical and pharmacy records to determine erectile dysfunction as an outcome and defined it as the need for medication prescribed for the treatment of erectile problems, or testosterone replacement therapy. Chronic opioid use was characterized in this study as ten or more prescribed fills of opioid medication in at least 90 days. Compared to non-opioid users, medications for erectile dysfunction or testosterone replacement therapy were more often prescribed for chronic opioid consumers (33). Finally, besides loss of libido, the case-report from Japan described erectile difficulties in a hospitalized patient as a result of hypogonadotropic hypogonadism as a consequence of his long-term fentanyl use (37).

Other domains of sexuality

Multiple studies examined other domains of sexuality apart from libido or erectile function. Lin et al. reported a 44% reduced sexual capability (28). In 2017, the same author described lower sexual satisfaction and performance in 57,9% of opioid users. Furthermore, also a lower intercourse frequency was found in 55,6% of patients (29). In the cross-sectional study of Ho et al. 68% of sexually active patients reported decreased capability, frequency and satisfaction (30). Birke et al. found, by means of a population based survey, that both long and short term opioid users appeared more likely to experience sexual dissatisfaction than the comparison groups. Sexual activity, defined as having had sexual intercourse during the past year, was significantly diminished in CNCP patients receiving long-term opioid therapy (56,7%), compared to short-term users (62,3%), non-opioid CNCP patients (67,7%) and persons without CNCP (76,5%) (31). As mentioned above, Rhodin et al. noted that 84% of opioid-treated patients reported sexual dysfunction, but besides libido also capability and orgasmic function were part of the self-reported data (32).

Standardized questionnaires for sexual dysfunction

The studies that used standardized questionnaires to measure sexual dysfunction found a positive association with chronic opioid use. Ajo et al. found that 72,4% of female CNCP patients and 77% of male CNCP patients confirmed self-reported sexual dysfunction using the FSFI and IIEF questionnaires respectively for women and men. The main focus of the IIEF is on erectile dysfunction, but other domains are also taken into account (25). Lamprecht et al. also found a significant impaired sexual function in both men and women using the same scales mentioned above in a study with 40 CNCP patients and 25 sex- and age-matched controls (27). Morasco et al. saw a significant yearly decline in MOS score during the course of their study. Their analysis was controlled for the effects of common variables such as patient demographics, comorbidities and pain (35).

Gender differences

Out of the thirteen included articles, ten articles had a mixed gender population. The case report from Tabuchi et al. had one male patient (37), and two articles, both database studies, had an exclusively male or female population (33,34). Most publications provided information on gender distribution, but not all studies analyzed differences between men and women. Ho et al. reported sexual dysfunction in 62 of 100 patients, without significant gender differences in patients suffering from problems regarding sexual desire, satisfaction, function and frequency (30). Lin et al. also reported no statistical gender differences in sexual desire and sexual function or capability (28).

Correlation with opioid type, dose or duration

Some articles provided information on correlations between sexual dysfunctioning and the opioid type, dose or duration. For example, Ajo et al. found a significant correlation between sexual dysfunction and higher morphine-equivalent dose (MED) in men. They also found lower IIEF scores with tapentadol, naloxone and oxycodone (25). In Deyo et al., prescriptions for erectile dysfunction or testosterone replacement increased with both duration and dose of treatment. Patients who were prescribed a daily MED treatment of 120 mg or more had a higher use of medication for erectile dysfunction or testosterone replacement than patients without opioid use, even with adjustment for

duration (33). The combination of long-term and high-dose opioid use seems most strongly associated with markers of sexual dysfunction. In the prospective study conducted by Morasco et al., 441 patients from two large medical centers were studied for two years and divided into two subgroups for analysis based on dose-escalation of opioids. Sexual functioning significantly worsened over time independent of dose escalation during treatment. In this study, high doses of MED >120 mg/day or more were excluded (35).

Correlation with hormonal imbalances

Several studies investigated the link between hormone levels and either sexual function or long-term opioid use. In Lamprecht et al., lower scores on the IIEF questionnaire were not correlated with lower testosterone scores. Although the testosterone levels of opioid users were lower compared to the control group, it failed to reach statistical significance. There was no gonadotropin suppression found in post-menopausal women, and not enough data on pre-menopausal women was available. As this study also examined the influence of opioids on the HPA-axis, they found dose-related secondary adrenal insufficiency (SAI) in more than 20% of patients with long-term opioid use. All participants with SAI received MED doses of more than 60 mg/day (27). In the study of Ho et al. low testerone levels were correlated with longer duration of opioid therapy. In women, they saw a correlation between estradiol levels and sexual desire with lower levels of estradiol for women with reduced sexual desire (30). In Wong et al. there was no association between low free testosterone (FT), total testosterone (TT) or high prolactin levels and decreased desire and/or erectile dysfunction in men, although testosterone levels in men with opioid use were significantly lower. Men who reported SD had lower FT regardless of opioid use. In women, they only found low TT levels in premenopausal women with decreased sexual desire and opioid use, but these results should be treated with caution given the small sample size (26). Finally, in the study of Valverde-Filho et al., significantly lower testosterone and DHEAS levels were found in the oral opioid group compared to controls (36).

Authors – Year Country	Results of chronic opioid use on aspects of sexuality
Ajo et al. 2016 (25) Spain	* 84/116 F with **sexual dysfunction**, confirmed with FSFI. Not related to type of opioid. * 72/94 M with **sexual dysfunction**, confirmed with IIEF. Significant correlation with MED.
Birke et al. 2018 (31) Denmark	* Long- and short-term opioid users more frequent **sexual dissatisfaction.** * Short- and long-term opioid use associated with **lack of/low desire**, long-term opioid use has higher odds of **low desire**. * **Sexual intercourse** during the past year: long-term opioid therapy (56,7%), short-term opioid therapy (62,3%), non-opioid (67,7%), non-CNCP (76,5%).
Deyo et al. 2013 (33) US	* Long-term use of opioids ~ greater use of medications for **erectile dysfunction** or testosterone replacement. * >120 mg MED ~ more use of medication for **erectile dysfunction** or testosterone replacement.
Ho ST et al. 2021 (30) Taiwan	* 62% **lower sexual desire.** * 68% sexually active patients had **decreased function/capability, frequency and satisfaction**, no gender differences. * Estradiol levels lower in F with **reduced sexual desire**. * Lower testosterone scores were present in 89,5% of F and 50% of M. * Duration of opioid therapy correlated with lower testosterone scores in M.
Lamprecht et al. 2018 (27) Australia	* **Impaired sexual function** in M and F opioid users. * Lower IIEF score not correlated with lower testosterone scores.
Lin et al. 2010 (28) Taiwan	* 48% **reduced desire**. * 44% **reduced capability.** * No gender differences.
Lin et al. 2017 (29) Taiwan	* 146/210 patients reported **reduced sexual desire**. * **Decrease in sexual performance** (57,9%), **frequency** (55,6%) and **satisfaction** (57,9%).
Morasco et al. 2020 (35) US	* **Sexual functioning** worsened over time, independent of dose escalation.
Rhodin et al. 2010 (32) Sweden	* 84% opioid-treated patients and 32% control patients reported **sexual dysfunction**.
Richardson et al. 2018 (34) UK	* No higher incidence of **loss of libido** in long-term opioid users.
Tabuchi et al. 2012 (37) Japan	* Presence of **libido loss and erectile dysfunction.** * Hypogonadotropic hypogonadism.
Valverde et al. 2016 (36) Brazil	* Opioid group had significantly **impaired libido**. * **Reduced potency** in M more frequent in the oral morphine group. * Low testosterone and DHEAS levels in oral group.
Wong et al 2011 (26) Canada	* M: **sexual dysfunction** equal in opioid and non-opioid users. * No association between low FT, TT, or high prolactin levels and **decreased desire/erectile dysfunction**. * F: no difference in frequency of **sexual dysfunction** in opioid and non-opioid users. * Premenopausal F with **decreased sexual desire** and opioid use had more frequently low TT levels.

Table 2: Results of chronic opioid use on aspects of sexuality. F: female, M: male, MED: Morphine Equivalent Dose, FT: Free Testosterone, TT: Total Testosterone

DISCUSSION

This review is the first scoping review that reports on research in which opioids were predominantly administered orally or transdermally, simulating prescription behavior in primary care settings. Our study is also one of few scoping reviews describing the effects of chronic treatment on all domains of sexuality.

Our results indicate that most studies found an overall negative effect of chronic opioid use on one or more aspects of sexuality (25,27-33,35-37). This is demonstrated by the high incidence rates of dysfunction in all studied domains of sexuality in opioid treatment groups, particularly the domains erectile dysfunction and reduced sexual desire. Remarkably, neither Wong et al. nor Richardson et al. noted any negative effects (26,34). Several factors might explain the contrast in results with other studies with similar design. First, the large matched cohort study of Richardson et al. is the only publication with research exclusively in women (34). This could be an important factor contributing to the different result. However, two other included studies compared both genders and found no apparent differences between men and women in the incidence of sexual dysfunction (31,36). Second, in their study they used encoded diagnoses and prescription information from a primary care database which could have been subject to inconsistent coding by physicians (34). Also, because of a prescription based definition of opioid use we cannot know the rate of compliance. Furthermore this study compared short-term versus long term opioid use, rather than comparison with non-opioid users. In contrast, the cross-sectional population based survey of Birke et al. with a similar prescription based study design observed a significant difference in low desire between short-term and long-term users. Compared to CNCP patients not using opioids, patients on short term opioid use did not report low desire more often, whereas patients with long term opioid use did report low desire more often (31). Lastly, this study had a rather low age range, with a population of women between the ages of 35 and 49 years old, whereas most other studies had a mean age of more than 50 years old and large ranges thus including elderly men and women. The cross-sectional study of Wong et al. used a small study population of 73 patients (male and female), and a control group of 24 persons of which 6 males and therefore does not hold a lot of power (26).

Whereas Wong et al. and Richardson et al. did not find a correlation between chronic opioid use and sexual dysfunction (26,34), the other included studies showed us a notable association (25,27-33, 35-37). This negative effect is consistent with existing literature. Similar results were found in systematic reviews concerning methadone maintenance therapy or opioid abuse, which was out of scope of this work. For example, the systematic review of Ortman and Siegel, concluded that methadone, frequently used as maintenance therapy in opioid abusers, has disruptive effects on the HPG-axis and self-reported sexual function (38). Yee et al. studied the prevalence of sexual dysfunction in male patients using maintenance therapy in a meta-analysis and concluded that sexual dysfunction was higher among those who used methadone as maintenance therapy , compared to buprenorphine (39). During our search, we assessed three articles from Egypt that studied tramadol-dependent men. They also found a significant increase in sexual dysfunction in this population, however the doses of tramadol were in most cases extremely high (>1000mg/day) and the indication for tramadol intake was often for social or psychological reasons, rather than pain treatment (40-42).

Notwithstanding the trend it is difficult to draw conclusions due to the substantial heterogeneity within and in between publications. Where Wong et al. indicates equal incidences of sexual dysfunction both in the opioid treatment group and the control group, Rhodin et al. reported an incidence of 84% sexual dysfunction in the treatment group but also 32% in the control group (26,32). In contrast, the cohort of Valverde-Filho et al. included an equally large control group of which 84% did not complain of sexual problems (36). This heterogeneity might be attributed to a number of factors. First, different patient characteristics, both between and within publications, can be an important factor. This was also reported as a limitation by some authors (27,34). Specifically for this review there is an overrepresentation of participants in Taiwan, Denmark, the United Kingdom and the United states (28-31,33-35). Second, in between studies there is considerable difference in both definition and the assessment of sexual dysfunction. The majority of studies used self-reported data which is subject to bias as it is unclear how the population defined sexual dysfunction or would answer questions about recollection (26,28-32,36,37). However, sexuality in all its facets remains a personal and subjective experience so it is logical self-reported data was frequently used. Although the 4-item MOS scale used by Morasco et al. is standardized, we did not encounter other publications that used the 4-item MOS scale, nor find evidence it is a validated questionnaire (35). Only two studies used validated questionnaires, such as FSFI and IIEF questionnaires which are amongst the most known and accepted (25,27). The two studies that assessed sexual dysfunction independently from patient input rely on correct coding of diagnoses and treatment in databases by healthcare workers (33,34). Both studies had considerable power, each analyzing information on prescriptions of well over 11.000 patients. Here, a striking heterogeneity in results is observed as well. The first study showed that patients, whose prescription-filling behavior met the definition of chronic opioid use, had greater use of medications for erectile dysfunction in men (33). The second study, which obtained information on long-term and short-term opioid use in women through a UK primary care database, did not observe a higher incidence of decreased libido in the first group. However as the comparison group used opioids as well, statements regarding opioids versus no opioid-based treatment cannot be made (34).

The median age in most studies was above fifty. This is relevant as several of the included studies recognized age as a possible confounder for sexual dysfunction (25,33-35). In a meta-analysis by Zhao et al. age was also identified as a risk for the development of erectile dysfunction, but when corrected for this variable the prevalence of erectile dysfunction in opioid users remained significant. For the greater part, this study included participants who used opioids for dependency, both legal and illegal and therefore we cannot generalize these findings for all opioid consumers (43). The majority of studies identified comorbidities amongst which obesity and depression as confounding factors (25,27-31,33-37). Excess weight may negatively impact hormone levels and induce metabolic changes (36). Wong et al. saw a higher prevalence of depression in their opioid treatment group whereas Lin et al. even observed the prevalence of depression in participants to be as high as 50% (26,29). A last important confounding factor is the presence of pain in all studies which negatively influences quality of life and psychological well being (32). As chronic pain was present in all studies we expect this to influence our findings little.

Some of the included studies examined the association with hormonal changes during opioid treatment (26,27,30,36,37). Several have found a decline in serum testosterone in men (30,36,37), which is consistent with known literature about hypogonadism in opioid users (OPIAD)(9,44). In women, hormonal changes have been less clear. A study from 2008 did find a correlation in hormonal changes in women on opioid treatment (45). Hormone levels were 39% lower in opioid consuming

women and 92% of the opioid treatment group complained of fatigue, depression, lower libido or lower sexual satisfaction. A limitation is the fact that this study includes participants on short-term opioid treatment (4 weeks). Also some of the women were on hormonal substitution therapy, which can be a confounding factor. Interestingly, in Wong et al. and Lamprecht et al. a decrease in testosterone did not correlate with sexual dysfunction symptoms (26,27). Even though there is evidence that hypogonadism is a possible side effect of chronic opioid use, the correlation with sexual dysfunction remains unclear. It is possible that other factors predispose patients to hormonal changes and/or sexual symptoms, such as smoking or BMI. Also, as previously mentioned, most studies use data from drug abusers and conclusions may not apply to the whole patient group taking opioids (46). However, testosterone replacement or substitution therapy is already being used as a valid treatment option in patients with hypogonadism, independently of sexual symptoms. Daniell et al. carried out an open-label study in which they treated patients taking opioids for noncancer pain with transdermal testosterone patches. In this study, an improvement in sexual function was seen, although the effects were incompletely resolved (47). Smith et al. conclude that both men and women with opioid-induced endocrinopathy can benefit from androgen replacement therapy, but there are significant side effects such as polycythemia, decrease of HDL-cholesterol, gynaecomastia, male pattern baldness, increased risk of prostate cancer in men, increased risk of breast cancer in women and virilisation of women (9).

The present work has several limitations that could not be avoided. First, this scoping review included only cross-sectional studies, a case report and cohort studies. Our methods were unable to identify randomized control trials and the eligible systematic reviews and meta-analysis were all based on already included or excluded research. Second, the majority of our included studies had a lack of sufficient power due to a small sample size. Third, not all of the discussed works clearly reported the application of opioid treatment. Through the context of study designs we assumed opioids were prescribed orally or transdermally, although we cannot guarantee this.

Contrary to existing publications on the effects of chronic opioid use on sexuality this review focuses on prescribed oral or transdermal opioids for indications other than dependence, which makes it more relevant in primary care settings where opioids are most commonly prescribed as an analgesic. After our selection process the remaining eligible studies all researched a population of chronic non-cancer pain patients although this was not a criterion for inclusion. Results between publications are however more comparable because of the presence of this population characteristic in all studies. Our study design allows us to chart a wide array of information on this topic regardless of publication date or design. Both opioid use and sexual health have become rising points of interest the last few decades as a result of which the discussed research is relatively recent.

Future research and practice

Current literature is lacking large, prospective studies or controlled trials to further determine the association between chronic opioid use, endocrinopathy and effects on sexuality. Therefore the value of routine hormone testing for manifestations of opioid-induced endocrine dysfunction needs to be further assessed. The possible confounding factors that add to sexual problems should be further investigated to understand to what extent the use of opioids itself contributes to sexual dysfunction. Medical professionals must become more aware of possible negative influences of opioid analgesics on sexuality and should aim to explore these routinely, preferably by form of standardized questioning, which is currently not common practice.

CONCLUSION

As the chronic use of opioids is increasing, the risk of side effects such as sexual dysfunction becomes substantial, possibly diminishing the quality of life of patients. In this scoping review, a correlation between chronic opioid use and negative effects on all domains of sexuality can be seen in most studies. Due to the heterogeneity of our included articles, this trend can not be seen in all participants. Several confounding factors such as age and depression seem to have an influence on these results. Further research is necessary to determine a definitive causal relationship and to implement clinical guidelines for screening and treatment.

REFERENCES

1. Hemmings Jr HC, Lambert DG. The good, the bad, and the ugly: the many faces of opioids. Br J Anaesth. 2019 Jun 1;122(6):e95–7.

2. Skolnick P. The Opioid Epidemic: Crisis and Solutions. Annual Review of Pharmacology and Toxicology Annu Rev Pharmacol Toxicol [Internet]. 2018;58:143–59. Available from: https://doi.org/10.1146/annurev-pharmtox-

3. Goesaert G, Baitar A. OPIOIDE PIJNSTILLERS dossier | opioïde pijnstillers [Internet]. 2018. Available from: www.epo.be

4. Organisation for Economic Co-operation and Development. Addressing Problematic Opioid Use in OECD Countries. OECD Publishing; 2019. p. 80.

5. Khademi H, Kamangar F, Brennan P, Malekzadeh R. Opioid Therapy and its side effects: A review. Arch Iran Med. 2016;19(12):870–6.

6. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Pain Physician 2008: Opioid Special Issue: 11:S105-S120. Pain Physician [Internet]. 2008;Opioid Special Issue(11):S105–20. Available from: www.painphysicianjournal.com

7. Richards GC, Mahtani KR, Muthee TB, Devito NJ, Koshiaris C, Aronson JK, et al. Factors associated with the prescribing of high-dose opioids in primary care: A systematic review and meta-Analysis. BMC Med. 2020 Mar 30;18(68).

8. Ajo R, Segura A, Mira L, Inda MDM, Alfayate R, Sánchez-Barbie A, et al. The relationship of salivary testosterone and male sexual dysfunction in opioid-associated androgen deficiency (OPIAD). Aging Male. 2017 Jan 2;20(1):1–8.

9. Smith HS, Elliott JA. opioid-induced androgen deficiency. Pain Physician. 2012;15(2150–1149):ES145–56.

10. Ho KWK. Opioid-induced androgen deficiency (OPIAD): prevalence, consequence, and efficacy of testosterone replacement. Vol. 6, Current Opinion in Endocrine and Metabolic Research. Elsevier Ltd; 2019. p. 54–9.

11. Coluzzi F, Billeci D, Maggi M, Corona G. Testosterone deficiency in non-cancer opioid-treated patients. Vol. 41, Journal of Endocrinological Investigation. Springer International Publishing; 2018. p. 1377–88.

12. Read S, King M, Watson J. Sexual dysfunction in primary medical care: Prevalence, characteristics and detection by the general practitioner. Journal of Public Health Medicine (United Kingdom). 1997;19(4):387–91.

13. Manninen SM, Kero K, Perkonoja K, Vahlberg T, Polo-Kantola P. General practitioners' self-reported competence in the management of sexual health issues–a web-based questionnaire study from Finland. Scand J Prim Health Care. 2021;39(3):279–87.

14. Burri A, Spector T. Recent and Lifelong Sexual Dysfunction in a Female UK Population Sample: Prevalence and Risk Factors. Journal of Sexual Medicine. 2011;8(9):2420–30.

15. McCabe MP, Sharlip ID, Lewis R, Atalla E, Balon R, Fisher AD, et al. Incidence and Prevalence of Sexual Dysfunction in Women and Men: A Consensus Statement from the Fourth International Consultation on Sexual Medicine 2015. Journal of Sexual Medicine. 2016 Feb 1;13(2):144–52.

16. Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual Problems and Distress in United States Women Prevalence and Correlates. Obstet Gynecol. 2008;112:970–8.

17. Parish SJ, Hahn SR. Hypoactive Sexual Desire Disorder: A Review of Epidemiology, Biopsychology, Diagnosis, and Treatment. Vol. 4, Sexual Medicine Reviews. Elsevier B.V.; 2016. p. 103–20.

18. Thomas DR. Medications and sexual function. Clin Geriatr Med. 2003;19:553–62.

19. Nappi RE, Cucinella L, Martella S, Rossi M, Tiranini L, Martini E. Female sexual dysfunction (FSD): Prevalence and impact on quality of life (QoL). Maturitas. 2016 Dec 1;94:87–91.

20. Clayton AH, Goldstein I, Kim NN, Althof SE, Faubion SS, Faught BM, et al. The International Society for the Study of Women's Sexual Health Process of Care for Management of Hypoactive Sexual Desire Disorder in Women. Mayo Clin Proc. 2018 Apr 1;93(4):467–87.

21. Kraus C, Kadriu B, Lanzenberger R, Zarate CA, Kasper S. Prognosis and improved outcomes in major depression: a review. Transl Psychiatry. 2019 Dec 1;9(127).

22. Grover S, Shouan A. Assessment Scales for Sexual Disorders—A Review. Journal of Psychosexual Health. 2020 Apr;2(2):121–38.

23. Basson R. Review: Testosterone therapy for reduced libido in women. Ther Adv Endocrinol Metab. 2010;1(4):155–64.

24. Hsieh A, DiGiorgio L, Fakunle M, Sadeghi-Nejad H. Management Strategies in Opioid Abuse and Sexual Dysfunction: A Review of Opioid-Induced Androgen Deficiency. Sex Med Rev. 2018 Oct 1;6(4):618–23.

25. Ajo R, Segura A, Inda M del M, Planelles B, Martínez L, Ferrández G, et al. Opioids Increase Sexual Dysfunction in Patients With Non-Cancer Pain. Journal of Sexual Medicine. 2016 Sep 1;13(9):1377–86.

26. Wong Bsc D, Gray Md Frcpc D, Simmonds M, Rashiq S, Bs Ms Frcpc BM, Sobolev I, et al. Opioid analgesics suppress male gonadal function, but opioid use in men and women does not correlate with symptoms of sexual dysfunction. Pain Res Manage [Internet]. 2011;16(5):311–6. Available from: www.physics.

27. Lamprecht A, Sorbello J, Jang C, Torpy DJ, Inder WJ. Secondary adrenal insufficiency and pituitary dysfunction in oral/transdermal opioid users with non-cancer pain. Eur J Endocrinol. 2018 Dec 1;179(6):353–62.

28. Lin TC, Hsu CH, Lu CC, Tsai YC, Ho ST. Chronic opioid therapy in patients with chronic noncancer pain in Taiwan. J Anesth. 2010 Dec;24(6):882–7.

29. Lin TC, Ger LP, Pergolizzi J V., Raffa RB, Wang JO, Ho ST. Long-term use of opioids in 210 officially registered patients with chronic noncancer pain in Taiwan: A cross-sectional study. Journal of the Formosan Medical Association. 2017 Apr 1;116(4):257–65.

30. Ho ST, Lin TC, Yeh CC, Cheng KI, Sun WZ, Sung CS, et al. Gender differences in depression and sex hormones among patients receiving long-term opioid treatment for chronic noncancer pain in Taiwan—A multicenter cross-sectional study. Int J Environ Res Public Health. 2021 Aug 1;18(15).

31. Birke H, Ekholm O, Højsted J, Sjøgren P, Kurita GP. Chronic pain, opioid therapy, sexual desire, and satisfaction in sexual life: A population-based survey. Pain Medicine (United States). 2019 Jun 1;20(6):1132–40.

32. Rhodin A, Stridsberg M, Gordh T. Opioid Endocrinopathy: A Clinical Problem in Patients With Chronic Pain and Long-term Oral Opioid Treatment. Clin J Pain [Internet]. 2010;26(5):374–80. Available from: www.clinicalpain.com

33. Deyo RA, Smith DHM, Johnson ES, Tillotson CJ, Donovan M, Yang X, et al. Prescription opioids for back pain and use of medications for erectile dysfunction. Spine (Phila Pa 1976). 2013 May 15;38(11):909–15.

34. Richardson E, Bedson J, Chen Y, Lacey R, Dunn KM. Increased risk of reproductive dysfunction in women prescribed long-term opioids for musculoskeletal pain: A matched cohort study in the Clinical Practice Research Datalink. European Journal of Pain (United Kingdom). 2018 Oct 1;22(9):1701–8.

35. Morasco BJ, Smith N, Dobscha SK, Deyo RA, Hyde S, Yarborough BJH. Outcomes of prescription opioid dose escalation for chronic pain: results from a prospective cohort study. Pain. 2020 Jun 1;161(6):1332–40.

36. Valverde-Filho J, Cunha Neto MBC da, Fonoff ET, Meirelles E de S, Teixeira MJ. Chronic Spinal and Oral Morphine-Induced Neuroendocrine and Metabolic Changes in Noncancer Pain Patients. Pain Medicine (United States). 2015 Apr 1;16(4):715–25.

37. Tabuchi Y, Yasuda T, Kaneto H, Kitamura T, Kozawa J, Otsuki M, et al. A case of hypogonadotropic hypogonadism caused by opioid treatment for nonmalignant chronic pain. Case Rep Med. 2012;2012.

38. Ortman HA, Siegel JA. The effect of methadone on the hypothalamic pituitary gonadal axis and sexual function: A systematic review. Drug Alcohol Depend. 2020 Feb 1;207.

39. Yee A, Loh HS, Hisham Hashim HM bt, Ng CG. The Prevalence of Sexual Dysfunction among Male Patients on Methadone and Buprenorphine Treatments: A Meta-Analysis Study. Journal of Sexual Medicine. 2014;11(1):22–32.

40. Bassiony MM, Youssef UM, El-Gohary H, Abdelghani M, Hassan MS, Salah El-Deen G. Sexual Dysfunction among Male Patients with Tramadol abuse: A Case-Control Study. International Journal of Sexual Health. 2019 Jan 2;31(1):109–14.

41. Soliman T, Shaher H, Mohey A, El-Shaer W, Sebaey A. Gonadotoxic effect of tramadol administration: A prospective controlled study. Arab J Urol. 2022;20(1):54–60.

42. Kabbash A, El Kelany R, Oreby M, El Gameel D. Effect of tramadol dependence on male sexual dysfunction. Interdiscip Toxicol. 2019 Dec 1;12(4):157–62.

43. Zhao S, Deng T, Luo L, Wang J, Li E, Liu L, et al. Association Between Opioid Use and Risk of Erectile Dysfunction: A Systematic Review and Meta-Analysis. Journal of Sexual Medicine. 2017 Oct 1;14(10):1209–19.

44. Bawor M, Bami H, Dennis BB, Plater C, Worster A, Varenbut M, et al. Testosterone suppression in opioid users: A systematic review and meta-analysis. Drug Alcohol Depend. 2015 Apr 1;149:1–9.

45. Daniell HW. Opioid Endocrinopathy in Women Consuming Prescribed Sustained-Action Opioids for Control of Nonmalignant Pain. Journal of Pain. 2008 Jan;9(1):28–36.

46. Benyamin R, Trescot AM, Datta S, Buenaventura Ricardo, Adlaka R, Sehgal N, et al. Opioid Complications and side effects. Pain Physician [Internet]. 2008;Opioid Special(11):105–20. Available from: www.painphysicianjournal.com

47. Daniell HW, Lentz R, Mazer NA. Open-label pilot study of testosterone patch therapy in men with opioid-induced androgen deficiency. Journal of Pain. 2006 Mar;7(3):200–10.

APPENDICES

Appendix 1: Research Ethics Committee approval

Scoping review about the effect of chronic opioid use on sexual desire and experience in non-cancer patients.

Dossiernr.:	MP018567
Masterproef:	Masterproef I HAIO, 2020 – 2023
Faculteit/opleiding:	Faculteit Geneeskunde - Master in de huisartsgeneeskunde
Studiefase:	eerste fase
Academiejaar:	2021-2022
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.

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.

Appendix 2: Approved protocol

THESIS PROTOCOL

The effect of chronic opioid use on sexuality in non-cancer patients.

1. APPLICANTS

Protocol - full title	**Scoping review about the effect of chronic opioid use on sexual desire and experience in non-cancer patients.**
Version 1: Date submission	Date: 01 june 2021
Version 2: Date resubmission	(to add in case of resubmission) Date:Click here to enter a date.
Version 3: Date third submission	(to add in case of third submission) Date:Click here to enter a date.
Principal Investigator – Promoter	Name: Van Nuland Marc
	Telephone: /
	E-mail:
Co-Investigator – Co-Promoter	Name: Coteur Kristien
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2. ABSTRACT

NA.

3. INTRODUCTION

Opioids are a group of well-known analgesics that inhibit pain perception by binding to opioid receptors in the central and peripheral nervous system (1). In 1804, the first opioid analgesic morphine was extracted from opium, the dried latex from the Papaver Somniferum. Morphine and other opium derivatives like heroin or codeine are called opiates, whereas the term opioids is used for all substances that interact with opioid receptors: the opiates, synthetic opioids (e.g. fentanyl) as well as the body's own opioid substances such as endorphins.

Opioid use has increased dramatically over the past decades in the United States, where more than 245 million prescriptions were made in 2014, testimony to an epidemic (2,3). The same trend can be seen in Belgium where the amount of opioid users has doubled between 2006 and 2017. More than 1,2 million people have received a prescription for opioids in 2017 of which more than 80% had been prescribed by their general practitioner (3). In fact, Belgium ranks in third place in Europe and fifth place worldwide when looking at daily use of opioids per million inhabitants (4).

Having gained fame for their role in acute or chronic pain management, some opioids have a wide range of non-pain related applications in primary care settings (1). Examples are codeine or dextromethorphan as cough suppressants or loperamide as an antidiarrheal drug. Although interactions with mu-receptors as well as kappa- or delta-receptors all mediate pain-inhibitory pathways, the mu-receptor plays the main role in pain alleviation but also in opioid-related side-effects (5).

Within the range of opioid-use associated adverse events, most commonly mentioned are nausea and constipation, but also dizziness, hypotension and hallucinations (6). Moreover, patients using opioids in high doses are more at risk to use other medications such as benzodiazepines and suffer from depression (7). Arguably, the most alarming side-effects of opioid use might be the development of tolerance and addiction, resulting in the use of progressively higher doses, risking respiratory depression and death by overdose (8).

Another less known side-effect of chronic opioid use is opioid-induced androgen deficiency (OPIAD) attributed to an inhibitory function on the hypothalamic-pituitary-gonadal (HPG) axis. Opioids inhibit the release of gonadotropin-releasing hormone (GnRH) resulting in a decrease of testosterone production and a stimulation of testosterone denaturation (9). The prevalence of OPIAD in chronic users has been reported up to 86% (10). This hypogonadism is associated with fatigue, depression, menstrual irregularities, loss of bone mass but also sexual dysfunction, possibly leading to a decreased quality of life for chronic opioid users (9,11).

Sexual dysfunction as a result of chronic opioid use is often overlooked and may be difficult to assess. Despite an increase in prescription of opioids and a higher than reported estimated prevalence of sexual dysfunction in chronic opioid consumers, general practitioners infrequently make inquiries as to patients' sexual health in general (12,13). 70% of the patients reported a need to discuss sexual problems with their general practitioner but in only 2% of all cases the general practitioner took note of the complaint (14).

Studies have reported the prevalence of sexual dysfunction in the general population as high as 15,5% in women and 25% in men, citing problems such as erectile dysfunction, vaginismus, loss of desire or premature

ejaculation (14,15,16). Considering sexual dysfunction to be this prevalent in the general population, making low-threshold inquiries towards associated symptoms when prescribing treatments that may diminish sexuality, like opioids, is important. For side-effects that are difficult to objectify, such as decreased sexual desire or altered sexual experiences, thorough questioning is even more vital**.** Patients are far more likely to report sexual dysfunction as an adverse drug event when asked directly by a physician compared to self-reportage. This phenomenon outlines the role of general practitioners in early detection of sexual side-effects to a treatment, but also helps explain the underestimation of sexual dysfunction prevalence, as this estimation relies predominantly on self-reported sexual dysfunction.(17) Impaired sexual dysfunction has shown to have a significant negative impact on quality of life.(18) This association has also been confirmed between depression and hypoactive sexual desire disorder which is the most prevalent sexual dysfunction in women and affects approximately 1 in 10 women. Patiënts suffering from sexual dysfunction have an associated increased risk of depression of over 130%, for which they sometimes receive medication that paradoxically may cause sexual dysfunction as well.(19) However early recognition of depressive symptoms leads to earlier treatment and better outcomes for the patient.(20)

Whereas several systematic reviews and meta-analyses exist on OPIAD, decreased testosterone and erectile dysfunction in men, there is no systematic research available about sexual desire and loss-of-libido. A wide array of questionnaires are used to objectify changes in sexual desire, but are subject to bias. In the diagnosis of OPIAD and consequently decreased libido, laboratory testing is little contributing, as there is no absolute lower hormone limit under which a person be diagnosed with hypogonadism (21). Furthermore, sex hormone levels tend to correlate poorly with loss of libido in women (22).

Due to its intrinsic subjective nature, changes in sexual desire are difficult to correlate to concomitant opioid use, and therefore little hard evidence exists on this topic. In our scoping review, we will produce an overview regarding information about changed sexual desire and overall sexual experience as an indication of sexual dysfunction as an adverse event to chronic opioid use.

Objective

The objective of this scoping review is to provide an overview of the current state of knowledge concerning the effect of chronic non-cancer related opioid use on the perception of sexual desire and sexual experience. Apart from describing opioid's effects on this part of sexual well-being, we aim to present insight into the incidence of changes in sexual desire in chronic opioid consumers as well as reliable tools for reporting. Our analysis of present-day literature aims to function as a foundation for future experimental research and outline gaps in our comprehension of this topic.

4. REVIEW QUESTION

hat is the effect of chronic prescribed oral or transdermal opioid use in non-cancer patients on different aspects of sexuality?

5. METHODS

Protocol and registration

This protocol has been registered and approved by the Belgian Research Ethics Committee.

Search strategy

We will conduct a literature search using the concepts “opioids” and “sexuality” by examining the following electronic databases: Pubmed, Embase, Web of Science, CINAHL, Cochrane library and PsycArticle. MeSH Terms and entry terms were identified through the MeSH Tree provided by the National Library of Medicine (NLM). The identified terms are also entered in the search as title/abstract(TIAB) terms. The search is tailored for optimal use in each of the forementioned databases. If one database identifies an additional subject heading, this is added to the search string. If possible, terms are exploded. Several terms are entered as Supplemental Concept in our Pubmed search, as no hits were obtained in any other field. Grey literature targeted searches will be performed in publicly available data sources to capture unpublished data. Following the snowball principle, we aim to identify additional relevant sources through searching reference lists.

Search string

Our search strategy of the electronic databases mentioned above will be carried out with both MeSH terms and free text terms pertaining to abstract or title.

Example of PubMed search

Concept 1: Opioids

"Analgesics, Opioid"[Mesh], "Opioid"[Title/Abstract], "Opioid analgesics"[Title/Abstract]

- 18,19-dihydroetorphine *(Supplementary Concept)*
- acetaminophen, hydrocodone drug combination *(Supplementary Concept)*
- acrylfentanyl *(Supplementary Concept)*
- Alfentanil *(MeSH Term)*
- Alphaprodine *(MeSH Term)*
- beta-casomorphins *(Supplementary Concept)*
- brorphine *(Supplementary Concept)*
- Buprenorphine *(MeSH Term)*
- Buprenorphine, Naloxone Drug Combination *(MeSH Term)*
- Butorphanol *(MeSH Term)*
- carfentanil *(Supplementary Concept)*
- Codeine *(MeSH Term)*
- crotonylfentanyl *(Supplementary Concept)*
- cyclopropylfentanyl *(Supplementary Concept)*
- deltorphin I, Ala(2)- *(Supplementary Concept)*
- dermorphin *(Supplementary Concept)*
- desomorphine *(Supplementary Concept)*
- Dextromoramide *(MeSH Term)*
- Dextropropoxyphene *(MeSH Term)*
- dezocine *(Supplementary Concept)*
- dihydrocodeine *(Supplementary Concept)*
- Dihydromorphine *(MeSH Term)*
- Diphenoxylate *(MeSH Term)*
- Dsuvia *(Supplementary Concept)*

- dynorphin (1-13) *(Supplementary Concept)*
- endomorphin 1 *(Supplementary Concept)*
- endomorphin 2 *(Supplementary Concept)*
- Enkephalin, Ala(2)-MePhe(4)-Gly(5)- *(MeSH Term)*
- Enkephalin, D-Penicillamine (2,5)- *(MeSH Term)*
- enkephalin-Met, Ala(2)- *(Supplementary Concept)*
- eseroline *(Supplementary Concept)*
- Ethylketocyclazocine *(MeSH Term)*
- Ethylmorphine *(MeSH Term)*
- Etorphine *(MeSH Term)*
- Fentanyl *(MeSH Term)*
- Heroin *(MeSH Term)*
- Hydrocodone *(MeSH Term)*
- Hydromorphone *(MeSH Term)*
- kappa-opioid agonist JT09 *(Supplementary Concept)*
- ketobemidone *(Supplementary Concept)*
- Levorphanol *(MeSH Term)*
- lofentanil *(Supplementary Concept)*
- Meperidine *(MeSH Term)*
- Meptazinol *(MeSH Term)*
- Methadone *(MeSH Term)*
- Methadyl Acetate *(MeSH Term)*
- Morphine *(MeSH Term)*
- Nalbuphine *(MeSH Term)*
- nocistatin *(Supplementary Concept)*
- normethadone *(Supplementary Concept)*
- O-demethyltramadol *(Supplementary Concept)*
- Opiate Alkaloids *(MeSH Term)*
- Opium *(MeSH Term)*
- Oxycodone *(MeSH Term)*
- Oxymorphone *(MeSH Term)*
- paracymethadol *(Supplementary Concept)*
- Pentazocine *(MeSH Term)*
- Phenazocine *(MeSH Term)*
- Phenoperidine *(MeSH Term)*
- Pirinitramide *(MeSH Term)*
- Promedol *(MeSH Term)*
- protopine *(Supplementary Concept)*
- Remifentanil *(MeSH Term)*
- Sufentanil *(MeSH Term)*
- Tapentadol *(MeSH Term)*
- Tilidine *(MeSH Term)*
- Tramadol *(MeSH Term)*
- tramadol, dexketoprofen drug combination *(Supplementary Concept)*
- tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine *(Supplementary Concept)*

<u>Concept 2: Sexuality</u>

"Sexual Dysfunction, Physiological"[Mesh] OR "Dyspareunia"[Mesh] OR "Erectile Dysfunction"[Mesh] OR “Premature Ejaculation”[Mesh] OR “Vaginismus”[Mesh] OR “Orgasm”[Mesh] OR “Sexual Behavior”[Mesh] OR “Sexual Arousal”[Mesh] OR “Sexuality”[Mesh] OR “Libido”[Mesh] OR “Coitus”[Mesh] OR

"Masturbation"[Mesh] OR "Ejaculation"[Mesh] OR "Penile Erection"[Mesh] OR "Sexual Partners"[Mesh] OR "Sexual*"[Title/Abstract] OR "Libido*"[Title/Abstract] OR "Lubrication"[Title/Abstract] OR "Vulvodynia"[Title/Abstract] OR "Anorgasmia"[Title/Abstract] OR "Orgasm*"[Title/Abstract] OR "Impotence*"[Title/Abstract] OR "Dyspareunia"[Title/Abstract] OR "Vaginismus"[Title/Abstract] OR "Masturbation"[Title/Abstract] OR "Coitus"[Title/Abstract] OR "Ejaculation"[Title/Abstract] OR "Erecti*"[Title/Abstract] OR "Sex Disorders"[Title/Abstract] OR "Penile Venous Leakage"[Title/Abstract] OR "Psychosexual Dysfunction"[Title/Abstract]OR "Psychosexual Disorder"[Title/Abstract] OR "Frigidity"[Title/Abstract] OR "Sex Behavior"[Title/Abstract] OR "Oral Sex"[Title/Abstract] OR "Sex Orientation"[Title/Abstract] OR "Anal Sex"[Title/Abstract] OR "First Intercourse"[Title/Abstract] OR "Coital Frequency"[Title/Abstract] OR "Coital Frequencies"[Title/Abstract] OR "Sex Partner"[Title/Abstract]

Selection of sources of evidence and eligibility criteria

Identified articles are screened by two independent reviewers on title and/or abstract for relevance. Duplicates were removed. Disagreement is solved by consulting a third researcher or (co-)promotor if necessary.

This scoping review has no limitation regarding study design, the year of publication or location where the research was performed. This review is restricted to only consider studies performed in humans, both male and female participants. Articles must be available in languages spoken by all researchers, which is either English or Dutch. Inclusion criteria are the legal use of prescribed oral or transdermal opioids in sexually active, adult, non-cancer patients for a duration of at least eight weeks. Both the presence and treatment of cancer have an important confounding effect on sexual well-being, for example receiving hormone or chemotherapy or the development of a disturbed body image, making it necessary to exclude this population (23,24). Publications are required to define which aspects of sexuality the outcome is about, providing numerical data. Exclusion criteria comprise the use of non-prescription opioids, the therapeutic use of opioids for sexual dysfunction, the presence of sexual dysfunction pre-exisiting the beginning of the study and the abuse of multiple drugs. Multi-drug dependency poses difficulties in monitoring drug intake and concomitant use of sexual health harming products results in important confounding effect (25). Our focus lies predominantly on primary care as this setting is for many patients their first contact with prescribed opioids, however studies in other settings may provide crucial insights and are therefore included as well.

Data charting

Data will be systematically extracted from papers included in this scoping review by three independent reviewers using a data extraction tool. The extracted data will include qualitative data and if mentioned quantitative data. An analysis of quantitative data will be carried out if enough numerical data is found in our search.

A draft extraction form is provided (see Addendum 1). The draft data extraction tool will be modified and revised as necessary during the process of charting data from each included evidence source. Any modifications will be detailed in the scoping review. Two reviewers will independently extract data from each source. Any disagreements that arise between the reviewers will be resolved through consulting a third reviewer. If necessary, authors of papers may be contacted to request missing or additional data.

Data items

This review will extract data concerning following domains: study characteristics (e.g. year of publication, publication type..), the size of the studied population and if mentioned their demography (e.g. sex, age,...), the type and dose of opioid that was administered and the duration of its consumption, the effect on reported

sexual desire and experience, detailed information on reported quality of life or other adverse effects, length of follow-up, confounding factors and possible treatment or care approaches. Furthermore we will collect information about the setting in which the study took place and the tools and questionnaires that were used to report the findings.

Critical appraisal of individual sources of evidence

Articles eligible for inclusion will undergo an appraisal by two independent reviewers. A third reviewer is consulted to discuss discrepancies.

6. RESULTS

NA.

7. DISCUSSION

NA.

8. FUNDING

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9. REFERENCES

1. Hemmings HC, Lambert DG. The good, the bad, and the ugly: the many faces of opioids. *Br J Anaesth*. 2019;122(6):705-707. doi:10.1016/j.bja.2019.04.003

2. Skolnick P. The Opioid Epidemic: Crisis and Solutions. *Annu Rev Pharmacol Toxicol*. 2018;58:143-159. doi:10.1146/annurev-pharmtox-010617-052534

3. G G. opioïde pijnstillers. *VAD -vlaams Expert alcohol en And drugs*. https://www.vad.be/assets/dossier_opioide_pijnstillers_web.

4. OECD (2019), *Addressing Problematic Opioid Use in OECD Countries*, OECD Health Policy Studies, OECD Publishing, Paris, https://doi.org/10.1787/a18286f0-en.

5. Kieffer BL, Gavériaux-Ruff C. Exploring the opioid system by gene knockout. *Prog Neurobiol*. 2002;66(5):285-306. doi:10.1016/S0301-0082(02)00008-4

6. Khademi H, Kamangar F, Brennan P, Malekzadeh R. Opioid therapy and its side effects: A review. *Arch Iran Med*. 2016;19(12):870-876. doi:0161912/AIM.0010

7. Richards GC, Mahtani KR, Muthee TB, et al. Factors associated with the prescribing of high-dose opioids in primary care: A systematic review and meta-Analysis. *BMC Med*. 2020;18(1):1-11. doi:10.1186/s12916-020-01528-7

8. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician*. 2008;11(SPEC. ISS. 2):105-120. doi:10.36076/ppj.2008/11/s105

9. Healy S, Hartman A, Gustin J. Opioid-induced androgen deficiency #284. *J Palliat Med*. 2014;17(11):1278-1279. doi:10.1089/jpm.2014.9398

10. Coluzzi F, Billeci D, Maggi M, Corona G. Testosterone deficiency in non-cancer opioid-treated patients. *J Endocrinol Invest*. 2018;41(12):1377-1388. doi:10.1007/s40618-018-0964-3

11. Flaminia Coluzzi, Maria Sole Scerpa MC. The Effect of Opiates on Bone Formation and Bone Healing. *Curr Osteoporos Rep*. 2020;18(5):433-438. doi:10.1007/s11914-020-00607-1

12. Heiman JR. Sexual dysfunction: overview of prevalence, etiological factors, and treatments. J Sex Res. 2002 Feb;39(1):73-8. doi: 10.1080/00224490209552124. PMID: 12476261.

13. Parish SJ, Hahn SR. Hypoactive Sexual Desire Disorder: A Review of Epidemiology, Biopsychology, Diagnosis, and Treatment. Sex Med Rev. 2016 Apr;4(2):103-120. doi: 10.1016/j.sxmr.2015.11.009. Epub 2016 Feb 6. PMID: 27872021.

14. Read S, King M, Watson J. Sexual dysfunction in primary medical care: Prevalence, characteristics and detection by the general practitioner. *J Public Heal (United Kingdom)*. 1997;19(4):387-391. doi:10.1093/oxfordjournals.pubmed.a024665

15. Burri A, Spector T. Recent and Lifelong Sexual Dysfunction in a Female UK Population Sample: Prevalence and Risk Factors. *J Sex Med*. 2011;8(9):2420-2430. doi:10.1111/j.1743-6109.2011.02341.x

16. McCabe MP, Sharlip ID, Lewis R, et al. Incidence and Prevalence of Sexual Dysfunction in Women and Men: A Consensus Statement from the Fourth International Consultation on Sexual Medicine 2015. *J Sex Med*. 2016;13(2):144-152. doi:10.1016/j.jsxm.2015.12.034

17. Thomas DR. Medications and sexual function. Clin Geriatr Med. 2003 Aug;19(3):553-62. doi: 10.1016/s0749-0690(02)00101-5. PMID: 14567007.

18. Nappi RE, Cucinella L, Martella S, Rossi M, Tiranini L, Martini E. Female sexual dysfunction (FSD): Prevalence and impact on quality of life (QoL). Maturitas. 2016 Dec;94:87-91. doi: 10.1016/j.maturitas.2016.09.013. Epub 2016 Sep 28. PMID: 27823751

19. Clayton AH, Goldstein I, Kim NN, Althof SE, Faubion SS, Faught BM, Parish SJ, Simon JA, Vignozzi L, Christiansen K, Davis SR, Freedman MA, Kingsberg SA, Kirana PS, Larkin L, McCabe M, Sadovsky R. The International Society for the Study of Women's Sexual Health Process of Care for Management of Hypoactive Sexual Desire Disorder in Women. Mayo Clin Proc. 2018 Apr;93(4):467-487. doi: 10.1016/j.mayocp.2017.11.002. Epub 2018 Mar 12. PMID: 29545008.

20. Kraus C, Kadriu B, Lanzenberger R, Zarate CA Jr, Kasper S. Prognosis and improved outcomes in major depression: a review. Transl Psychiatry. 2019;9(1):127. Published 2019 Apr 3. doi:10.1038/s41398-019-0460-3

21. Smith HS, Elliott JA. Opioid-induced androgen deficiency (OPIAD). Pain Physician. 2012 Jul;15(3 Suppl):ES145-56. PMID: 22786453.

22. Basson R. Review: Testosterone therapy for reduced libido in women. *Ther Adv Endocrinol Metab*. 2010;1(4):155-164. doi:10.1177/2042018810379588

23. Tripaldi C. Sexual function after stoma formation in women with colorectal cancer. Br J Nurs. 2019 Sep 12;28(16):S4-S15. doi: 10.12968/bjon.2019.28.16.S4. PMID: 31518529.

24. Candy B, Jones L, Vickerstaff V, Tookman A, King M. Interventions for sexual dysfunction following treatments for cancer in women. Cochrane Database Syst Rev. 2016 Feb 2;2:CD005540. doi: 10.1002/14651858.CD005540.pub3. PMID: 26830050.

25. Chou NH, Huang YJ, Jiann BP. The Impact of Illicit Use of Amphetamine on Male Sexual Functions. J Sex Med. 2015 Aug;12(8):1694-702. doi: 10.1111/jsm.12926. Epub 2015 Jul 6. PMID: 26147855

10. ADDENDA

Addendum 1: draft of data extraction form

Author Year Country	Journal	Design Setting	Population	Control group	Out-comes	Definition sexuality	Opioid: type dose	Definition chronic use	Results	Con-founders	Limita-tions	Conclusion	Gaps in literature

Appendix 3: Enumeration of search strategies

Pubmed

Concept 1: opioids

"Analgesics, Opioid"[Mesh] OR “18,19-dihydroetorphine”[Supplementary Concept] OR “acetaminophen, hydrocodone drug combination”[Supplementary Concept] OR “acrylfentanyl”[Supplementary Concept] OR “Alfentanil”[Mesh] OR “Alphaprodine”[Mesh] OR “beta-casomorphins”[Supplementary Concept] OR “brorphine”[Supplementary Concept] OR “Buprenorphine”[Mesh] OR “Buprenorphine, Naloxone Drug Combination”[Mesh] OR “Butorphanol”[Mesh] OR “carfentanil”[Supplementary Concept] OR “Codeine”[Mesh] OR “crotonylfentanyl”[Supplementary Concept] OR “cyclopropylfentanyl”[Supplementary Concept] OR “deltorphin I, Ala(2)-”[Supplementary Concept] OR “dermorphin”[Supplementary Concept] OR “desomorphine”[Supplementary Concept] OR “Dextromoramide”[Mesh] OR “Dextropropoxyphene”[Mesh] OR “dezocine”[Supplementary Concept] OR “dihydrocodeine”[Supplementary Concept] OR “Dihydromorphine”[Mesh] OR “Diphenoxylate”[Mesh] OR “Dsuvia”[Supplementary Concept] OR “dynorphin (1-13)”[Supplementary Concept] OR “endomorphin 1”[Supplementary Concept] OR “endomorphin 2”[Supplementary Concept] OR “Enkephalin, Ala(2)-MePhe(4)-Gly(5)-”[Mesh] OR “Enkephalin, D-Penicillamine (2,5)-”[Mesh] OR “enkephalin-Met, Ala(2)-”[Supplementary Concept] OR “eseroline”[Supplementary Concept] OR “Ethylketocyclazocine”[Mesh] OR “Ethylmorphine”[Mesh] OR “Etorphine”[Mesh] OR “Fentanyl”[Mesh] OR “Heroin”[Mesh] OR “Hydrocodone”[Mesh] OR “Hydromorphone”[Mesh] OR “kappa-opioid agonist JT09”[Supplementary Concept] OR “ketobemidone”[Supplementary Concept] OR “Levorphanol”[Mesh] OR “lofentanil”[Supplementary Concept] OR “Meperidine”[Mesh] OR “Meptazinol”[Mesh] OR “Methadone”[Mesh] OR “Methadyl Acetate”[Mesh] OR “Morphine”[Mesh] OR “Nalbuphine” [Mesh] OR “nocistatin”[Supplementary Concept] OR “normethadone”[Supplementary Concept] OR “O-demethyltramadol”[Supplementary Concept] OR “Opiate Alkaloids”[Mesh] OR “Opium”[Mesh] OR “Oxycodone”[Mesh] OR “Oxymorphone”[Mesh] OR “paracymethadol”[Supplementary Concept] OR “Pentazocine”[Mesh] OR “Phenazocine”[Mesh] OR “Phenoperidine”[Mesh] OR “Pirinitramide”[Mesh] OR “Promedol”[Mesh] OR “protopine”[Supplementary Concept] OR “Remifentanil”[Mesh] OR “Sufentanil”[Mesh] OR “Tapentadol”[Mesh] OR “Tilidine” [Mesh] OR “Tramadol”[Mesh] OR “tramadol, dexketoprofen drug combination”[Supplementary Concept] OR “tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine”[Supplementary Concept]

OR "Opioid*"[Title/Abstract] OR (“narcotic analgesic agent”[Title/Abstract]) OR “18,19-dihydroetorphine”[Title/Abstract] OR “acrylfentanyl”[Title/Abstract] OR “Alfentanil”[Title/Abstract] OR “Alphaprodine”[Title/Abstract] OR “beta-casomorphins”[Title/Abstract] OR “brorphine”[Title/Abstract] OR “Buprenorphine”[Title/Abstract] OR “Butorphanol”[Title/Abstract] OR “carfentanil”[Title/Abstract] OR “Codeine”[Title/Abstract] OR “crotonylfentanyl”[Title/Abstract] OR “cyclopropylfentanyl”[Title/Abstract] OR “deltorphin I, Ala(2)-”[Title/Abstract] OR “dermorphin”[Title/Abstract] OR “desomorphine”[Title/Abstract] OR “Dextromoramide”[Title/Abstract] OR “Dextropropoxyphene”[Title/Abstract] OR “dezocine”[Title/Abstract] OR “dihydrocodeine”[Title/Abstract] OR “Dihydromorphine”[Title/Abstract] OR “Diphenoxylate”[Title/Abstract] OR “Dsuvia”[Title/Abstract]

OR “dynorphin (1-13)”[Title/Abstract] OR “endomorphin 1”[Title/Abstract] OR “endomorphin 2”[Title/Abstract] OR “Enkephalin, Ala(2)-MePhe(4)-Gly(5)-”[Title/Abstract] OR “Enkephalin, D-Penicillamine (2,5)-”[Title/Abstract] OR “enkephalin-Met, Ala(2)-”[Title/Abstract] OR “eseroline”[Title/Abstract] OR “Ethylketocyclazocine”[Title/Abstract] OR “Ethylmorphine”[Title/Abstract] OR “Etorphine”[Title/Abstract] OR “Fentanyl”[Title/Abstract] OR “Heroin”[Title/Abstract] “Hydrocodone”[Title/Abstract] OR “Hydromorphone”[Title/Abstract] OR “kappa-opioid agonist JT09”[Title/Abstract] OR “ketobemidone”[Title/Abstract] OR “Levorphanol”[Title/Abstract] OR “lofentanil”[Title/Abstract] OR “Meperidine”[Title/Abstract] OR “Meptazinol”[Title/Abstract] OR “Methadone”[Title/Abstract] OR “Methadyl Acetate”[Title/Abstract] OR “Morphine”[Title/Abstract] OR “Nalbuphine” [Title/Abstract] OR “nocistatin”[Title/Abstract] OR “normethadone”[Title/Abstract] OR “O-demethyltramadol”[Title/Abstract] OR “Opiate Alkaloids”[Title/Abstract] OR “Opium”[Title/Abstract] OR “Oxycodone”[Title/Abstract] OR “Oxymorphone”[Title/Abstract] OR “paracymethadol”[Title/Abstract] OR “Pentazocine”[Title/Abstract] OR “Phenazocine”[Title/Abstract] OR “Phenoperidine”[Title/Abstract] OR “Pirinitramide”[Title/Abstract] OR “Promedol”[Title/Abstract] OR “protopine”[Title/Abstract] OR “Remifentanil”[Title/Abstract] OR “Sufentanil”[Title/Abstract] OR “Tapentadol”[Title/Abstract] OR “Tilidine” [Title/Abstract] OR “Tramadol”[Title/Abstract] OR “tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine”[Title/Abstract]

Concept 2: sexuality

"Sexual Dysfunction, Physiological"[Mesh] OR "Dyspareunia"[Mesh] OR "Erectile Dysfunction"[Mesh] OR “Premature Ejaculation”[Mesh] OR “Vaginismus”[Mesh] OR “Orgasm”[Mesh] OR “Sexual Behavior”[Mesh] OR “Sexual Arousal”[Mesh] OR “Sexuality”[Mesh] OR “Libido”[Mesh] OR “Coitus”[Mesh] OR “Masturbation”[Mesh] OR “Ejaculation”[Mesh] OR “Penile Erection”[Mesh] OR “Sexual Partners”[Mesh] OR “Sexual*”[Title/Abstract] OR “Libido*”[Title/Abstract] OR “Lubrication”[Title/Abstract] OR “Vulvodynia”[Title/Abstract] OR “Anorgasmia”[Title/Abstract] OR “Orgasm*”[Title/Abstract] OR “Impotence*”[Title/Abstract] OR “Dyspareunia”[Title/Abstract] OR “Vaginismus”[Title/Abstract] OR “Masturbation”[Title/Abstract] OR “Coitus”[Title/Abstract] OR “Ejaculation”[Title/Abstract] OR “Erecti*”[Title/Abstract] OR “Sex Disorders”[Title/Abstract] OR “Penile Venous Leakage”[Title/Abstract] OR “Psychosexual Dysfunction”[Title/Abstract]OR “Psychosexual Disorder”[Title/Abstract] OR “Frigidity”[Title/Abstract] OR "Sex Behavior"[Title/Abstract] OR "Oral Sex"[Title/Abstract] OR "Sex Orientation"[Title/Abstract] OR "Anal Sex"[Title/Abstract] OR “First Intercourse”[Title/Abstract] OR “Coital Frequency”[Title/Abstract] OR “Coital Frequencies”[Title/Abstract] OR "Sex Partner"[Title/Abstract]

Embase

Concept 1: opioids

‘Opiate’/exp OR ‘narcotic analgesic agent’/exp OR ’18 19-dihydroetorphine’/exp OR ‘acetaminophen, hydrocodone drug combination’/exp OR ‘acrylfentanyl’/exp OR ‘Alfentanil’/exp OR ‘Alphaprodine’/exp OR ‘beta casomorphine derivate’/exp OR ‘brorphine’/exp OR ‘Buprenorphine’/exp OR ‘buprenorphine plus naloxone’/exp OR ‘Butorphanol’/exp OR ‘carfentanil’/exp OR ‘Codeine’/exp OR ‘crotonylfentanyl’/exp OR ‘cyclopropylfentanyl’/exp OR ‘deltorphin I, Ala(2)-’/exp OR ‘dermorphin’/exp OR ‘desomorphine’/exp OR ‘Dextromoramide’/exp OR ‘Dextropropoxyphene’/exp OR ‘dezocine’/exp OR ‘dihydrocodeine’/exp OR ‘Dihydromorphine’/exp

OR 'Diphenoxylate'/exp OR 'sufentanil citrate'/exp OR 'dynorphin[1-13]'/exp OR 'endomorphin 1'/exp OR 'endomorphin 2'/exp OR 'enkephalin[2 dextro alanine 4 methylphenylalanine 5 glycine]'/exp OR 'Enkephalin[2,5 dextro penicillamine]'/exp OR 'enkephalin-Met, Ala(2)-'/exp OR 'eseroline'/exp OR 'ethylketazocine'/exp OR 'Ethylmorphine'/exp OR 'Etorphine'/exp OR 'Fentanyl'/exp OR 'Hydrocodone'/exp OR 'Hydromorphone'/exp OR 'kappa-opioid agonist JT09'/exp OR 'ketobemidone'/exp OR 'Levorphanol'/exp OR 'lofentanil'/exp OR 'pethidine'/exp OR 'Meptazinol'/exp OR 'Methadone'/exp OR 'acetylmethadol'/exp OR 'Morphine'/exp OR 'Nalbuphine'/exp OR 'nocistatin'/exp OR 'normethadone'/exp OR 'desmetramadol'/exp OR 'Oxycodone'/exp OR 'Oxymorphone'/exp OR 'paracymethadol'/exp OR 'Pentazocine'/exp OR 'Phenazocine'/exp OR 'Phenoperidine'/exp OR 'piritramide'/exp OR 'trimeperidine'/exp OR 'protopine'/exp OR 'Remifentanil'/exp OR 'Sufentanil'/exp OR 'Tapentadol'/exp OR 'Tilidine'/exp OR 'Tramadol'/exp OR 'dexketoprofen plus tramadol'/exp OR 'tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine'/exp

OR 'Opioid*':ab,ti OR 'narcotic analgesic agent':ab,ti OR '18 19-dihydroetorphine':ab,ti OR 'acrylfentanyl':ab,ti OR 'Alfentanil':ab,ti OR 'Alphaprodine':ab,ti OR 'beta casomorphine derivative':ab,ti OR 'brorphine':ab,ti OR 'Buprenorphine':ab,ti OR 'Butorphanol':ab,ti OR 'carfentanil':ab,ti OR 'Codeine':ab,ti OR 'crotonylfentanyl':ab,ti OR 'cyclopropylfentanyl':ab,ti OR 'deltorphin I, Ala(2)-':ab,ti OR 'dermorphin':ab,ti OR 'desomorphine':ab,ti OR 'Dextromoramide':ab,ti OR 'Dextropropoxyphene':ab,ti OR 'dezocine':ab,ti OR 'dihydrocodeine':ab,ti OR 'Dihydromorphine':ab,ti OR 'Diphenoxylate':ab,ti OR 'sufentanil citrate':ab,ti OR 'dynorphin [1-13]':ab,ti OR 'endomorphin 1':ab,ti OR 'endomorphin 2':ab,ti OR 'enkephalin[2 dextro alanine 4 methylphenylalalnine 5 glycine]':ab,ti OR 'enkephalin[2,5 dextro penicillamine]':ab,ti OR 'enkephalin-Met, Ala(2)':ab,ti OR 'eseroline':ab,ti OR 'ethylketazocine':ab,ti OR 'Ethylmorphine':ab,ti OR 'Etorphine':ab,ti OR 'Fentanyl':ab,ti OR 'Hydrocodone':ab,ti OR 'Hydromorphone':ab,ti OR 'kappa-opioid agonist JT09':ab,ti OR 'ketobemidone':ab,ti OR 'Levorphanol':ab,ti OR 'lofentanil':ab,ti OR 'pethidine':ab,ti OR 'Meptazinol':ab,ti OR 'Methadone':ab,ti OR 'acetylmethadol':ab,ti OR 'Morphine':ab,ti OR 'Nalbuphine':ab,ti OR 'nocistatin':ab,ti OR 'normethadone':ab,ti OR 'desmetramadol':ab,ti OR 'opiate':ab,ti OR 'Opium':ab,ti OR 'Oxycodone':ab,ti OR 'Oxymorphone':ab,ti OR 'paracymethadol':ab,ti OR 'Pentazocine':ab,ti OR 'Phenazocine':ab,ti OR 'Phenoperidine':ab,ti OR 'piritramide':ab,ti OR 'trimeperidine':ab,ti OR 'protopine':ab,ti OR 'Remifentanil':ab,ti OR 'Sufentanil':ab,ti OR 'Tapentadol':ab,ti OR 'Tilidine':ab,ti OR 'Tramadol':ab,ti OR 'tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine':ab,ti

Concept 2: sexuality

'Sexual Dysfunction'/exp OR 'Dyspareunia'/exp OR 'Erectile Dysfunction'/exp OR 'organic impotence'/exp OR 'Premature Ejaculation'/exp OR 'Vaginism'/exp OR 'Psychosexual disorder'/exp OR 'Orgasm'/exp OR 'Sexual Behavior'/exp OR 'Sexual Arousal'/exp OR 'Sexuality'/exp OR 'Libido'/exp OR 'Coitus'/exp OR 'Masturbation'/exp OR 'Ejaculation'/exp OR 'Penis erection'/exp OR 'Sexual*':ab,ti OR 'Libido*':ab,ti OR 'Orgasm*':ab,ti OR 'Impotence*':ab,ti OR 'Erecti*':ab,ti OR 'Lubrication':ab,ti OR 'Vulvodynia':ab,ti OR 'Anorgasmia':ab,ti OR 'Dyspareunia':ab,ti OR 'Premature Ejaculation':ab,ti OR 'Vaginismus':ab,ti OR 'Masturbation':ab,ti OR 'Coitus':ab,ti OR 'Ejaculation':ab,ti OR 'Penile Tumescence':ab,ti OR 'Sex Disorders':ab,ti OR 'Penile Venous Leakage':ab,ti OR 'Ejaculatio Praecox':ab,ti OR 'Psychosexual Dysfunction':ab,ti OR 'Psychosexual Disorder':ab,ti OR 'Frigidity':ab,ti OR 'Sex Behavior':ab,ti OR 'Oral Sex':ab,ti OR 'Sex Orientation':ab,ti OR 'Anal Sex':ab,ti OR 'First Intercourse':ab,ti OR 'Coital Frequency':ab,ti OR 'Coital Frequencies':ab,ti OR 'Sex Partner':ab,ti

Web Of Science

Concept 1: opioids

TS=(Opioid* OR "narcotic analgesic agent" OR 18,19-dihydroetorphine OR Acetaminophen, hydrocodone drug combination OR Acrylfentanyl OR Alfentanil OR Alphaprodine OR Beta-casomorphins OR Brorphine OR Buprenorphine OR Butorphanol OR Carfentanil OR Codeine OR Crotonylfentanyl OR Cyclopropylfentanyl OR Deltorphin I, Ala(2)- OR Dermorphin OR Desomorphine OR Dextromoramide OR Dextropropoxyphene OR Dezocine OR Dihydrocodeine OR Dihydromorphine OR Diphenoxylate OR Dsuvia OR Dynorphin (1-13) OR Endomorphin 1 OR Endomorphin 2 OR Enkephalin, Ala(2)-MePhe(4)-Gly(5)- OR Enkephalin, D-Penicillamine (2,5)- OR Enkephalin-Met, Ala(2)- OR Eseroline OR Ethylketocyclazocine OR Ethylmorphine OR Etorphine OR Fentanyl OR Heroin OR Hydrocodone OR Hydromorphone OR Kappa-opioid agonist JT09 OR Ketobemidone OR Levorphanol OR Lofentanil OR Meperidine OR Meptazinol OR Methadone OR Methadyl Acetate OR Morphine OR Nalbuphine OR Nocistatin OR Normethadone OR O-demethyltramadol OR "Opiate Alkaloids" OR Opium OR Oxycodone OR Oxymorphone OR Paracymethadol OR Pentazocine OR Phenazocine OR Phenoperidin OR Pirinitramide OR Promedol OR Protopine OR Remifentanil OR Sufentanil OR Tapentadol OR Tilidine OR Tramadol OR tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine)

Concept 2: sexuality

TS=(Sexual* OR Libido* OR Erecti* OR Impotence* OR Orgasm* OR Dyspareunia OR Vaginismus OR Coitus OR Masturbation OR Ejaculation OR Lubrication OR Vulvodynia OR Anorgasmia OR Penile Tumescence OR Sex Disorders OR Penile Venous Leakage OR Ejaculatio Praecox OR Psychosexual Dysfunction OR Psychosexual Disorders OR Frigidity OR Sex Behavior OR Oral Sex OR Sex Orientation OR Anal Sex OR First Intercourse OR Coital Frequency OR Coital Frequencies OR Sex Partner

CINAHL

Concept 1: opioids

MH("opioid*" OR "Alfentanil" OR "Alphaprodine" OR "Buprenorphine" OR "Buprenorphine, Naloxone Drug Combination" OR "Butorphanol" OR "Codeine" OR "Dextromoramide" OR "Dextropropoxyphene" OR "Dihydromorphine" OR "Diphenoxylate" OR "Enkephalin, Ala(2)-MePhe(4)-Gly(5)-" OR "Enkephalin, D-Penicillamine (2,5)-" OR "Ethylketocyclazocine" OR "Ethylmorphine" OR "Etorphine" OR "Fentanyl" OR "Heroin" OR "Hydrocodone" OR "Hydromorphone" OR "Levorphanol" OR "Meperidine" OR "Meptazinol" OR "Methadone" OR "Methadyl Acetate" OR "Morphine" OR "Nalbuphine" OR "Opiate Alkaloids" OR "Opium" OR "Oxycodone" OR "Oxymorphone" OR "Pentazocine" OR "Phenazocine" OR "Phenoperidine" OR "Pirinitramide" OR "Promedol" OR "Remifentanil" OR "Sufentanil" OR "Tapentadol" OR "Tilidine" OR "Tramadol" OR "18,19-dihydroetorphine"OR "acetaminophen, hydrocodone drug combination"OR acrylfentanyl OR "beta-casomorphins" OR Brorphine OR carfentanil OR crotonylfentanyl OR cyclopropylfentanyl OR "deltorphin I, Ala(2)-" OR dermorphin OR desomorphine OR dezocine OR dihydrocodeine OR Dsuvia OR "dynorphin (1-13)" OR "endomorphin 1" OR "endomorphin 2" OR "enkephalin-Met, Ala(2)-" OR eseroline OR "kappa-opioid agonist JT09" OR ketobemidone OR lofentanil OR nocistatin OR normethadone OR "O-demethyltramadol" OR paracymethadol OR protopine" OR "tramadol,

dexketoprofen drug combination" OR "tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine") OR

TI("opioid*" OR "Alfentanil" OR "Alphaprodine" OR "Buprenorphine" OR "Butorphanol" OR "Codeine" OR "Dextromoramide" OR "Dextropropoxyphene" OR "Dihydromorphine" OR "Diphenoxylate" OR "Enkephalin, Ala(2)-MePhe(4)-Gly(5)-" OR "Enkephalin, D-Penicillamine (2,5)-" OR "Ethylketocyclazocine" OR "Ethylmorphine" OR "Etorphine" OR "Fentanyl" OR "Heroin" OR "Hydrocodone" OR "Hydromorphone" OR "Levorphanol" OR "Meperidine" OR "Meptazinol" OR "Methadone" OR "Methadyl Acetate" OR "Morphine" OR "Nalbuphine" OR "Opiate Alkaloids" OR "Opium" OR "Oxycodone" OR "Oxymorphone" OR "Pentazocine" OR "Phenazocine" OR "Phenoperidine" OR "Pirinitramide" OR "Promedol" OR "Remifentanil" OR "Sufentanil" OR "Tapentadol" OR "Tilidine" OR "Tramadol" OR "18,19-dihydroetorphine"OR "acetaminophen, hydrocodone drug combination"OR acrylfentanyl OR "beta-casomorphins" OR brorphine OR carfentanil OR crotonylfentanyl OR cyclopropylfentanyl OR "deltorphin I, Ala(2)-" OR dermorphin OR desomorphine OR dezocine OR dihydrocodeine OR Dsuvia OR "dynorphin (1-13)" OR "endomorphin 1" OR "endomorphin 2" OR "enkephalin-Met, Ala(2)-" OR eseroline OR "kappa-opioid agonist JT09" OR ketobemidone OR lofentanil OR nocistatin OR normethadone OR "O-demethyltramadol" OR paracymethadol OR protopine" OR "tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine" OR "narcotic analgesic agent") OR

AB("opioid*" OR "Alfentanil" OR "Alphaprodine" OR "Buprenorphine" OR "Butorphanol" OR "Codeine" OR "Dextromoramide" OR "Dextropropoxyphene" OR "Dihydromorphine" OR "Diphenoxylate" OR "Enkephalin, Ala(2)-MePhe(4)-Gly(5)-" OR "Enkephalin, D-Penicillamine (2,5)-" OR "Ethylketocyclazocine" OR "Ethylmorphine" OR "Etorphine" OR "Fentanyl" OR "Heroin" OR "Hydrocodone" OR "Hydromorphone" OR "Levorphanol" OR "Meperidine" OR "Meptazinol" OR "Methadone" OR "Methadyl Acetate" OR "Morphine" OR "Nalbuphine" OR "Opiate Alkaloids" OR "Opium" OR "Oxycodone" OR "Oxymorphone" OR "Pentazocine" OR "Phenazocine" OR "Phenoperidine" OR "Pirinitramide" OR "Promedol" OR "Remifentanil" OR "Sufentanil" OR "Tapentadol" OR "Tilidine" OR "Tramadol" OR "18,19-dihydroetorphine"OR "acetaminophen, hydrocodone drug combination"OR acrylfentanyl OR "beta-casomorphins" OR brorphine OR carfentanil OR crotonylfentanyl OR cyclopropylfentanyl OR "deltorphin I, Ala(2)-" OR dermorphin OR desomorphine OR dezocine OR dihydrocodeine OR Dsuvia OR "dynorphin (1-13)" OR "endomorphin 1" OR "endomorphin 2" OR "enkephalin-Met, Ala(2)-" OR eseroline OR "kappa-opioid agonist JT09" OR ketobemidone OR lofentanil OR nocistatin OR normethadone OR "O-demethyltramadol" OR paracymethadol OR protopine" OR "tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine" OR "narcotic analgesic agent")

<u>Concept 2: sexuality</u>

MH("Sexual*" OR "Dyspareunia" OR "Erecti*" OR "Impotence*" OR "Premature Ejaculation" OR "Vaginismus" OR "Orgasm*" OR "Libido*" OR "Coitus" OR "Masturbation" OR "Ejaculation") OR
TI(Sexual* OR Libido* OR Dyspareunia OR Erecti* OR Impotence* OR OR Vaginismus OR Coitus OR Masturbation OR Ejaculation OR Lubrication OR Vulvodynia OR Orgasm* OR Dyspareunia OR Penile Tumescence OR Sex Disorders OR Penile Venous Leakage OR Frigidity OR Sex Behavior OR Oral Sex OR Sex Orientation OR Premarital Sex Behavior OR Anal Sex OR First Intercourse OR Coital Frequency OR

Coital Frequencies OR Sex Partner OR Multiple Sex Partners OR anorgasmia OR psychosexual disorder) OR

AB(Sexual* OR Libido* OR Erecti* OR Impotence* OR Orgasm* OR Dyspareunia OR Vaginismus OR Coitus OR Masturbation OR Ejaculation OR Lubrication OR Vulvodynia OR Anorgasmia OR Dyspareunia OR Penile Tumescence OR Sex Disorders OR Ejaculatio Praecox OR Penile Venous Leakage OR Frigidity OR Sex Behavior OR Psychosexual disorder OR Psychosexual Dysfunction OR Oral Sex OR Sex Orientation OR Anal Sex OR First Intercourse OR Coital Frequency OR Coital Frequencies OR Sex Partner)

Cochrane

Concept 1: opioids

[mh "Analgesics, Opioid"] OR [mh “Alfentanil”] OR [mh “Alphaprodine”] OR [mh “Buprenorphine”] OR [mh “Buprenorphine, Naloxone Drug Combination”] OR [mh “Butorphanol”] OR [mh “Codeine”] OR [mh “Dextromoramide”] OR [mh “Dextropropoxyphene”] OR [mh “Dihydromorphine”] OR [mh “Diphenoxylate”] OR [mh “Enkephalin, Ala(2)MePhe(4)Gly(5)”] OR [mh “Enkephalin, D-Penicillamine (2,5)”] OR [mh "Ethylketocyclazocine"] OR [mh “Ethylmorphine”] OR [mh “Etorphine”] OR [mh “Fentanyl”] OR [mh “Hydrocodone”] OR [mh “Hydromorphone”] OR [mh “Levorphanol”] OR [mh “Meperidine”] OR [mh “Meptazinol”] OR [mh “Methadone”] OR [mh “Methadyl Acetate”] OR [mh “Morphine”] OR [mh “Nalbuphine”] OR [mh “Opiate Alkaloids”] OR [mh “Opium”] OR [mh “Oxycodone”] OR [mh “Oxymorphone”] OR [mh “Pentazocine”] OR [mh “Phenazocine”] OR [mh “Phenoperidine”] OR [mh “Pirinitramide”] OR [mh “Promedol”] OR [mh “Remifentanil”] OR [mh “Sufentanil”] OR [mh “Tapentadol”] OR [mh “Tilidine”] OR [mh “Tramadol”] OR

("Opioid*" OR "Analgesics, Opioid" OR “18,19dihydroetorphine” OR “acetaminophen, hydrocodone drug combination” OR “acrylfentanyl” OR “Alfentanil” OR “Alphaprodine” OR “Buprenorphine” OR “Butorphanol” OR “beta-casomorphins” OR “brorphine” OR “carfentanil” OR “crotonylfentanyl” OR “cyclopropylfentanyl” OR “Codeine” OR “deltorphin I, Ala(2)” OR “dermorphin” OR “desomorphine” OR “dezocine” OR “dihydrocodeine” OR “Dsuvia” OR "Dynorphin" OR “Dextromoramide” OR “Dextropropoxyphene” OR “Dihydromorphine” OR “Diphenoxylate” OR "endomorphin" OR “Enkephalin, Ala(2)MePhe(4)Gly(5)” OR “Enkephalin, D-Penicillamine (2,5)” OR “eseroline” OR "Ethylketocyclazocine" OR “Ethylmorphine” OR “Etorphine” OR “Fentanyl” OR “Hydrocodone” OR “Hydromorphone” OR “ketobemidone” OR “lofentanil” OR “Levorphanol” OR “Meperidine” OR “Meptazinol” OR “Methadone” OR “Methadyl Acetate” OR “Morphine” OR “Nalbuphine” OR “nocistatin” OR “normethadone” OR “O-demethyltramadol” OR “Opiate Alkaloids” OR “Opium” OR “Oxycodone” OR “Oxymorphone” OR “Pentazocine” OR “Phenazocine” OR “Phenoperidine” OR “Pirinitramide” OR “Promedol” OR “paracymethadol” OR “protopine” OR “Remifentanil” OR “Sufentanil” OR “Tapentadol” OR “Tilidine” OR “Tramadol” OR "H-Tyr-Tic-Phe-Phe-OH"):ti,ab,kw

Concept 2: sexuality

[mh "Sexual Dysfunction, Physiological"] OR [mh "Dyspareunia"] OR [mh "Erectile Dysfunction"] OR [mh “Impotence, Vasculogenic”] OR [mh “Premature Ejaculation”] OR [mh “Vaginismus”] OR [mh “Sexual Dysfunctions, Psychological”] OR [mh “Orgasm”] OR [mh “Sexual Behavior”] OR [mh “Sexual

Arousal”] OR [mh “Sexuality”] OR [mh “Libido”] OR [mh “Coitus”] OR [mh “Masturbation”] OR [mh “Ejaculation”] OR [mh “Penile Erection”] OR [mh “Sexual Partners”]

OR (Sexual* OR Libido* OR “Lubrication” OR Orgasm* OR Impotence* OR Erecti* OR “Vulvodynia” OR “Anorgasmia” OR “Dyspareunia” OR “Ejaculation” OR “Vaginismus” OR “Masturbation” OR “Coitus” OR “Penile Tumescence” OR “Sex Disorder” OR “Penile Venous Leakage” OR “Ejaculatio Praecox” OR “Psychosexual Dysfunction” OR “Psychosexual Disorder” OR “Frigidity” OR "Sex Behavior" OR "Oral Sex" OR "Sex Orientation" OR "Anal Sex" OR “First Intercourse” OR “Coital Frequency” OR “Coital Frequencies” OR "Sex Partner"):ti,ab,kw

PsychArticles

Concept 1: opioids

MAINSUBJECT.EXACT.EXPLODE(“opioid analgesics” OR Buprenorphine OR Codeine OR Fentanyl OR Methadone OR Morphine OR Opiates OR Oxycodone OR Pentazocine OR Tramadol) OR

MAINSUBJECT.EXACT(“18,19-dihydroetorphine” OR “acetaminophen, hydrocodone drug combination” OR Acrylfentanyl OR Alfentanil OR Alphaprodine OR “beta-casomorphins” OR Brorphine OR “Buprenorphine, Naloxone Drug Combination” OR Butorphanol OR Carfentanil OR Crotonylfentanyl OR Cyclopropylfentanyl OR “deltorphin I, Ala(2)-” OR Dermorphin OR Desomorphine OR Dextromoramide OR Dextropropoxyphene OR Dezocine OR Dihydrocodeine OR Dihydromorphine OR Diphenoxylate OR Dsuvia OR “dynorphin (1-13)” OR “endomorphin 1” OR “endomorphin 2” OR “Enkephalin, Ala(2)-MePhe(4)-Gly(5)-” OR “Enkephalin, D-Penicillamine (2,5)-” OR “enkephalin-Met, Ala(2)-” OR Eseroline OR Ethylketocyclazocine OR Ethylmorphine OR Etorphine OR Heroin OR Hydrocodone OR Hydromorphone OR “kappa-opioid agonist JT09” OR ketobemidone OR Levorphanol OR lofentanil OR Meperidine OR Meptazinol OR “Methadyl Acetate” OR Nalbuphine OR Nocistatin OR Normethadone OR “O-demethyltramadol” OR “Opiate Alkaloids” OR Opium OR Oxymorphone OR paracymethadol OR Pentazocine OR Phenazocine OR Phenoperidine OR Pirinitramide OR Promedol OR Protopine OR Remifentanil OR Sufentanil OR Tapentadol OR Tilidine OR Tramadol OR “tramadol, dexketoprofen drug combination” OR “tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine” OR “narcotic analgesic agent”) OR

AB,TI(Opioid* OR “18,19-dihydroetorphine” OR “acetaminophen, hydrocodone drug combination” OR Acrylfentanyl OR Alfentanil OR Alphaprodine OR “beta-casomorphins” OR Brorphine OR Buprenorphine OR Butorphanol OR Carfentanil OR Codeine OR Crotonylfentanyl OR Cyclopropylfentanyl OR “deltorphin I, Ala(2)-” OR Dermorphin OR Desomorphine OR Dextromoramide OR Dextropropoxyphene OR Dezocine OR Dihydrocodeine OR Dihydromorphine OR Diphenoxylate OR Dsuvia OR “dynorphin (1-13)” OR “endomorphin 1” OR “endomorphin 2” OR “Enkephalin, Ala(2)-MePhe(4)-Gly(5)-” OR “Enkephalin, D-Penicillamine (2,5)-” OR “enkephalin-Met, Ala(2)-” OR Eseroline OR Ethylketocyclazocine OR Ethylmorphine OR Etorphine OR Fentanyl OR Hydrocodone OR Hydromorphone OR “kappa-opioid agonist JT09” OR Ketobemidone OR Levorphanol OR lofentanil OR Meperidine OR Meptazinol OR Methadone OR “Methadyl Acetate” OR Morphine OR Nalbuphine OR Nocistatin OR Normethadone OR “O-demethyltramadol” OR “Opiate Alkaloids” OR Opium OR Oxycodone OR Oxymorphone OR paracymethadol OR Pentazocine OR Phenazocine OR Phenoperidine

OR Pirinitramide OR Promedol OR protopine OR Remifentanil OR Sufentanil OR Tapentadol OR Tilidine OR Tramadol OR “tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine” OR “narcotic analgesic agent”)

Concept 2: sexuality

MAINSUBJECT.EXACT(“Sexual Dysfunction, Physiological” OR “Impotence, Vasculogenic” OR “Premature Ejaculation” OR Vaginismus OR “Sexual Dysfunctions, Psychological” OR “Sexuality” OR Ejaculation) OR

MAINSUBJECT.EXACT.EXPLODE(“Sexual Function Disturbances” OR Dyspareunia OR “Erectile Dysfunction” OR “Premature Ejaculation” OR Vaginismus OR Orgasm OR “Psychosexual Behavior” OR “Sexual Arousal” OR Libido OR “Sexual Intercourse (Human)” OR Masturbation OR “Erection (Penis)” OR “Sexual Partners”) OR

AB,TI(Sexual* OR Libido* OR Orgasm* OR Impotence* OR Erecti* OR “Lubrication” OR “Vulvodynia” OR “Anorgasmia” OR “Dyspareunia” OR “Ejaculation” OR “Vaginismus” OR “Masturbation” OR “Coitus” OR “Penile Tumescence” OR “Sex Disorders” OR “Penile Venous Leakage” OR “Ejaculatio Praecox” OR “Psychosexual Dysfunctions” OR “Psychosexual Disorder” OR “Frigidity” OR "Sex Behavior" OR "Oral Sex" OR "Sex Orientation" OR "Anal Sex” OR “First Intercourse” OR “Coital Frequency” OR “Coital Frequencies” OR "Sex Partner" OR "Multiple Sex Partners")

Appendix 4: Personal reflections of the authors

Persoonlijke reflectie Nicky Koster

Wij hebben dit onderwerp gekozen omdat één van de auteurs van deze thesis naast haar opleiding tot huisarts ook een master in de seksuologie volgt. Zij heeft mij overtuigd van de noodzaak tot verder onderzoek naar deze problematiek. Initieel hadden we een een review op het oog met een meer systematische aanpak, maar door de voor ons onderwerp beperkte bruikbare informatie die we op databases vonden, had onze eerste promotor professor Matheï ons overtuigd om het onderwerp open te trekken naar een scoping review.

Evaluatie van het groepsproces

Naar mijn gevoel is de samenwerking gedurende de afgelopen drie jaar steeds vlot verlopen. De sfeer tijdens de vergaderingen was steeds aangenaam en de planning van taken gebeurde steeds met groot respect voor elkaar en elkaars privéleven. De ontwikkeling van dit werk kwam het eerste jaar wat traag op gang omdat onze tijd in beslag genomen werd door de frequente seminaries, lessen en het examen op het einde van het eerste jaar. Hierdoor hebben we, voornamelijk dat eerste jaar, weinig van de vooropgestelde deadlines van onze tijdlijn gehaald. In retrospect lijkt onze tijdlijn voor die periode te streng geweest en hebben we verderop in het proces de verloren tijd vlotjes ingehaald. We hebben een protocol opgesteld en gezien het een literatuurstudie betrof, zonder vertraging de goedkeuring van de ethische commissie gekregen voor onze scoping review. Helaas kregen wij hierna bericht dat professor Matheï na een periode van ziekte ten overlijden is gekomen en professor Van Nuland haar rol als promotor zou waarnemen, bijgestaan door onze co-promotor Kristien Coteur. Vervolgens vonden er meerdere online vergaderingen plaats om de voortgang van ons project te bespreken en om onze zoekstrategie op te stellen. Naar mijn aanvoelen heeft dit onderdeel van de thesis de meeste tijd gevraagd omdat literatuuronderzoek staat en valt bij de juiste zoekstrategie. Bovendien is het doel van een scoping review dat deze inclusief is zodat er geen relevante informatie gemist wordt. Hierdoor is onze zoekstrategie lang en aangepast per databank, getuige de opsomming in appendix 2 van onze thesis. Deze werd afgewerkt tijdens ons tweede jaar van de opleiding, waarna er een datum werd gekozen om in alle databanken de zoekstrategie toe te passen. Sindsdien heeft naar mijn aanvoelen de thesis een meer concrete vorm gekregen, wat ons vertrouwen en motivatie tijdens de rest van het proces heeft vergroot. Er werd een taakverdeling voor de eerste screening van de publicaties afgesproken, die het werk gelijk verdeelde voor alle medewerkers. Discussies over het al dan niet includeren van publicaties verliepen steeds respectvol en efficiënt. De rest van het tweede jaar hebben we steeds na afronding van een volgende stap online of fysiek overleg gehouden om het overzicht over het proces te behouden. Tussendoor werd er af en toe feedback gevraagd aan de promotor en co-promotor, en de volgende stappen besproken. Door de achterstand die we op onze tijdlijn hadden opgelopen het eerste jaar, was er ook tijdens het tweede jaar een beperkte achterstand en werden een aantal vooropgestelde deadlines niet gehaald. Omdat een van de medeauteurs tijdens ons laatste jaar om medische redenen een paar weken minder aan de thesis kon bijdragen, werd een deel van de verwerking van de resultaten door mijn collega en mezelf gedaan. Dit is een beslissing die onderling zonder wrevel werd gemaakt en waar iedereen achter stond. Voor de correctheid van ons proces werd de analyse na afloop door onze medeauteur nagekeken na haar ziekteperiode. Tijdens het laatste jaar van onze opleiding zijn we in de spreekwoordelijke hogere versnelling geschakeld, ondanks het feit dat dit voor ons alle drie een druk jaar is geweest voor zowel onze opleiding als in ons privéleven. We hebben een nieuwe tijdlijn opgemaakt waarbij enkele deadlines werden herzien en ons hieraan gehouden. We spraken soms meermaals per week online af om de bemerkingen die we hadden bij

elkaars geschreven tekst te overlopen en te verbeteren op basis van constructieve feedback. Hierdoor hebben we in de laatste maanden voor onze deadline veel vooruitgang geboekt, en werd dit werk zonder veel tijdsdruk voltooid.

Naar mijn gevoel verliep de samenwerking met zowel de promotor, co-promotor en onderling tussen de hoofdauteurs van deze thesis opmerkelijk vlot en aangenaam. De online bijeenkomsten, maar ook de fysieke ontmoetingen waren efficiënt en in gemoedelijke sfeer. Als sommige weken de ene collega minder kon bijdragen, stak de rest een tandje bij en omgekeerd. Volgens mij heeft juist de samenwerking in groepsverband ervoor gezorgd dat wij elkaar bleven motiveren, dat ieders verschillende vaardigheden en sterkten complementair werkten en onze minder sterke punten door de groep werden opgevangen.

Persoonlijk aandeel

We hebben steeds gestreefd om een zo eerlijk mogelijke verdeling te maken van de taken waarbij elk lid van de groep probeerde de taak op zich te nemen die het beste inspeelde op diens vaardigheden of eerdere ervaringen. Bijgevolg zijn er weinig onderdelen van deze thesis die door slechts 1 auteur tot stand zijn gekomen. Mijn eerste taak was het opstellen en het beheer van de tijdlijn, waarbij ik de andere auteurs hielp herinneren aan de afgesproken deadlines. Nadat wij gezamenlijk de termen van de concepten hadden geïdentificeerd waarmee we een zoekopdracht wensten op te bouwen, was het mijn taak om deze te verfijnen omdat de eerste versie van de zoekstrategie te lang en onpraktisch was. Nadat alle publicaties in Rayyan waren opgeladen, was het ieders opdracht om 2/3 hiervan te screenen op titel en abstract. Dit waren meer dan zesduizend publicaties per persoon en heeft wat tijd en inspanning gevraagd. Ik heb de taak op mij genomen om parameters in de web-tool Rayyan in te geven om de volgende stappen in het proces te vereenvoudigen. Vervolgens werd per publicatie de volledige tekst doorgelicht voor de aanwezigheid van onze inclusie en exclusiecriteria. Tijdens de ziekteperiode van één van de medewerkers heb ik tijdelijk een deel van de datacharting van haar overgenomen totdat zij verder kon werken. Betreft het schrijven heb ik op basis van onze eerste versie de introductie herschreven en verfijnd, de resultaten betreffende erectiele dysfunctie en het gebruik van gestandaardiseerde vragenlijsten geschreven. Verder heb ik een deel van de discussie geschreven en gaf ik steeds feedback over de tekst die de andere medewerkers hebben geschreven. Vlak voor het indienen van de thesis heb ik ons dankwoord uitgewerkt en nam ik de taak op mij om deze meermaals te herlezen en de laatste fouten te corrigeren.

Impact op het werkveld

We hebben, omwille van het toenemend gebruik van opioïden, met dit werk geprobeerd om een breed overzicht te geven over de langetermijneffecten van opioïden op de seksualiteit die de setting waarin huisartsen werken zo goed mogelijk benadert. Ons werk omvat met zijn inclusieve zoekstrategie een screening van meer dan tienduizend publicaties, waardoor we naar mijn mening geslaagd zijn om ons onderzoek alomvattend te maken. Naast het algemeen negatieve effect van opioïden bespreken wij in onze discussie ook nog een aantal belangrijke limitaties en hiaten in de huidige beschikbare literatuur die ervoor zorgt dat we voorzichtig zijn met het trekken van conclusies met betrekking op de eerstelijnszorg. Hiermee kan onze thesis een aanzet zijn voor verder kwalitatief en kwantitatief onderzoek om weer een stap dichter te komen bij klinische richtlijnen voor huisartsen. Deze thesis draagt daarnaast bij aan het informeren en sensibiliseren van artsen omtrent potentiële bijwerkingen van analgetica op seksueel vlak.

Persoonlijke reflectie Marie Groffi

Aangezien ikzelf, naast Huisartsgeneeskunde, ook de Master Seksuologie volg, leek het me initieel zeer interessant om deze achtergrond te kunnen verwerken in een thesis met een medisch onderwerp. Samen met prof. Matheï, die met haar ervaring in de verslavingszorg reeds meerdere thesissen begeleid had met psychofarmaca als onderwerp, kozen we voor een literatuurstudie over de seksuele effecten van psychofarmaca. In overleg werd dit onderwerp verder verdiept naar opioïden, veelgebruikte analgetica met meerdere bijwerkingen en niet te onderschatten risico's voor de gezondheid van chronische gebruikers. Aangezien er nog niet veel gekend is in de literatuur over seksuele bijwerkingen bij chronisch gebruik van opioïden, werd er afgesproken een scoping review te maken om de bestaande literatuur samen te brengen tot één geheel, dewelke nuttig kan zijn in een eerstelijnssetting.

Evaluatie van het groepsproces

We gingen als een groep van drie samen aan de slag om deze thesis te maken. Dit hele proces is zeer vlot verlopen en we hebben steeds met respect en de nodige flexibiliteit met mekaar kunnen samenwerken. Het eerste jaar verliep nog wat moeizaam: we moesten ons nog inlezen en vertrouwd maken met de bestaande literatuur om zo concreter onze visie uit te werken, maar ook de werkdruk in de praktijk lag hoog en helaas viel prof. Matheï gedurende meerdere maanden met ziekte uit en kwam ze ook te overlijden aan haar ziekte. Nadien volgende een periode van onzekerheid hoe het verder moest, aangezien we hoopten met haar ervaring een goede start te kunnen maken. Gelukkig konden we rekenen op de hulp van Kristien, onze co-promotor, om te helpen waar nodig. Desondanks liepen we wel wat vertraging op in onze vooropgestelde tijdlijn, waarbij vooral Nicky de leiding nam in de deadlines te proberen behalen. Aan de start van het tweede jaar kregen we prof. Van Nuland toegewezen als vervangend promotor en konden we verder aan de slag. Toen hebben we onze focus gelegd op het bepalen van een zoekstrategie en deze aan te passen aan de verschillende databanken. Hierbij hebben we de zes databanken verdeeld en hebben we erg veel tijd gestoken in deze zo goed mogelijk uit te werken samen. Nadien hebben we samen op dezelfde dag de zoekstrategie uitgevoerd in de databanken en de gevonden artikels in Rayyan ingevoerd. Aangezien deze zoektocht zo'n 17.000 artikels uiteindelijk opleverde, kwam nadien de moeilijke taak deze te screenen: eerst alle duplicaten verwijderen, nadien screenen op titel en abstract en ten slotte screenen op volledige tekst. Per persoon deden we zo 2/3 van het totale aantal, zodat elke publicatie steeds door twee werd gescreend. Het werk was dus eerlijk verdeeld en iedereen voerde deze taak uit wanneer het paste in haar planning. Deze screening gebeurde blind, onafhankelijk van mekaar, waarna er werd overlegd bij conflicten.
Aangezien we dit heel nauwkeurig hebben uitgevoerd, en onze vrije tijd niet helemaal overeenkwam, werden onze deadlines in de tijdlijn niet meer haalbaar aangezien we hiermee pas klaar waren in het derde jaar. We hebben dan ook onze tijdlijn wat aangepast en de laatste maanden hard doorgewerkt om de data-extractie en uitschrijven van resultaten en discussie te vervolledigen. Tijdens de data-extractie hebben Nicky en ikzelf iets meer werk op ons genomen om Phoebe de nodige rust te gunnen toen dit nodig was. Na enkele weken zijn we dan alle drie terug aan de slag gegaan om alles tijdig af te werken.
Over het algemeen was het een fijne samenwerking met de groep, maar ook met promotor en co-promotor. Iedereen was onmisbaar in dit project en heeft zijn/haar steentje bijgedragen tot het succesvol afronden van de thesis.

Persoonlijk aandeel

In het eerste jaar was het niet altijd gemakkelijk om aan de thesis te werken, aangezien ik veel meer bezig was met het werken in de praktijk. Mits wat extra stimulans van Nicky, lukte het wel om samen aan de slag te gaan. We hebben steeds geprobeerd een verdeling van de taken te maken, zodat niet één persoon veel meer zou doen dan de rest. Ik vind dat we daar zeker in geslaagd zijn. Zo is het opstellen van de zoekstrategie zeker eerlijk verlopen, hoewel dit niet de makkelijkste taak was. Hierin hebben we dan ook mekaar af en toe geholpen als we niet verder konden. Tijdens het screenen van de artikels, deed iedereen het op haar eigen tempo, maar probeerden we wel steeds een deadline af te spreken met de nodige flexibiliteit. Ik was bijvoorbeeld sneller klaar met een deel van de screening omdat ik meer tijd had tijdens die periode, maar dat was niet noodzakelijk een rustige periode voor mijn groepsleden. De data-extractie hebben we tijdelijk met twee opgenomen, waardoor ik daarin iets meer tijd heb gestoken. Tijdens het schrijven van de tekst heeft iedereen bijgedragen tot een goed resultaat, waarbij niet iedereen dezelfde taak deed. Ik heb iets meer de focus gelegd op de tekst, abstract en data-extractie tabel, maar minder op de referenties.

Impact op het werkveld

Onze scoping review had als doel om een opsomming van de gekende literatuur met betrekking tot chronisch gebruik van opioïden en de seksuele bijwerkingen te maken. Hierbij werd er selectief gekeken naar een eerstelijnssetting, om het relevant te maken voor het werkveld van huisartsen.
Hoewel er geen causaal verband kan worden aangetoond, is het duidelijk dat medische professionals best geïnformeerd zijn over de mogelijke negatieve effecten van het chronisch gebruik van opioïden op seksualiteit. Aangezien het gebruik van opioïden gevoelig stijgt de afgelopen jaren, wordt het opsporen en behandelen van bijwerkingen ook belangrijker.
In de toekomst is het nuttig dat huisartsen en/of andere hulpverleners in de eerste lijn bekend zijn met dit probleem en hier dan ook de patiënten over kunnen informeren en screenen naar problemen op seksueel gebied.

Persoonlijke reflectie Phoebe Van der Donckt

We hebben bij het begin van onze opleiding gekozen voor het onderwerp ‘de invloed van opioïden op seksualiteit’. Dit onderwerp sprong vooral voor Marie naar voor omdat zij bijkomend nog een master seksualiteit volgt. Zij heeft Nicky en mij overtuigd om met haar dit onderwerp verder te bestuderen. Professor Matheï heeft ons bij het eerste gesprek meteen enthousiast gemaakt om dit onderwerp te bestuderen met behulp van een scoping review. Zij is met ons in het eerste jaar gestart met een informatiesessie over wat een scoping review juist is en hoe we hieraan moesten beginnen. Dit gaf meteen een goede basis om aan onze paper te beginnen.

Evaluatie van het groepsproces

Het volledige proces is heel vlot verlopen met veel respect voor en flexibiliteit naar elkaar. We zijn tijdens ons eerste jaar begonnen met het opstellen van een tijdlijn die voor ons allemaal comfortabel en haalbaar leek. Vervolgens zijn we met veel enthousiasme begonnen aan de introductie om ons meteen ook wat in te lezen in het onderwerp. Na enkele maanden is professor Matheï jammer genoeg ziek geworden waardoor het even wat moeizamer gelopen is, vooral door onzekerheid over hoe het nu verder ging lopen met onze paper. Nadat we meer informatie kregen over het opstellen van de zoekstrategie zonk de moed ons wat in de schoenen omdat dit proces een stuk complexer en minder evident bleek te zijn dan we dachten. Toen heeft Nicky enorm veel werk verzet en ons mee aan onze

mouw getrokken om toch de deadlines te halen. We hebben naar mijn aanvoelen na het eerste jaar, ondanks de niet zo evidente start, toch een mooi protocol kunnen afleveren. We hebben hier wel nog een beetje aan gesleuteld doorheen het proces, maar het was een goede basis om mee aan de slag te gaan in het 2de jaar.

Bij de start van het nieuwe HAIO-jaar zijn we dan ook officieel gewisseld van promotor na het overlijden van professor Matheï. Professor Van Nuland heeft de begeleiding toen definitief over genomen. We hebben ons in het 2de jaar vooral gefocust op het opstellen van de zoekstrategie in de verschillende databases en hebben toen het werk mooi verdeeld onder elkaar door elk een database voor onze rekening te nemen en de anderen bij te staan als er problemen optraden. We zijn in persoon samen gekomen om op dezelfde dag de verschillende databases te doorzoeken en alles te kunnen uploaden in Rayyan. Deze artikels hebben we vervolgens allemaal gescreend op duplicaten. Dit hebben we afwisselend gedaan omdat we op dat moment niet alle drie op hetzelfde moment evenveel tijd hadden door andere tijdsschema's in de praktijk of het ziekenhuis. Ik heb dit nooit als een probleem ervaren en ik denk dat iedereen toen zijn uiterste best heeft gedaan om te doen wat mogelijk was binnen het werkschema.

Na het verwijderen van de duplicaten zijn we overgegaan tot het screenen op titel en abstract. Hiervoor hebben we alle overgebleven artikels verdeeld en allemaal 2/3 van de artikels gescreend op titel en abstract en later op volledige tekst obv onze inclusie en exclusiecriteria. Vervolgens zijn we terug samen gekomen om de artikels te bespreken waarover we geen consensus hadden bereikt. Op dat moment werd ook de 3de auteur betrokken om beslissingen te nemen over artikels waarover geen consensus was bereikt.

Ondertussen waren we in het 3de jaar aangekomen en bleek dat we toch niet meer helemaal op schema van onze tijdlijn zaten. We hebben niet meteen gepanikeerd en hebben in onderling overleg onze tijdlijn aangepast om deze terug haalbaar te maken zodat we toch een richtlijn hadden en we op tijd klaar zouden geraken. We hebben vanaf dan ook allemaal nog een extra tandje bijgestoken.

Toen we gingen starten aan de data-extractie heb ik een positieve zwangerschapstest afgelegd en enkele dagen daarna een bloeding gedaan met een kans op een miskraam. Het was toen ook een heel moeilijk moment voor mij in de praktijk door het uitvallen van collega's. De vermoeidheid en stress door mijn zwangerschap hebben toen hun tol geëist. Mijn thesis partners zijn op dat moment enorm behulpzaam geweest en hebben mij een tijdje ontlast van de thesis zodat ik mij kon focussen op mijn gezondheid. Zij hebben hier nooit een probleem van gemaakt en hebben mij de nodige rust gegund, waarvoor ik hen heel dankbaar ben. Ik ben toen terug ingestapt als 3de auteur en ben gaan kijken voor oplossingen op punten waar zij het niet volledig eens geraakte, Ik heb ook geprobeerd om een tandje bij te steken in het schrijven van de definitieve tekst en ik heb mij toegelegd op het noteren van de referenties en het opstellen van de tabellen.

Over het algemeen hebben we dus een heel vlotte samenwerking gehad met veel respect voor elkaar en flexibiliteit in periodes dat het voor de anderen wat moeilijker was. Het hele proces heeft een aanzienlijke impact gehad op ons privéleven, maar we zijn nooit elkaar en elkaars gezondheid uit het oog verloren.

Persoonlijk aandeel

Ik ben over het algemeen iemand met wat uitstelgedrag en heb dus zeker in het begin ,als de deadline veraf is, iemand nodig die het proces wat trekt. Daar was Nicky gelukkig de geschikte persoon voor. Ik denk dat we zeker het meeste werk mooi hebben kunnen verdelen met toch duidelijke afspraken over de deadlines en dat ook ik mijn best heb gedaan om deze te respecteren. Op het einde van het proces ben ik even uitgevallen omwille van gezondheidsproblemen rond mijn prille zwangerschap. Mijn collega's hebben dit heel respectvol opgevangen waardoor ik even de nodige rust heb gekregen. Erna heb ik mijn partners wat proberen ontlasten door wat meer initiatief te nemen in het schrijven van de tekst, het juist zetten van de referenties en het opstellen van de uiteindelijke tabellen voor in de tekst. Naar mijn aanvoelen hebben we dus over het algemeen een mooie taakverdeling kunnen bekomen doorheen het proces en heeft iedereen op zijn manier zijn best gedaan om zijn steentje bij te dragen.

Impact op het werkveld

We hebben met deze scoping review geprobeerd om een overzicht te maken van de beschikbare literatuur over de invloed van opioïden op seksualiteit en deze zoveel mogelijk door te trekken naar de huisartsenpraktijk. Aan de hand van onze scoping review lijkt er een negatieve trend te zijn van de invloed van opioïden op seksualiteit. Er zijn jammer genoeg niet veel studies met hoge power beschikbaar over de invloed van orale of transdermale opioïden op seksualiteit en er zijn zeker nog andere limitaties die besproken worden in de discussie. Hierdoor is zeker meer onderzoek nodig. Het was niet het opzet van onze paper, maar we zien wel dat huisartsen te weinig bevragen welke impact op alle domeinen van seksualiteit de patiënt ervaart en dat dit dus te weinig besproken wordt. Het aantal voorschriften voor opioïden neemt de laatste jaren ook toe waardoor het onderbelichte probleem vermoedelijk ook frequenter gaat voorkomen en de impact nog groter zal worden. Het is dus heel belangrijk dat ook eventuele seksuele problemen besproken kunnen worden bij de huisarts en het taboe rond seksualiteit wat doorbroken wordt. Dit kan onder andere zeker door de huisartsen beter op te leiden zodat zij zich ook comfortabeler voelen om dit te bespreken. Onze thesis draagt dus bij tot het stimuleren van meer onderzoek over dit onderwerp zodat huisartsen nog beter geïnformeerd kunnen worden.