HHS Public Access

Author manuscript

Pain Med. Author manuscript; available in PMC 2016 March 21.

Published in final edited form as:

Pain Med. 2012 September ; 13(9): 1181–1211. doi:10.1111/j.1526-4637.2012.01467.x.

Medical and Psychological Risks and Consequences of Long-Term Opioid Therapy in Women

Beth D. Darnall, PhD[*], **Brett R. Stacey, MD**[*], and **Roger Chou, MD**[†]

[*]Department of Anesthesiology and Perioperative Medicine, Oregon Health & Science University, Portland, Oregon, USA

[†]Internal Medicine and Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland, Oregon, USA

Abstract

Background—Long-term opioid use has increased substantially over the past decade for U.S. women. Women are more likely than men to have a chronic pain condition, to be treated with opioids, and may receive higher doses. Prescribing trends persist despite limited evidence to support the long-term benefit of this pain treatment approach.

Purpose—To review the medical and psychological risks and consequences of long-term opioid therapy in women.

Method—Scientific literature containing relevant keywords and content were reviewed.

Results and Conclusions—Long-term opioid use exposes women to unique risks, including endocrinopathy, reduced fertility, neonatal risks, as well as greater risk for polypharmacy, cardiac risks, poisoning and unintentional overdose, among other risks. Risks for women appear to vary by age and psychosocial factors may be bidirectionally related to opioid use. Gaps in understanding and priorities for future research are highlighted.

Keywords

Opioids; Opioid; Women; Chronic Pain; Sex; Gender; Risks; Treatment

Introduction

Long-term opioid use has increased substantially in the United States over the past decade [1], with women outpacing men by a considerable margin [2,3]. Recent increases in long-term opioid prescription in the United States may partially reflect a rising prevalence of chronic pain [4] or be a manifestation of the general trend of increased effort directed toward treating chronic pain [5]. Regardless, opioid-prescribing practices in many European settings are considered conservative compared with the United States [6,7].

Reprint requests to: Beth D. Darnall, PhD, Department of Anesthesiology, Division of Pain Medicine, Stanford University, 450 Broadway Street Pavilion A, 1st Floor, MC 5340, Redwood City, CA 94063, USA. Tel: 650-723-6238; Fax: 650-721-3414; bdarnall@pain.stanford.edu.

Conflict of Interest Statement: Drs. Darnall and Chou wish to disclose no conflicts of interest. Dr. Stacey wishes to disclose the following: Teva Pharmaceuticals, consultant.

A number of studies of relatively short duration have shown that opioids reduce chronic pain levels [8]. However, increasing prescription opioid misuse overdose deaths and other poorly characterized adverse opioid effects led an interdisciplinary panel to recently label the situation an “urgent medical and social problem” [9]. While several reviews and guidelines suggest that opioids are appropriate in the continuum of care for some patients with chronic pain [10–12], other research suggests that chronic pain reduction from long-term opioid use may be minimal [13,14] and the evidence for improved quality of life or function is limited [15–17].

One population-based study showed that across age groups, the prevalence of opioid prescription in women has been increasing at a similar or greater rate than for men, with as many as 8–9% of women aged 65 and older on long-term opioid therapy [18]. Despite the increasing rate of opioid prescription in women, the specific risks and consequences of opioids in women have not been reviewed comprehensively. In recent years, the bulk of research on prescription opioids has focused on outcomes related to pain reduction and the associated risks of medication misuse or abuse, with less attention paid to the medical and psychological risks conferred by opioid therapy, or to the specific risks in women.

As such, the benefits of opioid analgesia are generally well appreciated, while the risks and consequences of long-term opioid use may be less recognized. The purposes of this review are to discuss the current evidence on the medical and psychological risks and consequences of long-term opioid therapy in women with non-cancer and non-end-of-life chronic pain, to describe gaps in understanding, and to highlight directions for future research. While we emphasize areas where sex/ gender differences exist, this article broadly addresses risks and consequences that pertain to women including gender-neutral risks.

Definitions and Methods of Inclusion

Opioids can be prescribed for acute self-limited pain, cancer-related pain, treatment of addiction/dependence, and chronic pain. Clearly, these situations represent different populations with unique circumstances and consequences of disease and therapy. Clinical studies on opioid administration often focus on specific indications for treatment, but the lines of distinction are at times blurred (e.g., opioids initially prescribed to treat acute pain that has transitioned into the chronic state; chronic pain patients with an acute pain issue, opioid naive chronic pain patients, patients with addiction and pain, and so forth). Nonetheless, evidence for prescribing for one indication may have variable applicability to other indications or conditions. For this article, we focused on studies of long-term opioid administration in subjects with ongoing pain.

Long-term or chronic opioid use has not been formally or consistently defined in the literature, but recent epidemiological studies have used 90 or more days with 120 or more total supply days calculated by a pharmacist at dispensation or 10 or more opioid dispensations [18–23]. Other studies have defined long-term opioid use as 3–6 months or longer. In this review, we considered studies that used any of these definitions to provide direct evidence on long-term opioid use, and we considered studies that explicitly included subjects with ongoing pain of at least 3 months’ duration to provide direct evidence on chronic pain patients. Some studies of shorter duration were included for background or

supporting evidence. A few relevant studies that described the consequences of opioid use in healthy samples were also included, and preclinical data are discussed in sections where human data are severely limited and only as background.

Medline Ovid and PubMed searches were conducted most recently in January 2012 for English language studies on human subjects using the following terms: opioid, opioids, oxycodone, morphine, oxymorphone, hydromorphone, hydrocodone, methadone, fentanyl, tap-entadol, buprenorphine, and codeine, for the years 1946– 2011. We refined the search using the "AND" function with the term "pain" combined with the terms "chronic," "chronic disease," or "chronic pain." Lastly, we further refined our search by adding the terms "sex," "sex differences," "women," or "gender" to yield the bulk of the studies reviewed herein.

In addition, subsidiary searches were conducted within the broad "opioid" and "pain" subset on each of the review subsections (e.g., sleep disturbance and sleep-disordered breathing, prescription, prescribing, polypharmacy, cardiac, arrhythmia, hyperalgesia, birth defects, and so forth); search results were reviewed for relevance.

Many studies did not keyword for sex or gender differences and this served as a barrier in conducting this comprehensive literature review. Articles that did not use sex or gender terminology as a keyword but were identified to have examined sex/gender differences were included.

Organization of Tables

Four tables provide a condensed view of risks and consequences for opioid use by category. The tables only include data from chronic pain studies. Table 1 reviews articles that included "opioid" or "opioids" as a keyword and "sex," "gender," or "women." The table describes findings for studies that present opioid-related data *specific* to women. In parallel with the organizational layout of the article, Table 2A describes the medical/physical risks and consequences, and Table 2B describes the psychological/behavioral risks and consequences of long-term opioid use. All studies included in Table 2A,B used mixed-sex samples, although few of them examined sex differences. We aimed to quantify female risk relative to that for men; accordingly, Table 2A,B include columns to describe whether there is an increased risk for women, no increased risk, an inferred increased risk (based on increased prevalence of the risk), or whether the relative risk was not assessed by sex. We underscore that a finding of "no increased risk for women" does *not* equate to "no risk." Indeed, all categories listed in Table 2A,B were found to be risks for women; we simply reported whether a significant sex difference was found, and if so, we describe the direction of the difference. Finally, Table 3 describes risks that are *unique* to women. Table 3 is stratified by menstrual status and this distinction functions as a gross proxy for age.

Medical/Physical Risks and Consequences

Factors Predicting Likelihood of Opioid Prescription and Risk for Misprescription

Compared with men, women have increased incidence of many painful chronic conditions, including migraine [24], fibromyalgia [25], irritable bowel disorder (IBD) [26], arthritic

conditions [27], and many musculoskeletal or inflammatory conditions [28]. Some pain conditions are female-specific, such as chronic pelvic pain, dyspareunia, menstrual pain, and vulvodynia. The author of a comprehensive review on sex differences in the clinical pain experience concluded that pain is more intense, of longer duration, of greater frequency, and is more widespread in women than it is in men [29]. A study recently replicated the finding for sex disparity in pain intensity in a large hospital database of 11,000 patients [30].

Given the sex/gender differences for pain, it is perhaps unsurprising that several large epidemiological studies have consistently shown older age and female sex predict opioid prescription [3,18,20,31], and other studies show that female sex predicts higher opioid dose [20,32]. For example, an epidemiological study conducted in conjunction with Kaiser Permanente Northern California and Group Health Cooperative examined a database with approximately 4 million individuals for the years 1997 and 2005 [18]. Across age groups, long-term opioid use was greater in women compared with men, and highest among older women, a finding replicated in another chronic opioid cohort study of 600,000 privately insured patients, in which older women made up the largest percentage of chronic opioid users [20]. These consistent practice pattern findings underscore the need for research to examine risks and consequences of opioids by sex, and to examine how risks may vary as a consequence of age.

Pain Conditions with Poor Efficacy Data for Opioid Use

Several pain conditions that predominate in women have little data to support opioid use in their treatment including most musculoskeletal pain conditions [33], IBD, and headache [34–38]. We found essentially no evidence to support the use of opioids for several primary pain conditions that disproportionately or exclusively involve women ranging from headache to chronic pelvic pain.

IBD—IBD represents a combination of abdominal pain and abnormal bowel habits without clear structural pathology. While generally regarded as afflicting women more than men in Western countries [39,40], this may not be the case in Asian countries [41]. IBD is associated with decreased pain thresholds at sites outside the abdomen, and is associated with other pain conditions typically more prevalent in women including migraine, temporomandibular disorders, and fibromyalgia [42–45]. While some guidelines suggest opioids as a treatment option for the treatment of diarrhea [38,46], we found no consistent evidence to support opioid treatment for IBD pain. In fact, constipation prominent IBD may be favorably impacted by an opioid antagonist [47].

Musculoskeletal Conditions—In the arena of musculoskeletal pain, women may not benefit from opioid therapy and may find their conditions worsened by opioid use [33]. Despite poor efficacy data, women with these conditions are disproportionately prescribed opioids. The authors of a national study of patients taking long-term opioid therapy for chronic pain reported that 37% of women were prescribed opioids for arthritis pain, compared with 27% of men [20]. Chronic low back pain is arguably the most common musculoskeletal condition, yet the role of opioid therapy remains unclear due to limited and

mixed evidence on effectiveness, and gender differences in effectiveness opioid therapy for this condition remain poorly characterized [12,48–51].

Fibromyalgia—There is no evidence of long-term efficacy for opioids in patients with fibromyalgia and at least suggestive evidence that opioids may worsen fibromyalgia symptoms [33,52–54]. In fact, treatment of fibromyalgia incorporating either analgesic (opioid) withdrawal [55] or treatment with an opioid antagonist [56] have better evidence to support them than the use of non-tramadol opioids.

Headache—Women are more likely to have more headache diagnoses than men [57] including migraine [58], chronic daily headache [35,58], tension type headaches [59], and medication overuse headache [60]. Women with headaches are more likely to have cooccurring allodynia [61], which is associated with greater pain and treatment resistance [42], and this may increase the likelihood for being prescribed opioids. Opioids are one of the medications that can cause medication overuse headache or lead to the "chronification" of episodic headache [36,62]. Additionally, limited direct evidence available suggests that opioids are typically ineffective for chronic headaches [37,63], and use of opioids may also decrease the effectiveness of other therapy [64]. Current guidelines suggest that opioids should be used rarely in the treatment for headache conditions [37].

Use of Opioids in Persons with Comorbidites—In a national epidemiological study of long-term opioid therapy for chronic pain, Cicero et al. found that women are more likely than men to be prescribed opioids when comorbid conditions such as chronic obstructive pulmonary disease (COPD) or endocrine disorders are present [20]. Such increased prescribing in these comorbid women may place them at greater risk for reduced oxygen saturation or respiratory depression in the case of COPD, or for compounded endocrinopathy in the case of women with preexisting endocrine disorder. However, we found no studies to examine the specific consequences of opioid use in these or other comorbid, at-risk populations, making it difficult to estimate risks and consequences.

Reduced Receipt of Preventive Care

Use of long-term opioid therapy in women may associate with other unintended consequences, such as lower quality of health care compared with women not taking opioids, despite receiving more medical services. Authors of a study of 704 adults at seven rural primary care clinics reported that women on long-term opioid therapy had more clinic visits than men on opioid therapy (18 vs 15) [65], as well as more emergency department visits and hospital stays, suggesting either poorer global health or more health care seeking behavior. Despite more clinic visits, women aged 35–65 on opioid therapy were less likely to undergo Pap cervical cancer screenings compared with non-opioid women, and women older than 50 years were less likely to undergo colorectal cancer screening. The reasons behind these associations are unknown but the researchers hypothesized that the complexity of opioid management may dominate medical visits, with a consequence being a tendency to neglect preventive care [65]. Future research that is either designed to control for number or type of medical conditions or to compare groups of patients with similar numbers of

comorbidities may provide even stronger evidence that opioid prescription is independently associated with reduced preventive care and is not simply a proxy for a sicker population.

Other studies are needed to confirm these findings in different settings and to determine factors associated with receipt of relevant preventive care in women aged 35 and younger on long-term opioid therapy; to our knowledge, these risks remain uninvestigated for women in this age group.

Immunosuppression

Laboratory data suggest that opioids have an inhibitory effect on the immune system, and like cytokines, modulate immune responses in the central nervous system and in the periphery [66]. The hypothalamic-pituitary-adrenal (HPA) axis is thought to be a primary mechanism by which opioids influence immune activity. Opioid exposure is associated with immunosuppression [66] and animal studies have shown a temporal relationship, with longer-term exposure leading to greater immunosuppression [33]. Indeed, preclinical work has shown that morphine tolerant animals exhibit enhanced susceptibility to negative effects of various stressful challenges on immune cell function [67]; to our knowledge, the clinical implications remain unknown as human studies have been largely limited to HIV or drug abuse populations.

Endocrinopathy and Fertility Risks

Studies have shown that opioid therapy leads to impaired endocrine function and dysregulated sex steroid balance in women [68–70]. The reader is directed to Vuong et al. for a comprehensive review of the effects of opioids on animal and human endocrine systems [69]. Importantly, the authors noted that one cannot assume that the known acute effects of opioids on the endocrine system are simply prolonged and of the same magnitude with chronic opioid therapy; rather, long-term use of opioids may have unique endocrine consequences that are of different magnitude and direction [69].

The endocrine system is intricately linked to pain processes in direct and indirect fashion. In terms of direct effects, modulation of estrogens and other sex steroids are associated with greater pain intensity [71,72]. The research on endocrinopathy related to prescribed oral opioids has focused more on men and thus the data are stronger for this sex [73,74]. Fewer studies have focused specifically on women, particularly women on long-term oral opioids. We review what is known for women in the following.

To better understand the effects of opioids on endocrine function in women, Daniell examined total and free testosterone, estradiol, dehydroepiandrosterone sulfate (DHEAS) in 47 women aged 30–75 taking long-acting oral or transdermal opioids for chronic pain and compared their data to 68 non-opioid-taking control subjects in an unmatched, cross-sectional study [68]. Results were broken down by age group to represent premenopausal and postmenopausal subgroups. More than half of the opioid-taking women aged 30–50 had nonsurgical amenorrhea (52%), compared with 20% of the control group ($P<0.05$), suggesting opioid-induced endocrinopathy. The author of the study noted that eight women became amenorrheic following the first use of opioid and another eight developed

amenorrhea later (often following opioid dose increase). Opioid users with intact ovaries had hormone values 48–57% lower than those in the control group. For women aged 50–70, hormone levels were 52–66% lower in the opioid-taking group compared to the non-opioid control group.

Another cohort study examined 39 patients treated with strong oral opioids for more than 1 year and compared endocrine outcomes with a group of 20 non-opioid-taking chronic pain patients; divergent findings based on opioid group were reported [75]. Importantly, the opioid and non-opioid participants were matched for age, pain duration, and type of pain. Women ≤50 years of age (N = 16) were found to have reduced estradiol compared with controls (N = 6; $P = 0.05$). Women taking long-term opioids were also found to have reduced levels of DHEAS ($P = 0.05$) and reduced peak values of leutenizing hormone ($P=0.01$). Women >50 (N = 6) prescribed opioids had reduced peak follicular stimulating hormone levels compared with controls that trended toward significance ($P= 0.055$). Combined analysis (men and women) showed that long-term opioid users had supernormal prolactin levels compared with controls ($P< 0.001$). The authors noted that their findings were consistent with those reported by Daniell, and may provide stronger evidence of endocrinopathy given that their study design matched for important confounders. Their findings were also consistent with other studies that found opioids associated with modulation of other hormones in women, including prolactin [76,77]. However, the specific consequences of such opioid-induced changes are not well characterized.

Opioid-induced endocrinopathy may diminish fertility in reproductive-aged women [68,69].

Echoing the results on menstrual cycle function reviewed previously, another cohort study found evidence for reduced fertility in women taking long-term opioids compared with non-opioid-taking women with chronic pain [75]. Only 2 of 16 women ≤50 years of age who were taking long-term opioids had normal menses (13 had amenorrhea or irregular menses and 1 had hysterectomy), while all 6 women ≤50 in the non-opioid control group had normal menses. Reduced libido and hypogonadism have been reported as consequences of oral [75] and intrathecal administration of opioids in patients with chronic pain [78,79]. Abs et al. prospectively examined the association between long-term intrathecal administration of opioids and endocrine parameters and menses. Hormonal data for 44 women with noncancer chronic pain (mean duration = 26.6 ± 16.3 months) were compared with data for an opioid-free chronic pain sample (N = 9) [70]. All of the premenopausal women receiving intrathecal opioids developed amenorrhea or irregular menses (N = 21), and only one woman in the opioid group ovulated, confirming findings from another study [79]. Serum leutinizing hormone, progesterone and estradiol were significantly lower in premenopausal women taking opioids compared with controls. Levels of growth hormone, cortisol, and insulin-like growth factor were significantly lower than controls. Roughly 15% of the opioid group also developed central hypocorticalism and growth hormone deficiency.

Findings for opioid-induced endocrinopathy are not entirely consistent, with at least one study reporting a null finding and attributing observed hormonal differences to other comorbidities such as obesity, and rather than opioid analgesia per se [80].

In summary, there is a need for randomized controlled trials and well-conducted prospective studies that appropriately account for potential confounders. The literature to date suggests an association between long-term opioid and endocrine dysregulation in both pre- and postmenopausal women in terms of sex steroids and HPA hormones.

Additional Risks for Reproductive-Aged Women

Reproductive age women prescribed opioids for chronic pain may have more years of opioid exposure than older women, potentially magnifying endocrine and other iatrogenic effects of opioids. One study found that roughly 25% of reproductive age women (18–45) seeking specialty outpatient chronic pain care for non-pelvic pain have had historical hysterectomy [81]. These limited data suggest that a substantial fraction of women younger than 45 seeking pain clinic consultation are likely hormonally compromised prior to opioid prescription and are most likely to be prescribed opioids. No studies exist to describe the additive endocrinopathic risks of opioids in young women with historical hysterectomy.

Despite the potential and not fully characterized risks of opioids in reproductive-aged women, evidence suggests that opioid use is increasing in this population. A study of trends for long-term opioid use across two large American health care systems showed that between 2000 and 2005 the estimated percent increase in opioid use in women aged 18–44 years to be 24% in a national commercially insured health network and 54% for the state Medicaid system [82]. Women aged 18–44 years also evidenced the largest estimated percent increase in opioid prescribing, with implications for the endocrine system, fertility, fetal, and newborn health.

Impact of Opioid Use During Pregnancy on Neonates

Despite apparent reductions in fertility associated with long-term opioids, pregnancy nonetheless occurs in women taking opioids with potential fetal implications. Most of the literature on pregnancy and opioids has focused on infants born to women with substance abuse histories [83,84], or women who used opioids for peripartum analgesia, rather than those on long-term opioid therapy for chronic pain. Because the research to date has almost exclusively focused on women who were addicted to opioids, it is difficult to separate the unique risks of long-term opioid use in women with chronic pain from the confounding factors that are inherent in addiction populations [85]. Nevertheless, the next sections review the impact of opioids on fetal and infant health.

Teratogenesis

The safety of maternal prescribed opioid use and the potentially teratogenic effects on the developing fetus are remarkably understudied. Without good safety data, some clinical providers of pregnant women with chronic pain may default to “safe until proven otherwise” when considering opioids [86,87]. Acetaminophen is commonly present in combination opioid products. Although considered to be safe in pregnancy [88], we could find no data specifically assessing safety of acetaminophen in combination with opioids. Two major groups of commonly used adjuvant medications—antidepressants and antiepileptics—have clearly established teratogenetic and fetal risks [89–92], thus limiting opioid alternatives. For pregnant women with heroin addiction, opioid replacement is considered the treatment

of choice in order to reduce the risks associated with opioid withdrawal, including spontaneous abortion, preterm labor, and fetal distress. Methadone is often used because of its longer half-life. An association between maternal first trimester use of opioids and congenital heart defects has been reported by case-control studies [93,94].

The position statement of the American Pain Society and the American Academy of Pain Medicine is that clinicians should provide counseling to pregnant women regarding the risks of opioids to the fetus, and they recommend minimal or no use of opioids with the exception of severe, disabling pain that only responds to opioid medication.

The U.S. Food and Drug Administration (FDA) has generally classified opioids in pregnancy with a “C” rating, meaning that while animal studies may have shown adverse effects, there are no adequate and well-controlled studies in pregnant women. The fetal effects recognized by the FDA for codeine specifically include cleft palate and inguinal hernia, although studies have been inconclusive [95,96]. Hydromorphone is an exception in that it has a B-category rating, meaning that that the FDA considers it relatively safe in pregnancy.

Researchers at the Centers for Disease Control examined the effect of maternal use of prescribed opioids on birth defects in women who took the medication between the month prior to pregnancy and the first trimester (3 months following conception) [97]. The study used the largest data set to date to evaluate the association between opioid exposure and congenital heart defects, among other birth defects, and was part of the National Birth Defects Prevention Study (1997–2005), an ongoing multisite, population-based, case-control study evaluating more than 30 major structural birth defects (nonstructural outcomes such as arrhythmias were excluded). Between 6 weeks and 2 years after their estimated delivery date, women were invited to participate in an hour-long computer-assisted telephone health history interview. Opioid exposure was coded for use of ≥1 opioid product, prescribed for any duration, dose, and frequency. All multivariate logistic regression models were adjusted for confounding demographic factors, including maternal age, body mass index, smoking status, race, education, and study center. Excluded from analyses were women with pre- and intrapartum diabetes (due to its independent association with birth defects) and women who reported illicit opioid use.

Prescribed opioid use was reported for 2.6% (454) of 17,449 case mothers and 2.0% (134) of 6,701 control mothers. Codeine (34.5%), hydrocodone (34.5%), and oxycodone (14.4%) were the most commonly prescribed opioids. Information regarding the reason of use was collected for only 66% of women exposed to opioids; the main reasons included surgical procedures (41%), infections (34%), and chronic diseases (20%; presumably where chronic pain would be captured). Maternal exposure to opioids was associated with cardiac defects in neonates including conoventricular septal defect, atrioventricular septal defect, atrial septal defect, hypoplastic left heart syndrome, tetralogy of Fallot, and pulmonary valve stenosis. Maternal exposure to opioids also was associated with noncardiac birth defects including spina bifida (odds ratio [OR] 2.0, 95% confidence interval [CI] 1.3–3.2) and gastroschiasis (OR 1.8, 95% CI 1.1–2.9). When the researchers narrowed their definition of opioid exposure to the month prior to conception and up to 2 months after conception, the

association between opioids and teratogenic effects strengthened. Using these criteria, hypoplastic left heart syndrome—a condition strongly linked to infant mortality [98]—had the highest OR (3.7, 95% CI 2.1–6.6). The researchers were unable to provide safety or risk rankings for the various opioids studied. Interpretation of this study is complicated by the fact that some unknown fraction of women in the study was presumably exposed to opioids for a relatively short duration to treat acute pain. The findings suggest that opioid drug use in the first trimester is associated with some teratogenic risk, with insufficient evidence to determine a safe level of exposure. Recommendations regarding cautious prescribing of opioids for chronic pain in pregnant women and in women contemplating pregnancy may be found elsewhere [99].

Additional Neonatal Risks

A common practice for women taking daily opioids during pregnancy is to continue the opioid schedule until delivery to mitigate possible consequences of opioid intrauterine fetal opioid withdrawal and risk for early labor and mortality [100]. While a continuation strategy may mitigate risks associated with withdrawal, it may promote several other severe health risks.

Chronic opioid use during pregnancy has been associated with low birth weight, premature birth, hypoxic-ischemic brain injury, prolonged QT syndrome, neonatal withdrawal syndrome, and neonatal death [101]. A challenge of opioid and fetal outcomes research is the convergence of other maternal factors that may contribute to poor outcomes [84]. For example, one study found that neonatal risk may be lower when methadone is prescribed for chronic pain management rather than for opioid dependence treatment [102], but other maternal factors may account for the observed differences in neonatal outcomes. Higher doses of antenatal methadone in tolerant mothers do not seem to increase complication rates [103]. Methadone is associated with dysrhythmias and prolonged QT intervals, and may cross the placenta with similar cardiac effects in neonates [104]. Parikh et al. examined electrocardiograms (ECGs) in newborns of mothers taking methadone therapy for opioid dependence (not for pain treatment) compared with matched control newborns born to women not taking methadone and noted significantly prolonged corrected QT (QTc) interval in on the first two days of life [83].

Breast-feeding

Opioids are commonly prescribed for women in the postnatal recovery period, and patients who were on chronic opioid therapy prepartum may continue taking the prescriptions while breast-feeding. A review of the literature reveals conflicting data and suggestions about the use of opioids in breast-feeding women.

Oxycodone concentrates in breast milk and is detectable in mothers' milk within 24 hours. Oxycodone levels found in breast milk correlate with maternal plasma levels and can result in detectable serum levels in the infant, although a recent study found the infant serum levels were below the arbitrary safety benchmark of 10% of a therapeutic concentration [105,106].

A recent pharmacokinetic study examined breast milk hydrocodone and hydromorphone levels in 30 mothers using hydrocodone bitartrate for acute postpartum pain [107]. The

authors of the study reported that on average fully breast-fed neonates received 1.6% of the maternal weight-adjusted hydrocodone dosage. While the total median opioid dosage from breast milk was 0.7% of a therapeutic dosage for older infants—well below the standard benchmark for acceptability during breast-feeding— the authors still cautioned against prolonged use of high doses of opioids in nursing mothers.

Codeine use while breast-feeding was associated with divergent findings in the literature. A review on the safety of codeine use by breast-feeding mothers reported an association between codeine and central nervous system events in breast-fed infants, including apnea, bradycardia, drowsiness, and cyanosis [108]. Women with a specific cytochrome P450 2D6 (CYP2D6) genotype rapidly metabolize codeine into morphine, which could result in high breast milk and plasma levels of full-term neonates [109]. In fact, an infant death caused by opioid toxicity has been reported in a breast-feeding woman taking postpartum codeine [110,111]. Genetic/pedigree screening for the P450 2D6 genotype is not standard practice [111] so women and the clinicians caring for them are typically unaware whether they are rapid metabolizers of codeine who may inadvertently expose newborns to increased risk of opioid toxicity [110].

Prior to the recent report of an infant death associated with codeine and breast-feeding, the American Academy of Pediatrics (2001), the U.S. FDA, and groups of researchers considered codeine compatible with breastfeeding, with minimal risks to the breast-feeding infant [106,112,113]. Notably, recommendations regarding opioid safety were established for short-term use of the drugs (e.g., 72 hours post-Cesarean section [106]; recovery from delivery) and not for indefinite scheduled dosing for a preexisting chronic pain condition. Subsequently, greater caution has been advised, with the 2007 warning issued by the FDA [114] suggesting a transition to non-opioids [115]; others called for the phasing out of codeine [116].

For all postpartum opioids, risks may be attenuated by the volume of exposure in the neonatal period, as infants ingest small amounts of breast milk in the first few days of life. In addition, newborns who were exposed to opioids in utero (either prescribed or illicit) may respond to postnatal opioid exposure via breast milk differently from those with de novo opioid exposure after birth. We found no studies describing risks specifically associated with breastfeeding in infants of mothers on regular opioid therapy for non-obstetric chronic pain, although findings from the acute pain literature suggest that there are likely to be risks in infants of breast-feeding mothers using opioids chronically. Some have cautioned that an increase in opioid dose during the nursing period has the potential for serious adverse effects [117]. There has been a call for maternal education, particularly in cases where long-term opioid use cannot be avoided, so that breast-feeding mothers may be vigilant for warning signs of toxicity in their infants [115].

Long QT Interval

Sex is a predictor of variability in QT intervals on the ECG. Sex differences in the QTc interval emerge at puberty [118] and decline at menopause. Normal QTc intervals are shorter for women than for men. Among acutely ill patients, women are more likely to have long QT intervals [119]. Long QT intervals are associated with torsades de pointes, a type of

ventricular tachycardia found to be more prevalent in women [120]. Sex steroids may influence women's susceptibility to torsades de pointes [121,122] based on studies suggesting the temporal occurrence of prolonged QTc during a woman's fertile years. The risk of torsades de pointes increases with longer QTc intervals, with severe QTc prolongation uncommon. Taken together, the evidence suggests that fertile women may be more susceptible to risks associated with drugs that prolong QT intervals than men. Methadone is a well-recognized cause of QT prolongation in adults that can result in torsades de pointes [123]. Because of this potential complication, American guidelines for adults recommend routine ECG screening of patients receiving methadone, although these recommendations are not based on data showing improvement in clinical outcomes after initiation of routine ECG screening, and have been the subject of controversy because of uncertain cost-effectiveness, particularly in low-risk patients on low doses [124,125]. The true prevalence of QT prolongation with methadone is unclear, with an estimate of QTc above 500 ms ranging from 2–10% [126] and the relationship of dose to QT prolongation is not linear [126].

Non-methadone studies on cardiac risk are sparse. Prolongation of the QTc interval has been reported with buprenorphine [127], a mixed agonist/antagonist opioid with multiple formulations and varied uses, and a warning of possible QT prolongation is included in some versions of the package insert for buprenorphine products. One cross-sectional study of chronic pain patients on long-term opioids showed that higher oxycodone dose was associated with longer QTc interval, thus suggesting increased risk associated with this drug [128]. The authors of the study speculated that high levels of oxycodone could lead to hERG channel inhibition, QTc prolongation, and sudden cardiac death [128]. The positive finding for cardiac risk described in this study was specific to high-dose oxycodone and was not observed with tramadol or morphine.

Sleep and Opioids

Sleep disturbance accompanies many or most chronic pain conditions [129–132] including diabetic neuropathy [133], fibromyalgia [134,135], chronic low back pain [136], and osteoarthritis [137]. Sleep discontinuity has been shown to impair endogenous pain-inhibitory function and increase spontaneous pain in women [138]. Disturbed sleep is itself a risk factor for chronic pain, and impaired endogenous pain-inhibitory function has been demonstrated in women with fibromyalgia [139].

It is true that some evidence supports improvement in subjective sleep outcomes with effective opioid therapy [140,141], but substantial data suggest that opioid use is associated with obstructive and central sleep apnea, disordered sleep, altered sleep architecture, daytime somnolence, and hypoxemia [142–149]. These opioid-induced sleep perturbations may promote pain pathophysiology and therefore attenuate analgesia.

It is generally accepted that men are at increased risk for sleep apnea [150], but at least one study that examined opioids and sleep noted a high rate in women studied (50%) [145]. Sleep apnea may be underdiagnosed in women, as some research suggests that they are less likely to undergo sleep studies [151]. In a study specifically looking at gender differences in sleep, Wahner-Roedler et al. noted that women undergoing polysomnography were more

than twice as likely to use sleep medications than men and more likely to have several conditions associated with abnormal sleep including obesity, fibromyalgia, depression, and IBD [152].

It is likely that opioids influence both central and obstructive sleep apnea. Central suppression of respiratory drive leading to apnea is a known effect of opioids and is the primary cause of opioid overdose death. Obstructive sleep apnea is generally more common and is more frequently diagnosed than central sleep apnea in patients taking opioids [146,149,153], although it is unlikely to be a causal association [144,148,154,155].

In a study of acute administration of opioids to healthy pain-free adults, opioids were associated with disrupted sleep architecture including reduced slow wave sleep and impaired rapid eye movement sleep compared to placebo [143,156]. Slow wave sleep (the early part of nocturnal sleep) is when growth hormone and cortisol (among other mediators) exert influence on the expression of pro- and anti-inflammatory cytokines. A study of healthy men revealed that disturbed sleep leads to the suppression of the immune system (decreased NK-cell activity and T-cell function), dysregulation of cytokine production, and decreased growth hormone [157]. As such, the slow wave sleep has been identified as being predominant in the regulation of the immune function during nocturnal sleep [157]. It is not known how this opioid effect on slow wave sleep impacts opioid endocrinopathy in women.

Polypharmacy

Women prescribed with opioids are at risk for polypharmacy. Fillingim et al. conducted a cross-sectional study of data from chronic spinal pain patients undergoing evaluation at a multidisciplinary pain treatment center [158]. They reported that women taking opioids were more likely to be taking a greater number of other medications than non-opioid-using women with chronic pain. Specifically, women using opioids were more likely to be on an anti-depressant ($P = 0.0005$), and more likely to be taking a muscle relaxant ($P = 0.03$), suggesting that women taking opioids tend to be more pharmaceutically complex [158]. Polypharmacy in women taking opioids presents additional risk for drug–drug interactions and additive side effects. For instance, researchers used a Medicare and a large commercial claims database to examine drug : drug interactions among osteoarthritis patients taking CYP450-metabolized opioids [159]. Women were found to be significantly more likely than men to experience a drug : drug adverse event (28.4% vs 21.0%, respectively).

Opioid-Induced Bowel Dysfunction (OBD)

OBD is the most common and persistent adverse effect of long-term opioid use [160]. Female gender is a risk factor for chronic constipation [161,162], the most common and frequently studied component of OBD. Other symptoms include nausea with or without emesis, reflux, pain, bloating, and cramping. OBD is a predictable risk for women but the data do not clearly indicate that women are at greater risk than men. Rosti et al. examined OBD in 2,324 patients; two-thirds of the sample had cancer pain, while the remaining one-third had chronic non-cancer pain [163]. The researchers found that 64% of opioid users experienced OBD despite laxative use in 90% of opioid users. Female sex and age >70 years were significant risk factors for OBD, although the sex and age differences were at least

partially accounted for by cancer status [163]. Other studies have either found no statistically significant sex differences in risk for OBD [164] or did not employ multivariate analysis to examine such differences [165,166]. The risk for constipation—the most common opioid bowel symptom—has been shown to increase with duration of opioid therapy and appears unrelated to opioid dosage [164] and to sex [163].

Tolerance, Opioid-Induced Hyperalgesia (OIH), and Physical Dependence/Withdrawal

Tolerance (the requirement for a higher dose to maintain effect), physical dependence (defined as a state in which an abstinence syndrome occurs when opioids are withdrawn suddenly or tapered too quickly, or when an opioid antagonist is administered), and OIH (the paradoxical lowering of nociceptive threshold with opioid administration) are physiological responses to opioid administration that have repeatedly been shown to differ across sexes in animal models [167]. In addition to hormonal and genetic factors, the opioid-receptor binding properties of the drug investigated, potency, and dose all appear to play a role in variable expression of these differences. In humans, the experimental and clinical data are less developed, making it difficult to draw clinical conclusions, particularly for chronic opioid administration [168,169]. We briefly review preclinical animal data to provide some context to interpret the relatively sparse human data.

In rodents, tolerance to morphine tends to be more prominent in intact male animals and is attenuated in both male castrated animals [170] and female ovariectomized animals [171]. Additionally, development of tolerance varies with the estrous cycle and estrogen supplementation [172]. N-methyl-D-aspartate (NMDA) antagonists do not appear to inhibit tolerance in female mice [173], while flumazenil (a benzodiazepine antagonist) diminished tolerance in female—but not male—rats [174], highlighting the complexities of sex differences in development and abatement of tolerance and rendering the implications of these findings uncertain in regard to humans.

Indeed, the human data are far from clear. Studies are limited and characterized by imprecise distinctions between tolerance and OIH, and most studies/ observations have focused on acute pain and short-term opioid administration. We did not identify any human studies that examined sex differences in opioid tolerance with long-term therapy, although at least one long-term prospective study did find more male than female tolerance [175].

In the taxonomy of pain issued by the International Association for the Study of Pain, hyperalgesia is defined as “increased pain from a stimulus that normally provokes pain” (http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Defi...isplay.cfm&ContentID=1728#Hyperalgesia), and OIH is not defined. In the past, hyperalgesia was heralded as a sign of neuropathic pain, but subsequent examination of many chronic pain conditions revealed a component of hyperalgesia in a subset of chronic pain patients without the presence of neuropathic pain. Many of these conditions—headache [176], fibromyalgia [177], and IBD [178], to name a few—disproportionally impact women, suggesting that many women are likely to experience hyperalgesia as part of their chronic pain experience, regardless of opioid exposure.

Regardless of underlying diagnosis, opioid administration may lead to decreased nociceptive threshold and OIH, with or without the presence of chronic pain, such as methadone maintenance treatment for opioid dependence [179–185]. OIH is variably assessed and defined in animal and human studies. In routine clinical practice, it may be difficult to distinguish OIH from tolerance, disease progression, limited coping skills, catastrophizing, or other confounding factors. The pro-nociceptive elements of OIH may lead to the clinical response of dose escalation, which may be variably labeled as tolerance or OIH. Limited evidence suggests that withdrawal of opioids may reduce OIH [186–189] and that gabapentin [190] or ketamine [191] may at least temporarily improve OIH. However, challenges in defining, identifying, and treating OIH contribute to discordance regarding its significance in clinical practice [192–200]. Several studies demonstrate that duration and dosage of opioid therapy correlate with OIH [201,202]. In one study, OIH was noted to develop within 1 month of initiation of opioid therapy for chronic low back pain [203]; sex differences were not explored. Clinically, the development of OIH with chronic administration is particularly relevant. Cohen et al. examined the response to a standardized painful stimulus (injection of 1 mL of lidocaine subcutaneously) in 355 patients with pain scheduled for an interventional procedure, asking them to rate both the pain and unpleasantness of the injection [201]. Not only did they find higher opioid dose and duration of opioid treatment were directly associated with more pain and unpleasantness, women also reported higher scores on both variables and baseline pain scores correlated with both measures as well. In a methadone maintenance population, Compton et al. investigated the hypothesis that adding the NMDA antagonist dextromethorphan would alter experimental pain tolerance [204]. There was no benefit to adding the dextromethorphan, and in fact there was a paradoxical effect with women, demonstrating decreased pain tolerance compared with men given dextromethorphan.

Chen et al. investigated OIH and found that chronic pain patients prescribed with opioids had decreased heat pain threshold and exacerbated temporal summation of the second pain to thermal stimulation compared with non-pain patients and chronic pain patients not prescribed with opioids [202]. Women were slightly overrepresented in the study population (61%). While many clinical factors were examined, gender differences on quantitative sensory testing (QST) were not assessed. The authors did note that morphine equivalent dose was a factor, with higher doses correlating with changes in QST. In a study looking at both cold pain perception and diffuse noxious inhibitory control (DNIC) in patients with and without opioid management of their chronic pain, only men taking opioids had decreased magnitude of DNIC, suggesting that women were less susceptible to this opioid effect [205].

In summary, the concept of OIH is a relatively new area for research in chronic opioid therapy, and the early data suggests sex-specific differences likely exist. Sex/gender differences may be magnified when baseline pain scores, duration of opioid exposure, and dose are independent risk factors for OIH, when one considers that women are more likely to be prescribed with opioids in the first place, stay on them for longer periods of time, and achieve higher doses [3,18,206].

Opioid dependence is a challenging term, because it can be used to describe two different situations. In mental health circles, the focus is on an individual’s inability to stop taking a

drug despite it being in her/his best interest to do so, accompanied by the inability to control drug-taking behavior. Adding the word “physical” shifts the focus to a state in which an individual has a physiological dependence on the substance, such that if it is withdrawn or an antagonist is administered they will experience characteristic behavioral and physiological symptoms and display physical signs of an abstinence syndrome. An individual may have physical dependence to a psychologically inert substance such as a cardiovascular drug [207,208], but in the case of opioids, clinical “dependence” involves the melding of psychological and physiological issues. While physical, observable signs may be noted (e.g., diarrhea, piloerection, restlessness, lacrimation, yawning, etc.), the psychological components are inextricably linked to the patient experience of withdrawal and assessment of withdrawal typically involves a mixture of signs and symptoms [209].

In animals, physical dependence and opioid withdrawal are associated with objective, quantifiable signs as weight loss, “wet-dog” shakes, diarrhea, and jumping. While sex differences have been found in mouse and rat models of withdrawal and dependence, the findings do not easily generalize to humans. The preclinical data vary by species [167], the timing for inducing withdrawal is short, antagonists are often used to precipitate withdrawal, some of the behaviors are unique and not exhibited in humans, and the psychological variables that accompany dependence (e.g., craving, social milieu, mood) cannot be replicated in animals.

Human studies of physical opioid dependence and withdrawal tend to focus on opioid-abusing patients with rec-reational use rather than pain treatment as the main reason for their physical dependence. In general this body of research has not assessed sex differences. An Austrian study compared withdrawal between women and men entering a maintenance program. The authors noted that gender differences were small, with women evidencing more physical symptoms of withdrawal (appetite, muscle twitching, vomiting, depression all at least 50% increase), and poorer self-reported quality of life, suggesting a larger burden of withdrawal for women [210].

Older Age

The risks of opioid therapy vary by age for women. Older women may be more susceptible to the negative consequences of opioids, such as respiratory depression, sedation, cognitive effects, constipation, drug–drug interactions (due to polypharmacy or impaired metabolism), and accidental overdose. A recent review and meta-analysis of outcomes associated with long-term opioid use in older adults concluded that the long-term safety, efficacy, and abuse potential remains undetermined [211], and the relevant sex differences remain poorly understood.

One study reported improved outcomes for elderly nursing home residents with persistent nonmalignant pain taking no analgesics (N = 1,467) or different classes of analgesics (N = 2,202) for at least 6 months [212]. Long-acting and short-acting opioids were analyzed separately. While data for men and women were not examined separately, the opioid sample was comprised mainly of women (87.5% for long acting, 88.9% for short acting). The authors reported a trend toward improved social engagement for those taking long-acting opioids compared with those in the non-opioid group. However, interpretation of these data

(and for other specific quality of life indicators) is limited by small cell sizes (e.g., 11–24 in the opioid groups being compared with as many as 237 in the no analgesics group) and limited statistical power to evaluate associations.

Fractures

Falls and fracture risks are greater in older women taking opioids compared with women with chronic pain not taking opioids [213], and risk appears to increase directly with opioid dose. Indeed, older women taking ≥50 mg/ day of morphine equivalents have a twofold increased risk of fracture. Another study of two statewide pharmaceutical programs examined risk of fracture in adults with arthritis ≥65 years of age (N = 17,310) initiating either opioids or nonsteroidal anti-inflammatory drugs (NSAIDs) [214]. The sample was overwhelming female (84%) with a mean age of 80 years (standard deviation = 7.0). The researchers reported 587 fractures among the opioid users and 38 among NSAID users (hazard ratio = 4.9, 95% CI 3.5–6.9) [214]. Fracture risk increased with greater dosage and with short-acting opioid use. Falls and fractures may be caused by dizziness [215], sedation, or other factors. While more research is needed to determine cause, the risk of falling suggests that caution should be used when prescribing opioids in women 60 or older— the age group that is currently the most likely to receive opioid prescriptions.

Given the previous findings, it has been suggested that fall risk may be attenuated by avoiding short-acting opioids in older women, although no studies have evaluated the effectiveness of such a strategy [214]. Fall risk may also be mitigated by a quick follow-up after initial opioid prescription to determine whether opioid initiation impaired cognitive, balance, or strength capacity, any such impairment may be considered relative contraindication for continued use due to a potential increase in risk for falling. It has been suggested that a fall risk management plan should be discussed with family and/or caregivers prior to prescription in older adults [216].

Outcomes for Surgery and Other Medical Procedures

One study examined the impact of chronic opioid use as a risk factor for postsurgical pain in women undergoing gynecological surgery. Information on pain characteristics, opioid use, and psychological factors were collected prior to and 6 months after surgery. Women taking long-term opioids prior to surgery were 2.0 times more likely (range 1.2–3.3) to report chronic postsurgical pain than those not taking opioids. Among women with preoperative pelvic pain, those taking opioids were 30% (RR = 1.3; 95% CI 0.8–1.9) more likely to report chronic postsurgical pain than those not taking opioids [217].

Recent research has examined long-term opioid use and found associations between long-term opioids and poorer outcomes for surgery [218] and epidural steroid injections [219]. Overall, the studies are small and sparse, sex differences analyses were not performed, and interpretation of findings is unclear due to limited matching of patient comorbidities.

Poisoning/Unintentional Overdose

Higher doses of opioids are directly associated with increased risk of opioid overdose for both sexes [220– 222]. While women are often prescribed higher doses than men [20], sex

differences for opioid overdose rates have been both confirmed [223] and disconfirmed [221], leaving an unclear determination of the relative risk for women. In terms of unintentional poisoning, overdose deaths have tripled among women since 1999, and the profile of poisoning agents has changed, with greater increases in opioid-related poisoning hospitalizations seen for women but not for men. One study examined rates of poisoning hospitalizations in young women (18–44 years of age) for the years 1998–2006 [224]. Opioids accounted for 6.5% of the total 635,886 poisoning hospitalizations (N = 41,333). Data were then broken down by type of poisoning: intentional (433,877), unintentional (101,680), and undetermined intent (99,706). The unintentional poisoning category included excessive opioid use for medical or recreational use. In the medical realm, examples of factors related to poisoning could include overprescription, overuse by the patient, adverse effects, or toxicity related to drug–drug interactions. While data were not broken down by substance abuse and mental disorder comorbidity or by poisoning agent, in aggregate, 41% of unintentionally poisoned women had comorbid substance abuse and 42% had mental disorder diagnosis. While coding of diagnoses has its limitations, the majority of unintentional overdoses (60%) were not coded as substance abuse related and thus are likely to reflect risk associated with medical use of opioids. Unintentional opioid poisoning increased sharply over the study period ($P < 0.0001$), indicating a worrisome trend in poisoning risk for women that has been confirmed by other researchers [225].

Researchers have noted that overdose trends mirror prescribing patterns [226]. At the individual level, prescription shopping and/or doctor shopping appears to predict risk for overdose in women. One state-wide study examined patterns of abuse among unintentional pharmaceutical overdose fatalities [227]. The researchers reported that prescribed opioids were present in 44% of fatality cases. Among decedents, women were more than twice as likely as men to have received prescriptions from ≥5 clinicians in the year prior to their death, as evidenced by controlled substance monitoring program records [227]. Women are more likely to receive opioids from doctors, and these data show they are also more likely to doctor shop with fatal consequences, suggesting that effective use of information from prescription drug monitoring programs might mitigate the risks. Other contributory factors to overdose risk may include psychiatric comorbidity, polypharmacy, and higher doses of opioids, although more research is needed to better describe the impact and relatedness of these factors.

Psychological/Behavioral Risks and Consequences

While it is tempting to conclude that greater pain intensity in women drives opioid prescription, the empirical evidence suggests that psychosocial factors often mediate the relationship between sex/gender and prescribing of opioids. A growing body of evidence from multiple groups of independent researchers has shown that psychological factors either predict or strongly associate with receipt of opioid prescription [81,228–232]. Psychological comorbidities are common in people with chronic pain [229,233,234], and one study suggested that symptoms of depression predict the longitudinal trajectory of chronic pain [235]. Certainly, chronic pain, pain-related functional deficits, and reductions in quality of life are associated with depressive symptoms. While it may be assumed that treating pain with opioids will lead to reductions in depressive symptoms, supportive data are limited and

some studies suggest that long-term opioid use is associated with increased levels of depression [236]. One important factor to consider is the limitation of opioids in treating pain. In fact, rarely do opioids "remove" or "cure" chronic pain. A pooled analysis of four studies of oral opioids showed a standard mean pain reduction of 1.6 points (on a 0–10 numeric rating scale) [237]. While such differences may be statistically and even clinically significant, for the majority of patients on opioids, chronic pain remains a condition that must be managed and one that remains heavily influenced by biopsychosocial factors. As such, the need for proper assessment and treatment of psychological comorbidities in women with chronic pain is underscored.

Most likely it is the *combination* of chronic pain and the presentation of psychopathology, emotional distress, and other factors that influences whether the female patient leaves her doctor's office with a prescription for opioids. There is at least suggestive evidence that higher levels of symptoms of psychopathology may associate with decreased opioid responsiveness in both sexes. One study examined the response to opioids of patients with chronic low back pain using a double-blind, placebo controlled, randomized crossover designed trial. Participants were stratified into three levels psychological symptom severity (low, moderate, and high). Participants in the higher psychological symptom severity groups (including anxiety, depression, and other factors) not only had more disability and less mobility, but also reported poorer pain relief with the acute administration of an opioid than those with less psychopathology [238]. Additionally, clinical trials on the safety and efficacy of analgesics including opioids typically exclude patients with anxiety and depression [239], so that the drugs are poorly studied in this patient population [21].

On the whole, data regarding long-term opioid use, psychological factors, and risks for women *relative* to men are lacking. Few studies have examined sex differences. In the following, we mainly review what is known regarding the risks for both sexes (as these data pertain to women) and focus on women-specific data where possible.

Depression

The literature suggests that a bidirectional relationship exists between depression and opioid use among people with chronic pain. One study of people with chronic pain found that those who take opioids regularly have a higher occurrence of depression compared with those who do not take opioids (28% vs 19%, $P = 0.012$) [236]. Viewed from the other direction, chronic pain patients who have experienced a recent depressive episode (within the past 2 years) are more likely to be prescribed opioids and to have concurrent use of sedative-hypnotic drugs than people with no recent history of depression [21]. Indeed, the gender-neutral association between opioid prescription and depression is robust, spans multiple independent research groups [21,236,240,241], supports the link between psychopathology and opioid prescription, and suggests a possible risk for polypharmacy because of the need to address both the depression and the pain.

The link between depression and opioid use is particularly relevant to women given their greater prevalence of both conditions. The lifetime female : male relative risk for major depressive episode is 1.7 [242]. One national database study of 131,535 adults showed that women are almost twice as likely as men to have depression (prevalence rate 9.1 vs 5.0,

respectively), and women with various chronic pain conditions were more likely have comorbid depression [243].

Women who have had a recent depressive episode or who exhibit negative affect (a symptom of depression) are more likely to be prescribed opioids [179,180,185]. A 10-year follow-up study of people with chronic pain who received multidisciplinary pain treatment revealed that people taking opioids 10 years post-inpatient treatment were more likely to be depressed than those who were not taking opioids [236]. Some work has suggested that underlying psychological characteristics, including anxiety and negative affect, are associated with reduced opioid analgesia in people with chronic pain [238]. Long-term opioid prescription in women may influence neurotransmitters, the immune system, sex steroids, the HPA axis, sleep, and cognitive function—all factors affecting mood. However, teasing out effects of opioids from the effects of chronic pain itself requires more definitive study.

Anxiety

Outside of the substance abuse literature, most studies on anxiety and opioid use have not examined sex effects. In general, for both sexes, anxiety is directly related to opioid use. One study examined the independent effect of anxiety disorder diagnosis and found it predicted heavy opioid utilization for privately insured patients only, and not for Medicaid patients [244]. In a population-based study (N = 9,279), Sullivan et al. showed that among persons with chronic pain, those who had a diagnosis of either panic disorder or generalized anxiety disorder within the past year were significantly more likely to report regular use of prescribed opioids [230]. Indeed, the likelihood for opioid use was roughly sixfold greater for those with panic disorder and almost fourfold greater for those with generalized anxiety disorder compared with those who had no opioid use in the past year.

Activation of the opioid system leads to anxiolytic responses in healthy people and in people with anxiety disorders [245]. The relationship between the opioid system and anxiolysis may serve an adaptive function. However, for women with chronic pain and concomitant anxiety —whether pain related or not—anxiolysis may serve to reinforce use of prescribed opioids. Clinical studies are needed to assess the effects of opioid use on anxiety (and vice versa) specifically in women with chronic pain.

Pain Catastrophizing

It is useful to broaden the conversation of opioids and psychological factors beyond anxiety and depression. While not a formal psychiatric diagnosis, pain catastrophizing is an important cognitive and emotional construct that has been shown to potently influence the experience of pain and pain outcomes [246–256]. Catastrophizing is composed of the cognitive aspects of rumination and magnification of pain, and the emotional aspect of feeling helplessness over pain [257]. Catastrophizing has been shown to predict poor response to opioid treatment in healthy adults [258,259]. While a female predilection for pain catastrophizing has been reported in healthy samples exposed to pain stressors [256,260,261], data are mixed [258]. The specific impact of catastrophizing on opioid use in women with chronic pain is poorly defined. One study linked catastrophizing to greater

usage of non-opioid pain medication in adolescent girls compared with boys [262]; future studies may determine whether this finding extends to opioid use in women in other age groups.

Patient Behaviors

The literature shows that individual characteristics and psychosocial factors strongly predict prescription for long-term opioid therapy [21,263] for both sexes [21,261]. Relevant individual characteristics include psychiatric diagnoses [230], frequency of medical service utilization [20,264], smoking status [265,266], and pain-related functional impairment [81,263]. A seminal study of predictors of physician opioid-prescribing patterns by Turk and Okifuji showed that male and female patient behaviors exhibited during the medical visit significantly predicted physicians' writing of opioid prescriptions, while pain intensity, demographic factors, and objective physical pathology were non-influential [263]. Specific behaviors included negative affect, facial expressions of distress, distorted ambulation or posture, and avoidance of activity. The authors noted that office visit pain behaviors may be the result of behaviors that have been reinforced over time. Other work has shown that negative affect predicts poorer response to opioid analgesia [267].

In terms of other behavioral predictors for opioid use, high spousal solicitousness has been associated with increased likelihood of opioid use for women with chronic pain but not for men [268]. More studies are needed to describe the psychosocial factors that influence the pathway by which women arrive at—and remain on—opioids.

Function

While the goal of opioid therapy may be pain reduction and associated functional improvement, a recent Cochrane review concluded that insufficient evidence exists to support a determination of long-term opioid use as beneficial on functional status in chronic pain patients of either sex [17]. Poorer function has been reported for women prescribed with opioids compared with those not prescribed opioids, consistent with other mixed-sex studies [81,269]. Lastly, another study examined follow-up outcomes for patients who attended a multidisciplinary pain treatment program 10 years prior [236]. The authors found that at 10-year follow-up, men and women taking opioids had significantly lower (worse) scores on the Short Form 36 (physical functioning, social functioning, general health, mental health, and vitality) compared with nonusers of opioids. Caution must be used in interpreting these associations, as matching for important patient characteristics within groups, such as medical comorbidity, is rare or absent. Regardless, we found no evidence to suggest women are at *greater* risk than men.

Smoking Status

Studies have shown that smoking status is associated with early opioid prescription following low back injury [270] and with long-term opioid use (24-month follow-up) in back pain patients [271]. One study of 5,292 individuals with chronic pain found that opioid and smoking status were strongly related. Opioid users were more than twice as likely to be a daily smoker than non-opioid users (OR = 2.19, 95% CI = 1.49–3.23) [272]. The data were adjusted for sex, and specific sex differences for smoking risk were not assessed. Smoking is

also associated with depression, greater pain intensity [266,273], and is a risk factor for greater use of opioids. Hooten et al. showed that current smoking status is associated with an average 27 mg increase in baseline morphine equivalent dose. This relationship between smoking and opioid dose is similar or *greater* for men than for women [266,270,271]. Similarly, the collective data suggest that smoking confers equal risk to women and men for receipt of opioid prescription [270] and duration of use [271].

Aberrant Behaviors/Misuse/Abuse

Use of prescription opioids is associated with some risk of abuse or misuse [274]. Studies on the effect of sex on opioid misuse among opioid-prescribed patients are inconsistent, with one study showing male sex predicted prescription drug use disorder among primary care patients with chronic pain [275]. A review conducted by Turk et al. reported that among five studies that addressed sex as a predictor of opioid misuse, none found a positive association with patient sex [276]. Studies from the substance abuse literature suggest that women are more likely to use opioids for nonmedical purposes [31] and to demonstrate analgesic drug problem use [31,277–279], although none of these studies were specific to chronic pain and only one study examined pain as a variable of interest [277]. One small study indicated that women are more likely to hoard unused medication (68% vs 48%, $P = 0.04$) than men [280], although this behavior could be a marker for either aberrant intention or for undertreated pain [281]. Knowledge regarding opioid misuse/abuse in women is limited because studies frequently do not examine sex differences [282–284].

Jamison et al. conducted a multisite longitudinal study using self-report measures, a structured interview, and results from a urine toxicology screen to examine sex differences in the clinical correlates of opioid misuse among patients taking opioids for chronic pain [285]. No sex differences were found for overall risk for aberrant drug behavior (as defined by abnormal urine screens and the Aberrant Drug Behavior Index). Risk for opioid misuse in women was predicted by history of physical and sexual abuse, psychiatric diagnoses, and individual mood disorder items of the Prescription Drug Use Questionnaire.

In contrast, a large epidemiological study (N = 31,844) examined the risks for possible and probable opioid misuse among recipients of chronic opioid therapy in commercial and Medicaid insurance plans and found increased risk for women [23]. The investigators calculated an opioid misuse score designed to detect patients receiving excess medication or accessing multiple opioid sources, composed of four factors: days supplied of short-acting opioids, days supplied of long-acting opioids, number of opioid pharmacies, and number of opioid prescribers [23]. This study utilized an index date as first use of opioids and examined data for each participant over the next 12 months. Study outcomes were risk for “possible” and “probable” misuse. Results showed that women comprised the majority of long-term opioid users (72% of Medicaid and 59% of commercially insured). For privately insured patients, women were more likely to possibly misuse (OR = 1.06, 95% CI 1.01, 1.12, $P = 0.025$) or probably misuse (OR = 1.09, 95% CI 0.98, 1.21, $P < 0.001$) opioids than men. Interestingly, among Medic-aid patients, there was no sex difference for possible misuse of opioids, and women were *less* likely to probably misuse opioids (OR = 0.69, 95% CI 0.52, 0.88, $P < 0.001$) suggesting sex differences by socioeconomic status. It did not

appear that the data were examined for age and gender interactions; however, the overall sex-neutral finding was that age was inversely related to misuse scores.

Cicero et al. showed that for men and women taking long-term opioid therapy for chronic pain, sex differences exist in the profile of substance abuse. The incidence of alcohol abuse predominated in men (2:1 alcohol vs opioid problem use), while women on long-term opioids were twice as likely to abuse their opioids than alcohol [20].

Indeed, women seeking treatment for opioid abuse are significantly more likely than men to report that their first opioid exposure was in the form of a legitimate prescription (85% vs 79%, respectively) [277]. Although women in each age group were more likely than men to receive prescribed medications, sex differences were significant only for the 21–30 and 31–40 age groups ($P < 0.05$ and $P < 0.01$, respectively); it should be noted that the researchers examined 11 drugs, 3 of which were non-opioid. Therefore, for women, the prominent pathway to aberrant opioid use appears to be medical and is more likely to be pain-*related*. While multiple studies have shown that women's greater likelihood for opioid receipt is influenced by individual and psychological characteristics, such as anxiety and depression [263], it is important to distinguish between psychological risk for opioid *prescription* and risk for opioid *misuse/abuse*. Unipolar depression and anxiety are predictors of opioid misuse for both genders in some studies [286–288], but not in others [284,289,290]. Such conflicting evidence makes it difficult to draw firm conclusions regarding the association between these psychopathologies and misuse behavior.

Another national study examined pathways to opioid abuse, 1,408 males and females seeking treatment for opioid abuse [277]. While this was not a pain study, 70% of women said their first-time opioid use was for pain control (vs 62% of men). Eighty-five percent of women and 79% of men reported first exposure to opioids from a legitimate medical prescription for pain treatment. Neither of these numeric differences achieved statistical significance; pain intensity ratings and incidence of chronic pain were also sex neutral. It is important to note that an interaction with age may obscure some sex differences. When the authors examined data by age category for drug source, they found that across age groups, women were numerically more likely to source drugs from a physician's prescription, and this was significantly true for women aged 21–30 ($P < 0.05$) and 31–40 years of age ($P < 0.01$).

An epidemiological study of people prescribed long-term opioids for chronic pain found that the rate for abuse or dependence was not statistically different between men and women (1.3% for both) [20]. However, the abuse rate for opioid-using men was 31 times greater than for men in the non-opioid group (1.31% vs 0.02%, respectively), and the abuse rate for opioid-using women was an astounding 128 times greater than the non-opioid group of women (1.27% vs 0.01%, respectively) [20]. The reasons for the risk disparity is unknown but is likely multifactorial and almost certainly includes psychological factors. For both sexes, opioid abuse among opioid-prescribed patients appears to be at least partially mediated by anxiety and depression [274]. One factor that may contribute to an increased predilection for opioid abuse in women is that mental suffering and physical pain may be more likely to be undifferentiated [21]. Prescribing for undifferentiated pain represents a

problematic treatment pathway, as patients with concomitant psychological distress may experience reduced analgesic benefit from opioids and be at greater risk for medication misuse [238,288]. Studies are needed to parse and illuminate the relationships between chronic pain, psychology, and opioid use/abuse in order to reduce the risk for poor outcome in women and to ensure women's pain and distress are treated properly.

Overall, women prescribed with opioids may be at higher risk for the unintended consequences of opioid abuse. It has been recommended that physicians pay careful attention to factors that predict opioid abuse in women, including psychopathology, history of substance abuse, and smoking status [277]. It has also been suggested that pain treatment programs may require a modification in structure to account for—and to attend to—differences across the sexes in these risk factors [277].

While opioid use is associated with psychological factors [263], poorer function [263], and greater illness in both sexes, these associations may be stronger for women. For instance, a study of opioid abusers showed that compared with men, women who abuse opioids are more physically and psychologically dysfunctional and ill [77], again suggesting a more complex picture for women and opioid abuse.

Research Needs and Direction

While we have endeavored to consolidate what is known about long-term opioid use in women, we underscore the vast unknowns. Broadly, there is a major need for all opioid studies to examine data by sex. Many studies examine whether there are sex differences in the composition of groups within a study; however, few studies actually examine whether sex independently influences the dependent variables of interest. The latter approach may reveal critical sex-specific findings that would inform our understanding of risks for both sexes. Additionally, there is an overarching need for opioid studies to consider comorbidities in the analyses, and when possible, to match for such characteristics across groups. Regardless of whether the opioid or other patient characteristics (or a combination of the two) are driving the associations, the data suggest that the woman who is prescribed with opioids is at greater risk for negative outcomes of various types, thus warranting further study, clinical consideration, and strategies for risk mitigation.

While opioid-induced endocrine dysregulation is widely recognized, studies are needed to characterize the specific, broad, and downstream effects in women. Gaps in understanding may be closed with studies that examine: 1) the association between opioid therapy and growth hormone deficiency; 2) the efficacy of hormonal supplementation in women on opioids who have endocrine deficiencies; 3) whether and how quickly hormonal homeostasis is reestablished following opioid discontinuation; and 4) whether risks vary as a consequence of body composition, as some research has suggested [291]. Endocrine dysregulation has broad impact on the human body, and thus future studies are needed on how opioid-induced endocrinopathy may influence other outcomes in women such as mood, cognition, insulin secretion, cardiovascular events, sexual function, bone loss, and fracture risk. Others have underscored the need for prospective studies to focus on opioid-induced endocrinopathy and its downstream effects [69]. For instance, more research is needed to

understand the psychobio-logical consequences of opioid use in women. Negative mood is known to be influenced by sex steroids [292], and functional magnetic resonance imaging studies have shown that estrogen moderates neural patterns associated with affective processing [293]. Women who experience opioid-induced endocrinopathy may be at greater risk for depressive symptoms and anxiety, whether at the symptom level or in terms of formal psychopathology. Longitudinal research is needed to determine the specific risks for women and the factors that mediate such risks.

More studies are needed to stratify endocrinopathy risks by age. Little is known about the specific risks and consequences of long-term opioid use in young women and fertile women (e.g., what are the incidence and long-term consequences of opioid-induced endocrinopathies in terms of fertility and progression of pain?). For younger women, prospective and epidemiologic studies are needed to better understand the risks of long-term opioid use and how the drugs may impact endocrine and immune status (and the clinical consequences of such impacts) over the course of many years of exposure. It remains unknown whether such effects are additive or synergistic with many years of exposure as data describing the long-term consequences of opioid therapy in women are lacking.

While research indicates that opioids confer risks for fertility and pregnancy, many specifics remain unknown due to the limited scope of studies that have focused on substance abuse populations. Research should extend beyond substance abuse and methadone maintenance populations to women using long-term opioids for chronic pain. For instance, is it more difficult for a woman taking opioids to become pregnant? Without comparative data for women with chronic pain using opioids during pregnancy who do not have substance abuse, it is impossible to adequately evaluate the true risks of opioid use in these women and their children, including risk of birth defects, perinatal complications, and altered neonatal physiology. Clearly, ethical concerns would require a thoughtful study design, perhaps one in which women with chronic pain unable to taper opioid use prior to pregnancy were followed longitudinally and neonatal outcomes tracked. Additionally, the different strategies of continued opioids in pregnancy vs ceasing opioids and relying on non-opioid alternative treatments during pregnancy have not been compared. Such studies could determine group differences in outcome, and whether outcome is predicted by pain intensity, other factors, or the long-term opioid therapy itself.

In terms of childbirth, studies are needed to separate effects of opioids for acute postsurgical pain from the effects of anesthesia or other surgical drugs, and the impacts of chronic pain and long-term opioid use on these outcomes. Opioid use in women of childbearing age is increasing and therefore fetal therapeutic opioid exposure should be made a research priority, particularly given the impact of potential birth defects. Opioid use birth defects may negatively impact the child throughout their lifespan and potentially pose a substantial societal burden from associated medical costs and mortality.

Sex-specific differences appear to be present in animal models examining pain physiology responses to opioids including hyperalgesia, but clinical data are lacking. As more women are exposed to opioids at higher average doses, and they experience many chronic pain conditions associated with hyperalgesia and allodynia more often than men, it is possible

that women may be at increased risk for OIH. Studies are needed to better characterize sex-specific changes in pain physiology with long-term opioid use and their clinical implications.

Depression predicts opioid prescription in women, but less is known about how opioids impact mood in women, including whether women are at increased risk for negative mood effects. More research is needed to better define the influence of anxiety, depression, and catastrophizing on physician's pharmaceutical decision making, and to understand whether its influence varies as a function of the sex of the patient and/or of the sex of the physician. Prior research in other health-related areas has shown that sex may impact treatment approach in medical settings [294] and therefore opioid-prescribing studies could be improved by including the sex of the patient—and of the doctor—as variables of interest. The literature to date suggests that interpersonal factors (e.g., physician- or spouse -related) predict likelihood of opioid prescription for women, opening another area for research on all of the environmental and interpersonal components (patients, prescribers, spouses, family members) impacting each patient. Future studies may focus specifically on developing patient opioid education interventions for optimizing patient behaviors and outcomes.

Summary/Conclusions

This review discussed evidence that supports five major considerations in regard to women and long-term opioid use: 1) women could be at higher risk for the negative medical and psychological effects of opioids because they have more persistent pain than men, and may be prescribed opioids more often and at higher doses than men; 2) multiple psychophysiological factors may contribute to certain risks and consequences of chronic opioid therapy; 3) risks in pregnancy and breast-feeding impact mother and neonate/infant; 4) as in men, risks that are unique to women may increase concomitantly with greater exposure to opioids (in terms of frequency and dosage); and 5) as in men, risks for women appear to vary at different ages. Evidence reviewed here confirms prior work which found a generally low or uncertain benefit : risk ratio for long-term opioid use; here, we specifically extend this conclusion to women.

Women in the United States are prescribed opioids for pain more often than are men and at higher doses. In the past decade, opioid prescribing has risen disproportionately for women in the United States, and a similar trend has been reported in Australia [295]. The direct and indirect adverse effects of opioids are important issues for women across all ages. Although many women will have improved pain control and function as a result of long-term opioid therapy, others will not achieve favorable outcomes or experience significant negative results with opioids. Adverse effects associated with opioids that may affect women more than men or are particularly relevant in women include endocrinopathy, polypharmacy, prolonged QT syndrome, unintentional poisoning, hyperalgesia, tolerance, doctor shopping, sleep pathology, bowel dysfunction, and reduced receipt of cancer screenings. Adverse medical effects may be compounded by: 1) demographic factors (e.g., age); 2) psychological factors (e.g., depression, catastrophizing, drug abuse, etc.); 3) health status (comorbid conditions); and 4) dose. Older women are the most likely group to be prescribed opioids; age-specific risks include falls and fractures for postmenopausal women, reduced fertility in

premenopausal women, birth defects in pregnant women, and neonatal toxicity risk for breast-feeding women and neonatal withdrawal following in utero exposure. Psychological risks and consequences of opioids include increased depression or negative affect, abuse/misuse of medication, and unintentional poisoning.

Knowledge of the specific risks of opioids in women has been limited by: 1) few focused studies on the topic; 2) small sample sizes; and 3) lack of longitudinal and controlled studies. Gaps in understanding have been complicated by other factors, such as the preponderance of opioid medication trials having been funded by the companies who make opioids [12,48–51,296–303]; additionally, safety and (short-term) efficacy studies have largely excluded women with comorbid mental illness or women who are pregnant, breast-feeding, or contemplating pregnancy.

Although a number of major gaps in understanding exist, important research priorities include defining the risks and consequences of long-term opioid use in young women, fertile women, and pregnant women who do not have substance abuse. Knowledge and treatment may be improved by developing and testing interventions, which target opioid risk management in women. Finally, given the sex differences discussed here, future work may determine whether gender-specific interventions are needed for patients and prescribers to ensure that the medical and psychological factors that contribute to increased pain and distress are treated appropriately in women.

References

1. Korff MV, Saunders K, Thomas Ray G, et al. De facto long-term opioid therapy for noncancer pain. Clin J Pain. 2008; 24(6):521–527. [PubMed: 18574361]
2. Compton WM, Volkow ND. Abuse of prescription drugs and the risk of addiction. Drug Alcohol Depend. 2006; 83(suppl 1):S4–S7. [PubMed: 16563663]
3. Parsells Kelly J, Cook SF, Kaufman DW, et al. Prevalence and characteristics of opioid use in the US adult population. Pain. 2008; 138(3):507–513. [PubMed: 18342447]
4. Freburger JK, Holmes GM, Agans RP, et al. The rising prevalence of chronic low back pain. Arch Intern Med. 2009; 169(3):251–258. [PubMed: 19204216]
5. Martin BI, Deyo RA, Mirza SK, et al. Expenditures and health status among adults with back and neck problems. JAMA. 2008; 299(6):656–664. [PubMed: 18270354]
6. Sullivan MD, Edlund MJ, Fan MY, et al. Trends in use of opioids for non-cancer pain conditions 2000–2005 in commercial and Medicaid insurance plans: The TROUP study. Pain. 2008; 138(2): 440–449. [PubMed: 18547726]
7. Lindenhovius AL, Helmerhorst GT, Schnellen AC, et al. Differences in prescription of narcotic pain medication after operative treatment of hip and ankle fractures in the United States and The Netherlands. J Trauma. 2009; 67(1):160–164. [PubMed: 19590328]
8. Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: A review of the evidence. Clin J Pain. 2008; 24(6):469–478. [PubMed: 18574357]
9. Chapman CR, Lipschitz DL, Angst MS, et al. Opioid pharmacotherapy for chronic non-cancer pain in the United States: A research guideline for developing an evidence-base. J Pain. 2010; 11(9): 807–829. [PubMed: 20430701]
10. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010; 17(9):1113. e88. [PubMed: 20402746]
11. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: An overview and literature update. Mayo Clin Proc. 2010; 85(3 suppl):S3–S14. [PubMed: 20194146]

12. Chou R, Huffman LH. American Pain Society, American College of Physicians. Medications for acute and chronic low back pain: A review of the evidence for an American Pain Society/ American College of Physicians clinical practice guideline. Ann Intern Med. 2007; 147(7):505–514. [PubMed: 17909211]
13. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: Opioid treatment for chronic back pain: Prevalence, efficacy, and association with addiction. Ann Intern Med. 2007; 146(2):116–127. [PubMed: 17227935]
14. Sullivan MD, Ballantyne JC. Examination of long-term opioid therapy. Arch Intern Med. 2012; 172(5):433–434. [PubMed: 22412109]
15. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: A meta-analysis of effectiveness and side effects. CMAJ. 2006; 174(11):1589–1594. [PubMed: 16717269]
16. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. Pain. 2004; 112(3):372–80. [PubMed: 15561393]
17. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. 2010; (1) CD006605.
18. Campbell CI, Weisner C, Leresche L, et al. Age and gender trends in long-term opioid analgesic use for noncancer pain. Am J Public Health. 2010; 100(12):2541–2547. [PubMed: 20724688]
19. Boudreau D, Von Korff M, Rutter CM, et al. Trends in long-term opioid therapy for chronic non-cancer pain. Pharmacoepidemiol Drug Saf. 2009; 18(12):1166–1175. [PubMed: 19718704]
20. Cicero TJ, Wong G, Tian Y, et al. Co-morbidity and utilization of medical services by pain patients receiving opioid medications: Data from an insurance claims database. Pain. 2009; 144(1–2):20–27. [PubMed: 19362417]
21. Braden JB, Sullivan MD, Ray GT, et al. Trends in long-term opioid therapy for noncancer pain among persons with a history of depression. Gen Hosp Psychiatry. 2009; 31(6):564–570. [PubMed: 19892215]
22. Edlund MJ, Martin BC, Fan MY, et al. Risks for opioid abuse and dependence among recipients of chronic opioid therapy: Results from the TROUP study. Drug Alcohol Depend. 2010; 112(1–2): 90–98. [PubMed: 20634006]
23. Sullivan MD, Edlund MJ, Fan MY, et al. Risks for possible and probable opioid misuse among recipients of chronic opioid therapy in commercial and medicaid insurance plans: The TROUP study. Pain. 2010; 150(2):332–339. [PubMed: 20554392]
24. Stewart WF, Shechter A, Rasmussen BK. Migraine prevalence. A review of population-based studies. Neurology. 1994; 44(6 suppl 4):S17–S23. [PubMed: 8008222]
25. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum. 1995; 38(1):19–28. [PubMed: 7818567]
26. Payne S. Sex, gender, and irritable bowel syndrome: Making the connections. Gend Med. 2004; 1(1):18–28. [PubMed: 16115580]
27. Symmons D, Turner G, Webb R, et al. The prevalence of rheumatoid arthritis in the United Kingdom: New estimates for a new century. Rheumatology (Oxford). 2002; 41(7):793–800. [PubMed: 12096230]
28. Yacoub Wasef SZ. Gender differences in systemic lupus erythematosus. Gend Med. 2004; 1(1): 12–17. [PubMed: 16115579]
29. Unruh AM. Gender variations in clinical pain experience. Pain. 1996; 65(2–3):123–167. [PubMed: 8826503]
30. Ruau D, Liu LY, Clark JD, Angst MS, Butte AJ. Sex differences in reported pain across 11,000 patients captured in electronic medical records. J Pain. 2012; 13(3):228–234. [PubMed: 22245360]
31. Simoni-Wastila L, Ritter G, Strickler G. Gender and other factors associated with the nonmedical use of abusable prescription drugs. Subst Use Misuse. 2004; 39(1):1–23. [PubMed: 15002942]
32. Williams RE, Sampson TJ, Kalilani L, Wurzelmann JI, Janning SW. Epidemiology of opioid pharmacy claims in the United States. J Opioid Manag. 2008; 4(3):145–152. [PubMed: 18717509]
33. Crofford LJ. Adverse effects of chronic opioid therapy for chronic musculoskeletal pain. Nat Rev Rheumatol. 2010; 6(4):191–197. [PubMed: 20357788]

34. Sun-Edelstein C, Bigal ME, Rapoport AM. Chronic migraine and medication overuse headache: Clarifying the current International Headache Society classification criteria. Cephalalgia. 2009; 29(4):445–452. [PubMed: 19291245]
35. Midgette LA, Scher AI. The epidemiology of chronic daily headache. Curr Pain Headache Rep. 2009; 13(1):59–63. [PubMed: 19126373]
36. Bigal ME, Lipton RB. Overuse of acute migraine medications and migraine chronification. Curr Pain Headache Rep. 2009; 13(4):301–307. [PubMed: 19586594]
37. Saper JR, Lake AE3rd. Continuous opioid therapy (COT) is rarely advisable for refractory chronic daily headache: Limited efficacy, risks, and proposed guidelines. Headache. 2008; 48(6):838–849. [PubMed: 18549361]
38. Camilleri M, Heading RC, Thompson WG. Clinical perspectives, mechanisms, diagnosis and management of irritable bowel syndrome. Aliment Pharmacol Ther. 2002; 16(8):1407–1430. [PubMed: 12182741]
39. Higgins PD, Johanson JF. Epidemiology of constipation in North America: A systematic review. Am J Gastroenterol. 2004; 99(4):750–759. [PubMed: 15089911]
40. Wilson S, Roberts L, Roalfe A, Bridge P, Singh S. Prevalence of irritable bowel syndrome: A community survey. Br J Gen Pract. 2004; 54(504):495–502. [PubMed: 15239910]
41. Gwee K-A, Bak Y-T, Ghoshal UC, et al. Asian consensus on irritable bowel syndrome. J Gastroenterol Hepatol. 2010; 25(7):1189–1205. [PubMed: 20594245]
42. Tietjen GE, Brandes JL, Peterlin BL, et al. Allodynia in migraine: Association with comorbid pain conditions. Headache. 2009; 49(9):1333–1344. [PubMed: 19788473]
43. Grossi ML, Goldberg MB, Locker D, Tenenbaum HC. Irritable bowel syndrome patients vs responding and nonresponding temporomandibular disorder patients: A neuropsychologic profile comparative study. Int J Prosthodont. 2008; 21(3):201–209. [PubMed: 18548956]
44. Chang L, Mayer EA, Johnson T, FitzGerald LZ, Naliboff B. Differences in somatic perception in female patients with irritable bowel syndrome with and without fibromyalgia. Pain. 2000; 84(2–3): 297–307. [PubMed: 10666535]
45. Piche M, Arsenault M, Poitras P, Rainville P, Bouin M. Widespread hypersensitivity is related to altered pain inhibition processes in irritable bowel syndrome. Pain. 2010; 148(1):49–58. [PubMed: 19889500]
46. Talley NJ. Pharmacologic therapy for the irritable bowel syndrome. Am J Gastroenterol. 2003; 98(4):750–758. [PubMed: 12738451]
47. Hawkes ND, Rhodes J, Evans BK, et al. Naloxone treatment for irritable bowel syndrome—A randomized controlled trial with an oral formulation. Aliment Pharmacol Ther. 2002; 16(9):1649–1654. [PubMed: 12197844]
48. Altman RD, Smith HS. Opioid therapy for osteoarthritis and chronic low back pain. Postgrad Med. 2010; 122(6):87–97. [PubMed: 21084785]
49. Deshpande A, Furlan A, Mailis-Gagnon A, Atlas S, Turk D. Opioids for chronic low-back pain. Cochrane Database Syst Rev. 2007; (3) CD004959.
50. Franklin GM, Rahman EA, Turner JA, Daniell WE, Fulton-Kehoe D. Opioid use for chronic low back pain: A prospective, population-based study among injured workers in Washington state, 2002–2005. Clin J Pain. 2009; 25(9):743–751. [PubMed: 19851153]
51. Volinn E, Fargo JD, Fine PG. Opioid therapy for nonspecific low back pain and the outcome of chronic work loss. Pain. 2009; 142(3):194–201. [PubMed: 19181448]
52. Bennett RM, Schein J, Kosinski MR, et al. Impact of fibromyalgia pain on health-related quality of life before and after treatment with tramadol/ acetaminophen. Arthritis Rheum. 2005; 53(4):519–527. [PubMed: 16082646]
53. Holman AJ, Myers RR. A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. Arthritis Rheum. 2005; 52(8):2495–2505. [PubMed: 16052595]
54. Ngian G-S, Guymer EK, Littlejohn GO. The use of opioids in fibromyalgia. Int J Rheum Dis. 2010; 14(1):6–11. [PubMed: 21303476]

55. Hooten WM, Townsend CO, Sletten CD, Bruce BK, Rome JD. Treatment outcomes after multidisciplinary pain rehabilitation with analgesic medication withdrawal for patients with fibromyalgia. Pain Med. 2007; 8(1):8–16. [PubMed: 17244099]
56. Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: A pilot study. Pain Med. 2009; 10(4):663–672. [PubMed: 19453963]
57. Stovner LJ, Andree C. Prevalence of headache in Europe: A review for the Eurolight project. J Headache Pain. 2010; 11(4):289–299. [PubMed: 20473702]
58. Bigal ME, Lipton RB. The epidemiology, burden, and comorbidities of migraine. Neurol Clin. 2009; 27(2):321–334. [PubMed: 19289218]
59. Crystal SC, Robbins MS. Epidemiology of tension-type headache. Curr Pain Headache Rep. 2010; 14(6):449–454. [PubMed: 20865353]
60. Colas R, Munoz P, Temprano R, Gomez C, Pascual J. Chronic daily headache with analgesic overuse: Epidemiology and impact on quality of life. Neurology. 2004; 62(8):1338–1342. [PubMed: 15111671]
61. Bigal ME, Ashina S, Burstein R, et al. Prevalence and characteristics of allodynia in headache sufferers: A population study. Neurology. 2008; 70(17):1525–1533. [PubMed: 18427069]
62. Bigal ME, Lipton RB. Excessive opioid use and the development of chronic migraine. Pain. 2009; 142(3):179–182. [PubMed: 19232469]
63. Saper JR, Lake AE3rd, Hamel RL, et al. Daily scheduled opioids for intractable head pain: Long-term observations of a treatment program. Neurology. 2004; 62(10):1687–1694. [PubMed: 15159463]
64. Ho TW, Rodgers A, Bigal ME. Impact of recent prior opioid use on rizatriptan efficacy. A post hoc pooled analysis. Headache. 2009; 49(3):395–403. [PubMed: 19222588]
65. Buckley DI, Calvert JF, Lapidus JA, Morris CD. Chronic opioid therapy and preventive services in rural primary care: An Oregon rural practice-based research network study. Ann Fam Med. 2010; 8(3):237–244. [PubMed: 20458107]
66. Vallejo R, de Leon-Casasola O, Benyamin R. Opioid therapy and immunosuppression: A review. Am J Ther. 2004; 11(5):354–365. [PubMed: 15356431]
67. Ballard KA, Pellegrino TC, Alonzo NC, Nugent AL, Bayer BM. Enhanced immune sensitivity to stress following chronic morphine exposure. J Neuroim-mune Pharmacol. 2006; 1(1):106–115.
68. Daniell HW. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. J Pain. 2008; 9(1):28–36. [PubMed: 17936076]
69. Vuong C, Van Uum SH, O'Dell LE, Lutfy K, Friedman TC. The effects of opioids and opioid analogs on animal and human endocrine systems. Endocr Rev. 2010; 31(1):98–132. [PubMed: 19903933]
70. Abs R, Verhelst J, Maeyaert J, et al. Endocrine consequences of long-term intrathecal administration of opioids. J Clin Endocrinol Metab. 2000; 85(6):2215–22. [PubMed: 10852454]
71. Craft RM. Modulation of pain by estrogens. Pain. 2007; 132(suppl 1):S3–S12. [PubMed: 17951003]
72. Craft RM, Mogil JS, Aloisi AM. Sex differences in pain and analgesia: The role of gonadal hormones. Eur J Pain. 2004; 8(5):397–411. [PubMed: 15324772]
73. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. J Pain. 2002; 3(5): 377–384. [PubMed: 14622741]
74. Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, Kaur G, Bruera E. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. Cancer. 2004; 100(4):851–858. [PubMed: 14770444]
75. 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. 2010; 26(5):374–380. [PubMed: 20473043]
76. Gindoff PR, Jewelewicz R, Hembree W, Wardlaw S, Ferin M. Sustained effects of opioid antagonism during the normal human luteal phase. J Clin Endocrinol Metab. 1988; 66(5):1000–1004. [PubMed: 3129443]

77. Steardo L, Monteleone P, Tamminga CA, et al. Differential responses in prolactin levels induced by naloxone in humans. Psychoneuroendocrinology. 1985; 10(2):203–209. [PubMed: 4034850]
78. Paice JA, Penn RD, Ryan WG. Altered sexual function and decreased testosterone in patients receiving intraspinal opioids. J Pain Symptom Manage. 1994; 9(2):126–131. [PubMed: 7517429]
79. Finch PM, Roberts LJ, Price L, Hadlow NC, Pullan PT. Hypogonadism in patients treated with intrathe-cal morphine. Clin J Pain. 2000; 16(3):251–254. [PubMed: 11014399]
80. Merza Z, Edwards N, Walters SJ, Newell-Price J, Ross RJ. Patients with chronic pain and abnormal pituitary function require investigation. Lancet. 2003; 361(9376):2203–2204. [PubMed: 12842375]
81. Darnall B, Li H. Hysterectomy and predictors for opioid prescription in a chronic pain clinic sample. Pain Med. 2011; 12(2):196–203. [PubMed: 21223499]
82. Thielke SM, Simoni-Wastila L, Edlund MJ, et al. Age and sex trends in long-term opioid use in two large American health systems between 2000 and 2005. Pain Med. 2010; 11:248–256. [PubMed: 20002323]
83. Parikh R, Hussain T, Holder G, Bhoyar A, Ewer AK. Maternal methadone therapy increases QTc interval in newborn infants. Arch Dis Child Fetal Neonatal Ed. 2011; 96(2):F141–F143. [PubMed: 21081591]
84. Fajemirokun-Odudeyi O, Sinha C, Tutty S, et al. Pregnancy outcome in women who use opiates. Eur J Obstet Gynecol Reprod Biol. 2006; 126(2):170–175. [PubMed: 16202501]
85. Chou R, Ballantyne JC, Fanciullo GJ, Fine PG, Miaskowski C. Research gaps on use of opioids for chronic noncancer pain: Findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. J Pain. 2009; 10(2):147–159. [PubMed: 19187891]
86. Ross, L.; Koren, G.; Steiner, M. Clinical management of substance use during pregnancy. In: Koren, G., editor. Medication Safety in Pregnancy and Breastfeeding. New York: The McGraw-Hill Companies, Inc; 2007. p. 165
87. Fox AW, Diamond ML, Spierings EL. Migraine during pregnancy: Options for therapy. CNS Drugs. 2005; 19(6):465–481. [PubMed: 15962998]
88. Scialli AR, Ang R, Breitmeyer J, Royal MA. A review of the literature on the effects of acetaminophen on pregnancy outcome. Reprod Toxicol. 2010; 30(4):495–507. [PubMed: 20659550]
89. Galbally M, Roberts M, Buist A. Perinatal Psychotropic Review Group. Mood stabilizers in pregnancy: A systematic review. Aust N Z J Psychiatry. 2010; 44(11):967–977. [PubMed: 21034180]
90. Hill DS, Wlodarczyk BJ, Palacios AM, Finnell RH. Teratogenic effects of antiepileptic drugs. Expert Rev Neurother. 2010; 10(6):943–959. [PubMed: 20518610]
91. Nijenhuis CM, ter Horst PGJ, van Rein N, Wilffert B, de Jong-van den Berg LTW. Disturbed development of the enteric nervous system after in utero exposure of selective serotonin re-uptake inhibitors and tricyclic antidepressants. Part 2: Testing the hypotheses. Br J Clin Pharmacol. 2012; 73(1):126–134. [PubMed: 21848990]
92. Udechuku A, Nguyen T, Hill R, Szego K. Antidepressants in pregnancy: A systematic review. Aust N Z J Psychiatry. 2010; 44(11):978–996. [PubMed: 21034181]
93. Bracken MB. Drug use in pregnancy and congenital heart disease in offspring. N Engl J Med. 1986; 314(17):1120. [PubMed: 3960086]
94. Shaw GM, Malcoe LH, Swan SH, Cummins SK, Schulman J. Congenital cardiac anomalies relative to selected maternal exposures and conditions during early pregnancy. Eur J Epidemiol. 1992; 8(5):757–760. [PubMed: 1426180]
95. Bracken MB, Holford TR. Exposure to prescribed drugs in pregnancy and association with congenital malformations. Obstet Gynecol. 1981; 58(3):336–344. [PubMed: 7266953]
96. Saxen I. Associations between oral clefts and drugs taken during pregnancy. Int J Epidemiol. 1975; 4(1):37–44. [PubMed: 1116890]
97. Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol. 2011; 204(4):314.e1–314.e11. [PubMed: 21345403]

98. Boneva RS, Botto LD, Moore CA, et al. Mortality associated with congenital heart defects in the United States: Trends and racial disparities, 1979–1997. Circulation. 2001; 103(19):2376–2381. [PubMed: 11352887]

99. Darnall BD, Stacey BR. Sex differences examined in long-term opioid use: Cautionary notes for prescribing in women. Arch Intern Med. 2012; 172(5):431–432. [PubMed: 22412108]

100. Briggs, G.; Freeman, R.; Yaffe, S. Drugs in Pregnancy and Lactation. 3rd. Baltimore, MD: Williams and Wilkins; 1990.

101. Hadi I, da Silva O, Natale R, Boyd D, Morley-Forster PK. Opioids in the parturient with chronic nonmalignant pain: A retrospective review. J Opioid Manag. 2006; 2(1):31–34. [PubMed: 17319115]

102. Sharpe C, Kuschel C. Outcomes of infants born to mothers receiving methadone for pain management in pregnancy. Arch Dis Child Fetal Neonatal Ed. 2004; 89(1):F33–F36. [PubMed: 14711851]

103. McCarthy JJ, Leamon MH, Parr MS, Anania B. High-dose methadone maintenance in pregnancy: Maternal and neonatal outcomes. Am J Obstet Gynecol. 2005; 193(3 Pt 1):606–610. [PubMed: 16150249]

104. Hussain T, Ewer AK. Maternal methadone may cause arrhythmias in neonates. Acta Paediatr. 2007; 96(5):768–769. [PubMed: 17376175]

105. Ito S. Drug therapy for breast-feeding women. N Engl J Med. 2000; 343(2):118–126. [PubMed: 10891521]

106. Seaton S, Reeves M, McLean S. Oxycodone as a component of multimodal analgesia for lactating mothers after Caesarean section: Relationships between maternal plasma, breast milk and neonatal plasma levels. Aust N Z J Obstet Gynaecol. 2007; 47(3):181–185. [PubMed: 17550483]

107. Sauberan JB, Anderson PO, Lane JR, et al. Breast milk hydrocodone and hydromorphone levels in mothers using hydrocodone for postpartum pain. Obstet Gynecol. 2011; 117(3):611–617. [PubMed: 21343764]

108. Madadi P, Shirazi F, Walter FG, Koren G. Establishing causality of CNS depression in breastfed infants following maternal codeine use. Paediatr Drugs. 2008; 10(6):399–404. [PubMed: 18998750]

109. Willmann S, Edginton AN, Coboeken K, Ahr G, Lippert J. Risk to the breast-fed neonate from codeine treatment to the mother: A quantitative mechanistic modeling study. Clin Pharmacol Ther. 2009; 86(6):634–643. [PubMed: 19710640]

110. Madadi P, Koren G, Cairns J, et al. Safety of codeine during breastfeeding: Fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine. Can Fam Physician. 2007; 53(1):33–35. [PubMed: 17872605]

111. Madadi P, Ciszkowski C, Gaedigk A, et al. Genetic transmission of cytochrome P450 2D6 (CYP2D6) ultrarapid metabolism: Implications for breastfeeding women taking codeine. Curr Drug Saf. 2011; 6(1):36–39. [PubMed: 21241245]

112. Transfer of drugs and other chemicals into human milk. Pediatrics. 2001; 108(3):776–789. [PubMed: 11533352]

113. Bar-Oz B, Bulkowstein M, Benyamini L, et al. Use of antibiotic and analgesic drugs during lactation. Drug Saf. 2003; 26(13):925–935. [PubMed: 14583068]

114. FDA. [(accessed October 2011)] FDA public health advisory. Use of codeine by some breastfeeding mothers may lead to life-threatening side effects in nursing babies. 2007. Available at: http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm054717.htm

115. Madadi P, Moretti M, Djokanovic N, et al. Guidelines for maternal codeine use during breastfeeding. Can Fam Physician. 2009; 55(11):1077–1078. [PubMed: 19910591]

116. MacDonald N, MacLeod SM. Has the time come to phase out codeine? CMAJ. 2010; 182(17): 1825. [PubMed: 20921244]

117. Handal M, Engeland A, Ronning M, Skurtveit S, Furu K. Use of prescribed opioid analgesics and co-medication with benzodiazepines in women before, during, and after pregnancy: A population-based cohort study. Eur J Clin Pharmacol. 2011; 67(9):953–960. [PubMed: 21484468]

118. Stramba-Badiale M, Spagnolo D, Bosi G, Schwartz PJ. Are gender differences in QTc present at birth? MISNES Investigators. Multicenter Italian Study on Neonatal Electrocardiography and Sudden Infant Death Syndrome. Am J Cardiol. 1995; 75(17):1277–1278. [PubMed: 7778558]
119. Pickham D, Helfenbein E, Shinn JA, et al. High prevalence of corrected QT interval prolongation in acutely ill patients is associated with mortality: Results of the QT in Practice (QTIP) study. Crit Care Med. 2012; 40(2):394–399. [PubMed: 22001585]
120. Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. JAMA. 1993; 270(21):2590–2597. [PubMed: 8230644]
121. Benton RE, Sale M, Flockhart DA, Woosley RL. Greater quinidine-induced QTc interval prolongation in women. Clin Pharmacol Ther. 2000; 67(4):413–418. [PubMed: 10801251]
122. Rautaharju PM, Zhou SH, Wong S, et al. Sex differences in the evolution of the electrocardiographic QT interval with age. Can J Cardiol. 1992; 8(7):690–695. [PubMed: 1422988]
123. Stringer J, Welsh C, Tommasello A. Methadone-associated Q–T interval prolongation and torsades de pointes. Am J Health Syst Pharm. 2009; 66(9):825–33. [PubMed: 19386945]
124. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment: The CSAT consensus guideline. Ann Intern Med. 2009; 150(6):387–395. [PubMed: 19153406]
125. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment. Ann Intern Med. 2009; 150(6):387–395. [PubMed: 19153406]
126. Martin JA, Campbell A, Killip T, et al. QT interval screening in methadone maintenance treatment: Report of a SAMHSA expert panel. J Addict Dis. 2011; 30(4):283–306. [PubMed: 22026519]
127. Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC. QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. Arch Intern Med. 2007; 167(22):2469–2475. [PubMed: 18071169]
128. Fanoe S, Jensen GB, Sjogren P, Korsgaard MP, Grunnet M. Oxycodone is associated with dose-dependent QTc prolongation in patients and low-affinity inhibiting of hERG activity in vitro. Br J Clin Pharmacol. 2009; 67(2):172–179. [PubMed: 19159406]
129. Fishbain DA, Cole B, Lewis JE, Gao J. What is the evidence for chronic pain being etiologically associated with the DSM-IV category of sleep disorder due to a general medical condition? A structured evidence-based review. Pain Med. 2010; 11(2):158–179. [PubMed: 19788712]
130. Roehrs TA. Workshop Participants. Does effective management of sleep disorders improve pain symptoms? Drugs. 2009; 69(suppl 2):5–11. [PubMed: 20047347]
131. Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. Sleep Med Rev. 2004; 8(2):119–132. [PubMed: 15033151]
132. Tang NKY, Wright KJ, Salkovskis PM. Prevalence and correlates of clinical insomnia co-occurring with chronic back pain. J Sleep Res. 2007; 16(1):85–95. [PubMed: 17309767]
133. Viala-Danten M, Martin S, Guillemin I, Hays RD. Evaluation of the reliability and validity of the Medical Outcomes Study sleep scale in patients with painful diabetic peripheral neuropathy during an international clinical trial. Health Qual Life Outcomes. 2008; 6:113. [PubMed: 19091084]
134. Crawford BK, Piault EC, Lai C, Sarzi-Puttini P. Assessing sleep in fibromyalgia: Investigation of an alternative scoring method for the Jenkins Sleep Scale based on data from randomized controlled studies. Clin Exp Rheumatol. 2010; 28(6 suppl 63):S100–S109. [PubMed: 21176429]
135. Theadom A, Cropley M. “This constant being woken up is the worst thing”—Experiences of sleep in fibromyalgia syndrome. Disabil Rehabil. 2010; 32(23):1939–1947. [PubMed: 20919892]
136. O’Donoghue GM, Fox N, Heneghan C, Hurley DA. Objective and subjective assessment of sleep in chronic low back pain patients compared with healthy age and gender matched controls: A pilot study. BMC Musculoskelet Disord. 2009; 10:122. [PubMed: 19799778]

137. Hawker GA, French MR, Waugh EJ, et al. The multidimensionality of sleep quality and its relationship to fatigue in older adults with painful osteoarthritis. Osteoarthritis Cartilage. 2010; 18(11):1365–1371. [PubMed: 20708004]

138. Smith MT, Edwards RR, McCann UD, Haythornthwaite JA. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. Sleep. 2007; 30(4):494–505. [PubMed: 17520794]

139. Lautenbacher S, Rollman GB. Possible deficiencies of pain modulation in fibromyalgia. Clin J Pain. 1997; 13(3):189–196. [PubMed: 9303250]

140. Turk DC, Cohen MJM. Sleep as a marker in the effective management of chronic osteoarthritis pain with opioid analgesics. Semin Arthritis Rheum. 2010; 39(6):477–490. [PubMed: 19136144]

141. Brennan MJ, Lieberman JA 3rd. Sleep disturbances in patients with chronic pain: Effectively managing opioid analgesia to improve outcomes. Curr Med Res Opin. 2009; 25(5):1045–1055. [PubMed: 19292602]

142. Alattar MA, Scharf SM. Opioid-associated central sleep apnea: A case series. Sleep Breath. 2009; 13(2):201–206. [PubMed: 18807080]

143. Dimsdale JE, Norman D, DeJardin D, Wallace MS. The effect of opioids on sleep architecture. J Clin Sleep Med. 2007; 3(1):33–36. [PubMed: 17557450]

144. Farney RJ, Walker JM, Cloward TV, Rhondeau S. Sleep-disordered breathing associated with long-term opioid therapy. Chest. 2003; 123(2):632–639. [PubMed: 12576394]

145. Guilleminault C, Cao M, Yue HJ, Chawla P. Obstructive sleep apnea and chronic opioid use. Lung. 2010; 188(6):459–468. [PubMed: 20658143]

146. Mogri M, Desai H, Webster L, Grant BJB, Mador MJ. Hypoxemia in patients on chronic opiate therapy with and without sleep apnea. Sleep Breath. 2009; 13(1):49–57. [PubMed: 18683000]

147. Walker JM, Farney RJ, Rhondeau SM, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. J Clin Sleep Med. 2007; 3(5):455–461. [Erratum appears in J Clin Sleep Med 2007;3(6):Table of contents]. [PubMed: 17803007]

148. Wang D, Teichtahl H. Opioids, sleep architecture and sleep-disordered breathing. Sleep Med Rev. 2007; 11(1):35–46. [PubMed: 17141540]

149. Webster LR, Choi Y, Desai H, Webster L, Grant BJB. Sleep-disordered breathing and chronic opioid therapy. Pain Med. 2008; 9(4):425–432. [PubMed: 18489633]

150. Al Lawati NM, Patel SR, Ayas NT. Epidemiology, risk factors, and consequences of obstructive sleep apnea and short sleep duration. Prog Cardiovasc Dis. 2009; 51(4):285–293. [PubMed: 19110130]

151. Jordan AS, McEvoy RD. Gender differences in sleep apnea: Epidemiology, clinical presentation and pathogenic mechanisms. Sleep Med Rev. 2003; 7(5):377–389. [PubMed: 14573374]

152. Wahner-Roedler DL, Olson EJ, Narayanan S, et al. Gender-specific differences in a patient population with obstructive sleep apnea-hypopnea syndrome. Gend Med. 2007; 4(4):329–338. [PubMed: 18215724]

153. Sharkey KM, Kurth ME, Anderson BJ, et al. Obstructive sleep apnea is more common than central sleep apnea in methadone maintenance patients with subjective sleep complaints. Drug Alcohol Depend. 2010; 108(1–2):77–83. [PubMed: 20079978]

154. Farney RJ, Walker JM, Boyle KM, Cloward TV, Shilling KC. Adaptive servoventilation (ASV) in patients with sleep disordered breathing associated with chronic opioid medications for non-malignant pain. J Clin Sleep Med. 2008; 4(4):311–319. [PubMed: 18763421]

155. Javaheri S, Malik A, Smith J, Chung E. Adaptive pressure support servoventilation: A novel treatment for sleep apnea associated with use of opioids. J Clin Sleep Med. 2008; 4(4):305–310. [PubMed: 18763420]

156. Shaw IR, Lavigne G, Mayer P, Choiniere M. Acute intravenous administration of morphine perturbs sleep architecture in healthy pain-free young adults: A preliminary study. Sleep. 2005; 28(6):677–682. [PubMed: 16477954]

157. Lange T, Dimitrov S, Born J. Effects of sleep and circadian rhythm on the human immune system. Ann N Y Acad Sci. 2010; 1193:48–59. [PubMed: 20398008]

158. Fillingim RB, Doleys DM, Edwards RR, Lowery D. Clinical characteristics of chronic back pain as a function of gender and oral opioid use. Spine. 2003; 28(2):143–150. [PubMed: 12544931]

159. Pergolizzi JV Jr, Labhsetwar SA, Puenpatom RA, et al. Exposure to potential CYP450 pharmacokinetic drug-drug interactions among osteoarthritis patients: Incremental risk of multiple prescriptions. Pain Pract. 2011; 11(4):325–336. [PubMed: 21199317]

160. Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. Am J Surg. 2001; 182(5A suppl):11S–18S. [PubMed: 11755892]

161. Cook IJ, Talley NJ, Benninga MA, Rao SS, Scott SM. Chronic constipation: Overview and challenges. Neurogastroenterol Motil. 2009; 21(suppl 2):1–8. [PubMed: 19824933]

162. Peppas G, Alexiou VG, Mourtzoukou E, Falagas ME. Epidemiology of constipation in Europe and Oceania: A systematic review. BMC Gastroenterol. 2008; 8:5. [PubMed: 18269746]

163. Rosti G, Gatti A, Costantini A, Sabato AF, Zucco F. Opioid-related bowel dysfunction: Prevalence and identification of predictive factors in a large sample of Italian patients on chronic treatment. Eur Rev Med Pharmacol Sci. 2010; 14(12):1045–1050. [PubMed: 21375137]

164. Tuteja AK, Biskupiak J, Stoddard GJ, Lipman AG. Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain. Neurogastroenterol Motil. 2010; 22(4):424–430. e96. [PubMed: 20100280]

165. Bell TJ, Panchal SJ, Miaskowski C, et al. The prevalence, severity, and impact of opioid-induced bowel dysfunction: Results of a US and European Patient Survey (PROBE 1). Pain Med. 2009; 10(1):35–42. [PubMed: 18721170]

166. Hjalte F, Berggren AC, Bergendahl H, Hjortsberg C. The direct and indirect costs of opioid-induced constipation. J Pain Symptom Manage. 2010; 40(5):696–703. [PubMed: 20727708]

167. Bodnar RJ, Kest B. Sex differences in opioid analgesia, hyperalgesia, tolerance and withdrawal: Central mechanisms of action and roles of gonadal hormones. Horm Behav. 2010; 58(1):72–81. [PubMed: 19786031]

168. Dahan A, Kest B, Waxman AR, Sarton E. Sex-specific responses to opiates: Animal and human studies. Anesth Analg. 2008; 107(1):83–95. [PubMed: 18635471]

169. Niesters M, Dahan A, Kest B, et al. Do sex differences exist in opioid analgesia? A systematic review and meta-analysis of human experimental and clinical studies. Pain. 2010; 151(1):61–68. [PubMed: 20692097]

170. South SM, Wright AW, Lau M, Mather LE, Smith MT. Sex-related differences in antinociception and tolerance development following chronic intravenous infusion of morphine in the rat: Modulatory role of testosterone via morphine clearance. J Pharmacol Exp Ther. 2001; 297(1): 446–457. [PubMed: 11259573]

171. Shekunova EV, Bespalov AY. Estrous cycle stage-dependent expression of acute tolerance to morphine analgesia in rats. Eur J Pharmacol. 2004; 486(3):259–264. [PubMed: 14985047]

172. Shekunova EV, Bespalov AY. Effects of memantine on estrogen-dependent acute tolerance to the morphine analgesia in female rats. Eur J Pharmacol. 2006; 535(1–3):78–85. [PubMed: 16546163]

173. Bryant CD, Eitan S, Sinchak K, Fanselow MS, Evans CJ. NMDA receptor antagonism disrupts the development of morphine analgesic tolerance in male, but not female C57BL/6J mice. Am J Physiol Regul Integr Comp Physiol. 2006; 291(2):R315–R326. [PubMed: 16601258]

174. Holtman JR Jr, Sloan JW, Jing X, Wala EP. Modification of morphine analgesia and tolerance by flumazenil in male and female rats. Eur J Pharmacol. 2003; 470(3):149–156. [PubMed: 12798952]

175. Rowbotham MC, Lindsey CD. How effective is long-term opioid therapy for chronic noncancer pain? Clin J Pain. 2007; 23(4):300–302. [PubMed: 17449989]

176. Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R. Frequency of headache is related to sensitization: A population study. Pain. 2006; 123(1–2):19–27. [PubMed: 16630694]

177. Staud R, Nagel S, Robinson ME, Price DD. Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input: A randomized, double-blind, placebo-controlled study. Pain. 2009; 145(1–2):96–104. [PubMed: 19540671]

178. Moshiree B, Price DD, Robinson ME, Gaible R, Verne GN. Thermal and visceral hypersensitivity in irritable bowel syndrome patients with and without fibromy-algia. Clin J Pain. 2007; 23(4): 323–330. [PubMed: 17449993]

179. Colvin LA, Fallon MT. Opioid-induced hyperalgesia: A clinical challenge. Br J Anaesth. 2010; 104(2):125–127. [PubMed: 20086062]
180. Konopka KH, van Wijhe M. Opioid-induced hyperalgesia: Pain hurts? Br J Anaesth. 2010; 105(5):555–557. [PubMed: 20952429]
181. Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: Molecular mechanisms and clinical considerations. Clin J Pain. 2008; 24(6):479–496. [PubMed: 18574358]
182. Compton P, Charuvastra VC, Ling W. Pain intolerance in opioid-maintained former opiate addicts: Effect of long-acting maintenance agent. Drug Alcohol Depend. 2001; 63(2):139–146. [PubMed: 11376918]
183. Compton P, Charuvastra VC, Kintaudi K, Ling W. Pain responses in methadone-maintained opioid abusers. J Pain Symptom Manage. 2000; 20(4):237–245. [PubMed: 11027904]
184. Compton P. Pain tolerance in opioid addicts on and off naltrexone pharmacotherapy: A pilot study. J Pain Symptom Manage. 1998; 16(1):21–28. [PubMed: 9707654]
185. Hay JL, White JM, Bochner F, et al. Hyperalgesia in opioid-managed chronic pain and opioid-dependent patients. J Pain. 2009; 10(3):316–322. [PubMed: 19101210]
186. Siniscalchi A, Piraccini E, Miklosova Z, et al. Opioid-induced hyperalgesia and rapid opioid detoxification after tacrolimus administration. Anesth Analg. 2008; 106(2):645–646. table of contents. [PubMed: 18227327]
187. Baron MJ, McDonald PW. Significant pain reduction in chronic pain patients after detoxification from high-dose opioids. J Opioid Manag. 2006; 2(5):277–282. [PubMed: 17319259]
188. Crisostomo RA, Schmidt JE, Hooten WM, et al. Withdrawal of analgesic medication for chronic low-back pain patients: Improvement in outcomes of multidisciplinary rehabilitation regardless of surgical history. Am J Phys Med Rehabil. 2008; 87(7):527–536. [PubMed: 18574345]
189. Hooten WM, Mantilla CB, Sandroni P, Townsend CO. Associations between heat pain perception and opioid dose among patients with chronic pain undergoing opioid tapering. Pain Med. 2010; 11(11):1587–1598. [PubMed: 21029354]
190. Compton P, Kehoe P, Sinha K, Torrington MA, Ling W. Gabapentin improves cold-pressor pain responses in methadone-maintained patients. Drug Alcohol Depend. 2008; 109(1–3):213–219. [PubMed: 20163921]
191. Kapural L, Kapural M, Bensitel T, Sessler DI. Opioid-sparing effect of intravenous outpatient ketamine infusions appears short-lived in chronic-pain patients with high opioid requirements. Pain Physician. 2010; 13(4):389–394. [PubMed: 20648208]
192. Lee M, Silverman SM, Hansen H, Patel VB, Manchi-kanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011; 14(2):145–161. [PubMed: 21412369]
193. Schneider JP, Kirsh KL. Defining clinical issues around tolerance, hyperalgesia, and addiction: A quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. J Opioid Manag. 2010; 6(6):385–395. [PubMed: 21268999]
194. Bannister K, Dickenson AH. Opioid hyperalgesia. Curr Opin Support Palliat Care. 2010; 4(1):1–5. [PubMed: 20019618]
195. Silverman SM. Opioid induced hyperalgesia: Clinical implications for the pain practitioner. Pain Physician. 2009; 12(3):679–684. [PubMed: 19461836]
196. Fishbain DA, Cole B, Lewis JE, Gao J, Rosomoff RS. Do opioids induce hyperalgesia in humans? An evidence-based structured review. Pain Med. 2009; 10(5):829–839. [PubMed: 19594845]
197. Mitra S. Opioid-induced hyperalgesia: Pathophysiology and clinical implications. J Opioid Manag. 2008; 4(3):123–130. [PubMed: 18717507]
198. Angst MS, Clark JD. Opioid-induced hyperalgesia: A qualitative systematic review. Anesthesiology. 2006; 104(3):570–587. [PubMed: 16508405]
199. Bekhit MH. Opioid-induced hyperalgesia and tolerance. Am J Ther. 2010; 17(5):498–510. [PubMed: 20844348]
200. Reznikov I, Pud D, Eisenberg E. Oral opioid administration and hyperalgesia in patients with cancer or chronic nonmalignant pain. Br J Clin Pharmacol. 2005; 60(3):311–318. [PubMed: 16120071]

201. Cohen SP, Christo PJ, Wang S, et al. The effect of opioid dose and treatment duration on the perception of a painful standardized clinical stimulus. Reg Anesth Pain Med. 2008; 33(3):199–206. [PubMed: 18433669]
202. Chen L, Malarick C, Seefeld L, et al. Altered quantitative sensory testing outcome in subjects with opioid therapy. Pain. 2009; 143(1–2):65–70. [PubMed: 19237249]
203. Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: A preliminary prospective study. J Pain. 2006; 7(1):43–48. [PubMed: 16414554]
204. Compton PA, Ling W, Torrington MA. Lack of effect of chronic dextromethorphan on experimental pain tolerance in methadone-maintained patients. Addict Biol. 2008; 13(3–4):393–402. [PubMed: 18507735]
205. Ram KC, Eisenberg E, Haddad M, Pud D. Oral opioid use alters DNIC but not cold pain perception in patients with chronic pain—New perspective of opioid-induced hyperalgesia. Pain. 2008; 139(2):431–438. [PubMed: 18583047]
206. Simoni-Wastila L. The use of abusable prescription drugs: The role of gender. J Womens Health Gend Based Med. 2000; 9(3):289–297. [PubMed: 10787224]
207. Daiber A, Munzel T, Gori T. Organic nitrates and nitrate tolerance—State of the art and future developments. Adv Pharmacol. 2010; 60:177–227. [PubMed: 21081219]
208. Morikawa Y, Mizuno Y, Harada E, et al. Nitrate tolerance as a possible cause of multidrug-resistant coronary artery spasm. Int Heart J. 2010; 51(3):211–213. [PubMed: 20558913]
209. Tompkins DA, Bigelow GE, Harrison JA, et al. Concurrent validation of the Clinical Opiate Withdrawal Scale (COWS) and single-item indices against the Clinical Institute Narcotic Assessment (CINA) opioid withdrawal instrument. Drug Alcohol Depend. 2009; 105(1–2):154–159. [PubMed: 19647958]
210. Giacomuzzi SM, Riemer Y, Ertl M, et al. Gender differences in health-related quality of life on admission to a maintenance treatment program. Eur Addict Res. 2005; 11(2):69–75. [PubMed: 15785067]
211. Papaleontiou M, Henderson CR Jr, Turner BJ, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: A systematic review and meta-analysis. J Am Geriatr Soc. 2010; 58(7):1353–1369. [PubMed: 20533971]
212. Won A, Lapane KL, Vallow S, et al. Long-term effects of analgesics in a population of elderly nursing home residents with persistent nonmalignant pain. J Ger-ontol A Biol Sci Med Sci. 2006; 61(2):165–169.
213. Saunders KW, Dunn KM, Merrill JO, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. J Gen Intern Med. 2010; 25(4):310–315. [PubMed: 20049546]
214. Miller M, Sturmer T, Azrael D, Levin R, Solomon DH. Opioid analgesics and the risk of fractures in older adults with arthritis. J Am Geriatr Soc. 2011; 59(3):430–438. [PubMed: 21391934]
215. Roth SH, Fleischmann RM, Burch FX, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: Placebo-controlled trial and long-term evaluation. Arch Intern Med. 2000; 160(6):853–860. [PubMed: 10737286]
216. Blalock SJ, Casteel C, Roth MT, et al. Impact of enhanced pharmacologic care on the prevention of falls: A randomized controlled trial. Am J Geriatr Pharmacother. 2010; 8(5):428–440. [PubMed: 21335296]
217. VanDenKerkhof EG, Hopman WM, Goldstein DH, et al. Impact of perioperative pain intensity, pain qualities, and opioid use on chronic pain after surgery: A prospective cohort study. Reg Anesth Pain Med. 2012; 37(1):19–27. [PubMed: 22157741]
218. Zywiel MG, Stroh DA, Lee SY, Bonutti PM, Mont MA. Chronic opioid use prior to total knee arthroplasty. J Bone Joint Surg Am. 2011; 93(21):1988–1993. [PubMed: 22048093]
219. Kirpalani D, Mitra R. Is chronic opioid use a negative predictive factor for response to cervical epidural steroid injections? J Back Musculoskeletal Rehabil. 2011; 24(3):123–127.
220. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA. 2011; 305:1315–1321. [PubMed: 21467284]

221. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: A cohort study. Ann Intern Med. 2010; 152(2):85–92. [PubMed: 20083827]
222. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med. 2011; 171(7):686–691. [PubMed: 21482846]
223. Prosser JM, Perrone J, Pines JM. The epidemiology of intentional non-fatal self-harm poisoning in the United States: 2001–2004. J Med Toxicol. 2007; 3(1):20–24. [PubMed: 18072154]
224. Cox S, Kuo C, Jamieson DJ, et al. Poisoning hospi-talisations among reproductive-aged women in the USA, 1998–2006. Inj Prev. 2011; 17(5):332–337. [PubMed: 21296799]
225. Coben JH, Davis SM, Furbee PM, et al. Hospitaliza-tions for poisoning by prescription opioids, sedatives, and tranquilizers. Am J Prev Med. 2010; 38(5):517–524. [PubMed: 20409500]
226. Wisniewski AM, Purdy CH, Blondell RD. The epidemiologic association between opioid prescribing, non-medical use, and emergency department visits. J Addict Dis. 2008; 27(1):1–11. [PubMed: 18551883]
227. Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA. 2008; 300(22):2613–2620. [PubMed: 19066381]
228. Doan BD, Wadden NP. Relationships between depressive symptoms and descriptions of chronic pain. Pain. 1989; 36(1):75–84. [PubMed: 2919097]
229. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: A literature review. Arch Intern Med. 2003; 163(20):2433–2445. [PubMed: 14609780]
230. Sullivan MD, Edlund MJ, Steffick D, Unutzer J. Regular use of prescribed opioids: Association with common psychiatric disorders. Pain. 2005; 119(1–3):95–103. [PubMed: 16298066]
231. Hanson KA, Loftus EV Jr, Harmsen WS, et al. Clinical features and outcome of patients with inflammatory bowel disease who use narcotics: A case-control study. Inflamm Bowel Dis. 2009; 15(5):772–777. [PubMed: 19107782]
232. Sullivan MD, Edlund MJ, Zhang L, Unutzer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. Arch Intern Med. 2006; 166(19):2087–2093. [PubMed: 17060538]
233. Von Korff M, Dworkin SF, Le Resche L, Kruger A. An epidemiologic comparison of pain complaints. Pain. 1988; 32(2):173–183. [PubMed: 3362555]
234. Demyttenaere K, Bruffaerts R, Lee S, et al. Mental disorders among persons with chronic back or neck pain: Results from the World Mental Health Surveys. Pain. 2007; 129(3):332–342. [PubMed: 17350169]
235. Schieir O, Thombs BD, Hudson M, et al. Symptoms of depression predict the trajectory of pain among patients with early inflammatory arthritis: A path analysis approach to assessing change. J Rheumatol. 2009; 36(2):231–239. [PubMed: 19132790]
236. Jensen MK, Thomsen AB, Hojsted J. 10-year follow-up of chronic non-malignant pain patients: Opioid use, health related quality of life and health care utilization. Eur J Pain. 2006; 10(5):423–433. [PubMed: 16054407]
237. Seehusen DA. Opioid therapy for chronic noncancer pain. Am Fam Physician. 2010; 82(1):40. [PubMed: 20590067]
238. Wasan AD, Davar G, Jamison R. The association between negative affect and opioid analgesia in patients with discogenic low back pain. Pain. 2005; 117(3):450–461. [PubMed: 16154274]
239. Dworkin RH, Turk DC, Peirce-Sandner S, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. Pain. 2010; 149(2):177–193. [PubMed: 20207481]
240. Ciccone DS, Just N, Bandilla EB, et al. Psychological correlates of opioid use in patients with chronic non-malignant pain: A preliminary test of the downhill spiral hypothesis. J Pain Symptom Manage. 2000; 20(3):180–192. [PubMed: 11018336]
241. Breckenridge J, Clark JD. Patient characteristics associated with opioid vs nonsteroidal anti-inflammatory drug management of chronic low back pain. J Pain. 2003; 4(6):344–350. [PubMed: 14622692]

242. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey I: Lifetime prevalence, chronicity and recurrence. J Affect Disord. 1993; 29(2–3):85–96. [PubMed: 8300981]

243. Munce SE, Stewart DE. Gender differences in depression and chronic pain conditions in a national epidemiologic survey. Psychosomatics. 2007; 48(5):394–399. [PubMed: 17878497]

244. Edlund MJ, Martin BC, Fan MY, et al. An analysis of heavy utilizers of opioids for chronic noncancer pain in the TROUP study. J Pain Symptom Manage. 2010; 40(2):279–289. [PubMed: 20579834]

245. Colasanti A, Rabiner EA, Lingford-Hughes A, Nutt DJ. Opioids and anxiety. J Psychopharmacol. 2011; 25(11):1415–1433. [PubMed: 20530588]

246. Severeijns R, Vlaeyen JW, van den Hout MA, Weber WE. Pain catastrophizing predicts pain intensity, disability, and psychological distress independent of the level of physical impairment. Clin J Pain. 2001; 17(2):165–172. [PubMed: 11444718]

247. Spinhoven P, Ter Kuile M, Kole-Snijders AM, et al. Catastrophizing and internal pain control as mediators of outcome in the multidisciplinary treatment of chronic low back pain. Eur J Pain. 2004; 8(3):211–219. [PubMed: 15109971]

248. Jensen MP, Turner JA, Romano JM. Changes in beliefs, catastrophizing, and coping are associated with improvement in multidisciplinary pain treatment. J Consult Clin Psychol. 2001; 69(4):655–662. [PubMed: 11550731]

249. Pavlin DJ, Sullivan MJ, Freund PR, Roesen K. Catastrophizing: A risk factor for postsurgical pain. Clin J Pain. 2005; 21(1):83–90. [PubMed: 15599135]

250. Keefe FJ, Lefebvre JC, Egert JR, et al. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: The role of catastrophizing. Pain. 2000; 87(3):325–334. [PubMed: 10963912]

251. Weissman-Fogel I, Sprecher E, Pud D. Effects of catastrophizing on pain perception and pain modulation. Exp Brain Res. 2008; 186(1):79–85. [PubMed: 18030455]

252. Thibault P, Loisel P, Durand MJ, Catchlove R, Sullivan MJ. Psychological predictors of pain expression and activity intolerance in chronic pain patients. Pain. 2008; 139(1):47–54. [PubMed: 18430518]

253. Haythornthwaite JA, Clark MR, Pappagallo M, Raja SN. Pain coping strategies play a role in the persistence of pain in post-herpetic neuralgia. Pain. 2003; 106(3):453–460. [PubMed: 14659529]

254. Martin MY, Bradley LA, Alexander RW, et al. Coping strategies predict disability in patients with primary fibromyalgia. Pain. 1996; 68(1):45–53. [PubMed: 9251997]

255. Forsythe ME, Dunbar MJ, Hennigar AW, Sullivan MJ, Gross M. Prospective relation between catastrophizing and residual pain following knee arthroplasty: Two-year follow-up. Pain Res Manag. 2008; 13(4):335–341. [PubMed: 18719716]

256. Sullivan M, Tripp DA, Santor D. Gender differences in pain and pain behavior: The role of catastrophizing. Cognit Ther Res. 2000; 24:121–134.

257. Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: Development and validation. Psychol Assess. 1995; 7:524–532.

258. Weissman-Fogel I, Sprecher E, Pud D. Effects of catastrophizing on pain perception and pain modulation. Exp Brain Res. 2008; 186(1):79–85. [PubMed: 18030455]

259. Fillingim RB, Hastie BA, Ness TJ, et al. Sex-related psychological predictors of baseline pain perception and analgesic responses to pentazocine. Biol Psychol. 2005; 69(1):97–112. [PubMed: 15740828]

260. Sullivan MJ, Thorn B, Haythornthwaite JA, et al. Theoretical perspectives on the relation between catastrophizing and pain. Clin J Pain. 2001; 17(1):52–64. [PubMed: 11289089]

261. Edwards RR, Haythornthwaite JA, Sullivan MJ, Fill-ingim RB. Catastrophizing as a mediator of sex differences in pain: Differential effects for daily pain vs laboratory-induced pain. Pain. 2004; 111(3):335–341. [PubMed: 15363877]

262. Bedard G, Reid GJ, Mcgrath P, Chambers CT. Coping and self-medication in a community sample of junior high school students. Pain Res Manag. 1997; 2:145–150.

263. Turk DC, Okifuji A. What factors affect physicians' decisions to prescribe opioids for chronic noncancer pain patients? Clin J Pain. 1997; 13(4):330–336. [PubMed: 9430814]

264. Masson CL, Sorensen JL, Batki SL, et al. Medical service use and financial charges among opioid users at a public hospital. Drug Alcohol Depend. 2002; 66(1):45–50. [PubMed: 11850135]

265. Hooten WM, Townsend CO, Bruce BK, et al. Effects of smoking status on immediate treatment outcomes of multidisciplinary pain rehabilitation. Pain Med. 2009; 10(2):347–355. [PubMed: 18721171]

266. Hooten WM, Shi Y, Gazelka HM, Warner DO. The effects of depression and smoking on pain severity and opioid use in patients with chronic pain. Pain. 2011; 152(1):223–229. [PubMed: 21126821]

267. Wasan AD, Kaptchuk TJ, Davar G, Jamison RN. The association between psychopathology and placebo analgesia in patients with discogenic low back pain. Pain Med. 2006; 7(3):217–228. [PubMed: 16712621]

268. Fillingim RB, Doleys DM, Edwards RR, Lowery D. Spousal responses are differentially associated with clinical variables in women and men with chronic pain. Clin J Pain. 2003; 19(4): 217–224. [PubMed: 12840615]

269. Kidner CL, Mayer TG, Gatchel RJ. Higher opioid doses predict poorer functional outcome in patients with chronic disabling occupational musculoskeletal disorders. J Bone Joint Surg Am. 2009; 91(4):919–927. [PubMed: 19339577]

270. Stover BD, Turner JA, Franklin G, et al. Factors associated with early opioid prescription among workers with low back injuries. J Pain. 2006; 7(10):718–725. [PubMed: 17018332]

271. Krebs EE, Lurie JD, Fanciullo G, et al. Predictors of long-term opioid use among patients with painful lumbar spine conditions. J Pain. 2010; 11(1):44–52. [PubMed: 19628436]

272. Ekholm O, Gronbaek M, Peuckmann V, Sjogren P. Alcohol and smoking behavior in chronic pain patients: The role of opioids. Eur J Pain. 2009; 13(6):606–612. [PubMed: 18774317]

273. Fishbain DA, Lewis JE, Cole B, et al. Variables associated with current smoking status in chronic pain patients. Pain Med. 2007; 8(4):301–311. [PubMed: 17610452]

274. Edlund MJ, Sullivan M, Steffick D, Harris KM, Wells KB. Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? Pain Med. 2007; 8(8):647–656. [PubMed: 18028043]

275. Liebschutz JM, Saitz R, Weiss RD, et al. Clinical factors associated with prescription drug use disorder in urban primary care patients with chronic pain. J Pain. 2010; 11(11):1047–1055. [PubMed: 20338815]

276. Turk DC, Swanson KS, Gatchel RJ. Predicting opioid misuse by chronic pain patients: A systematic review and literature synthesis. Clin J Pain. 2008; 24(6):497–508. [PubMed: 18574359]

277. Cicero TJ, Lynskey M, Todorov A, Inciardi JA, Surratt HL. Co-morbid pain and psychopathology in males and females admitted to treatment for opioid analgesic abuse. Pain. 2008; 139(1):127–135. [PubMed: 18455314]

278. Tetrault JM, Desai RA, Becker WC, et al. Gender and non-medical use of prescription opioids: Results from a national US survey. Addiction. 2008; 103(2):258–268. [PubMed: 18042194]

279. Kelly SM, Schwartz RP, O'Grady KE, et al. Gender differences among in- and out-of-treatment opioid-addicted individuals. Am J Drug Alcohol Abuse. 2009; 35(1):38–42. [PubMed: 19152205]

280. Back SE, Payne RA, Waldrop AE, et al. Prescription opioid aberrant behaviors: A pilot study of sex differences. Clin J Pain. 2009; 25(6):477–484. [PubMed: 19542794]

281. Portenoy RK. Opioid therapy for chronic nonmalignant pain: A review of the critical issues. J Pain Symptom Manage. 1996; 11(4):203–217. [PubMed: 8869456]

282. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. Pain Med. 2008; 9(4):444–459. [PubMed: 18489635]

283. Naliboff BD, Wu SM, Schieffer B, et al. A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. J Pain. 2011; 12(2):288–296. [PubMed: 21111684]

284. Schieffer BM, Pham Q, Labus J, et al. Pain medication beliefs and medication misuse in chronic pain. J Pain. 2005; 6(9):620–629. [PubMed: 16139781]

285. Jamison RN, Butler SF, Budman SH, Edwards RR, Wasan AD. Gender differences in risk factors for aberrant prescription opioid use. J Pain. 2010; 11(4):312–320. [PubMed: 19944648]

286. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. Pain. 2007; 129(3):355–362. [PubMed: 17449178]

287. Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: A prospective cohort study. BMC Health Serv Res. 2006; 6:46. [PubMed: 16595013]

288. Wasan AD, Butler SF, Budman SH, et al. Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. Clin J Pain. 2007; 23(4):307–315. [PubMed: 17449991]

289. Michna E, Ross EL, Hynes WL, et al. Predicting aberrant drug behavior in patients treated for chronic pain: Importance of abuse history. J Pain Symptom Manage. 2004; 28(3):250–258. [PubMed: 15336337]

290. Chabal C, Erjavec MK, Jacobson L, Mariano A, Chaney E. Prescription opiate abuse in chronic pain patients: Clinical criteria, incidence, and predictors. Clin J Pain. 1997; 13(2):150–155. [PubMed: 9186022]

291. Villa P, Valle D, Mancini A, et al. Effect of opioid blockade on insulin and growth hormone (GH) secretion in patients with polycystic ovary syndrome: The heterogeneity of impaired GH secretion is related to both obesity and hyperinsulinism. Fertil Steril. 1999; 71(1):115–121. [PubMed: 9935127]

292. Amin Z, Canli T, Epperson CN. Effect of estrogen-serotonin interactions on mood and cognition. Behav Cogn Neurosci Rev. 2005; 4(1):43–58. [PubMed: 15886402]

293. Amin Z, Epperson CN, Constable RT, Canli T. Effects of estrogen variation on neural correlates of emotional response inhibition. Neuroimage. 2006; 32(1):457–464. [PubMed: 16644236]

294. Kattainen A, Salomaa V, Jula A, et al. Gender differences in the treatment and secondary prevention of CHD at population level. Scand Cardiovasc J. 2005; 39(6):327–333. [PubMed: 16352484]

295. Roxburgh A, Bruno R, Larance B, Burns L. Prescription of opioid analgesics and related harms in Australia. Med J Aust. 2011; 195(5):280–284. [PubMed: 21895598]

296. Gordon A, Rashiq S, Moulin DE, et al. Buprenorphine transdermal system for opioid therapy in patients with chronic low back pain. Pain Res Manag. 2010; 15(3):169–178. [PubMed: 20577660]

297. Hale M, Khan A, Kutch M, Li S. Once-daily OROS hydromorphone ER compared with placebo in opioid-tolerant patients with chronic low back pain. Curr Med Res Opin. 2010; 26(6):1505–1518. [Erratum appears in Curr Med Res Opin 2010;26(8):1904]. [PubMed: 20429852]

298. Hale ME, Ahdieh H, Ma T, Rauck R, Oxymorphone ERSG. Efficacy and safety of OPANA ER (oxymor-phone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: A 12-week, randomized, double-blind, placebo-controlled study. J Pain. 2007; 8(2):175–184. [PubMed: 17145204]

299. Katz N, Rauck R, Ahdieh H, et al. A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naive patients with chronic low back pain. Curr Med Res Opin. 2007; 23(1):117–128. [PubMed: 17257473]

300. Peniston JH, Gould E. Oxymorphone extended release for the treatment of chronic low back pain: A retrospective pooled analysis of enriched-enrollment clinical trial data stratified according to age, sex, and prior opioid use. Clin Ther. 2009; 31(2):347–359. [PubMed: 19302907]

301. Peniston JH, Xiang Q, Gould EM. Factors affecting acceptability of titrated oxymorphone extended release in chronic low back pain—An individual patient analysis. Curr Med Res Opin. 2010; 26(8):1861–1871. [PubMed: 20521870]

302. Rauck RL, Bookbinder SA, Bunker TR, et al. A randomized, open-label study of once-a-day AVINZA (morphine sulfate extended-release capsules) vs twice-a-day OxyContin (oxycodone hydrochloride controlled-release tablets) for chronic low back pain: The extension phase of the ACTION trial. J Opioid Manag. 2006; 2(6):325–328. [PubMed: 17326594]

303. Vorsanger GJ, Xiang J, Gana TJ, Pascual MLG, Fleming RRB. Extended-release tramadol (tramadol ER) in the treatment of chronic low back pain. J Opioid Manag. 2008; 4(2):87–97. [PubMed: 18557165]

Table 1

Studies that examined sex-specific opioid use and risks*

Author (Year; Citation Number)	Design	Summary of Findings/Author Conclusions
Thielke et al. (2010; [82])	Analysis of administrative pharmacy data to calculate changes in prevalence of long-term opioid prescription (≥90 days within a calendar year). Data for private (N = 2,716,163) and Medicaid (N = 115,914) insured patients were compared and analyzed by sex and age.	35–50% increase in long-term opioid prescription between 2000–2005. Doses did not increase. Equal risk for both sexes. Younger women on Medicaid may be more at risk for long-term use and associated iatrogenic consequences. 40–53% increase in long-term use for Medicaid, with the steepest increase in women 18–44 (53.5%; CI = 43.2–63.9%). For privately insured, greatest increase found for women 65 and older (both long- and short-acting opioids).
Jamison et al. (2010; [285])	Sex differences in risk factors for aberrant prescription opioid use were examined. M = 275, F = 335 prescribed opioids completed SOAPP-R screener then interviewed 5 months later with PDUQ screener, urine analysis, and physician behavior checklist for substance misuse (POTQ).	Women scored higher on items relating to psychological distress (men reported more legal and behavioral issues). At 5-month follow-up, women had higher PDUQ scores (prescription drug use questionnaire).
Darnall and Li (2011; [81])	Study examined surgical and psychological factors associated with opioid prescription. Retrospective cross-sectional chart review of women aged 18–45 seeking treatment at a chronic pain clinic (N = 323).	Hysterectomy and pain-related dysfunction were significantly and independently associated with opioid prescription after adjusting for age and pain intensity. More than 85% of women with hysterectomy and pain-related dysfunction had opioid prescription.
Daniell (2008; [68])	Prospective study examined association between endocrinopathy and opioid use. Observational opioid cohort (N = 31) with non-opioid control comparison (N = 42); sample age range 30–75.	Endocrinopathy was observed in pre- and postmenopausal women taking opioids (inhibited ovarian sex hormone and adrenal androgen production, $P < 0.05$). Related consequences for premenopausal women were altered menstrual flow and probable associated reduced fertility.
Handal et al. (2011; [117])	Study examined opioid risks in pregnant women. Population-based cohort study linking two national registries in Norway before, during, and after singleton pregnancy (N = 194,937).	Increased use of postpartum opioids may pose risk. Tramadol the second most frequently prescribed opioid to pregnant women despite lack of safety data. Women taking opioids more likely to be concurrently prescribed benzodiazepines.
Campbell et al. (2010; [18])	Incident and prevalent opioid use retrospectively estimated using health care data from two large health plans (F = 10,508; M = 6,933).	Women had higher opioid use than men; older women had the highest prevalence of long-term opioid use (8–9% in 2005). Women more likely to have concurrent use of sedative-hypnotic medications.
VanDenKerkhof et al. (2012; [217])	Prospective cohort study (N = 433) examined impact of opioid use on chronic pain following gynecologic surgery.	Women taking preoperative opioids were twice as likely to report chronic postsurgical pain than those not taking opioids. Among patients with preoperative pelvic pain, those taking long-term opioids were 30% more likely to report chronic postsurgical pain than those not taking opioids.
Hanson et al. (2009; [231])	Case-controlled cohort study of IBD patients (N = 361) identified 100 IBD patients receiving narcotics (cases); 100 IBD controls were matched to cases.	Women were more likely to be prescribed opioids for IBD pain than were men (64% cases vs 45% controls). Other significant associations included anxiety, depression, history of sexual abuse, and substance abuse.

* As defined by having a sex/gender keyword MeSH term.

SOAPP-R = Screener and Opioid Assessment for Patients with Pain-Revised; PDUQ = Prescription Drug Use Questionnaire; POTQ = Prescription Opioid Therapy Questionnaire.

Table 2

A Medical/physical risks pertaining to both sexes (with between sex comparison)

Medical/Physical Opioid Risks Documented in Both Sexes	Citations (Year; Citation Number)	Type of Evidence (Direct, Indirect)	Increased Risk for Women Compared with Men? Yes, No, Inferred, Not Assessed (NA)
Reduced preventive care (colorectal screenings in those ≥50 years of age)	Buckley et al. (2010; [65])	Direct	NA
Immunosuppression	Vallejo et al. (2004; [66]), review	Indirect	Inferred
Endocrinopathy	Abs et al. (2000; [70])	Direct	See Table 3
	Rhodin et al. (2010; [75])	Direct	NA
	Vuong et al. (2010; [69]), review	Indirect	See Table 3
	Finch et al. (2000; [79])*	Direct	See Table 3
Prolonged QT interval	Benton et al. (2000; [121])	Direct	Yes
	Fanoe et al. (2009; [128])	Direct	NA
Sleep disturbance and sleep-disordered breathing	Wang and Teichtahl (2007; [148]), review Walker et al. (2007; [147])	Direct Direct	NA NA
	Farney et al. (2003; [144]), case series	Direct	NA (N = 3)
Polypharmacy	Campbell et al. (2010; [18])	Direct	Yes
	Parsells Kelly et al. (2008; [3])	Direct	Yes
	Manchikanti (2009)	Direct	Yes
	Boudreau et al. (2009; [19])	Direct	NA, Inferred
Drug : drug interactions	Pergolizzi et al. (2011; [159])	Direct	Yes
Bowel dysfunction	Rosti et al. (2010; [163])	Direct	No
	Tuteja et al. (2010; [164])	Direct	No
	Furlan et al. (2006; [15]), review	Direct	No or NA
	Kalso et al. (2004; [16]), review	Direct	No or NA
	Bell et al. (2009; [165])	Direct	NA
Hyperalgesia	Cohen et al. (2008; [201])	Direct	Yes
	Chen et al. (2009; [202])	Direct	NA
	Hooten et al. (2010; [189])	Direct	NA
	Ram et al. (2008; [205])	Direct	No
Fractures in adults ≥ 65 years	Miller et al. (2011; [214])	Direct	Inferred (sample 84% female)
	Saunders et al. (2010; [213])	Direct	Inferred (sample 65% female)
Poorer surgical outcome	Zywiel et al. (2011; [218])	Direct	NA
	VanDenKerkhof et al. (2012; [217])	Direct	See Table 3
Reduced response to epidural steroid injection	Kirpalani and Mitra (2011; [219])	Direct	NA
Drug : drug interactions	Pergolizzi et al. (2011; [159])	Direct	Yes
Unintentional overdose	Dunn et al. (2010; [221])	Direct	Numeric increase NA
	Hall et al. (2008; [227])	Direct	NA
	Bohnert et al. (2011; [220])	Direct	NA (VA sample 93% male)
	Coben et al. (2010; [225])	Direct	Yes
	Gomes et al. (2011; [222])	Direct	NA

A Medical/physical risks pertaining to both sexes (with between sex comparison)

Medical/Physical Opioid Risks Documented in Both Sexes	Citations (Year; Citation Number)	Type of Evidence (Direct, Indirect)	Increased Risk for Women Compared with Men? Yes, No, Inferred, Not Assessed (NA)
Higher dose	Williams et al. (2008; [32])	Direct	Yes
	Campbell et al. (2010; [18])	Direct	No (risk greater for men)
Poorer function	Kidner et al. (2009; [269])	Direct	No
	Jensen et al. (2006; [236])	Direct	NA
	Turk and Okifuji (1997; [263])	Direct	NA
	Darnall and Li (2011; [81])	Direct	See Table 3

B Behavioral/psychological risks pertaining to both sexes (with between sex comparison)

Psychological Opioid Risks Documented in Both Sexes	Author (Year; Citation Number)	Type of Evidence (Direct, Indirect)	Increased Risk for Women Compared with Men? Yes, No, Inferred, Not Assessed (NA)
Depression	Breckenridge and Clark (2003; [240])	Direct	No
	Jensen et al. (2006; [236])	Direct	No
	Braden et al. (2009; [21])	Direct	NA (data adjusted for gender)
	Sullivan et al. (2006; [232])	Direct	Inferred
	Sullivan et al. (2005; [230])	Direct	No
	Hanson et al. (2009; [231])	Direct	Yes
	Cicero et al. (2009; [20])	Direct	Yes
	Thielke et al. (2010; [82])	Direct	No
Anxiety			
No association	Breckenridge and Clark (2003; [240])	Direct	No
	Jensen et al. (2006; [236])	Direct	No
Positive association	Sullivan et al. (2006; [232])	Direct	No
	Sullivan et al. (2005; [230])	Direct	No
	Hanson et al. (2009; [231])	Direct	Yes
	Cicero et al. (2009; [20])	Direct	Yes
	Thielke et al. (2010; [82])	Direct	No
Catastrophizing Psychological factors	Jensen et al. (2006; [236])	Direct	NA
Predict prescription	Wasan et al. (2007; [288]) (longer duration of prescription)	Direct	No
	Edlund et al. (2010; [22])	Direct	NA
Predict analgesia	Turk and Okifuji (1997; [263])	Direct	NA
	Wasan et al. (2005; [238])	Direct	No
Poorer function	Kidner et al. (2009; [269])	Direct	No
	Jensen et al. (2006; [236])	Direct	NA
	Turk and Okifuji (1997; [263])	Direct	NA
	Darnall and Li (2011; [81])	Direct	See Table 3
Smoking	Stover et al. (2006; [270])	Direct	No
	Krebs et al. (2010; [271])	Direct	No
	Hooten et al. (2011; [266])	Direct	No

B Behavioral/psychological risks pertaining to both sexes (with between sex comparison)

Psychological Opioid Risks Documented in Both Sexes	Author (Year; Citation Number)	Type of Evidence (Direct, Indirect)	Increased Risk for Women Compared with Men? Yes, No, Inferred, Not Assessed (NA)
	Ekholm et al. (2008; [272])	Direct	NA (adjusted for sex)
Abuse/aberrant behaviors	Manchikanti (2007)	Direct	No
	Turk et al. (2008; [276]), review	Direct	No or NA
	Edlund et al. (2010; [22])	Direct	NA
	Sullivan et al. (2010; [23])	Direct	Yes
	Liebschutz et al. (2010; [275])	Direct	No
	Martell et al. (2007; [13]), review	Direct	NA
	Ives et al. (2006; [287])	Direct	No
Doctor shopping* with fatal consequences	Hall et al. (2008; [227])	Direct	Yes

*Intrathecal route.

*Opioid prescriptions from ≥5 physicians at time of death.

Table 3

Medical and psychological risks specific to women

Menstrual Status	Risk Category	Level of Evidence/Risk (Direct, Indirect, Inferred)	Author (Year; Citation Number)
Premenopausal	Amenorrhea/reduced fertility	Direct, indirect, and inferred	Abs et al. (2000; [70]) Daniell et al. (2008; [68]) Vuong et al. (2010; [69]) review
	Teratogenesis	Direct and inferred	Handal et al. (2011; [117])
	Breastfeeding	Direct and indirect	Madadi et al. (2008; [108]) Madadi et al. (2009; [115]) Madadi et al. (2007; [110]) Sauberan et al. (2011; [107]) Handal et al. (2011; [117]) Seaton et al. (2007; [106])
	Sex-specific endocrinopathy	Direct	Abs et al. (2000; [70]) Daniell et al. (2008; [68]) Finch et al. (2000; [79])*
		Indirect and inferred	Vuong et al. (2010; [69]) review
	Predictors for prescription		
	Historical hysterectomy	Direct	Darnall and Li (2011; [81])
	Pain-related dysfunction	Direct	Darnall and Li (2011; [81])
	Polypharmacy in pregnancy	Direct; also inferred fetal risks	Handal et al. (2011; [117])
Pre- and Postmenopausal	Reduced cervical cancer screening between ages 35 and 65	Direct	Buckley et al. (2010; [65])
	High spousal solicitousness predicts greater opioid use	Direct	Fillingim et al. (2003; [268])
	Poorer surgical outcome following gynecological surgery	Direct	VanDenKerkhof et al. (2012; [217])
Postmenopausal	Endocrinopathy	Direct	Abs et al. (2000; [70]) Finch et al. (2000; [79])*
	Older women have highest prevalence of long-term use	Direct	Campbell et al. (2010; [18])
	Fractures	Direct	Miller et al. (2011; [214])

*Intrathecal route.