CHRONIC PAIN, OPIOIDS AND OVARIAN HORMONES

by

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Abstract

Sex differences in pain perception have led researchers to hypothesize that ovarian hormones might mediate these differences. The animal and human literature demonstrates that ovarian hormones modulate pain and its treatments in female rodents as well as women in their reproductive years. While rife with inconsistencies in study design, the general agreement of the clinical literature raises the question as to whether this sex difference and role of ovarian hormones is taken into account in clinical practice. A chart review of 254 patient records of a specialist pain clinic in a large Canadian city revealed sex differences in types of chronic non-cancer pain (CNCP) conditions, treatments, and in sheer numbers of patients. The majority of patients were women in their reproductive years and many had co-occurring pelvic pain. Interestingly, women’s charts included no information on ovarian hormones or phase of the menstrual cycle suggesting that ovarian hormones are an overlooked aspect of CNCP treatment.
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CNCP: Chronic Non-Cancer Pain
TMD: Temporomandibular Disorder
MSP: Musculoskeletal Pain
RA: Rheumatoid Arthritis
IBS: Irritable Bowel Syndrome
UC: Ulcerative Colitis
CD: Crohn’s Disease
CPP: Chronic Pelvic Pain
Ocs: Oral Contraceptives
PPT: Pain Pressure Threshold
VAS: Visual Analogue Scale
PMDS: Premenstrual Distress Syndrome
MM: Menstrual Migraine
TCR: Trigeminocervical Reflex
MA: Migraine with Aura
MO: Migraine without Aura
HRT: Hormonal Replacement Therapy
PMDD: Premenstrual Dysphoric Disorder
MPC: Multiple Pain Conditions.
UOT: Under Opioid Treatment
POU: Problematic Opioid Use
NOT: No Opioid Treatment
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Chapter 1

Introduction

Pain has come to be understood as a disease of its own. Pain is viewed as the body’s protective tool. It is through pain signals which are sent to the brain that the individual is motivated to withdraw from damaging situations to protect a damaged body part while it heals. Nevertheless, sometimes pain persists despite removal of the stimulus and apparent healing of the body. Sometimes pain even arises in the absence of any detectable damage. Therefore, pain that may seem useful at the beginning can—and often does—cause severe problems for patients. Chronic pain is usually not associated with a definitive pathology, and is—most of the time—resistant to most medical treatments.

Chronic pain that is not caused by cancer (CNCP) is not only a notoriously challenging problem, but it is also a growing one for Canadians, estimated to affect between 15% to 29% of the population (Moulin et al., 2002). In fact, CNCP accounts for up to one third of visits to emergency departments in Canada and the United States as a presenting complaint (Todd et al. 2007). Moreover, the cost of chronic pain management is enormous, both to individuals and to society; as it leads to a severe decline in the quality of life and a startling rise in the degree of disability. According to the Chronic Pain Association of Canada, the annual cost of chronic pain, including medical expenses, lost income, and lost productivity was estimated to exceed $10 billion, in 2010 (Reitsma et al., 2008). The reason behind this enormous economic repercussion is that CNCP is often inadequately assessed and treated; leaving many patients struggling everyday against the limitations imposed by their pain. Even though, the medical use of the most potent analgesic drug — opioids — for pain treatment has increased recently, the evidence for
effectiveness of opioids in managing CNCP is still undetermined. Therefore, pain research is exerting continuous efforts to enhance our understanding for this complex condition and to help individuals with CNCP manage their pain more effectively.

1.1 Pain

Pain has been defined according to the International Association for the Study of Pain as “an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (IASP, 2001; Bonica, 1979). In the healthy person, acute pain always acts as a warning signal for possible damage. Chronic pain, on the other hand, does not function in most cases as a warning sign. In the case of chronic pain, pain is usually not associated with a definitive pathology and the degree of pain usually does not reflect at all the severity of the original tissue damage.

1.2 Chronic Pain

1.2.1 Definition

Chronic pain (CP) is typically defined as “Pain lasting longer than 3 months or beyond the expected period of healing of tissue pathology; where pain is not correlated with the amount of damage and symptoms can persist long after tissue damage from an antecedent injury resolves. Chronic pain can develop as a result of persistent stimulation of or changes to nociceptors due to localized tissue damage from an acute injury or disease, or damage to the peripheral or central nervous system, or both” (Turk et al., 2011).
Chronic pain is generally separated into two categories based on whether or not it is caused by cancer (Ashburn & Staats, 1999; Jacobson & Mariano, 2001; Merskey, 1986; Russo & Brose, 1998; Schaible & Richter, 2004). Pain whose cause is not related to cancer is called chronic non-cancer pain (CNCP). CNCP is usually presented as an assorted set of chronic pain conditions that includes: migraine headache, temporomandibular disorder (TMD), fibromyalgia, rheumatoid arthritis (RA) and a variety of chronic pelvic pains (CPP), including endometriosis, irritable bowel syndrome (IBS), ulcerative colitis (UC), crohn’s disease (CD) and menstrual pain.

### 1.2.2 Prevalence

CNCP is the most common reason for seeking health care. In fact, CNCP accounts for up to one-third of visits to emergency departments in Canada and the United States as a presenting complaint (Todd et al. 2007). Many Canadian studies have reported estimates of the prevalence as high as 29% (Moulin et al., 2002). Growing evidence shows that approximately 17% of Canadians—3.9 million individuals aged 15 years and older—suffer from CNCP and suboptimal pain management (Moulin et al., 2002).

### 1.2.3 Health and Economic Impact

CNCP is associated with significant economic, societal, and health impact. The cost of uncontrolled chronic pain is enormous, both to individuals and to society; as it leads to a severe decline in the quality of life and a startling rise in the incidence of disability. In 2010, the Chronic Pain Association of Canada reported that, “…the annual cost of chronic pain, including medical expenses, lost income, and lost productivity, but not the social costs, is estimated to exceed $10 billion.” (Reitsma et al., 2008).
The repercussions of CNCP on the economy and health as well as its shockingly high prevalence coupled with long life expectancy are important reasons for studying this complex condition in order to devise better treatments.

1.2.4 Management

CNCP management is a clinical challenge. Even though pain is one of the most common reasons for seeking health care, CNCP is usually difficult to assess and rarely respond to the usual forms of medical management. Available treatments of CNCP are antidepressant medications, anticonvulsants, nerve blocks, local steroid injections, Botox injections, physiotherapy, massage, acupuncture, psychotherapy, mindfulness, chiropractic, and opioid analgesics. However, nothing has actually proved its effectiveness in curing CNCP; and no matter the kind of treatment, it more often than not fails to achieve adequate relief.

In the realm of pain medications, opioids are considered the most potent of pain treatment. During the last 25 years, the medical use of the four most common opioids used for pain treatment has increased. For example: morphine 73%, hydromorphone 96%, fentanyl 226%, hydrocodone 244%, and oxycodone 403% (Joranson et al., 2000; Gilson et al., 2004). Despite this rise, the use of opioids in pain management is always met with considerable resistance and debate because opioids are addictive as well as analgesic and some patients will develop physical dependence after long term use. For this reason, unlike the use of opioids to manage pain associated with cancer which has been well validated, the use of opioids in CNCP has been always associated with concerns about efficacy, safety, and the possibility of problematic opioid misuse (Savage, 1996; Bendtsen et al., 1999; Sjøgren et al., 2000; Breivik, 2001; Ballantyne & Mao, 2003). Therefore, despite the fact that opioids are the most potent analgesia, its effectiveness and use in treating CNCP is undetermined.
1.2.5 CNCP and Opioids

Balancing between risks and benefits of opioid use in CNCP management is challenging (Gallagher and Rosenthal, 2008; Ballantyne, 2007). Health care providers must always consider whether or not it is really worthwhile to prescribe opioid medication. Physicians must always consider the risk of addiction, which patients may not always recognize or divulge. This dilemma regarding opioids use is usually compounded by the complexity nature on CNCP. Therefore, this ambiguous situation has prompted many scientists to study CNCP, and opioids within the same context hoping to reach a better understanding of the nature of chronic pain as well as providing some key information that can be used to deliver more adequacies in pain relief. Recently, pain research has taken important strides toward shedding light on the current state and is increasingly exploring the role of multiple factors in modulating CNCP such as age, genetics, culture, race, and ethnicity. However, one dimension in which most pain research is critically under-informed: the multifaceted and embedded ways in which sex mediate individual experiences of pain and opioids use.

1.3 Sex differences and pain

For decades, sex differences in pain have been an under-researched area of medicine. In the past, most pain studies have only used men or male animals. It was not until 1997 that Health Canada published guidelines for the study designs in clinical trials; these guidelines advocated the inclusion of women at all stages of research and urged their inclusion in sufficient numbers to enable the detection of any significant sex differences. Due to this inclusion of women participants, several differences between males and females in response to pain, including individual’s risk and response to pain treatment have been discovered (Berkley et al., 2002;
LeResche, 2000). Since then and over the last 20 years, a number of experimental pain studies in humans have been carried to investigate sex differences (Procacci et al., 1972; Goolkasian, 1985; Velle, 1987; Lander et al., 1990; Feine et al., 1991; Maixner and Humphrey, 1993; Lautenbacher and Rollman, 1993; Ellermeier and Westphal, 1994; Fillingim and Maixner, 1995). When differences are observed under carefully controlled experimental circumstances, it is often the case that women are more sensitive, have lower thresholds or rate similar stimuli as more painful or have less tolerance for pain stimuli than do men (Paller et al., 2009; Riley et al., 1998; Wiesenfeld-Hallin, 2005).

1.4 Sex differences and Opioids

As in the case of pain itself, sex differences have been observed in the potency and efficacy of pain medications, in particular, opioids. Although, most of our knowledge about sex differences in opioids mainly comes from animal studies, the available human findings also indicate the presence of sex differences. For example, in their literature review, Nisters and colleagues (2010) analyzed data from postoperative pain studies for a variety of surgeries using mu (µ) opioid agonists (e.g., morphine, fentanyl, buprenorphine and meperidine). They reported a significant greater opioid effect in women in comparison to men. Similarly, in a review of postsurgical opioid consumption, Miaskowski et al. (2000) found that in 10 out of 18 studies, women’s doses were significantly lower than men’s. Additionally, in experimental studies in human in which pain was induced using a variety of tests: cold presser, pressure, and electrical pain, researchers reported a significantly greater analgesic effect among women than men (Zacny et al., 2002; Dahan et al., 1998; Sarton et al., 1999).
In addition to μ-opioid agonists like morphine, kappa (κ)–opioid drugs (e.g. pentazocine, nalbuphine, butorphanol) were also studied in this context. Gear et al (1996) reported that pentazocine, which acts predominantly at κ-receptors, produced significantly better postoperative analgesia in females than in males. In another study, Gear et al looked at whether there were sex differences associated with the analgesic efficacy of two other predominantly κ-opioid analgesics, nalbuphine and butorphanol. These were administered to both males and females who underwent surgery for the removal of third molar teeth with both nalbuphine and butorphanol producing significantly greater analgesia in females as compared to males.

Notably, however, no systematic sex effect was observed in one experimental human pain study. In his study, Fillingim (2002) performed an experimental RCT where both men and women were randomly given either pentazocine or placebo after inducing pain pressure, heat pain or ischemic pain. Fillingim found no sex differences in pentazocine analgesia. This suggests that the efficacy and difference in action of analgesics might depend on the type of pain---surgical or experimental---and the mode.

A variety of reasons have been proposed to account for these sex differences reported in both pain and opioids. Several researchers have hypothesized that psychosocial factors such as gender role expectancies, depression, and anxiety account for the greater pain sensitivity among women (Dubreuil et al., 1986; Levine et al., 1991). However, the most frequently investigated factor is sex hormones, in particular, ovarian hormones (Punnet &Herbert, 2000; Denton et al., 2004).
1.5 Ovarian Hormones and the Physiology of the Menstrual Cycle

One significant biological difference between men and women is that the latter build an environment for a fertilized egg and ovulate and the former do not. During women’s reproductive years, this occurs in a cyclic fashion usually referred to as the menstrual cycle. Studies of pain in humans suggest that pain perception and sensitivity in females might vary with the menstrual cycle (see section I. III). The menstrual cycle is a set of physiological changes associated with variations in ovarian hormonal levels that occur due to the ovarian cycle (fig. 1). The menstrual cycle is not the only time that levels of ovarian hormones change. Throughout women’s lives, there are numerous events associated with changes in ovarian hormonal serum levels: pregnancy and post-partum, pre and menopausal periods, as well as the taking of oral contraceptives (OC) and hormonal replacement therapy (HRT) (Ecochard & Gougeon, 2000; Ferin, 1996; Ferin, Jewelewicz, & Warren, 1993).

The menstrual cycle is under the control of the hypothalamic/pituitary/ovarian axis (Ferin, et al., 1993). The regular release of ovarian hormones requires the coordinated activity of: the hypothalamus, which secretes gonadotropin-releasing hormone (GnRH); the pituitary, which secretes luteinizing hormone (LH) and follicle stimulating hormone (FSH); and the ovary, which in turn secretes estrogen and progesterone. The menstrual cycle is commonly divided into four phases: menses, the follicular phase, ovulatory and the luteal phase. The average length of the menstrual cycle is 28 days, with a range of 25-32 days (Ecochard & Gougeon, 2000; Ferin, 1996; Ferin, et al., 1993; Greenberg, Bruess, & Conklin, 2007).

Menstrual cycles are counted from the first day of the shedding of the uterine lining.
(menses, menstrual bleeding). After menses ends, the follicular phase starts, in which both FSH and LH are secreted, and estrogen gradually increases, peaking just before ovulation. Around mid-cycle, a peak in LH leads to the release of small amounts of progesterone. Ultimately, the follicle ruptures, resulting in ovulation and the beginning of the luteal phase. Shortly after ovulation, the corpus luteum forms and itself secretes large amounts of progesterone.

Progesterone peaks during the mid-luteal phase and estrogen increases as well, though this increase is not as high as it was in the follicular phase. These increasing levels of estrogen and progesterone provide negative feedback to the pituitary, resulting in decreased secretion of LH and FSH across the luteal phase. This, in turn, decreases secretion of estrogen and progesterone, which, in the absence of fertilization, leads to the shedding of the uterine lining, menses, and a new menstrual cycle beginning (Ferin, 1996; Ferin, et al., 1993).
For the reasons discussed above, the role of ovarian hormones has been the focus of many experimental pain studies. In their review article, Fillingim and Ness (2000) provided considerable evidence from several studies that sex-related differences in pain responses might be attributed to the fluctuation of ovarian hormones encountered across the menstrual cycle. In another review article examining fluctuations in women’s perception of experimentally induced pain, Riley and colleagues presented a significant body of evidence regarding menstrual cycle related variability in pain perception and pain scores (Riley et al., 1999). In the studies examined,
Experimental pain scores varied in association with the fluctuations of ovarian hormones. Pain scores were higher during phases of low estrogens and were lower during other phases when estrogen was high (Fig. 2). In spite of this strong body of evidence, the mechanisms through which ovarian hormones modulate pain remain obscure.

**Fig. 2**: Schematic showing estrogen and progesterone levels and Pain Scores during a typical 28-day menstrual cycle.
1.7 Mechanisms by which ovarian hormones might modulate pain

Although the mechanisms through which ovarian hormones modulate pain are still unclear, there is a consensus that ovarian hormones have an effect on pain. Estrogens receptors have been identified in peripheral sensory neurons, the spinal cord, and various areas of the brain involved with pain perception (Fig. 3) (Bereiter & Barker, 1980; Fillingim & Ness, 2000; Papka et al., 1997).

![Diagram showing potential sites for ovarian hormonal modulation](image)

**Fig. 3:** Potential sites for ovarian hormonal modulation include the following: (1) peripheral afferent nerve fibers; (2) the spinal cord; (3) higher brain centers (Tavaris & Martins, 2013).
Peripheral afferent nerve fibers: Primary afferent nerve fibers are responsible for transmitting nociceptive impulses from the periphery to the spinal cord. In animal studies, changes were reported in pain sensitivity at these peripheral fibers after administering different amounts of estrogens. Therefore they concluded that estrogens affect nociception at the level of the primary afferent nerve fibers (Fillingim & Ness, 2000). These studies also found that estrogens might modulate signal transduction and the transmission of nociceptive information (Aloisi, 2003; Bereiter & Barker, 1980; Bradshaw & Berkley, 2000; Papka, et al., 1997; Taleghany et al., 1999).

In the spinal cord, estrogen receptors have been identified in the substantia gelatinosa and in the area surrounding the central canal. In animal studies, the density of estrogen receptors changed in tandem with changes in estrogen levels over the estrous cycle in rats, suggesting that these receptors might be estrogen sensitive (Aloisi, 2003; Amandusson et al., 1995). Additionally, estrogen receptors were found to be located in the dorsal root ganglia where peripheral afferent nerve fibers usually relay nociceptive signals, suggesting that any changes in the density of these estrogen sensitive receptors might modulate pain sensitivity (Aloisi, 2003; Amandusson & Blomqvist, 2001; Amandusson, et al., 1995).

In the brain, animal studies showed that estrogen receptors were prevalent in regions that modulate pain perception, such as the: periaqueductal grey, thalamus, medial and cortical amygdaloid nuclei, and mesencephalic central gray. Similarly, neurons in the ventral tegmental area, locus ceruleus, and dorsal raphe had also been reported to synthesize estrogens in varying amounts (Shughrue, Lane, & Merchenthaler, 1997; Simerly, Chang, Muramatsu, & Swanson,
1990; Stumpf, Sar, & Keefer, 1975), which again suggest that any change in estrogen levels might affect the activation of these brain areas and hence, pain perception (Aloisi, 2003).

Additionally, ovarian hormones were found to affect pain perception by modulating numerous neurotransmitters including serotonin, dopamine, β-endorphins and γ-amino-butyric acid (GABA). In fact, the interaction between estrogen and GABA was documented to be one of the most important mechanisms in modulating pain as GABA is one of the important neuromodulators in pain sensation (Aloisi, 2003; Kelly, Loose, & Ronneklev, 1992; Shughrue & Merchenthaler, 2000). Moreover, several animal studies showed that estrogen (i) increased glutamic acid decarboxylase (GAD, an enzyme necessary for GABA synthesis) activity in neurons, (ii) induced GABA release, (iii) upregulated GABA receptors, and (iv) increased the GABA receptor binding affinity (Kelly, et al., 1992; Saleh & Saleh, 2001; Shughrue & Merchenthaler, 2000).

Animal studies also reported that ovarian hormones might affect other neurotransmitters involved in the multiple inhibitory and excitatory systems known to control nociceptive signals transmission from the periphery to the central nervous system. These systems had been reported to be affected by changes in the levels of ovarian hormones, which in turn may alter nociceptive responses. Serotonin (5-HT) played a potentiating role in these inhibitory and excitatory systems. In human, studies reported that any declines in 5-HT levels led to a decrease in this inhibitory system which led to more perceived pain. Marcus showed that estrogen regulated 5-HT release and any decline in 5-HT levels was accompanied with a decline in estrogen levels, which in turn reduced the inhibitory system effects of 5-HT (Marcus et al., 1995). This phenomenon was, also, correlated with the occurrence of migraine headaches (Silberstein, 2001).
In sum, while much research is still needed to fully understand the pain pathway as a whole and to identify the mechanisms through which ovarian hormones influence pain perception, ovarian hormones (estrogens in particular) have been found to play a role at several key points along the pain pathway. Changes in estrogen levels have been shown to affect receptor density and expression and thus modulate transmission of pain signals. Additionally, estrogens interact with several important neurotransmitters which have been implicated in modulating pain perception. Thus, the waxing and waning of estrogen levels over the menstrual cycle may be one factor that modulates pain perception.

1.8 Ovarian hormones and opioids

The observation of sex differences in opioid analgesia has raised the question of whether ovarian hormones modulate sensitivity to opioids. Therefore, similar to pain, many researchers have been interested in studying mechanisms through which ovarian hormones might influence sensitivity to opioids. Studies have revealed that ovarian hormones might set the threshold to opioid analgesics both during development of the organism in utero (organizational effects) and/or during adulthood (activational effects) (Sandner-Kiesling & Eisenach, 2002). Additionally, studies reveal that ovarian hormones might modulate opioid analgesia by influencing opioid pharmacokinetics and/or opioid pharmacodynamics.

1.8.1 Organizational effects

Two recent studies demonstrated this role in modulating sensitivity to opioid analgesia in adult rodents (Cicero et al., 2002; Krzanowska et al., 2002). In these studies, female rat pups were de-feminized by the administration of testosterone on postnatal day 1–2; conversely, de-feminization and masculinization were prevented in male rat pups by orchidectomy on postnatal
day 1–2. These manipulations were proven to permanently alter reproductive physiology and behavior in rodents (Sachs & Meisel, 1988; Pfaff & Schwartz-Giblin, 1988). De-feminized female and orchidectomized male rates were then tested for sensitivity to morphine-induced analgesia as adults (approximately 3 months old). The de-feminized females had greater morphine sensitivity than the regular females and equivalent sensitivity compared to normal adult males, whereas the orchidectomized males had less morphine sensitivity than the regular males but equivalent sensitivity compared to normal adult females. In other words, the neonatal gonadal hormone manipulations abolished the sex differences in sensitivity to morphine analgesia normally observed in adults. These studies suggest that the neural substrates involved in opioid analgesia are sensitive to sex hormones during development of the organism.

1.8.2 Activational effects

A significant literature has examined the activational role for sex hormones in modulating opioid analgesia. In general, three different strategies have been employed to examine the activational role of ovarian hormones’ modulation of analgesia: 1. Comparison of analgesia in gonadally intact versus gonadectomized animals; 2. Comparison of analgesia in menopausal humans with and without hormone replacement therapy; and 3. Comparison of analgesia in women at different stages of the menstrual cycle: follicular, ovulatory, luteal and menses (Craft et al., 2004). A review by Craft and his colleagues looking at studies investigating cycle-related changes in opioid analgesia in female rodents, concluded that high levels of estrogen were associated with increased opioid analgesia among gonadally intact cycling female rodents compared to females tested in other stages when levels of estrogen were low (Craft et al., 2004). These studies found that gonadally intact males and gonadectomized males given testosterone showed greater opioid analgesia than did gonadectomized males not receiving hormone.
replacement testosterone. These findings are highly suggestive that activational effects of sex hormones may also contribute to sex differences in analgesia.

Two human studies were performed by Gear and his colleagues in which they administrated nalbuphine, pentazocine and butorphanol to female patients who underwent dental surgery for the removal of their third molars. They compared analgesic response in females with respect to the phase in their menstrual cycle. Women were subdivided into two groups according to number of days after the onset of menses. The analgesic response of those undergoing surgery within 10 days of onset of menses were compared with those undergoing surgery more than 10 days after the onset of menses. Each patient established their pain rating just before (the baseline pain level) and after pentazocine administration. The magnitude of the analgesic effect for each participant was determined as the difference between the pain rating at each time point following opioid administration and the baseline pain rating. Researchers confirmed their previous finding that pentazocine produces greater analgesia in females than in males; however, no significant difference was observed in analgesia among females in different phases of the menstrual cycle (Gear, et al., 1996a).

A different result was reached, however, in a recent study, in which researchers examined the analgesic effect of morphine and pentazocine among healthy women. Sixty-five healthy women, 35 taking oral contraceptives (OCP) and 30 normally cycling underwent experimental pain assessment both before and after intravenous administration of morphine or pentazocine compared to saline placebo. Both active drug and placebo were administered once during the follicular phase and once during the luteal phase. Measures of heat, ischemic, and pressure pain sensitivity were obtained before and after drug administration. Changes in pain scores were recorded to determine morphine and pentazocine analgesic responses and any side effects. Normally cycling women showed slightly lesser pain sensitivity in the follicular compared to
luteal phase, while the reverse pattern emerged for women using OCP. Regarding analgesic responses, normally cycling women showed greater morphine analgesia for pain during the follicular versus the luteal phase (Ribeiro-Dasilva et al., 2011). This study concluded that during phases when estrogen levels are high, pain sensitivity was at its lowest and morphine efficacy was at its highest. These findings suggest that sex hormones influence pain sensitivity as well as opioid responses.

Each of these studies (animal and humans studies) has yielded valuable information about the possible role of ovarian hormones in modulating the efficacy of opioids. However, variations in methodology, determination of menstrual stages by different methods e.g. vaginal cytology, daily diaries or plasma hormonal levels, and animal studies being compared to humans with a different reproductive cycle ---- known as the estrous cycle in rodents and the menstrual cycle in humans --- limits the interpretation of these studies. Thus studies using unified methods and clearly identified menstrual stages are required in order to obtain answers to whether and how steroid hormones modulate opioid analgesics. However, from the animal studies it is clear that both activational and organizational effects of sex steroids may contribute to sex differences in opioid analgesia (Sandner-Kiesling & Eisenach, 2002).

1.8.3 Opioid pharmacokinetics and pharmacodynamics

Sex hormones may modulate opioid analgesia by influencing opioid pharmacokinetics and/or opioid pharmacodynamics (Fillingim & Ness, 2000; Craft, 2003a, b). With regards to pharmacokinetics, several animal studies have demonstrated that sex hormones change the absorption, the distribution, and the metabolism of opioids to active and inactive metabolites (pharmacokinetics) (Ratka, 1995; Blanck et al., 1990; South et al., 2001; Baker & Ratka, 2002).
Additionally, many animal studies have shown that, with regards to pharmacodynamics, ovarian hormones – 17-beta-estadiol – modulate brain opioid peptide mRNA levels, opioid peptide levels, opioid receptor density, and opioid receptor-mediated signal transduction (pharmacodynamics) (Hahn & Fishman, 1985; Craft et al., 2004; Hammer, 1990; Weiland & Wise, 1990; Maggi et al., 1991; Holtzman et al., 1997; Carter & Soliman, 1998; Ekersell et al., 1998; Smith et al., 1998; Sinchak et al., 2000; Kelly et al., 2002, 2003). Estrogens also have been shown to attenuate the effects of endogenous and exogenous opioids by binding directly to opioid receptors in humans (Schwarz & Pohl, 1994).

Notably, the relation between ovarian hormones and opioids is bi-directional. There is a growing body of literature showing that long term opioid therapy for CNCP significantly reduces sex hormones in both men and women (Gordon, 2010; Vuong et al., 2010).

1.9 Conclusion

Although sex differences in pain and opioids have garnered much attention, the exact reasons behind these differences remain elusive. In fact, these differences can be attributed to multiple factors, from genes and reproductive hormones to socio-cultural and environmental factors. However, evidence is continuously developing leading to the suggestion that sex hormones modulate both pain sensitivity and opioid efficacy (Craft et al., 2004).

Coupled with the fact that women are the majority of CNCP patients with a peak prevalence during the reproductive years, this evidence regarding the role of ovarian hormones in modulating pain and opioids has generated the hypothesis that ovarian hormones may modulate CNCP conditions as well (Fillingim & Ness, 2000; Turner, et al., 2004). Therefore, a growing number of studies using various study designs and paradigms in humans have hypothesized that
any changes in the levels of these ovarian hormones will be associated with the severity of CNCP conditions (Riley, et al., 1998; Unruh, 1996).
Chapter 2

Literature Review

2 Ovarian Hormones and Chronic Non-Cancer Pain

In order to understand more completely what is known about this possible link between ovarian hormones and CNCP conditions, we undertook a review of the literature focusing our attention on CNCP conditions that are more prevalent in women. These conditions are: musculoskeletal pain (MSP), migraine headache, TMD, and CPP.

2.1 Methods

Relevant articles were identified through searches of the Medline, PubMed, and Google Scholar databases as well as through the reference lists of identified publications that reviewed the relationship between the menstrual cycle, ovarian hormones and pain; citation searches enable locating potentially relevant studies that may not have been retrieved by traditional subject searching. The key words searched were: chronic pain, chronic non-cancer pain, migraine headache, temporomandibular joint disorder, irritable bowel syndrome, fibromyalgia, rheumatoid arthritis, and chronic pelvic pain each in turn crossed separately with ovarian hormones/steroids, estrogen/progesterone, hormonal replacement therapy, oral contraceptives, menopause and menstrual cycle.

Inclusion criteria chosen to ensure relevance were: (i) human studies only, (ii) participants who were clinically diagnosed with CNCP condition and seeking help at an outpatient clinic, (iii) studies investigating the relation between the severity of these CNCP
conditions and events related to changes in the levels of ovarian hormones such as: hormonal treatment, the menstrual cycle, pregnancy, abortion, or menopause. The search was limited to the English language. Any studies that were not clinically based (i.e. a survey or community based studies) were excluded.

The search was unlimited by any specific dates or time interval in order to capture as many studies as possible.

### 2.2 Results

The search produced 385 papers (dates ranging from 1983-2012) focusing on CNCP conditions and their relation to hormonal changes. We excluded any that did not fulfil our inclusion criteria leaving a total of 50 studies: eight for MSP such as: fibromyalgia and RA, nine for migraine headache, five for TMD, and 28 for CPP (including IBS and endometriosis). All recruited patients were diagnosed with a CNCP condition and pain was assessed by using a self-report. All studies observed participants with pain, recording changes in pain severity either by querying current pain using visual analogue scale (VAS), and/or McGill Questionnaire or by inducing/measuring physiological changes accompanying the condition (e.g., grip strength testing, finger joint size, and pain pressure threshold (PPT), rectal sensitivity, or stool consistency).
2.2.1 Musculoskeletal pain

A total of eight clinical studies were found which investigated the relationship between either fibromyalgia or RA severity and the different phases of the menstrual cycle (Table 1).

1. Fibromyalgia

Fibromyalgia is a chronic MSP characterized by widespread pain (Okifuji & Turk, 2006). Fibromyalgia is one of many CNCP conditions that tend to occur predominately in women and more frequently during reproductive ages. Therefore, there has been a growing interest regarding the relation between fibromyalgia and ovarian hormones.

A total of five studies investigated fibromyalgia specifically and its relation to the menstrual cycle and/or pregnancy, abortion and menopause (Ostensen et al., 1997; Anderberg et al., 1999; Alonso et al., 2004; Pamuk & Cakir, 2005; Okifuji & Turk, 2006). All but two studies were consistent in finding an increase in severity during phases considered by the researchers as low in estrogen levels (Alonso et al., 2004; Okifuji & Turk, 2006). Despite a general agreement, differences in methodology hinder any detailed comparison between studies.

The studies varied greatly in terms of participant age, number of participants and comparative groups. In three studies, comparing premenopausal to menopausal participants, researchers found that postmenopausal participants reported higher pain scores than were reported by premenopausal participants (Alonso et al., 2004; Anderberg et al., 1999; Pamuk & Cakir, 2005).

In another study of 26 female participants, researchers compared pain severity of their chronic pain condition between four different groups; pregnant women, normally cycling women, women using OC and women who underwent abortion. In this study, pregnancy was correlated with high pain severity scores for fibromyalgia, with the last trimester being the worst.
Normally cycling participants reported more pain in the premenstrual phase. Women post abortion or using OC reported no changes in pain severity (Ostensen, et al., 1997). Again, these findings suggest that pain severity changes with changes in the levels of ovarian hormones.

As with regards to mechanisms which were used to determine pain sensitivity, they varied widely. In addition to self-report which were used by all studies for recording changes in symptom severity, three studies used pressure dolorimetry with an algometer to apply pressure and detect changes in pain pressure threshold (PPT) (Alonso et al, 2004; Anderberg et al., 1999 Hapidou & Rollman, 1998) and one study performed ischemic pain testing (Okifuji & Turk, 2006). Despite these differences, three studies out of five showed an increase in pain severity during phases when estrogen levels were low (Ostensen, et al., 1997; Anderberg, et al., 1999 Pamuk, & Cakir,, 2005). In contrast, two studies, one of which used daily urine measurements for ovarian hormones, reported no changes in pain scores across the menstrual cycle (Alonso et al, 2004; Okifuji & Turk, 2006).

Taken together, these studies suggest that fibromyalgia pain symptoms may be greatest when estrogens are low.

2. **Rheumatoid arthritis (RA)**

RA is a CNCP condition characterized by inflammation, morning stiffness and ultimately, reduced activity due to chronic pain (Latman, 1983). Since ovarian hormones have been considered as anti-inflammatory agents (Bruce-Keller et al., 2000), researchers have studied the impact of ovarian hormones on the severity of RA.

Two studies compared variation in pain sensitivity across the menstrual cycle in cycling women with RA (Latman, 1983, Rudge, et al., 1983). While both studies used self-report questionnaires, Rudge and colleagues (1983) used objective pain and symptom measurements
(finger joint size, grip strength, and body weight) without measuring pain severity for the studied pain condition. Despite differences in methodologies, both studies found that the severity of RA varied with the phases of the menstrual cycle. However, there was no consensus on which menstrual cycle phase correlated with greater pain symptoms. While, Latman (1983) reported less joint pain and morning stiffness during the luteal phase which, in his schema, was a phase when estrogen and progesterone plasma levels are high, Rudge and colleagues (1983) found a decrease in grip strength during menses and an increase in the joint size in the first six days after menses compared with other time periods of the menstrual cycle which he considered as a low estrogen phase. Thus, while menstrual cycle phase seemed to be associated with changes in the pain severity, there was no agreement as to which phase is associated with higher pain scores.

3. **Chronic back, neck, ankle, and knee pain**

Only one study investigated how MSP in various areas (e.g., neck, shoulder, back, joints) varied with menstrual cycle phase (Hellström & Anderberg, 2003). This study found that pain severity was greater during premenstrual and menstrual phases compared with mid-menstrual and ovulatory phases, suggesting that pain sensitivity was greatest when estrogen levels were low. Taken together, these studies suggest that MSP symptoms vary over the course of women’s reproductive phases, and in most cases are most intense at low estrogen phases (i.e. menopause, early follicular phase, late luteal phase).
Table 1: Clinical studies investigating the relationship between MSP and phases of the menstrual cycle

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>CNCP Condition</th>
<th>Comparative participants</th>
<th>Blinded</th>
<th>Menstrual Cycle</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
</table>
| Ostensen, et al., 1997      | Fibromyalgia   | 26 female patients        | N       | Self-report     | Retrospective self-report of pain severity changes during pregnancy/abortion/use of OC/breast feeding | - more pain during last trimester in pregnancy  
- more pain in 72% pre-menstrual  
- no changes in pain among women using OC, or during abortion |
| Anderberg, et al., 1999     | Fibromyalgia   | 17 premenopausal with FM - 18 menopausal with FM - 13 postmenopausal controls | N       | Self-report     | - self-report questionnaires -daily pain intensity ratings - PPT (algometer) | -more pain among postmenopausal than pre-menopausal patients  
- more pain in perimenstrum vs. ovulatory phase among pre-menopausal |
| Alonso et al., 2004         | Fibromyalgia/RA | fibromyalgia RA healthy controls | N       | Self-report     | using dolorimetry tender point palpation and self-reported pain diaries | no significant differences in pain severity or number of tender points between the follicular and luteal phases |
- more pain and fatigue in menstrual, luteal phases vs. other phases among pre-menopause |
| Okifuji & Turk, 2006        | Fibromyalgia   | 74 cycling with FM -74 cycling controls | N       | blood sampling for nine days to measure ovulation | - Tender Point Palpation - grip strength testing - ischemic pain threshold and tolerance testing | - no difference in pain across phases  
- lower pain threshold & tolerance in patients |
| Latman, 1983                | RA             | 14 cycling with RA        | Y       | Self-report     | - self-report questionnaires | - less joint pain, morning stiffness during luteal phase vs. early follicular phase |
| Rudge, et al., 1983         | RA             | 7 cycling with RA         | N       | Self-report     | - daily finger joint size, grip strength, body weight measurements | - decrease in grip strength & increase in joint size during menses |
| Hellstrom, & Anderberg, 2003 | Chronic back, neck, ankle, knee pain; fibromyalgia | 20 cycling with chronic pain | Y       | Self-report     | - self-report questionnaire | - more pain during premenstrual and menstrual phases than mid-menstrual and ovulatory phases. |

FM: Fibromyalgia; OC: Oral Contraceptives; PPT: Pain Pressure Threshold; RA: Rheumatoid Arthritis; VAS: Visual Analogue Scale.
2.2.2 Migraine

The finding that nearly half of all women, who are diagnosed with migraine headache, are actually within their reproductive age underscores the idea that ovarian hormones play a role in modulating these painful attacks (Stewart et al., 1992; MacGregor & Hackshaw, 2004). Perhaps due to this, migraine headaches pose a special case in the literature of chronic pain in that they have been subdivided based on whether or not the attacks occur just prior to and during menses, as well as by headache features. Retrieved migraine studies also showed more understanding of the role of ovarian hormones in pain treatment with some of these studies observing that hormonal treatment was effective in treating menstrual migraines in particular (MacGregor & Hackshaw, 2004; MacGregor et al., 1990).

Despite an extensive body of literature discussing the relationship between migraine headaches’ occurrence at different phases of the menstrual cycle, only nine clinical studies specifically investigated the effect of the menstrual cycle on the severity of attacks (Table 2). Across the nine studies, there was a great variability in terms of study design and migraine terminology. We grouped the nine studies according to the way the studies themselves, classified them.

1. Migraine attacks (without further classifications)

Two studies investigated the relation between the menstrual cycle and migraine attacks in general with regards to prevalence, severity, and response to hormonal treatment among cycling participants (MacGregor & Hackshaw, 2004; Martin et al., 2005). While both studies used self-reported questionnaires to record pain severity changes over the course of three menstrual cycles, each study used a different way to identify different phases of menstrual cycle. In the first study,
MacGreagor et al. (2004) used daily diaries, while Martin and his colleagues (2005) collected daily urine samples to evaluate hormonal levels directly to identify different phases of the menstrual cycle. Despite this discrepancy, the two studies concluded that migraine attacks were more prevalent two days before and two days after menses (perimenstrum); and that those attacks tended to be more severe than other attacks occurring at other times of the cycle. As well perimenstrual attacks were more responsive to hormonal treatment.

Thus, these studies suggest that migraine headaches are most severe at stages of low estrogen and can be treated with estrogens.

2. **Menstrual migraine attacks (MM)**

Three studies divided migraine attacks with respect to their relation to the menstrual cycle; menstrual migraine (MM) and other migraine attacks occurring at other phases of the menstrual cycle (MacGregor et al., 1990; Varlibas & Erdemoglu, 2009; Granella et al., 2004). In these studies, MM was defined as attacks of migraine without aura occurring exclusively just before or during menstruation; this definition reflects the fact that MM are viewed as being related to the fluctuation of ovarian hormones across the menstrual cycle.

Two of these studies compared between MM attacks which occur in women in their reproductive years and other migraine attacks that did not meet the above definition in menopausal women (MacGregor et al., 1990; Granella et al., 2004). The investigators found that MM attacks which were prevalent among premenopausal women and occurred in the perimenstrum were more severe, longer in duration, associated with significantly greater work-related disability, and less responsive to non-hormonal treatment (β-blockers, calcium antagonists, anti-depressant medication, antiepileptic drugs, etc.) than other migraine attacks. Using a different design, one electrophysiological study evaluated the brainstem excitability in
MM patients (Varlibas & Erdemoglu, 2009). Brainstem excitability was measured because pain severity occurring during the migraine attacks is correlated to the electrophysiological parameters of the trigeminocervical reflex (TCR). When brainstem excitability using TCR was compared between MM patients and healthy controls, there was no statistically significant difference in the electrophysiological parameters measured for the TCR between the different phases of the menstrual cycle in controls. However, in MM patients, there were significant differences in brainstem excitability and the mean reflex latencies during the perimenstruum and follicular phases. As well, the latencies of MM patients were significantly longer during the follicular period (headache free) than during the perimenstrual phase (headache period).

Taken together these studies suggest that low estrogen is associated with migraine attacks that might be the reason that these attacks are more responsive to hormonal treatment.

3. **Migraine attacks classified by headache features**

Four studies classified migraine attacks by headache features which include migraine with aura (MA), migraine without aura (MO), tension-type, and all other migraine headaches (Johannes, et all, 1995; Stewart, et al., 2000; Cupini, et al., 1995; Mattson, et al., 2003). These four studies investigated whether type of migraine attacks varies with changes in hormonal status. Consistently, all four found that the risk for MO was significantly more prevalent during the first three days of menstruation, while risk for MA was not significantly increased during the two days immediately preceding onset of menstruation or on the estimated day of ovulation. Additionally, in her study, Cupini found that MA was more prominent during pregnancy (Cupini et al., 1995). In contrast, no significant difference between MA and MO were reported among women during menarche, or women using OC or menopausal women. Therefore, researchers
concluded that estrogen plays a role in mediating the characteristics of migraine headaches such as the presence of aura prior to migraine attacks.

In sum, despite variability in classification and study design, these studies are consistent regarding one aspect of their results with respect to migraine and the menstrual cycle: migraine attacks occurring around menses are usually characterized as being without aura, more severe, more responsive to hormonal treatment and less responsive to non-hormonal treatment and appear to reduce significantly in menopause.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Condition</th>
<th>Participants</th>
<th>Blinded (Y/N)</th>
<th>Menstrual Cycle</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacGregor &amp; Hackshaw, 2004</td>
<td>Migraine</td>
<td>- 155 cycling patients</td>
<td>N</td>
<td>Self-report</td>
<td>- self-report questionnaire</td>
<td>more pain during perimenstrum</td>
</tr>
<tr>
<td>Martin, et al., 2005</td>
<td>Migraine</td>
<td>- 21 cycling patients</td>
<td>Y</td>
<td>Daily urine samples</td>
<td>- self-report questionnaire</td>
<td>- more attacks during menses than during mid-cycle</td>
</tr>
<tr>
<td>MacGregor et al., 1990</td>
<td>Migraine</td>
<td>- 55 cycling patients</td>
<td>Y</td>
<td>Self-report</td>
<td>- self-report questionnaire</td>
<td>- 4 patients had MM without aura</td>
</tr>
<tr>
<td>Varlibas, A. &amp; Erdemoglu, A. K. (2009)</td>
<td>Migraine</td>
<td>- 31 cycling patients - 22 healthy controls</td>
<td>N</td>
<td>Self-report</td>
<td>- electromyography from stimulation of trigeminal nerve</td>
<td>- MM attacks are more severe, longer in duration, and have greater work-related disability than non-menstrual attacks</td>
</tr>
<tr>
<td>Granellaet al., 2004</td>
<td>Migraine</td>
<td>- 64 cycling patients</td>
<td>N</td>
<td>Self-report</td>
<td>- self-report questionnaire</td>
<td>- MM attacks are more severe, longer in duration, and have greater work-related disability than non-menstrual attacks</td>
</tr>
<tr>
<td>Johannes et al., 1995</td>
<td>Migraine</td>
<td>- 74 cycling patients</td>
<td>N</td>
<td>Self-report</td>
<td>- self-report questionnaire</td>
<td>- more MO during first three days of menstruation</td>
</tr>
<tr>
<td>Cupinl et al., 1995</td>
<td>Migraine</td>
<td>- 232 cycling - 268 menarche - 156 pregnant - 122 using OC - 36 menopausal patients</td>
<td>N</td>
<td>Self-report</td>
<td>-self-report questionnaire</td>
<td>- more MO attacks during menses</td>
</tr>
<tr>
<td>Stewart et al., 2000</td>
<td>Migraine</td>
<td>- 81 cycling patients</td>
<td>N</td>
<td>Self-report</td>
<td>- self-report questionnaire</td>
<td>- more MO attacks during menses</td>
</tr>
<tr>
<td>Mattson, 2003</td>
<td>Migraine</td>
<td>-728 cycling patients</td>
<td>N</td>
<td>Self-report</td>
<td>- self-report questionnaire</td>
<td>- 21% of women suffer from MO</td>
</tr>
</tbody>
</table>

MA: Migraines with Aura; MM: Menstrual Migraines; MO: Migraines without Aura; OC: Oral Contraceptives.
2.2.3 Temporomandibular Joint Disorder (TMD)

Many epidemiological studies have reported that the prevalence rates of TMD are higher among women and tend to increase especially during the reproductive years (LeResche et al., 2003). Moreover, the age of onset is almost always after menarche raising the question of whether the ovarian hormones play a role in modulating TMD. We found a total of five clinical studies investigating the relation between TMD and ovarian hormones (Table 3).

Three studies looked at variations in pain severity across the menstrual cycle, while comparing between regularly cycling patients to patients using OC (Dao et al., 1998; LeResche et al., 2003; Sherman et al., 2005). Although, one study (LeResche et al., 2003) actually used ovulation kits to determine different phases of the menstrual cycle while the other two did not measure hormone levels directly, using daily diaries instead. All three studies reported variations in daily pain severity ratings in cycling women with TMD, with pain levels reaching their maximum during menses and the mid-luteal phase. In spite of this agreement, however, reports of variations in pain scores in participants on OC were inconsistent. While Doa et al found greater variability in pain severity among cycling patients than in their counterparts on OC suggesting that pain thresholds and severity become more stable after abolishing the effect of hormonal fluctuations while LeResche, in contrast, reported that changes in TMD pain levels (more pain during menstruation) occurred similarly in both normally cycling women and women on OC.

In addition to measuring pain severity using VAS, one study also used pain pressure threshold (PPT) to measure changes in pain sensitivity as well (Isselee et al., 2002). This study found that PPT was highest during follicular and luteal phases and lowest during the perimenstrum suggesting that low estrogen might lower PPT.
Another study evaluated the effect of hormonal replacement therapy (HRT) on TMD pain in postmenopausal women (Isselee et al., 2002). Wise and colleagues found that women who received HRT had higher TMD pain intensity scores than those not receiving HRT, which suggests that there may be differences in effect between endogenous and exogenous hormonal effects on chronic pain conditions.

While the effects of OC on TMD pain vary between studies, taken together, all the studies demonstrated a pain pattern similar to other CNCP conditions that are more common in women, with pain sensitivity changes across the menstrual cycle. Most studies suggested that increased pain sensation was correlated with low estrogen levels. However, there are some that suggest that changes in TMD are due to hormonal fluctuation rather than absolute levels.
Table 3: Clinical studies investigating the relation between TMD and the menstrual cycle

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>CNCP Condition</th>
<th>Comparative participants</th>
<th>Participants Blinded (Y/N)</th>
<th>Menstrual Cycle</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dao et al., 1998</td>
<td>TMD</td>
<td>- 7 cycling patients</td>
<td>Y</td>
<td>Self-report</td>
<td>- self-report questionnaire - VAS</td>
<td>- greater variability in pain severity among cycling patients than patients using OC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 5 using OC patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wise et al., 2000</td>
<td>TMD</td>
<td>- 34 menopausal patients not using HRT</td>
<td>N</td>
<td>Self-report</td>
<td>- MPQ - self-report questionnaire for pain intensity ratings</td>
<td>- more pain for HRT group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 53 menopausal patients using HRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isselee et al., 2002</td>
<td>TMD</td>
<td>- 10 cycling patients</td>
<td>N</td>
<td>Self-report</td>
<td>- VAS - PPT (pressure algometry) - McGill Pain Questionnaire</td>
<td>- PPT highest during follicular and luteal phases, lowest during perimenstrum</td>
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<td></td>
</tr>
<tr>
<td>LeResche et al., 2003</td>
<td>TMD</td>
<td>- 35 cycling patients</td>
<td>N</td>
<td>Ovulation kit</td>
<td>- self-report questionnaire for pain</td>
<td>- more pain during menstruation for cycling and those using OC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 35 patients on OC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 35 cycling controls</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 21 males patients</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sherman et al., 2005</td>
<td>TMD</td>
<td>- 18 cycling patients</td>
<td>N</td>
<td>Self-report</td>
<td>- PPT (algometer) - Ischemic arm pain task.</td>
<td>- more pain at menses, mid-luteal phase in cycling women with TMD - more pain during late luteal phase among women with TMD on OC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 25 patients on OC</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- 25 cycling controls</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>- 26 controls on OC</td>
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</tbody>
</table>

2.2.4 Chronic Pelvic Pain (CPP)

CPP is another CNCP condition more prevalent among women, especially during their reproductive years (Ghaly & Chain, 2000). Until now, the underlying pathology of CPP has been poorly understood. Moreover, the relation between menstrual cycle and CPP has not been well recognized leading to two different definitions: one as “noncyclic pain of at least six months duration, localized to the pelvis, anterior abdominal wall, at or below the umbilicus and lower back and buttocks” (Reiter et al., 1999; Lamvu et al., 2006) and another as, “continuous or intermittent pain in the lower abdomen, lasting for at least 6 months and not exclusively related to menstrual period or sexual intercourse” (Weijenborg et al., 2007; William et al., 2004). In spite of these two different definitions, estimates suggest that many of the probable causes of CPP (e.g., endometriosis, interstitial cystitis and irritable bowel syndrome) are actually modulated by the menstrual cycle. Additionally, a considerable overlap often tends to occur between these causes making it difficult at some point to distinguish between them (Warren et al., 2011; Slocumb, 1990).

A total of 28 clinical studies (6 for IBS and 22 for CPP) were found which investigated the relationship between cyclic causes of CPP and any changes in the levels of ovarian hormones.

1. Irritable Bowel Syndrome (IBS)

IBS has been considered as one of the common non-gynecological causes of CPP and may account for up to 60% of referrals for CPP (Matheis et al., 2007; Verceillini et al., 2009). IBS is a chronic pain syndrome characterized by alterations in bowel habits and increased visceral sensitivity. Many population based studies have reported that women experience more
frequent and loose stools, abdominal cramping and distension at the time close to their menses, which raises the possible relation between IBS symptoms and the menstrual cycle.

Six clinical studies investigated changes in gastrointestinal symptoms (bowel discomfort, abdominal pain, bloating, and alteration in bowel movements) across the different phases of the menstrual cycle (Table 4). A variation in gastrointestinal symptoms including altered motility and/or enhanced perception of gastrointestinal symptoms (e.g. bloating, distension) and even rectal sensitivity (examined by rectal response to balloon distension) during different phases of the menstrual cycle was observed in three studies (Chang, et al., 2001; Houghton et al., 2002; Heitkemper, et al., 2003). Two of these studies consistently reported more abdominal pain and bloating during menses as compared with all other phases of the menstrual cycle which suggests that low estrogen is correlated with an increase in the severity of IBS symptoms (Chang, et al., 2001; Houghton et al., 2002). However, one study, which used direct hormone measurements by blood samples and used those to determine different phases of menstrual cycle and to confirm ovulation, found no difference in pain across phases (Heitkemper, et al., 2003).

Another two studies compared changes in severity between Crohn’s disease (CD) and ulcerative colitis (UC), and IBS across the menstrual cycle (Bernstein et al., 2012; Kane et al., 1998). Both studies reported more abdominal pain during premenstrum among patients than their healthy controls.

Thus, as with other studies of CNCP, although there are conflicting results, the weight of the evidence suggests that IBS symptoms including altered motility and/or enhanced perception of normal gastrointestinal events are greater in the perimenstrum, a low estrogen milieu, suggesting the role for ovarian hormones in modulating abdominal symptoms.
Table 4: Clinical studies investigating changes in IBS across the menstrual cycle.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>CNCP condition</th>
<th>Comparative participants</th>
<th>Participants Blinded (Y/N)</th>
<th>Menstrual Cycle Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kane et al., 1998</td>
<td>IBS</td>
<td>- 49 cycling with UC</td>
<td>Y</td>
<td>Retrospective self-report</td>
<td>- self-report on variations in symptoms across menstrual cycle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 49 cycling with CD</td>
<td></td>
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<td></td>
<td></td>
<td>- 46 cycling with IBS</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- 90 cycling controls</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Chang, et al., 2001</td>
<td>IBS</td>
<td>- 77 female with bloating</td>
<td>N</td>
<td>Self-report</td>
<td>- VAS - self-report questionnaire on bowel symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 303 female patients</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>with bloating and</td>
<td></td>
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<td></td>
<td></td>
<td>distension</td>
<td></td>
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<tr>
<td>Houghton et al., 2002</td>
<td>IBS</td>
<td>- 29 cycling with IBS</td>
<td>N</td>
<td>Self-report</td>
<td>- rectal response to balloon distension - self-report questionnaire</td>
</tr>
<tr>
<td>Heitkemper, et al., 2003</td>
<td>IBS</td>
<td>- 93 cycling with IBS</td>
<td>N</td>
<td>Blood sample during mid-luteal phase, ovulation kit</td>
<td>- self-report questionnaire</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 56 using OC with IBS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- 35 cycling control</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>- 7 using OC control</td>
<td></td>
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</tr>
<tr>
<td>Altman, 2006</td>
<td>IBS</td>
<td>- 38 with dysmenorrhea &amp; PMDS &amp; IBS</td>
<td>N</td>
<td>Self-report</td>
<td>- self-report questionnaire</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 59 with PMDS &amp; IBS</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>- 15 with dysmenorrhea &amp; IBS</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- 114 with IBS only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bernstein et al., 2012</td>
<td>IBS</td>
<td>- 151 premenopausal with CD</td>
<td>N</td>
<td>Retrospective self-report</td>
<td>- self-report questionnaire</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 87 premenopausal with UC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 156 premenopausal</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>controls</td>
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</tbody>
</table>

2. *Endometriosis*

Endometriosis is another pain condition that represents one third of the probable causes behind CPP and is widely acknowledged to be an estrogen-dependent condition (Azemi et al., 2009; Gambone et al., 2002; Ghaly & Chain, 2000; Vercellini et al., 1997, 2009; Howard, 1994). Although the relationship between CPP and the menstrual cycle is not well recognized, as mentioned before, the relation between CPP associated with endometriosis and ovarian hormones has been well established in the literature. Endometriosis is found almost exclusively in menstruating women of reproductive age. It is not reported before menarche and generally disappears with menopause (unless the woman is on an HRT regimen) (Kitawaki et al., 2003). In fact, estrogen directly stimulates the growth and influence the proliferation of the ectopic endometrial tissue. Therefore, hormonal treatments (e.g. OC and gonadotropin releasing hormone (GnRH) analogues, progestins, and danazol (an androgen agonist) have been used successfully to alleviate CPP associated with endometriosis in about 70% of patients (Lamvu et al., 2006; David et al., 2011; Huang, 2008; Olive et al., 2004; Stratton & Berkley, 2010; Cumiskey et al., 2008; Goodman et al., 1989; Missmer et al., 2004; Kennedy et al., 2005).

In spite of the fact that it is well acknowledged that endometriosis itself waxes and wanes with the level of ovarian hormones, perhaps because one definition of CPP excludes any relation to the menstrual cycle, there are no studies of how the CPP associated with endometriosis might also change with changes in the ovarian hormonal levels across the menstrual cycle. Instead, 22 randomized controlled trials (RCTs) were retrieved that presented evidence for the efficacy of the hormone therapy in alleviating CPP due to endometriosis by comparing it to either: a placebo, another hormonal therapy, or surgery (Table 5).

Seven RCTs of a total of 22 compared the efficacy of hormone therapy to placebo (Harada et al., 2008; Dlugi et al. 1990; Fedele et al. 1993; Bergqvist et al.1998; Ling 1999;
Telimaa et al., 1987a; Telimaa et al., 1987b). Women diagnosed with CPP associated with endometriosis were randomly assigned to receive either one of the hormonal therapy or placebo. Pain scores were most often assessed by a VAS and a verbal rating scale (VRS). One RCT evaluated the efficacy of OC for patients with CPP associated with endometriosis (Harada et al., 2008); four studies performed RCTs to investigate the efficacy of a GnRH agonist versus placebo (Dlugi et al. 1990; Fedele et al. 1993; Bergqvist et al. 1998; Ling 1999) and two studies compared progestin to placebo (Telimaa et al., 1987a; Telimaa et al., 1987b). Results revealed that pain scores were reduced significantly during treatment using any of the above mentioned hormonal treatments compared to placebo.

Fourteen RCTs compared the efficacy of hormone therapy to one another (Vercellini et al., 1993 Guzick et al., 2011; Henzel et al., 1988; Wheeler et al., 1992; Crosignani et al., 1992; Admoson et al., 1994; Crikel et al., 1995, Petta et al., 1993; Tekin et al., 2011; Overton et al., 1985; Strowaitzki et al., 2012; Strowaitzki et al., 2012; Telimaa et al., 1987a; Telimaa et al., 1987b; Fedele et al., 1989; Vercillini et al., 1996). Two studies compared the efficacy of OC and GnRH analogues to manage CPP associated with endometriosis (Vercellini et al 1993; Guzick and colleagues, 2011). Five studies compared GnRH analogues and danazol (Henzel et al., 1988; Wheeler et al., 1992; Crosignani et al., 1992; Admoson et al., 1994; Crikel et al., 1995). Two RCTs compared the efficacy of Levonorgestrel-Releasing Intrauterine System (LNG-IUS) and GnRH analogues (Petta and colleagues, 1993; Tekin et al., 2011). One RCT investigated the efficacy of dienogest versus leuprolide acetate (a GNRH analogue) for the treatment of pelvic pain associated with endometriosis (Strowaitzki et al., 2012). A total of four studies compared danazol and progestins (Telimaa et al., 1987a; Telimaa et al., 1987b; Fedele et al., 1989; Vercillini et al., 1996), two of which also compared both drugs to placebo (Telimaa et al., 1987b; Fedele et al., 1989), and one of which compared progestins to danazol combined with OC
(Vercillini et al. (1996). As in the other studies, all of these studies demonstrated that any of the hormone therapies provided virtually identical CPP relief. Thus, it appears that all hormonal therapies tried are superior in treating the CPP associated with endometriosis to a placebo, and no one hormonal treatment seems to be significantly superior to another (Olive et al., 2002).

One study that compared surgical treatment with hormonal treatment (Vercellini et al., 2011) found that after twelve month follow up both were equally effective in alleviating CPP associated with endometriosis.

As a result of these findings, researchers have advocated the importance of identifying any temporal patterns or cyclicity in CPP during patient assessments and have explicitly stated that hormonal variation is an important factor that needs to be considered during consultations with CPP patients (Vincent, 2009; Howard, 2003).
<table>
<thead>
<tr>
<th>Author(S)</th>
<th>Groups</th>
<th>#/Group</th>
<th>Pain Scale</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harada et al., 2008</td>
<td>OC vs. Placebo</td>
<td>-51 OC - 49 placebo</td>
<td>- VRS - VAS</td>
<td>reduce pain in OC group</td>
</tr>
<tr>
<td>Dlugi et al. 1990</td>
<td>LA vs. Placebo</td>
<td>- 26 LA - 26 placebo</td>
<td>- VAS</td>
<td>more pain relief for GnRH group</td>
</tr>
<tr>
<td>Fedele et al., 1993</td>
<td>Buserelin acetate vs. Placebo</td>
<td>- 16 placebo - 19 buserelin acetate</td>
<td>analogue &amp; multi-dimensional</td>
<td>more pain relief for GnRH group</td>
</tr>
<tr>
<td>Bergqvist et al., 1998</td>
<td>Triptorelin vs. Placebo</td>
<td>- 24 triptorelin - 25 placebo</td>
<td>- VAS</td>
<td>more pain relief for GnRH group</td>
</tr>
<tr>
<td>Ling, 1999</td>
<td>LA vs. Placebo</td>
<td>- 46 placebo - 49 LA</td>
<td>- VAS</td>
<td>more pain relief for GnRH group</td>
</tr>
<tr>
<td>Vercellini et al., 1993</td>
<td>OCs vs. Goserelin</td>
<td>- 29 goserelin - 28 OCs</td>
<td>-VAS - VRS</td>
<td>pain scores reduced for both groups</td>
</tr>
<tr>
<td>Guzick et al., 2011</td>
<td>OCs vs. LA</td>
<td>- 26 OCs - 49 LA</td>
<td>-VAS</td>
<td>no significant differences between groups.</td>
</tr>
<tr>
<td>Henzel et al., 1988</td>
<td>Nafarelin vs Danazol</td>
<td>213</td>
<td>-VAS</td>
<td>reduction in both groups GnRH analogues fewer side effects</td>
</tr>
<tr>
<td>Wheeler et al., 1992</td>
<td>LA vs. Danazol</td>
<td>270</td>
<td>-VAS</td>
<td>reduction in both groups</td>
</tr>
<tr>
<td>Crosignani et al., 1992</td>
<td>LA vs. Danazol</td>
<td>67</td>
<td>-VAS</td>
<td>pain reduced in both groups</td>
</tr>
<tr>
<td>Admoson et al., 1994</td>
<td>Naferelins vs. Danazol</td>
<td>213</td>
<td>-VAS</td>
<td>both treatments provided significant relief</td>
</tr>
<tr>
<td>Crikel et al., 1995</td>
<td>Triptorelin vs Danazol</td>
<td>- 30 triptorelin - 25 danazol</td>
<td>-VAS</td>
<td>dysmenorrhea treated successfully by both</td>
</tr>
<tr>
<td>Petta et al., 1993</td>
<td>LNG-IUS vs depot GnRH analogue</td>
<td>- 39 LNG-IUS - 43 GnRH analogue</td>
<td>-VAS</td>
<td>significant decrease in CPP in both groupspies</td>
</tr>
<tr>
<td>Tekin et al., 2011</td>
<td>Mirena vs Zoladex</td>
<td>- 20 Mirena - 20 Zoladex</td>
<td>-VAS - TESP</td>
<td>GnRH analogue led to significant decrease in both VAS &amp; TESP scores</td>
</tr>
<tr>
<td>Overton et al., 1985</td>
<td>Dydrogesterone vs placebo</td>
<td>62</td>
<td>-VAS - PRs</td>
<td>pain scores were reduced significantly for the dydrogesterone group</td>
</tr>
<tr>
<td>Strowaitzki et al., 2010</td>
<td>Dienogest vs Placebo</td>
<td>- 96 Placebo - 102 Dienogest</td>
<td>-VAS</td>
<td>Dienogest is significantly more effective than placebo for treating endometriosis-associated CPP.</td>
</tr>
<tr>
<td>Strowaitzki et al., 2012</td>
<td>Dienogest vs LA</td>
<td>- 124 Dienogest - 128 LA</td>
<td>-VAS</td>
<td>Dienogest has equivalent efficacy to depot LA in relieving the pain of endometriosis.</td>
</tr>
<tr>
<td>Study</td>
<td>Treatment</td>
<td>VAS</td>
<td>Outcome</td>
<td></td>
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<td>-------------------------------------------------------------------------</td>
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<tr>
<td>Telimaa et al., 1987a</td>
<td>MPA vs. Danazol vs placebo</td>
<td>- VAS</td>
<td>significant relief from both danazol and MPA</td>
<td></td>
</tr>
<tr>
<td>Telimaa et al., 1987b</td>
<td>MPA vs danazol vs placebo</td>
<td>- VAS</td>
<td>significant reduction of pain by both danazol and a high dose MPA treatment</td>
<td></td>
</tr>
<tr>
<td>Fedele et al., 1989</td>
<td>MPA vs danazol</td>
<td>- VAS</td>
<td>pain was relieved in both groups, however, dysmenorrhea recurred in 66% of the MPA group and 58% of the danazol group</td>
<td></td>
</tr>
<tr>
<td>Vercillini et al., 1996</td>
<td>MPA vs OC + danazol</td>
<td>- VAS</td>
<td>more pain relief in MPA group dysmenorrhea scores significantly greater in the OC/danazol group</td>
<td></td>
</tr>
<tr>
<td>Vercellini et al., 2012</td>
<td>Progestins vs surgery</td>
<td>- VAS</td>
<td>both equally effective in pain relief.</td>
<td></td>
</tr>
</tbody>
</table>

CPP: Chronic Pelvic Pain; GNRH: Gonadotropin Releasing Hormone; LA: leuprolide acetate; LNG-IUS: Levonorgestrel-Releasing Intrauterine System; MPA: Medroxyprogesterone acetate; OC: Oral Contraceptives; TESP: Total Endometriosis Severity Profile; VAS: Visual Analogue Scale; VRS: Verbal Rating Scale.
2.3 Discussion

The fact that CNCP conditions are more common in women and have been reported to worsen particularly during the peak reproductive years raises the question regarding the role of ovarian hormones in modulating the severity of CNCP conditions. The objective of this review was to determine what is known about the effects of the menstrual cycle or ovarian hormones on CNCP conditions more common in women: MSP, IBS, migraine, TMD and CPP. This is the first review of the literature focusing on clinical studies investigating the relation between the severity of these CNCP conditions more common in women with any events associated with changes in the levels of ovarian hormones via the menstrual cycle, pregnancy, abortion, menopause and/or the use of any hormonal treatment.

We found that despite placing no time constraint on our search, we found only 50 clinical studies spanning three decades across four CNCP conditions: MSP, migraine, TMD and CPP. Thus, the present literature review has revealed a paucity of research on the effects of ovarian hormones and the menstrual cycle on CNCP despite women being overrepresented in chronic pain conditions. This is especially surprising given the numerous advances in our understanding of a host of possible points that support the notion that estrogen can affect pain perception in both human and animal models (Craft, 2007).

Among these 50 studies, paradigms varied widely. Four studies compared women with CNCP of reproductive age with those who were menopausal (Anderberg, et al., 1999; Pamuk, & Cakir,, 2005 Cupini et al., 1995; Wise et al., 2000), five compared cycling women and women on OC (Sherman et al., 2005; LeResche et al., 2003; Dao et al., 1998; Cupini et al., 1995;
Heitkemper, et al., 2003) and six others compared women with CNCP conditions to controls without CNCP. Seven studies gave hormones or placebo to women with pain conditions to determine whether or not hormonal treatments were efficacious treatments suggesting that hormonal treatment might be a potential effective treatment providing pain relief for CNCP conditions.

Although most studies agreed that the increase in pain symptoms and perception was correlated with low estrogen, there were inconsistencies in which phases were associated with lower levels of estrogen, even for the same CNCP condition. For example, though Pamuk, & Cakir (2005) reported that MSP symptoms increase during the luteal phase, and Latman, (1983) reported an increase in the follicular phase, both concluded that the pain increases were due to low levels of estrogen. At first glance, while one might think that there were inconsistencies regarding which phase was characterized by low estrogen, nevertheless, hormonal levels in both luteal and follicular phases are varying continuously. For example, the early luteal phase is characterized by high levels of estrogen, while the late luteal phase has low levels of estrogen. Hence, it is not possible to know what hormone levels are by simply identifying menstrual cycle phases; changes in hormone concentrations may be the more relevant factor and measuring hormones directly, the clearest method demonstrating that.

Only seven out of 50 studies were carried out with participants blinded to the hypothesis that chronic pain is related to the menstrual cycle (Hellstrom & Anderberg, 2003; Latman, 1983, MacGregor et al., 1990; Doa et al., 1998; Hapidow &Rollman, 1998; Kane & Hanauer, 1998; Martin et al., 2005). It is well established that the menstrual cycle, itself, carries many negative connotations which may affect a person’s pain perception and therefore yield
information on a socially constructed phenomenon’s effect on pain symptoms but not specifically that of ovarian hormones (Romans et al., 2012). Past research has shown that self-identifying in the premenstrum or being aware of a menstrual focus in a research study may exert a significant effect on self-reported negative symptoms (Klebanov & Jemmott, 1992; Marvan & Escobedo, 1999; Woods, 1987). When participants are blinded to the menstrual cycle purpose of a study and hormones are measured directly, there is no significant relationship between either positive or negative mood in a community sample of non-help seeking women. In fact, the two strongest correlations with mood are psychosocial factors: perceived stress and health (Schwartz, et al., 2012). Since pain and mood are highly correlated, it may be that psychosocial factors also play a role in pain perception (Belle et al., 2011; Chang et al., 2006).

Given the menstrual cycle’s negative cultural overlays unless participants are blinded to the menstrual focus of a study, it is difficult to tease apart negative attitudes toward menstruation and pain perception.

Most studies used the menstrual cycle as a proxy for ovarian hormones, collecting menstrual phase information via daily diaries with only a few confirming these reports using ovulation tests, or blood samples to directly measure hormonal levels (Martin et al. 2005; Heitkemper et al., 2003; LeResche et al., 2003; Okifuji & Turk, 2006). However, it is also well established that there are individual differences in hormonal levels across cycles, occurrence of ovulation and ovarian cycle length both within and between women making it impossible to know the actual hormonal levels of a given participant (Guerrero, et al., 1976; Landgren, Unden, & Diczfalusy, 1980). Only three studies measured estrogens and progestagens directly. Of these three, two studies (Okifuji & Turk, 2006; Heitkemper et al., 2003) found no difference in pain across phases, while one study (Martin, 2005) found more migraine attacks during
menses than during mid-cycle. Therefore, daily, direct measurement of ovarian hormones is critical to determine whether there is any relation between ovarian hormones and pain intensity and thresholds (Martin et al., 2009).

Two CNCP conditions stood out as having strong consensus on the correlation of the pain with the menstrual cycle: menstrual migraine and endometriosis. Because there was good evidence of cyclicity to the pain, investigators were able to provide a more nuanced view on how the cycle influenced symptoms or treatments for these conditions. With respect to migraine, a specific type of migraine, menstrual migraine, has been identified and differentiated in treatments from other types of migraines. As well, the symptoms of migraines occurring perimenstrually have been differentiated from those that occur at any time: menstrual migraines occur without an aura and non-menstrual migraines with an aura, suggesting the recruitment of different neural circuits for each type. With respect to endometriosis, whether considered CPP, its waxing and waning with the menstrual cycle has led to an RCT that determined that hormone therapy is as efficacious in relieving pain as surgery. These findings raise an important question about the relative benefits of surgery even for diagnosis of CPP secondary to endometriosis, especially for cases in which minimal disease is present or lesions are atypical in appearance where surgery based on visualization is difficult (Ling, 1999). Additionally, as with all surgeries, there is a risk of tissue or nerve damage during laparoscopy which may aggravate or indeed even cause CPP. Thus, understanding the role of ovarian hormones in the exacerbation of pain has led to the suggestion that for a select group of patients with CPP secondary to clinically suspected endometriosis, beginning the diagnostic process should be started with noninvasive tests and a trial of medical therapy with GnRH agonists rather than laparoscopy as the more appropriate treatment approach (Ling, 1999; Howard, 1993).
It is important to note that different CNCP conditions have different characteristics. Migraine headaches are characterized as ‘attacks’ and are thus limited in time while fibromyalgia is characterized as a constant pain that might wax and wane but which never goes away. These differences required different methods of assessing pain. Studies used daily questionnaires to acquire women’s pain scores over a number of months, relying on self-reports of pain or VAS. A few studies used objective pain measurements such as finger joint size, grip strength, or pain pressure dolorimetry. Some studies asked about the actual presence of pain; others asked about the changes in the severity of the pain condition or number of times the pain occurred over the course of a month. There were, unfortunately, inconsistencies in methodology within a given pain condition and as the numbers of studies grow, this variation in approaches for a given condition limited our ability to perform a meta-analysis that could provide evidence on which treatment decisions could be made.

Oddly, although studies looked at women who had a CNCP condition, most did not consider treatment for the pain as one of the variables to be investigated or controlled for. Unless the study was about giving hormones as a treatment, none reported whether patients were undergoing treatment, the type of treatment, the degree of pain relief, or the adequacy of the pain treatment. None of these studies reported on the use of opioid medications or even the use of psychotropic drugs commonly used to treat either CNCP conditions in itself or psychiatric comorbidities which could have an effect on patients’ pain severity (Doressman et al., 2000). This seems like a serious oversight since it has been reported that ovarian hormones might modulate pain medications, especially opioids, and in turn may affect their potency, efficacy and selectivity (Craft, 2003b; Craft, Mogil, & Aloisi, 2004). Moreover, it is possible
that different medications might be more or less effective as a treatment and being on different medications with the same condition might affect whether or not the pain of a given condition varied with menstrual cycle stage. For example, some opioids are less effective in women than others (Craft, 2003b; Fillingim & Gear, 2004; Gear, et al., 1996; Sarton, et al., 2000; Sarton, Teppema, & Dahan, 1999). Additionally, it is possible that if women were being treated, it might be the medication that was more or less effective at different stages of the menstrual cycle. Pain medications themselves are known to be affected by estrogen and progesterone (Craft, 2003b; Craft, Mogil, & Aloisi, 2004). Alternatively, if women were being treated using mindfulness or cognitive behavioral therapy, other symptoms of the menstrual cycle such as bloating and cramping might affect their ability to carry out these therapies thereby affecting their pain levels. Thus, treatment is an important variable to be considered in any study of the relationship of chronic pain conditions and ovarian hormones.

With the exception of the acknowledgement that endometriosis often overlaps with IBS, all of the 50 studies investigated the relation between the menstrual cycle and only one CNCP condition. This is surprising since it is well known that CNCP conditions rarely occur as single entities but rather as multiple conditions with overlapping symptoms (McNeill, 1997; Rollman & Gillespie, 2000). In fact it may be more appropriate to think of CNCP as a constellation of conditions. Dao and colleagues (1997), who found that 70% of the fibromyalgia patients reported orofacial pain, suggested that facial pain may be part of the clinical presentation of fibromyalgia. Similarly, Klineberg et al. (1998) suggested that generalized or localized pain may be variations of a similar problem. Moreover, many studies suggested that associations between pain conditions make it difficult to reach adequacy in pain treatment (Von Korff, Le Resche, & Dworkin, 1993; John, Miglioretti, LeResche, Von Korff, & Critchlow, 2003; Raphael &
Marbach, 2001). In a study by Fillingim and his colleagues, women experiencing premenstrual dysphoric disorder (PMDD) showed higher ischemic pain sensitivity than controls during menses (Fillingim et al., 1995), supporting the notion that mood conditions that cycle might affect pain chronicity. In another study, Fillingim and his colleagues showed that females with PMDD are more vulnerable to TMD than women without PMDD (Fillingim et al., 2004). In fact, CPP has been reported to overlap with other CNCP conditions in many studies (Warren et al., 2011). Perhaps then, most important with respect to periodicity of pain related to the menstrual cycle would be the co-incidence of CNCP conditions that themselves are involved in the menstrual cycle such as cyclic CPP (for example: endometriosis, IBS, migraine) (Fillingim et al., 2005; Wesselmann et al., 2006). With this in mind, it is possible that underlying cyclic CPP or cyclic mood disorders such as PMDD is responsible for the noted variations of pain severity across the menstrual cycle in the literature.
2.4 Conclusion

In the past decade, numerous findings in animals and humans studies have indicated the role of ovarian hormones in modulating pain and opioids. Additionally, many studies have reported that women are the majority of CNCP patients with peak prevalence during the reproductive years. It is therefore not surprising that growing number of studies have examined the contribution of ovarian hormones in modulating CNCP conditions using various study designs and paradigms and, indeed, many studies have reported the role of ovarian hormones.

After reviewing these studies and despite all the discrepancies and inconsistencies in definitions of the menstrual cycle phases as well as methodologies used to measure pain, we concluded that the majority of studies find some variations in pain severity or sensitivity that is correlated with phases of the menstrual cycle. Moreover, apart from whether these variations are related to low levels of estrogen or fluctuations in the levels of ovarian hormones and regardless of which phase of the menstrual cycle is related to increase pain intensity or sensitivity, the role of ovarian hormones in modulating CNCP conditions under investigation and even in successfully alleviating some of these pain conditions is compelling. However, the fact, that none of these studies had considered neither type of treatment for the pain nor the possibility of co-occurrence of more than one pain conditions as one of the variables to be investigated or controlled for, undermines the usefulness of the extant literature for formulating treatment protocols leaving a huge gap in the literature on ovarian hormones and CNCP conditions.
Chapter 3

Retrospective Chart Review of Three Patient Groups at a Specialized Pain Clinic

3.1 Purpose

In light of the conclusions presented at the end of chapter 2, it seemed timely to carry out a chart review of a clinical practice to determine how what is in the literature had been adopted in clinical settings. Therefore, a retrospective chart review was conducted of CNCP patients referred to a specialized chronic pain clinic in a large, Canadian city. The pain clinic studied is a multidisciplinary pain center for outpatients focusing on providing multidisciplinary approaches to patients with CNCP with the goal of improving quality of life and facilitating a return to regular daily activities. Beside pain and psychotropic prescriptions, physicians incorporate other pain management modalities to help each patient, for example: cognitive-behavioral therapy sessions, biofeedback and relaxation training, stress management, and cognitive restructuring to decrease pain catastrophizing and pain anxiety. All patients at this clinic are referred from primary care facilities as they are considered as complicated cases, refractory to regular approaches and needing of more sophisticated pain management. Once at the clinic, patients are triaged by a nurse practitioner according to the single most severe pain complaint.

Charts for both sexes were reviewed in order to ascertain any sex differences in practice. As well comparing the pain characteristics of the women and the men might provide insight into what conditions and responses were more likely due to fluctuations in estrogens. The primary
objective of this cart review was to determine whether or not the severity of CNCP conditions varied across the menstrual cycle or with any other events associated with changes in the levels of ovarian hormones. Specifically, charts were scanned for: (i) the type of information gathered from males and females, as well as, type of opioids used; and (ii) any information about ovarian hormones including menstrual fluctuation to pain.

3.2 Hypotheses

Based on the animal as well as the human literature, the hypotheses were that: (i) there would be more women than men seeking clinical help, (ii) women would be the majority of patients with CPP; (iii) women would be the majority of patients receiving opioid treatment; (iv) more women would be in their reproductive years; (v) ovarian hormones level would correlate with the severity of the pain scores; (vi) women would be treated preferentially with kappa opioids and men with mu opioids; (vii) women would experience differences in the efficacy of their opioid treatment with different stages of the menstrual cycle; (viii) without adjustment of opioid dosage to the menstrual cycle, cycling women would show more problematic use of opioids.

3.3 Methods

After obtaining approval from the Research Ethics Board from both The University of Toronto and Mount Sinai Hospital (Appendix: B, C), a retrospective chart review was conducted of three different practices within the center. Each practice treated a different type of patients:
Practice 1; patients receiving opioid medications (neurologist), Practice 2; patients who were experiencing problematic opioid use (addiction specialist), Practice 3; patients not being treated with opioids (Dentist). From July 1, 2012 until July 31, 2013, 264 patients were uniquely represented in one of these three practices. Patients with cancer pain were excluded and patients with missing data were omitted, leaving only 254 patients with CNCP. Patients referred from one practice to another were only counted in one practice (e.g., someone in the non-opioid prescribing practice moving over to the opioid prescribing practice would only be counted in the latter).

We chose the term Problematic Opioid Use as it reflects the group of patients whose symptoms ranged from misuse (opioid misuse = the intentional or unintentional use of prescribed medication other than prescribed), abuse (abuse = the intentionally self-administration of medication for non-medical purpose) and addiction (addiction = the impaired control over drug use compulsive use continued despite harm) (Smith et al., 2013). From reviewing the charts alone, we could not differentiate between these three conditions. Therefore, we used this term that indicated a problem with the opioids prescribed for pain. This term was also commonly used in the charts themselves.

Data collected included: sex, age, pain condition, duration of pain condition, the long form of McGill Pain Questionnaire ; (Pain Rating Index, PRI) (Melzack, 1983), Pain Intensity Scale scores (Hawker et al., 2011), Pain Catastrophizing Scale scores (Sullivan et al., 1995), history of surgery or trauma, types of pain medications, Hamilton Anxiety Scale (HAS) (Hamilton, 1969), Beck Depression Inventory (BDI) for depression (Beck, 2006), history of drug abuse, and whether or not patient had an opioid misuse (Appendix: A). Data were collected at the
Pain Management Centre and was, then, analyzed at the laboratory for Cognitive Neuroscience and Women’s Health in the Department of Psychology, University of Toronto.

### 3.4 Confidentiality

To maintain confidentiality and anonymity of patients for the chart review, a key code was developed for each patient. The key code that contained the patient’s name, medical record number, and patient study number was stored at the clinic in a locked file cabinet in the research coordinator’s office. De-identified data were entered into a password protected electronic spreadsheets and kept on an encrypted USB. The chart review de-identified data collection spreadsheet was transferred from the clinic according the Data Sharing Agreement (Appendix: D) to be analyzed at the laboratory for Cognitive Neuroscience and Women’s Health in the Department of Psychology, University of Toronto.

### 3.5 Statistical Analysis

Data were analyzed using SPSS (SPSS 15.0.1, 2006, Chicago - Illinois. Software Inc.) According to opioids use, patients were divided into three groups: patients under opioid treatment, (UOT), patients with problematic opioid use, (POU) and patients not under opioid treatment (NOT).

Mean and standard deviation were calculated for patient characteristics that were in the form of continuous numerical variables. In order to study sex differences between nominal
variables, a comparison between female and male patients with CNCP was made for each group. P values <0.05 were considered significant and Pearson chi-square test was used.

To test for age differences in female patients, the age as a variable was divided into two periods: those who were 18-48 (as a proxy for women’s reproductive years; 49-71 (as a proxy for women in menopause). Therefore, the continuous variable of age was transformed into a nominal variable. In order to compare between the two age groups in female patients with MPC, CPP and problematic opioid use, we used a Pearson chi-square test. Patients with missing data were omitted from the total number of charts reviewed.

3.6 Results

Number of Patients

After exclusion of cancer patients and all patients with missing data, there were a total of 254 charts comprising female and male patients all three practices: 174 females and 80 males. Similar to other studies, this retrospective chart review found that in these three groups, women were disproportionately affected by CNCP conditions; overall, two-thirds were women. Thus, there was a significant sex difference in the number of patients (women =174 (69%); men = 80 (31%)) (χ² =34.787, df= 1, p=0.000). Notably, although there was no statistically significant sex difference in number of patients in the POU group, there was a significantly higher prevalence of history of drug abuse among male patients compared to female patients. There were also far more women than men in the NOT group; this may simply reflect the fact that this practice was primarily of people with TMD which is known to be more prevalent in women (LeResche et al., 2003).
Table 6: Number of patients in the three groups.

<table>
<thead>
<tr>
<th>Patients groups</th>
<th>Women # (%)</th>
<th>Men # (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>UOT</td>
<td>85 (70)</td>
<td>37 (30)</td>
<td>122</td>
</tr>
<tr>
<td>POU</td>
<td>44 (56)</td>
<td>35 (44)</td>
<td>79</td>
</tr>
<tr>
<td>NOT</td>
<td>45 (85)</td>
<td>8 (15)</td>
<td>53</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>174 (69)</strong></td>
<td><strong>80 (31)</strong></td>
<td><strong>254</strong></td>
</tr>
</tbody>
</table>

UOT: Patients under opioid treatment  
POU: Patients with problematic opioid use  
NOT: patients not under opioid treatment

**Patient Characteristics**

The mean age of patients at their initial visit was 43(SD: ±13, ranged 21-71) years.

Patients reported having CNCP condition for a mean duration of 10 years (SD: ± 8, ranged 2 -16 years) prior to referral to the Clinic. No other patients’ demographics were found, for example: no data were found regarding race and ethnicity, culture and socioeconomic status, or level of education.
Table 7: Patients’ characteristics (*A statistically significant sex difference)

<table>
<thead>
<tr>
<th>Groups</th>
<th>UOT</th>
<th>POU</th>
<th>NOT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>*No. of patients (%)</td>
<td>85(70)</td>
<td>37(30)</td>
<td>44(56)</td>
</tr>
<tr>
<td>Age (yrs): Mean (SD)</td>
<td>42(12)</td>
<td>46(15)</td>
<td>43(13)</td>
</tr>
<tr>
<td>Duration (yrs): Mean (SD)</td>
<td>10(8)</td>
<td>9(9)</td>
<td>14(11)</td>
</tr>
<tr>
<td>McGill Pain Questionnaire (PRI): Mean (SD)</td>
<td>35(11)</td>
<td>29(14)</td>
<td>34(14)</td>
</tr>
<tr>
<td>Pain Catastrophizing scale: Mean (SD)</td>
<td>29(11)</td>
<td>29(11)</td>
<td>28(12)</td>
</tr>
<tr>
<td>Pain Intensity: mean (SD)</td>
<td>7(2)</td>
<td>6(2)</td>
<td>7(2)</td>
</tr>
<tr>
<td>Depression (BDI): Mean (SD)</td>
<td>22(13)</td>
<td>24(16)</td>
<td>31(13)</td>
</tr>
<tr>
<td>Anxiety (HAS): Mean (SD)</td>
<td>10(5)</td>
<td>12(6)</td>
<td>12(6)</td>
</tr>
<tr>
<td>*H/o of surgery (%)</td>
<td>42(49)</td>
<td>10(27)</td>
<td>29(65)</td>
</tr>
<tr>
<td>*H/o drug abuse (%)</td>
<td>22(26)</td>
<td>10(27)</td>
<td>13(30)</td>
</tr>
<tr>
<td>H/o sexual abuse (%)</td>
<td>5(6)</td>
<td>-</td>
<td>6(14)</td>
</tr>
</tbody>
</table>

UOT: Patients under opioid treatment
POU: Patients with problematic opioid use
NOT: Patients not under opioid treatment
H/O: History of surgery, drug, sexual abuse
The charts did not contain any data that reflect that sex differences in pain and treatment were considered. This meant that there was no information regarding the levels of ovarian hormones or the relationship of the menstrual cycle to either the pain condition(s) or treatment. Differences did emerge however. For example, all patients were asked if they had a history of sexual abuse. Women answered this question with 14 across the three groups reporting that they did. Men, did not fill out this question saying neither yes nor no answered the question and positively reported a history of sexual abuse, none of the men answered this question did. While asked of men, none answered this question.

**Fig. 4: Sex differences in the number of patients presenting with CNCP conditions between the three groups.**

<table>
<thead>
<tr>
<th>Patients' groups</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>UOT</td>
<td></td>
</tr>
<tr>
<td>POU</td>
<td></td>
</tr>
<tr>
<td>NOT</td>
<td></td>
</tr>
</tbody>
</table>

UOT: Patients under opioid treatment
POU: Patients with problematic opioid use
NOT: patients not under opioid treatment
Women with CNCP

Not only were women the majority of CNCP patients, 74% of these women were in their reproductive years (n=124) ($\chi^2=29.793$, df =1, p=0.000, Table 8). Among patients in the two groups using opioids, 74% (n=96) of those patients were in their reproductive years.

Table 8: Number of women in their reproductive years

<table>
<thead>
<tr>
<th>Patient groups</th>
<th>Women patients #</th>
<th>Women patients in reproductive years # (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UOT</td>
<td>85</td>
<td>63 (74)</td>
</tr>
<tr>
<td>POU</td>
<td>44</td>
<td>33 (75)</td>
</tr>
<tr>
<td>NOT</td>
<td>45</td>
<td>28 (62)</td>
</tr>
<tr>
<td>Total</td>
<td>174</td>
<td>124 (74)</td>
</tr>
</tbody>
</table>

UOT: Patients under opioid treatment
POU: Patients with problematic opioid use
NOT: patients not under opioid treatment
Fig. 5: Women with CNCP in their reproductive years

UOT: Patients under opioid treatment
POU: Patients with problematic opioid use
NOT: patients not under opioid treatment
Frequencies of different CNCP conditions

Sex differences were found in the frequencies of types of CNCP. In women, CPP was the most common pain condition (45%) followed by Fibromyalgia, TMD, Low Back Pain (LBP) and Migraines, while in men, LBP was the most common (39%) followed by fibromyalgia and TMD.

Table 9: Frequencies of different CNCP conditions

<table>
<thead>
<tr>
<th>CNCP conditions</th>
<th>Patients’ groups</th>
<th>CPP</th>
<th>TMD</th>
<th>Fibro.</th>
<th>LBP</th>
<th>Migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>W</td>
<td>M</td>
<td>W</td>
<td>M</td>
<td>W</td>
<td>M</td>
</tr>
<tr>
<td>UOT</td>
<td>42</td>
<td>7</td>
<td>10</td>
<td>6</td>
<td>38</td>
<td>14</td>
</tr>
<tr>
<td>POU</td>
<td>25</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>NOT</td>
<td>13</td>
<td>2</td>
<td>45</td>
<td>8</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
<td>12</td>
<td>62</td>
<td>16</td>
<td>78</td>
<td>24</td>
</tr>
</tbody>
</table>
Fig. 6: Sex differences in frequencies of CNCP

Sex difference in frequencies of CNCP conditions

<table>
<thead>
<tr>
<th>Patients' groups</th>
<th>CPP</th>
<th>LBP</th>
<th>Fibro</th>
<th>TMD</th>
<th>Migraines</th>
</tr>
</thead>
<tbody>
<tr>
<td>UOT ♂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UOT ♂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POU ♂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POU ♂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOT ♂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOT ♂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

UOT: Patients under opioid treatment  
POU: Patients with problematic opioid use  
NOT: patients not under opioid treatment
Chronic Pelvic Pain

A statistically significant sex difference was found between men and women within CPP ($\chi^2=22.764$, df = 1, p=0.000). The prevalence of CPP was 46% in women, and only 15% in men. In patients under opioid treatment, the prevalence of CPP was also much higher among women than among men: 52% in women, and only 14% in men. In patients suffering from problematic opioid misuse, the prevalence of CPP was 57% in women, and 9% in men.

Table 10: Number of patients with CPP in the three groups

<table>
<thead>
<tr>
<th>Patients groups</th>
<th>Women with CPP # (%)</th>
<th>Men with CPP # (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UOT</td>
<td>42 (49)</td>
<td>7 (19)</td>
</tr>
<tr>
<td>POU</td>
<td>25 (57)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>NOT</td>
<td>13 (29)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Total</td>
<td>80 (46)</td>
<td>12 (15)</td>
</tr>
</tbody>
</table>

UOT: Patients under opioid treatment  
POU: Patients with problematic opioid use  
NOT: patients not under opioid treatment
Fig. 7: Sex differences in CPP

UOT: Patients under opioid treatment
POU: Patients with problematic opioid use
NOT: Patients not under opioid treatment
Women with CPP

In addition to the high prevalence among women in comparison to men, CPP in women was statistically significantly more likely to occur during the reproductive years within the population of women for this study ($\chi^2 = 4.643$, df= 1, p<0.05).

Table 11: Number of women patients with CPP in the three groups

<table>
<thead>
<tr>
<th>Patients groups</th>
<th>Women #</th>
<th>Women with CPP # (%)</th>
<th>Women with CPP in reproductive years # (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UOT</td>
<td>85</td>
<td>42 (49)</td>
<td>34 (81)</td>
</tr>
<tr>
<td>POU</td>
<td>44</td>
<td>25 (57)</td>
<td>21 (84)</td>
</tr>
<tr>
<td>NOT</td>
<td>45</td>
<td>13 (29)</td>
<td>8 (79)</td>
</tr>
<tr>
<td>Total</td>
<td>174</td>
<td>80 (46)</td>
<td>63 (80)</td>
</tr>
</tbody>
</table>

UOT: Patients under opioid treatment
POU: Patients with problematic opioid use
NOT: patients not under opioid treatment
Fig. 8: Women with CPP in their reproductive years

<table>
<thead>
<tr>
<th>% of patients</th>
<th>UOT: Patients under opioid treatment</th>
<th>POU: Patients with problematic opioid use</th>
<th>NOT: patients not under opioid treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>81%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>84%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>79%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Multiple pain conditions

The number of CNCP conditions in MPC ranged from one pain condition to five pain conditions. Hundred and twenty seven of 174 (72%) female patients reported MPC, while 22 out of 80 (28%) of the male patients did so. Thus, there was a statistically significant sex difference between female and male patients with MPC ($\chi^2 =46.673$, df= 1, p=0.000).

Table 12: Number of patients with MPC in the three groups

<table>
<thead>
<tr>
<th>Patients groups</th>
<th>Women with MPC # (%)</th>
<th>Men with MPC # (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UOT</td>
<td>62 (73)</td>
<td>9 (24)</td>
</tr>
<tr>
<td>POU</td>
<td>38 (86)</td>
<td>10 (29)</td>
</tr>
<tr>
<td>NOT</td>
<td>27 (60)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Total</td>
<td>127 (72)</td>
<td>22 (28)</td>
</tr>
</tbody>
</table>

UOT: Patients under opioid treatment  
POU: Patients with problematic opioid use  
NOT: patients not under opioid treatment
Fig. 9: Sex differences in MPC

Women with MPC

Out of 106 women patients (total number of women patients who were in their reproductive years, 95 (90%) of those patients had MPC. Additionally, the number of women present with MPC was statistically significant higher for those in their reproductive years than those in their menopause ($\chi^2 = 5.450$, df = 1, p = 0.020).
Table 13: Number of women with MPC in their reproductive years

<table>
<thead>
<tr>
<th>Patient groups</th>
<th>Women patients #</th>
<th>Women patients with MPC # (%)</th>
<th>Women patients with MPC in reproductive years # (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UOT</td>
<td>85</td>
<td>62 (73)</td>
<td>48 (77)</td>
</tr>
<tr>
<td>POU</td>
<td>44</td>
<td>38 (86)</td>
<td>31 (82)</td>
</tr>
<tr>
<td>NOT</td>
<td>45</td>
<td>27 (60)</td>
<td>16 (59)</td>
</tr>
<tr>
<td>Total</td>
<td>174</td>
<td>127 (72)</td>
<td>95 (75)</td>
</tr>
</tbody>
</table>

Fig 10: Women with MPC in their reproductive years

UOT: Patients under opioid treatment
POU: Patients with problematic opioid use
NOT: Patients not under opioid treatment
MPC associated with CPP

There was a statistically significant sex difference in CPP as one of the MPC ($\chi^2$=11.521, df =1, p=0.001). The prevalence of CPP in patients with MPC was 53% in women (n= 67), and 14% in men (n=3). Notably, in both groups where patients were under opioid treatment (UOT and POU), the prevalence of CPP in patients with MPC was 56% in women and only 5% in men.

Table 14: Number of patients with CPP & MPC

<table>
<thead>
<tr>
<th>Patients groups</th>
<th>Women with MPC # (%)</th>
<th>Women with MPC &amp; CPP #(%)</th>
<th>Men with MPC # (%)</th>
<th>Men with MPC&amp;CPP # (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UOT</td>
<td>62 (73)</td>
<td>34(53)</td>
<td>9 (24)</td>
<td>0(0)</td>
</tr>
<tr>
<td>POU</td>
<td>38 (86)</td>
<td>22(58)</td>
<td>10 (29)</td>
<td>1(10)</td>
</tr>
<tr>
<td>NOT</td>
<td>27 (60)</td>
<td>11(37)</td>
<td>3 (38)</td>
<td>2(67)</td>
</tr>
<tr>
<td>Total</td>
<td>127 (72)</td>
<td>67(53)</td>
<td>22( 28)</td>
<td>3(14)</td>
</tr>
</tbody>
</table>

UOT: Patients under opioid treatment
POU: Patients with problematic opioid use
NOT: patients not under opioid treatment
Women with MPC and CPP

Women with MPC and CPP were significantly more likely to be within their reproductive years (n= 53; 79%) ($\chi^2=5.945$, df=1, p=0.015).
Table 15: Number of Women patients with MPC and CPP in their reproductive years

<table>
<thead>
<tr>
<th>Patients groups</th>
<th>Women with MPC #(%)</th>
<th>Women with MPC and CPP # (%)</th>
<th>Women with MPC and CPP in their reproductive years #(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UOT</td>
<td>62 (73)</td>
<td>34 (53)</td>
<td>27 (79)</td>
</tr>
<tr>
<td>POU</td>
<td>38 (86)</td>
<td>22 (58)</td>
<td>20 (95)</td>
</tr>
<tr>
<td>NOT</td>
<td>27 (60)</td>
<td>11 (37)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Total</td>
<td>127 (72)</td>
<td>67 (53)</td>
<td>53 (79)</td>
</tr>
</tbody>
</table>

UOT: Patients under opioid treatment  
POU: Patients with problematic opioid use  
NOT: patients not under opioid treatment

Fig 12: Women with MPC and CPP in their reproductive years

UOT: Patients under opioid treatment  
POU: Patients with problematic opioid use  
NOT: patients not under opioid treatment
Types of opioids used

Each chart was examined for the types of treatments patients were given. Therapies varied both in type and in modalities. On average, patients had been prescribed six different kinds of treatment, ranging from antidepressant medications (Cymbalta; duloxetine, serotonin-norepinephrine reuptake inhibitor (SNRI), Elavil; amitriptyline, tricyclic antidepressants), and anticonvulsants (Lyrica; pregabalin, gabapentin, carbamazepine; anticonvulsant and mood stabilizer) to nerve blocks, local steroid injections, Botox injections, physiotherapy, massage, acupuncture, psychotherapy, mindfulness, chiropractor, and aggressive treatment such as opioids. No statistically significant difference was found between men and women in type of opioids prescribed. Additionally, there were no sex differences in number of patients with problematic opioid use (POU). However, more men than women transitioned to opioid abuse.

Fig. 13: Sex differences in types of opioids used

Sex differences in opioids

UOT: Patients under opioid treatment
POU: Patients with problematic opioid use
NOT: patients not under opioid treatment
Notably, although we didn’t find any sex differences in number of patients with problematic opioid use (POU), there was, however, a statistically significant positive correlation between duration of the pain condition and development of problematic opioid use, especially among women ($r=361$, $p=0.000$).

**Fig. 14: Duration and Problematic opioid use**
Women with Problematic Opioids Use

Women who suffer from problematic opioid use were statistically significantly more likely to be in their reproductive years (n= 33, 75%) ($\chi^2=4.506$, df=1, p=0.034).

Table 16: Number of female patients with Problematic Opioids Use in their reproductive years

<table>
<thead>
<tr>
<th>Patients group</th>
<th>Women with Problematic Opioids Use #</th>
<th>Women with Problematic Opioids Use in their reproductive years #(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POU</td>
<td>44</td>
<td>33 (75)</td>
</tr>
</tbody>
</table>

Fig. 15: Women with POU in their reproductive years

POU: Patients with problematic opioid use
History of Surgery

History of surgery differed between women and men across the three practices ($\chi^2 = 28.675$, df =1, p=0.000). Moreover, a significant positive association was found between history of surgery and MPC ($\chi^2 = 6.310$, df =1, p=0.012). Additionally, 66% of women who had a history of surgery, had their surgical procedures conducted in the abdominopelvic area with surgeries ranging from hysterectomy and laparoscopy. These may have been treatment for CPP but that was not clear from the charts.

Table 17: Sex differences in history of surgery

<table>
<thead>
<tr>
<th>Patients groups</th>
<th>Women with History of Surgery # (%)</th>
<th>Men with History of Surgery # (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UOT</td>
<td>42 (49)</td>
<td>10 (27)</td>
</tr>
<tr>
<td>POU</td>
<td>29 (65)</td>
<td>16 (46)</td>
</tr>
<tr>
<td>NOT</td>
<td>10 (21)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Total</td>
<td>81 (46)</td>
<td>27 (33)</td>
</tr>
</tbody>
</table>

UOT: Patients under opioid treatment  
POU: Patients with problematic opioid use  
NOT: patients not under opioid treatment
Fig. 16: Sex differences in history of surgery

Sex differences in History of Surgery

<table>
<thead>
<tr>
<th>Sex</th>
<th>UOT</th>
<th>POU</th>
<th>NOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>50%</td>
<td>60%</td>
<td>20%</td>
</tr>
<tr>
<td>Men</td>
<td>50%</td>
<td>40%</td>
<td>30%</td>
</tr>
</tbody>
</table>

UOT: Patients under opioid treatment
POU: Patients with problematic opioid use
NOT: Patients not under opioid treatment

Table 18: Types of surgeries

<table>
<thead>
<tr>
<th>Types of Surgeries</th>
<th>Number of Surgeries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopy</td>
<td>20</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>25</td>
</tr>
<tr>
<td>Cystoscopy or gastroscopy</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
</tr>
</tbody>
</table>
3.7 Discussion

This is the first chart review of a specialized pain clinic with a focus on comparing the charts of males and females and for females, determining any correspondence of pain conditions and treatment with ovarian hormones. It is also the first study to obtain data in patients, diagnosed with CNCP referred to a tertiary clinic, regarding sex differences and multiple pain conditions (MPC). This is an important first step to understanding how what is known in the experimental literature is put into practice in the clinic.

Based on the literature reviewed, eight hypotheses were formulated: (i) there would be more women than men seeking clinical help, (ii) women would be the majority of patients with CPP; (iii) women would be the majority of patients under opioid treatment (iv) more women would be in their reproductive years, (v) ovarian hormone levels would correlate with the severity of the pain scores, (vi) women would be treated preferentially with kappa opioids and males with mu opioids, (vii) women would experience differences in the efficacy of their opioid treatment with different stages of the menstrual cycle; (viii) without adjustment of opioid dosage to the menstrual cycle, cycling women would show more problematic use of opioids.

A total of 256 charts of female and male patients from three main different practices at the clinic were reviewed retrospectively. Surprisingly, no difference in type of information gathered from male and female patients was found. One area of fairly serious silence was on the question of sexual abuse. Consequently, no data were found on the levels of ovarian hormones in female patients or any possible relationship between ovarian hormones or the menstrual cycle and the treated pain condition. Specifically, there was no information in the charts as to whether or not pain severity varied across the menstrual cycle or even with any other events associated with changes in the levels of ovarian hormones such as: pregnancy, menopause, or the use of
exogenous intake of ovarian hormones such as OCP or HRT. This was the case even in the charts of women with CPP which is often associated or treated with sex hormones or their analogues. This lack of information made it difficult to acquire information directly about hypotheses iii, v, and vi. It was, however, clear that in spite of successful RCTs of hormone administration for CPP treatment, no hormonal treatment methods were used in this clinic and there were important signs that gathering such information might be useful (see section 2.2.4).

As hypothesized, women were the majority of patients representing a full two-thirds of CNCP patients in the three practices. In comparing the charts of men and women, no sex differences were found regarding McGill Pain Scale scores (Pain Rating Index, PRI), Pain Intensity Scale scores, or Pain Catastrophizing Scale scores. These findings suggest that the both men and women seek relief for pain when it reaches the same perceived intensity and despite having the burden of different pain conditions, catastrophize equally about their pain.

Surprisingly, little or no demographic data were collected regarding patients’ race, ethnicity or socioeconomic status; although evidence that both gender and the social world as well as sex and the biological, as factors that strongly influence the patient’s pain experience is increasingly emerging with the realm of pain (Bailey et al., 2013; Mailis-Gagnon et al., 2007; Chang et al., 2006). While some questions were asked, they received no answers. For example, while some women answered the question on whether they had suffered sexual abuse (14 answered in the affirmative), this seems like a seriously low percentage and men never answered the question. A history of sexual abuse has been closely correlated to CPP both in both men and women (Paras et al., 2009; Itza et al., 2010; Laumann et al., 1999), thus, this seems like a serious omission.
As hypothesized, women were also the majority of CPP patients. Surprisingly, in spite of the fact that the greatest number of women had CPP, no information was documented about the menstrual cycle or any correlation of pain or failure of treatment during different phases of the menstrual cycle. Since opioid efficacy is known to vary with ovarian steroid levels and the majority of women with CPP were being treated with opioids, information about ovarian steroid levels might be important to successful treatment. Indeed, this chart review revealed that the number of women with problematic opioid use in their reproductive years was a full one third. CPP was the most common CNCP condition to occur in women; while in men, LBP was the most common. One reason for the preponderance of CPP is that this clinic is known to treat CPP. This might also account for what seems to be a high (albeit lower) preponderance of CPP in men. It may even be that CPP levels are higher for men than represented with LBP acting as a proxy in men for CPP (Davis et al., 2013).

The study revealed that, at least in this practice, CNCP conditions rarely occur as single entities but rather as multiple pain conditions with overlapping symptoms. Although, other studies had previously reported that CNCP usually exist as a constellation of conditions (McNeill, 1997; Rollman & Gillespie, 2000), little is known about the pattern and frequencies of different CNCP condition occurring within this constellation. This study is the first to demonstrate that these MPC span different pain conditions that include chronic headaches, TMD, fibromyalgia and CPP. Interestingly, most of these MPC included CPP, suggesting that hormone treatment or study might be helpful.

This retrospective chart review is the first study to obtain data in patients with MPC that includes a comparison by sex in the prevalence and the pattern of overlapping CNCP conditions. In fact, women were disproportionally affected by MPC when compared to men. With respect to the pattern of MPC, the prevalence of CPP in patients with MPC was 55% in women and only
9% in men, which suggests that a sensitivity of pain conditions to ovarian steroids could very well be due to a co-existing condition of CPP. Our literature review revealed no published studies investigating any relationship between another CNCP conditions and CPP. In fact, most of these studies had considered women with CPP an exclusion criterion (Doa et al., 1998; Okifuji & Turk, 2006; Latman, 1983).

Moreover, although very few women in the present study had CPP in the absence of underlying pathology, the majority who had a CPP co-occurring with other CNCP conditions had endometriosis (an estrogen dependent disease), dyspareunia (deep pain with sexual intercourse), IBS and pelvic inflammatory disorders. These estrogen-sensitive conditions co-occurred with other CNCP conditions such as fibromyalgia, chronic migraines, TMD and LBP, again suggesting that one estrogen-dependent condition might influence the others. This chart review also revealed that the prevalence rates were higher in women than in men; the prevalence rates of women suffering from CNCP conditions, MPC and CPP peaked during their reproductive years. This surprisingly high prevalence is also suggestive of a potential role of ovarian hormones in modulating the severity of their CNCP conditions. A significant positive correlation was found between history of surgery especially hysterectomy and laparoscopy and MPC, indicating the possibility of existing endometriosis and MPC. Again, this evidence suggests the role of ovarian hormones.

The chart review also revealed that patients with CNCP receive different types of treatments with the average number of treatments patients being six. These include antidepressant and anticonvulsant medications, nerve blocks, local steroid injections, Botox injections, physiotherapy, massage, acupuncture, psychotherapy, mindfulness, chiropractor, and more aggressive treatment such as opioids.
One hypothesis was that women receiving opioids would receive kappa opioids and men, mu. However, there was no difference between men and women in type of opioids prescribed for men and women, all were prescribed varieties that act mostly at the mu receptor. This is surprising since women tend to respond better to kappa (κ) – opioid drugs and men, to mu (μ) – opioids (Gear et al., 1996). The finding that the prevalence of problematic opioid misuse was higher among women in their reproductive years suggests that prescribing kappa opioids to women exclusively as well as monitoring their effects with different stages of the menstrual cycle might produce more successful pain management.

Interestingly, even though the percentage of women treated with opioids was higher than that of men, men were more likely to transition to opioid misuse. However, in spite of some women being given kappa opioids as well as mu, many also transitioned to problematic opioid use.

Another hypothesis was that women might transition to problematic opioid use because opioid efficacy is altered by changes in the levels of ovarian hormones and thus they are not receiving optimal relief leaving them to develop problematic opioid use. The occurrence of problematic opioid use may also be due to the fact that some women received mu and some men, kappa opioids. Attention to the type of opioid prescribed might be beneficial. There was also a statistically significant positive correlation between duration of pain condition and problematic opioid use in women within their reproductive years. This finding supports the idea that their opioids are not as effective due to the fluctuations of ovarian hormones. This, in turn, might make women more vulnerable for problematic opioid use over time, and susceptible to relapse at certain phases of their cycle.

Taken together, the data from this chart review is highly suggestive of an underlying role for ovarian hormones both in modulating and in the efficacy of pain treatment.
Strengths and Limitations of the study

The major strength of this study was that it was a chart review focused on determining the characteristics of both patients and their treatments in a tertiary care pain clinic. Charts were searched specifically to determine if there were sex differences in the practices and if understandings about the role of ovarian hormones in pain perception as well as treatment efficacy were incorporated. By doing so, the chart review revealed important lacunae in knowledge underscoring the difficulty of bringing research to bear on clinical practice.

As for the weakness of this study, that retrospective chart reviews often utilize data that are not originally collected for a research purpose. Therefore, as with all retrospective reviews, the data were limited. Data were not collected prospectively in a standardized fashion. As well, data for each variable were not available in every chart. Third, the patient population studied was only of those patients referred to a tertiary chronic pain clinic knowing for treating CPP. Therefore, it is not possible to generalize these findings to the population of people with CNCP as a whole. In spite of these limitations, however, this retrospective chart review provides a snapshot of what is and is not incorporated into clinical practice from the research literature and opens further paths for future research capable of bringing new knowledge into practice.
Chapter 4

Conclusion and Future Directions

4.1 Conclusion

Chronic pain is a worldwide problem with much of the burden being carried by women in their reproductive years (Fillingim & Ness, 2000; Turner, et al., 2004). Successful treatments are few and far between with one of the most efficacious treatments, opioid analgesics, creating problems of misuse, dependency, and other physiologically debilitating side-effects when used long term (Savage, 1996; Bendtsen et al., 1999; Sjøgren et al., 2000; Breivik, 2001; Ballantyne & Mao, 2003). One promising area of research with the potential of improving care for women is that of sex differences which highlights the emerging understanding of the role of ovarian hormones in modulating both pain and its treatments, including opioids. This research would seem especially pertinent since women bear disproportionately the burden of chronic pain conditions suggesting that this might require sex-specific solutions. This approach is in line with the emerging field of personalized medicine and, more pertinently, with the philosophies and practices of many tertiary pain clinics.

Before changing practice, however, it is important to determine what is and is not known and to ascertain the best evidence. A review of the literature on sex differences in pain revealed that it is well accepted in both animal and human models that females have lower pain thresholds and respond differently to opioid analgesics than males (Chapter 1). Indeed, the International
Society for the Study of Pain has published several extensive reviews of the pain literature showing that sex differences should be taken into account; one highly influential paper goes so far as to describe best practices in accounting for and measuring hormones in women in their reproductive years (Greenspan et al., 2007). Animal studies provide mechanisms for the role of ovarian hormones on pain sensation in females showing that estrogen receptors are located in every region of the central nervous system engaging in the pain response.

A review of the literature on the role of ovarian hormones on the pain associated with CNCP conditions specifically associated with women—MSP, migraine headache, TMD, and CPP—revealed that there was a paucity of clinical literature studying these conditions. After thoroughly reviewing these studies, almost all of them had reported that when estrogen levels were high, pain severity was actually at its lowest, and correspondingly, when estrogen levels were low, pain was the highest (see chapter 2). However, the lack of consistency in study design, methodology, and even in the interpretation of the findings impeded comparison between the studies and not allowing the strength of the different studies’ findings to accrue. No meta-analysis was possible.

However, despite all the discrepancies and inconsistencies in these studies, one CNCP condition stood out as being well advanced in understanding the role of ovarian hormones on pain: migraine headache. In this literature, a specific type of migraine, menstrual migraine, was identified and differentiated in treatments from other types of migraines. This then allowed RCTs to study the effectiveness of hormone treatments on headaches occurring in the perimenstrum compared to hormone treatments of migraines occurring at other times of the month. These studies found that MM was well-treated with hormone therapies.
Although little attention was paid to whether or not overlapping pain condition made a difference or what type of treatments were used, the majority of studies were consistent in finding variations in pain severity associated with changes in the levels of ovarian hormones. Therefore, we hypothesized that the lessons learned in the literature would be carried through to clinical practice. These would include: (i) more women than men seeking clinical help, (ii) women would be the majority of patients with CPP; (iii) women would be the majority of patients under opioid treatment; (iv) more women would be in their reproductive years, (v) sex differences ovarian hormone levels would correlate with the severity of the pain scores, (vi) women would be treated preferentially with kappa opioids and males with mu opioids, (vii) women would experience differences in the efficacy of their opioid treatment with different stages of the menstrual cycle; (viii) without adjustment of opioid dosage to the menstrual cycle, cycling women would show more problematic use of opioids.

A chart review of both women and men seeking pain relief at a specialty clinic in a large Canadian city revealed a major disconnect between the research literature and the practice of pain management. While numerous sex differences consistent with the literature were found, no sex-specific questions were asked of patients either in their histories or in their pain questionnaires. In this sense, women might have benefited from being asked about ovarian hormones and men, more pointedly about sexual abuse. Further, sex specific medications were not used nor was stage of the menstrual cycle or reproductive history or life stage taken into account for women’s treatments.

However, while this retrospective chart review study could not report directly on the relation of ovarian hormones and CNCP conditions under treatment, the chart review does reveal evidence suggesting the potential role of ovarian hormones such as (i) significantly more women
in treatment than men; (ii) significantly more women in their reproductive years than not; (iii) higher percentage of migraine in women than in men; (iv) CPP as an overlapping pain condition represented more in women than men; (v) a CPP known to be dependent on estrogens, endometriosis, highest among the CPP conditions; (vi) the significant history of pelvic surgery, including oophorectomy, in women; (vii) problematic opioid used greatest for women in their reproductive years. Taken together all of these suggest that in this practice, ovarian steroids might be a significant variable in both modulating and treating pain. The literature plus the chart review suggest that not considering ovarian steroids in the treatment of women might make them more vulnerable for problematic opioid use over time, and susceptible to relapse at certain phases of their cycle.

**In sum, the primary novel finding of this study is that it demonstrates a significant gap between the pain research literature and pain treatment with respect to the role that ovarian hormones play in both modulating and treating CNCP conditions.**

This is not an uncommon split between research and practice. A chart review of another Canadian tertiary pain clinic revealed an important gap in information about culture and ethnicity, information that was also not collected in the clinic records reviewed in the current study (Mailis-Gagnon et al., 2007). This is unfortunate, but not surprising given what is already known about the time it takes to translate research results into clinical practice, even in the best of clinics (Balas & Boren, 2000). Previous estimates suggested that as few as 14 per cent of evidence from discovery enters day-to-day clinical practice (Westfall et al., 2007). The lack of translation from discovery to clinical practice is especially not surprising in this case given the lack of clarity of the literature itself as to what phase of the menstrual cycle should be used for aggressive and less aggressive treatments, particularly with opioids. Any practicing physician
reading this literature would likely as not wonder how to put it into practice since in their clinics women present with multiple, overlapping pain conditions (Chapter 3) and in the literature on ovarian steroids and pain women present as having only one condition (Chapter 2). In addition, at the tertiary pain clinic, women are triaged to one practice or another based on one presenting complaint.

How might these gaps therefore be rectified?

4.2 Future Recommendation

4.2.1 In the Pain Clinic

Based on the extant literature there are steps that clinical pain practices might take to achieve more successful pain treatment for women and men. Some demographic questions would be helpful to add such as: ethnicity, work, and active questioning as to whether or not a patient has a history of sexual abuse, especially those who have CPP. Men, especially, are unlikely to answer this question if it is on a questionnaire and an affirmative answer might affect the modality of pain treatments.

Repeatedly reported sex differences such as in the use of different opioid types should be put into practice. As well, ovarian hormone changes might also be considered; disregarding their possible influence while treating patients with CNCP may hinder successful pain treatment.

We recommend querying all patients upon intake regarding any association of overlapping pain conditions and not triaging them to practices dealing with only one pain condition before noting all the overlapping conditions in their charts. Whether CPP is one of the overlapping conditions should be queried directly of both women and men during the first steps
of pain management and throughout follow up visits because as our study revealed, MPP conditions grow in number over time. Women with history of hysterectomy and or oophorectomy, laparoscopy or gastroscopy should be asked about the cause for the surgery if they have not offered the information. It may be that an undetermined CPP condition is co-occurring with the pain condition under treatment.

Additionally, clinicians should be aware of the potential role of ovarian hormones in modulating CNCP in women. Abundant evidence supports the idea that women with CNCP—especially those who are within their reproductive years—will experience variations in the severity of their pain in synchrony with their menstrual cycles. It would be helpful to women patients if clinicians asked about whether or not there are any changes in the severity of their pain conditions with any event characterized by alterations in the levels of ovarian hormones (i.e., menstrual cycle, pregnancy, use of any hormonal treatment, menopause). This is particularly important if women have migraine headaches. Likewise, if decisions are to be made to prescribe opioids, treatment might be improved if clinicians considered the possibility of changes in treatment efficacy and potency with ovarian changes. This might include tailoring the opioid dose to phases of the menstrual cycle.

If a patient has CPP or migraines correlated with the menstrual cycle (MM) it has already been shown that hormonal treatments are helpful—in the case of CPP, as helpful than surgery. Thus, hormonal therapies should be tried as one of the pain management modalities. With regards to menopausal women, it would be important to query whether their menopause was surgically induced or natural as well as whether or not she is receiving any hormone replacement therapy.

In determining overlapping pain conditions, if CPP is present, it is important to determine whether its underlying cause is endometriosis. It is currently believed that peripheral
sensitization due to endometriosis significantly influences pain processing through the connection between the central nervous system and the sensitized inputs from the ectopic endometrial growths. These endometrial growths can actually influence neuronal activity by modulating both the inhibitory and excitatory mechanisms that in turn modulate pain signals transferred to central pain areas (Stratton & Berkley, 2011). The literature confirms that the hormonal treatment is of benefit for CPP associated with endometriosis (Craft et al., 2004; Greenspan et al., 2007) thus suggesting the necessity of evaluation for the presence of co-occurring CPP condition especially among women with MPC within their reproductive years. In addition, these findings suggest the potential benefit of a hormonal therapy in managing their pain, especially among women with co-occurring endometriosis.

4.2.2 Future Pain Studies

It is clear that the magnitude of the role of ovarian hormones has not been well characterized and additional research is obviously needed to facilitate the clinical application of findings regarding the role of ovarian hormones in the experience of pain. After all, this potential role has only been supported by observational research and not addressed by RCTs or clinical trials. Additionally, it may be that the inconsistencies in methodologies of the literature may have impeded a definitive understanding and by doing so, contributed to the failure of hormonal effects being translated into medical practice.

In fact, after reviewing studies investigating the role of ovarian hormones in modulating CNCP condition, we found that several methodological shortcomings have undermined the strength of their conclusions and have limited generalization across studies. Therefore, while abundant evidence demonstrates the potential role of ovarian hormones, clearly, more convergent evidence from appropriate long-term clinical trials is needed to provide the evidence
necessary to adequately discern whether or not and how CNCP is correlated with ovarian hormones thereby clearing the way for determining how treatment efficacy might also depend on ovarian hormones.

Ultimately, the aim is to devise effective pain management for women. The evidence that we have presented through this thesis lays the groundwork for future research studies.

**Clarifying the role of ovarian hormones in pain and opioid efficacy in women**

Carefully carried out RCTs taking estrogen levels into account might provide both comprehensible and sufficient data to influence clinical practice. From Chapter 2 as well as what is known about best practices in assessing the role of hormones in CNCP (Greenspan et al., 2007), it is clear that any study needs to:

(i) Use standard pain measurements;

(ii) Take direct and daily measures of hormone levels correlating them with pain threshold, intensity, and symptomology;

(iii) Blind participants to the menstrual focus of the study;

(iv) Include any co-occurring pain conditions—CPP in particular—in the analysis and interpretation of the results.

With the goal of eventually lowering the prevalence of opioid addiction among women with CNCP a protocol to study how titrating pain medication with levels of ovarian steroids might improve outcomes in treatment for CNCP with opioids might look as follows:

First, recruit women with CPP from a tertiary pain clinic. Ensure that all women are taking kappa opioids. Study one group that has been identified with problematic drug behaviors and another that has not.
Second, divide these two groups into three subgroups each:

(i) Women with regular menstrual cycles;
(ii) Women taking oral contraceptive pills;
(iii) Women in menopause.

Third, after completing the Pain Medication Questionnaire (PMQ) (Appendix E), all potential study participants will be instructed in how to rate their pain scores each day during three successive menstrual cycles, according to a Pain Intensity Scale (scale I) using a daily questionnaire (Appendix E). Record pain medication doses and duration will be taken for every patient. The researcher will stress the importance of completing the daily diary and will work with participants to incorporate diary completion into their daily routines.

Fourth, women should be asked to provide a daily urine sample for 42 days to determine how the levels of ovarian steroids correlate with increasing or decreasing pain; increasing or decreasing pain medication doses.

Fifth, both of the main groups will be studied, through the daily questionnaire (Appendix E), for:

1. The pain intensity using Pain Intensity Scale (see scale I).
2. The effect of the menstrual cycle on their pain intensity.
3. Opioid dose and estimated morphine equality.
4. The pain relief satisfaction score using the Likert scale (see scale II).
5. What drugs they have shown aberrant related behaviors to, e.g. alcohol, cocaine or prescribed opioids.
6. The effect of the menstrual cycle on their aberrant drug-related behaviors.
7. The relation between possible inadequacies of their pain treatment

Sixth, if pain intensity / relief varies with ovarian steroids, participants would be divided into two groups randomly:

1\textsuperscript{st} group: pain medication doses adjusted according to the participants own pattern of fluctuation with the menstrual cycle.

2\textsuperscript{nd} group: pain medication doses held constant throughout their menstrual cycle regardless of the observed pain pattern.

This study design is presented as just one possible study design to clarify the role of ovarian steroids in pain management. Studying all three of the initial groups and then the latter two for three to six months might provide the information necessary to determine the adequacy of pain treatment over the menstrual cycle, determine the degree of each participant’s satisfaction with treatment after individualizing their opioid prescription and monitor for any problematic drug-related behaviors.

\textbf{Conclusion}

The benefits of knowing whether opioid efficacy varies according to pain scores over the menstrual cycle might be three-fold:

(i) Titrating the initial dosage of pain medication to the varying levels of a woman’s own hormones might lower the risk of desensitization of opioid receptors from the outset of treatment thereby decreasing the likelihood that more opioids would be needed over the entire cycle;

(ii) Weaning women with problematic opioid use off opioids might be more successful if started at a time of the month when estrogens were high or kept, artificially high, during the earliest stages of withdrawal.
(iii) Hormone replacement might potentiate the effects of opioids for women in menopause thus requiring them to take a lower dose for treatment effects.

**In sum:** CNCP is a complex and multifactorial condition (Fillingim & Ness, 2000). All the aforementioned evidence suggests a potential role of ovarian hormones—as one of many factors—in modulating CNCP. And, building on these findings, if this role were considered there might be potentially important clinical implications. Therefore, it might be the case that major advances in improving our understanding of and alleviating CNCP would occur if sex differences in pain and pain treatments were considered.
References


Appendices

Appendix A

Data Collection Form

- Code number:

- Demographics:
  i) Sex: □ F □ M
  ii) Age: (years)

- Cause of referral:

- Pain Condition:
  □ Chronic pelvic pain □ Temporomandibular joint □ Irritable bowel syndrome
  □ Migraine headaches □ Fibromyalgia □ Chronic back pain

- Duration of pain condition: (years)

- Pain Scales Scores:
  i) McGill Pain Questionnaire PRI:
  ii) Pain Intensity scores:
  iii) Pain Catastrophizing Scale:

- Psychological assessment:
  i) Depression scale score BDI:
  ii) Anxiety scale score HAM:

- Medications / Treatments:
  i) Opioid Medications:
  ii) Other treatment approaches (e.g. nerve blocks, local steroid inj., Botox injections, physiotherapy, massage, acupuncture, psychotherapy, mindfulness, and chiropractor):

- Any Opioid use problems:

- Medical History:
  i) History of Drug/ sexual abuse
  ii) History of Surgery
  iii) History of Trauma
  iv) Related Family History

- Physician notes:
Appendix B

Research Ethics Board
600 University Avenue, Room 10-21
Toronto, Ontario, Canada, N5G 2W1
(416) 586-8675 ext 6135
www.reb.msh.ca

Notification of REB Approval for Access to Retrospective Data for Research Purposes

Date: July 22, 2013

To: Dr. Allan Gordon
Wellcome Trust Management Centre
Division of Neurology
Mount Sinai Hospital
Room 1199
600 University Avenue
Toronto, Ontario

Re: 14-MUS-0023
Sex Differences in Chronic Non-Cancer Pain: Cytokines: A Retrospective Chart Review

REB Initial Approval Date: 22 July, 2013
REB Expiry Date: 22 July, 2014
Funding: None

We wish to remind you that access to personal health records for research purposes without patient consent is a privilege granted by the REB. Please be sure to adhere to all timelines in the MSH Policy on Information and Data Security as noted in the Confidentiality Agreement signed as part of this submission. A copy of this approval letter and the completed REB Application for Access to Health Records form must be presented to the Health Records Manager. A Health Records fee may be applicable.

If during the course of the research, there are any confidentiality concerns, changes in the approved project, or any new information that must be considered with respect to the project, these should be brought to the immediate attention of the REB. In the event of a privacy breach, you are responsible for reporting the breach to the MSH REB and the MSH Corporate Privacy Office (in accordance with Ontario Health Privacy Legislation - Personal Health Information Protection Act, 2004). Additionally, the MSH REB requires reports ofany personal information and use of the information.

The MSH Research Ethics Board operates in accordance with the Tri-Council Policy Statement 2, TCPS2
Guidelines and Part C, Division 5 of the Food and Drug Regulations of Health Canada.

Sincerely,
Appendix C

PROTOCOL REFERENCE # 20321

August 29, 2013

Dr. Gillian Einstein  Ms. Samah Hassan
DEPT OF PSYCHOLOGY  DEPT OF PSYCHOLOGY
FAC OF ARTS & SCIENCE  FAC OF ARTS & SCIENCE

Dear Dr. Einstein and Ms. Samah Hassan,

Re: Your research protocol entitled, "Sex differences in chronic non-cancer pain conditions: A retrospective chart review"

ETHICS APPROVAL

Original Approval Date: August 29, 2013
Continuing Review Level: 1

We are writing to advise you that the Health Sciences Research Ethics Board (REB) has granted approval to the above-named research protocol under the REB's delegated review process. Your protocol has been approved for a period of one year and ongoing research under this protocol must be renewed prior to the expiry date.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events in the research should be reported to the Office of Research Ethics as soon as possible.

Please ensure that you submit an Annual Renewal Form or a Study Completion Report 16 to 30 days prior to the expiry date of your current ethics approval. Note that annual renewals for studies cannot be accepted more than 30 days prior to the date of expiry.

If your research is funded by a third party, please contact the assigned Research Funding Officer in Research Services to ensure that your funds are released.

Best wishes for the successful completion of your research.

Yours sincerely,

[Signature]

OFFICE OF RESEARCH ETHICS
McMichael Building, 12 Queen's Park Crescent West, 2nd Floor, Toronto, ON M5S 1S5 Canada
Tel: +1 416 946-3773 • Fax: +1 416 946-5780 • ethics.review@utoronto.ca • http://www.research.utoronto.ca/for-researchers/administrators/ethics/
Appendix D

DATA & BIOLOGICAL SAMPLE TRANSFER AGREEMENT

This Agreement is made by and among:

MOUNT SINAI HOSPITAL ("Disclosing Party")
With an address at: 600 University Avenue, Toronto, Ontario M5G 1X5

Contact Information:
For the Study:
Dr. Allan Gordon ("Disclosing Investigator")
Director, Wasser Pain Management Center
Mount Sinai Hospital
600 University Avenue, Room 1170
Toronto, Ontario M5G 1X5
Tel: 416-586-4800 ext 5181
Fax: 416-586-8430 or 5067
Email: agordon@mtsinai.on.ca

For the Disclosing Party’s Administration:
Terry Donaghe
Director, Technology Transfer and Industrial Liaison
600 University Avenue, Room 843
Toronto, Ontario M5G 1X5
Tel: 416-586-8225
Fax: 416-586-8244
Email: donaghe@lunenfeld.ca

and

The Governing Council of the University of Toronto ("Receiving Institution" or "UofT")
With an address at: 100 College St., Suite 413, Toronto, ON M5S 1L5

Contact Information:
For Receiving Party’s Administration:
University of Toronto
Innovations & Partnerships Office
Banting Institute
100 College St., Suite 413
Toronto, ON M5S 1L5
Attention: Lauren Gogo, Contracts Officer
Tel: 416-978-1212
Fax: 416-978-6952
Email: lauren.gogo@utoronto.ca

and

Dr. Gillian Einstein ("Receiving Investigator" and, together with Receiving Institution, "Receiving Party")

With an address at: Department of Psychology, University of Toronto, 100 St. George Street, Toronto, Ontario M5S 3G3, Office Tel: 416-978-0896, Email: gillian.einstein@utoronto.ca

with respect to data and/or biological samples that the Disclosing Party will provide to Receiving Party for the

May 2010
study entitled “Sex Differences in Chronic Non-cancer Pain Conditions: A Retrospective Chart Review” (the “Study”).

MSH REB #11-0195-C
The study is a retrospective chart review.

This Agreement is made in compliance with section 44(5) of the Personal Health Information Protection Act, 2004, S.O. 2004, c. 3 (“PHIPA”).

The parties hereby agree as follows:

1. Definitions. As used in this Agreement, the term:
   a) “Data” means all personal information (including without limitation medical data and information and other personal health information) that has been collected for the purpose of the Study at Disclosing Party and is provided to the Receiving Party for the purpose of carrying out the Study;

2. Compliance. In transferring the Data the parties shall comply with all applicable laws, regulations, guidelines and policies (“Applicable Law”). The Disclosing Party will prepare and furnish the Data in accordance with PHIPA including without limitation obtaining all appropriate consents. The Data will not be collected and/or transferred until the Disclosing Party’s research ethics board (“REB”) and, if applicable the Receiving Party’s REB, have: a) approved the Study protocol; and b) approved the Study informed consent forms or waived the requirement to obtain consent.

The Disclosing Party retains the right but not the obligation to conduct audits of Receiving Party’s compliance with this Agreement upon reasonable advance written notice to Receiving Party and at mutually acceptable times. If there is a breach of the Agreement by Receiving Party, Disclosing Party may require that all Data be returned promptly to Disclosing Party or destroyed in a secure manner at Disclosing Party’s option. The Disclosing Party retains the right, acting on reasonable grounds, to refuse the transfer of the Data requested hereunder.

3. Non-Disclosure of Data. The Receiving Party shall limit access to the Data only to its internal personnel and/or agents who need access for the purposes herein and who are bound by the same confidentiality obligations herein (“Study Staff”). Without limiting the obligation set out in s. 2, the Receiving Party agrees that it/he/she shall, and shall require its/its/her Study Staff, to:
   a) maintain Data in confidence, and not disclose Data except as permitted by this Agreement;
   b) use Data solely for the purposes of the Study or other expressly consented purposes, in compliance with:
      (i) the Study protocol as approved by the Disclosing Party’s REB and as amended from time to time, provided that amendments are approved by the Disclosing Party’s REB (the “Protocol”);
      (ii) any written conditions imposed by the Disclosing Party’s or Receiving Party’s REB;
      (iii) the Study subject’s consent consistent with the informed consent form approved by the Disclosing Party’s REB (the “Consent”) or, if the requirement to obtain consent has been waived, or otherwise determined to be unnecessary, by the Disclosing Party’s REB, the waiver of consent given by the Disclosing Party’s REB (the “Waiver”);
      (iv) any other conditions or restrictions imposed by Disclosing Party relating to the use, security, disclosure, return or disposal of the Data as set out in this Agreement.
   c) not use the Data to identify any individuals.

May 2010
d) not transfer the Data to any third parties without the prior written consent of the Disclosing Party and without obligating such third parties to comply with the terms and conditions hereof. Notwithstanding the forgoing, the Receiving Party may transfer the Data:

(i) to regulatory authorities, provided that the Receiving Party gives prior written notice of such intended disclosure to the Disclosing Party;
(ii) as otherwise permitted by the Consent or Waiver; or
(iii) in order to comply with Applicable Law or judicial process, or with a court or regulatory order, provided that the Receiving Party gives prior written notice of such intended disclosure to the Disclosing Party and takes all lawful actions that are reasonable in the circumstances to minimize the extent of such disclosure and obtain confidential treatment for such disclosure.

e) securely destroy the Data as required by the Protocol or instructed by the Disclosing Party and provide a written confirmation of the manner of destruction in a form acceptable to Disclosing Party.

5. Safeguards and Notification. The Receiving Party shall use appropriate safeguards (including without limitation with respect to encrypting identifying numbers, linking files, storing and retrieving files from secured locations) to prevent any unauthorized use or disclosure of the Data and shall promptly report to Disclosing Party any unauthorized use or disclosure of which Receiving Party becomes aware. Receiving Party shall immediately provide written notification to the Disclosing Party in the case of a breach of this Agreement or of s. 44(6) of PHIPA, or in the case of a suspected breach of s. 44(6), or where PHI is lost, stolen or accessed by unauthorized persons.

6. Contact with Subjects/Individuals. The Receiving Party shall not make contact or attempt to make contact with an individual unless the Disclosing Party first obtains the individual’s consent to be contacted, except to the extent that the Receiving Party is otherwise the individual’s health information custodian.

7. Financial Matters and Intellectual Property. Except as expressly provided herein, no right, title or interest in and to the Data is granted to the Receiving Party or implied hereunder. The Receiving Party shall own the analyzed Data that has been stripped of personally-identifying information and incorporated into its Study database. All other applicable financial matters and intellectual property terms are attached as Schedule "D" hereto.

8. Publication. Receiving Party shall have the right to use a) the analyzed, de-identified data derived from the use of the Data; and b) information and results arising out of analysis of the Data, as part of a publication or presentation of the results of the Study. The Receiving Party shall not include any personally identifying information in any publication or presentation. Disclosing Party’s investigator’s contribution to the Study shall be acknowledged appropriately in any such publication or presentation in accordance with academic standards.

9. Study Documents. The following Study documents are attached hereto and/or incorporated by reference:

| Schedule A – Study Protocol | [Attached] [Not Applicable] [Incorporated by Reference] |
| Schedule B – Written Conditions of REB; and/or REB Approval Letter | [Not Applicable] [Attached] [Incorporated by Reference] |
| Schedule C – Consent or Waiver | [Attached] [Not Applicable] [Incorporated by Reference] |

10. General Terms and Conditions.

(a) No party shall be entitled to assign or transfer this Agreement or the rights and obligations hereunder to
any third party without the prior written approval of the other parties.
(b) This Agreement including the attached Schedules represents the entire understanding between or among the parties related to the Study and supersedes all previously or contemporaneously executed agreements related to the Study.
(c) This Agreement shall not be amended, modified, varied or supplemented except in writing signed by each of the parties.
(d) No failure or delay on the part of any party hereto to exercise any right or remedy under this Agreement shall be construed or operate as a waiver thereof.
(e) The parties hereto are independent contractors. Nothing contained herein shall be deemed or construed to create between or among the parties hereto a partnership or joint venture or employment or principal-agent relationship. No party shall have the authority to act on behalf of any other party or to bind another party in any manner.
(f) Each party to this Agreement assumes responsibility for its own obligations under this Agreement.
(g) No party shall use, or authorize others to use, the name, symbols, or marks of another party hereto or its staff for any endorsement purposes without prior written approval from the party whose name, symbols or marks are to be used.
(h) This Agreement shall be governed by and construed in accordance with the laws of the Province of Ontario and the federal laws of Canada applicable therein.
(i) Counterparts This Agreement may be executed in any number of counterparts with the same effect as if all parties had signed the same document. All of these counterparts will for all purposes constitute one agreement, binding on the parties, notwithstanding that all parties are not signatories to the same counterpart. A faxed or emailed PDF copy or photocopy of this Agreement executed by a party in counterpart or otherwise will constitute a properly executed, delivered and binding agreement or counterpart of the executing party.

Acknowledged and agreed by:

Disclosing Party
MOUNT SINAI HOSPITAL

Receiving institution:
THE GOVERNING COUNCIL OF THE UNIVERSITY OF TORONTO

Name: James K. Woodgett
Title: Director

Name: Lino De Acencis
Title: Director, Partnerships

Date: November 12, 2013

Acknowledged by: Disclosing Investigator:
Dr. Allan Gordon

Date: Nov 12/13

Date: November 4, 2013

Dr. Gillian Einstein

May 2010
Appendix E

Daily questionnaire

Code #: 

Today’s Date: / MM/DD

Please answer all the questions as completely as possible.

- How severe is your pain today? Please, place a circle on the number below to indicate how bad you feel your pain today.

Y          N

Have you taken your pain treatment today?

Y          N

- Please, place a circle on the number below to rank your pain relief on a scale from 0 to 6 with 0 as no relief and 7 as pain free.

1  2  3  4  5  6  7

No Pain  Mild Pain  Moderate Pain  Severe Pain  Very Severe  Worst Pain

Is there any associated pain you are experiencing in addition to your actual pain today?

Y          N
<table>
<thead>
<tr>
<th></th>
<th>Y</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Would you feel better with a higher dosage of your pain medication today?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you feel anxious and sad or need help sleeping today?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you drink alcohol to help control your pain?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you borrow pain medication from your friends or family to get relief?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you feel that you need an extra dose or another drug to control your pain today?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have your period today?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **If you are menstruating, please answer these questions:**

<table>
<thead>
<tr>
<th></th>
<th>Y</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you have your period today?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, Do you feel any pain associated with your period?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If no, Have you received a phone call to start your ovulation test today?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, Have you complete your ovulation test today?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, Is the results positive today?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **If you are on any of the Oral Contraceptive Pills, please answer this question:**

<table>
<thead>
<tr>
<th></th>
<th>Y</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any recent changes with your pain?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **If you are on your menopause, please answer this question:**

<table>
<thead>
<tr>
<th></th>
<th>Y</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any recent changes with your pain?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you on Hormonal Replacement Therapy?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thank you for your time in answering all the questions as completely as possible.
Scales

Scale I

Pain Intensity Scales

Pain scales usually used to assess pain intensity (Hawker et al., 2011).

Visual Analogue Scale

| No Pain | Worst Possible Pain |

Wong-Baker FACES Pain Rating Scale

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain</td>
<td>Mild, annoying pain</td>
<td>Nagging, uncomfortable, troublesome pain</td>
<td>Distressing, miserable pain</td>
<td>Intense, dreadful, horrible pain</td>
<td>Worst possible, unbearable, excruciating pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Verbal Pain Intensity Scale

No Pain    Mild Pain    Moderate Pain    Severe Pain    Very Severe Pain    Worst Possible Pain
Scale II

7-point Likert scale to determine whether the Effectiveness of medication and pain intensity after taking the medication varies with the menstrual cycle rated on a scale (Trochium, 2006; Uebersax, 2006)

1= no reduction to 7= almost pain free (satisfaction scores for the treatment)

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Pain Relief</td>
<td>Pain Free</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>