Sex Differences in Overlapping Chronic Non-cancer Pain Conditions in a Tertiary Pain Clinic

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Abstract

Sex differences have been reported repeatedly in pain and response to opioid analgesia with women representing the majority of chronic non-cancer pain (CNCP) patients as well as a growing population of opioid users and misusers. However, none of these reports has investigated sex differences in the prevalence of overlapping multiple pain conditions (MPC), especially among patients under opioid therapy. Two hundred eighty-three charts were reviewed of patients attending a tertiary pain clinic with multiple sub-practices in a large Canadian city over a one-year period. 201 patients suffering from CNCP and under opioid therapy were selected. A significant sex difference was found in the number of patients, while no statistically significant sex difference was found in type of opioids prescribed. Moreover, significant sex differences were found in the prevalence and types of overlapping CNCP conditions as well as in the pattern of opioid misuse. With respect to overlapping pain conditions, Chronic pelvic pain (CPP) was the most common pain condition to co-occur in women, while in men, fibromyalgia was the most common. Taken together, all of these suggest that sex differences are significant in patients with overlapping CNCP conditions, and taking them into consideration might provide more comprehensive pain management.

Keywords: Chronic non-cancer pain (CNCP); CNCP conditions; Opioid treatments

Introduction

Chronic non-cancer pain (CNCP) is one of the most common reasons for seeking health care with one in five Canadians suffering from CNCP [1]. Moreover, CNCP accounts for up to 78% of visits to emergency care facilities, and usually leads to both a severe decline in the quality of life and a startling rise in the incidence of disability [2]. Successful treatments are few and far between with one of the most potent analgesics, opioid medications, associated consistently with concerns about problematic opioid use (POU) (i.e. misuse, abuse or addiction) [3-6].

Sex differences in both the incidence and types of chronic pain conditions have gained increasing attention as an area of research with the potential to lead to a better understanding the differences in CNCP patients’ response to treatments [7-9]. Clinical pain studies have reported repeatedly that women represent the majority of patients suffering from CNCP conditions like Fibromyalgia, Chronic Headaches; Temporomandibular disorder (TMD) Pain; and Chronic Pelvic Pain (CPP) [2,7,10]. All of the CNCP conditions are often treated with opioids and, as with pain, the available human studies have reported a significantly greater analgesic effect in women in comparison to men [11-15]. Moreover, recent studies report that women now represent a growing population suffering from POU after long-term opioid treatment [12,16-18].

Based on these findings, sex differences would seem especially pertinent in understanding both the reasons and treatments for CNCP. However, work in this area consists of studies investigating of only one CNCP condition at a time [19]. This approach leaves a serious gap in our understanding because it is well known that CNCP conditions most often co-occur as a constellation of multiple pain conditions (MPC) with overlapping symptoms [19-25]. Moreover, most studies investigating sex differences in clinical pain have not controlled for the current treatments participants might be prescribed especially with respect to opioids or an often note treatment outcome, POU [19]. Consequently, we decided to review charts of CNCP patients under opioid medication in order to determine whether there are sex differences in the prevalence of overlapping MPC and if so, the constellation of types of condition between women and men under opioid therapy.

Methods

After obtaining approval from the Research Ethics Boards of both the University of Toronto and Mount Sinai Hospital, a chart review was conducted of all patients under opioid treatment referred to three different practices at the Wasser Pain Management Centre, a tertiary pain clinic in Toronto, ON from July 1, 2012 until July 31, 2013. Two hundred eighty-three charts were reviewed in total; 82 patients were excluded because they were ineligible (10 patients had cancer and 72 CNCP patients were not using opioids 56 (87%) of which were women), leaving 201 patients with CNCP under opioid treatment. If patients could be cross-referred to more than one practice, they were counted only once.

Data collected included: sex, age, pain condition or conditions, type of treatment, duration of pain condition, responses to the long form McGill Pain Questionnaire (Pain Rating Index, PRI) [26], Pain Intensity Scale scores [27], Pain Catastrophizing Scale scores [28], history of surgery or trauma, types of pain medication, Hamilton Anxiety Scale (HAS) [29], Beck Depression Inventory (BDI) [30], history of drug abuse, and whether or not a patient was diagnosed with POU.

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Statistical analysis

Data were analyzed using SPSS (SPSS 15.0.1, 2006, Chicago - Illinois. Software Inc.). Means and standard deviations were calculated for the above patient characteristics 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 using a Student t-test and Pearson Chi-square test for non-parametric data. P-values of <0.05 were considered significant.

Results

Patient characteristics

A total of 283 charts comprising a mix of women and men were reviewed. Women were disproportionately represented in this pain clinic, 185 (68%) patients were women, while 88 (32%) were men.

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.

During this year, 201 patients were under opioid treatment and 88 were not. Oxycodone was the most prescribed opioid for both female and male patients, followed by morphine, methadone and fentanyl. While, no statistically significant difference was found between men and women in type of opioids prescribed, a significant sex difference was found in the number of CNCP patients under opioid treatment (n=201), (women: n=129 (64%); men: n=72 (36%) χ²=32.677 df=1, p<0.01). Moreover, out of the total of 201 patients under opioid treatment, of the 79 suffering from POU, 56% were women and 44% were men. Interestingly, although no significant sex difference was found in the percentage of patients with POU (χ²=4.074, df=1, p=0.44), men were significantly more likely to have a history of drug abuse compared to women: 44% of men and only 19 % of women (χ²=16.470, df=1, p<0.01) (Table 2).

Note that the full percentages do not all add up to 100% as the CNCP conditions are overlapping

Moreover, 38% of the women suffering from MPC had POU while 53% of the men had POU. In women with POU, CPP was also the most common co-occurring CNCP (56%) followed by fibromyalgia (49%), LBP (33%), chronic headaches (29%) and TMD (16%). In contrast, in men, fibromyalgia was the most common co-occurring CNCP (68%) followed by chronic headaches (53%), TMD (47%), LBP (42%), and CPP (5%). The sex difference in the most common overlapping condition was significant (χ²=16.470, df=1, p<0.01) (Table 2). Notably, in women, endometriosis and/or irritable bowel syndrome (IBS) together were the most common reasons for co-occurring CPP in women with 36 out of 56 (64%) having one or both of these conditions.

Relationship of chronic pain to reproductive years

The mean age of female patients at their initial visit was 42(SD ±13) and male patients was 45(SD ±15). While there was no sex difference in the mean age between patients, when the range of ages were divided into groups: those who were 18-48 (as a proxy for women's reproductive years) and 49-71 (as a proxy for women in menopause), we found that women in their reproductive years (18-49) represented 90% (n=95) of the women with MPP, 75% (n=33) of women with POU and 79% (n=53) of women with co-occurring CPP. For men who had MPC, POU, or co-occurring CPP, there was no difference between the two age groups.

Discussion

This retrospective chart review is the first chart review of CNCP patients that includes a comparison by sex in the prevalence of common co-occurring condition. It provides valuable insights into the differences in treatment and prevalence of CNCP in women and men, highlighting the need for more tailored and sex-specific approaches to pain management.
A total of 283 charts were reviewed across one year. Each chart was examined for the chronic pain conditions represented and the types of treatments patients were given. From the 283 charts, 201 patients were under opioid treatment. A significant sex difference was found in the number of patients under opioid treatment with women comprising 64% of those treated with opioids. No statistically significant difference was found between men and women in type of opioids prescribed for men and women with the most commonly prescribed being Oxycodon. It might be useful to consider this sex difference in the future. It is currently believed that peripheral sensitization due to endometriosis significantly influences pain processing via the connection between the central nervous system and the sensitized inputs from ectopic endometrial growths [37,38]. 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 [37,39]. Hence, while the chart could not report directly on the relation of the women's CNCP condition and their menstrual and reproductive status, nor their levels of ovarian hormones, the fact that CPP co-occurs with other CNCP conditions such as fibromyalgia, chronic migraines, TMD and LBP, suggests that estrogen might as well modulate other co-occurring conditions. The effects of hormonal variation might be important to follow up in these types of patients.

Additionally, the literature confirms that hormonal treatment specifically is of benefit for CPP associated with endometriosis [19,25], thus suggesting the necessity of evaluation for the presence of co-occurring CPP condition especially among women with MPC and CPP within their reproductive years and the potential benefit of hormonal therapy for managing their pain [37,39-43]. Moreover, it is also known that opioid efficacy waxes and wanes with the cyclic variations in reproductive hormones, and since those women were on opioid therapy for managing their pain [37,39], the fact that CPP co-occurs with other CNCP conditions such as fibromyalgia, chronic migraines, TMD and LBP, suggests that estrogen might as well modulate other co-occurring conditions. The effects of hormonal variation might be important to follow up in these types of patients.

Strengths and Weaknesses of the Study

An important strength of this study is that it is the first chart review of a Tertiary Pain Clinic to look at the intersection of sex differences, multiple chronic pain conditions, and opioid treatment. Our findings suggest that more such studies should be done in order to obtain more generalizable knowledge and to verify the treatment recommendations below.

A weakness of this study is that there were so few men, as compared with women, being treated by this pain clinic in the year studied. This may be due to the particular focus of this pain clinic as well as to the already identified disproportionate burden of chronic pain for women. Never the less, with even a small sample of men it is possible to gain a
snapshot of the types of their pain, the fact that they, too, present with overlapping pain conditions, and that they bear the brunt of a history of problematic opioid use while women bear the brunt of surgery. Another weakness of this study, as is the case for all chart reviews, is that it utilized data that were not originally collected for research purposes. Therefore, data were limited and were not collected prospectively in a standardized fashion. In spite of these limitations, however, this chart review provides a snapshot of how CNCP patients present at a clinical practice and opens further paths for future research capable of bringing new knowledge into practice.

**Recommendations**

A number of concrete recommendations for improved pain treatment for women and men emerge from our study. First, while abundant evidence demonstrates sex differences in pain, and opioid treatment, clearly more convergent evidence from appropriate long-term clinical trials is needed to provide the evidence necessary to adequately convince clinicians of whether or not and how CNCP is modulated by sex. Stronger evidence would clear the way for determining how treatment efficacy might depend on sex.

Second, we, also, recommend querying all patients upon intake regarding any association of overlapping pain conditions. The practice of triaging patients to practices dealing with only one pain condition before noting all the overlapping conditions in their charts limits the understanding of the whole pain condition. 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.

Additionally, adding some demographic questions such about ethnicity, work, and history of sexual abuse as well as other adverse childhood experiences, especially for those who have CPP would be helpful in understanding the larger context of the pain condition and might present treatment options [44,45]. As well, if CPP is present in women, it is important to determine whether its underlying cause is endometriosis.

**Conclusions**

These findings from one year’s intake to a tertiary pain clinic demonstrate that women and men present differently with CNCP have different types of overlapping pain conditions, and develop POU differently. Our findings suggest that additional types of information should be gathered for women and men allowing the physician to better understand any correspondence between CNCP conditions and the menstrual cycle or hormone variation as well as any changes in treatment efficacy with the menstrual cycle. The type of opioid administered might also require specificity by sex. Taken together, considering the sex of a patient with the possible concomitant sex differences in the types of conditions, prevalence of multiple pain conditions, type of opioid administered, and an already established POU as well as the effect of varying hormone levels on opioid efficacy might improve the efficacy of treatment for both men and women with CNCP conditions.

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