Biennial Review of Pain

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Sex and gender differences in pain: past, present, and future

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1. Introduction

Understanding why people vary in their experience and response to pain is central to the development of better, more targeted, personalised, treatments for pain. Sex and gender differences provide a key source of variation and are widely observed,[19,57,60,70] with women generally experiencing more pain across the lifespan when compared with men. This review will focus on what we currently know about the role that sex and gender have in pain. It will present a brief overview of the evidence that has accumulated over the past 25 years for differences in men and women's pain (the past), as well as some of the reasons why such differences occur. There will also be a focus on the variation in findings, as well as consideration of the factors that might moderate and/or mediate such effects. A key theme that will emerge is that although there is good evidence for male–female differences, there are inconsistencies that need to be explained (the present). There is a need to move beyond an overreliance on binary categories to fully understand how and why sex and gender impact on pain. There will be a particular focus on gender, and gender concepts, because these help to illustrate how it is possible to develop a conceptually driven approach and better understand the variation in men and women's pain. This focus is also because there have been excellent reviews of preclinical sex differences and the identification of potential biological mechanisms.[123,125,171] This review will conclude by highlighting knowledge gaps and areas for further investigation (the future).

2. Defining sex and gender, and the focus of this review

Given the focus of this review is on sex and gender, it is useful to start with some definitions and consider the relevant debates.[27] Fortunately, the CIHR Institute of Gender and Health provides some useful definitions.[39] They note that sex is often associated with biological factors, such as genetics, sex hormones, and physiology, and usually involves comparisons between men and women. Conversely, gender is associated with psychological and sociocultural factors, such as beliefs, expectations, and stereotypes, and how men and women behave and interact with one another. Binary categories are commonly used (eg, male/female, man/woman, and boy/girl), although gender is not constrained to this and encompasses broader aspects.

Although the biological and psychosocial distinction points to different underlying mechanisms, caution should be exercised in exclusively equating sex with biology, and gender with social psychological factors, because this implies that they are completely independent and/or dissociated.[17,78,80] After all, sex-related mechanisms can be shaped and influenced by environmental exposure, whereas gender constructs, such as masculinity and femininity, are ultimately mediated through neural mechanisms within an individual. The term sex/gender has started to be used,[80,132] highlighting the continuing difficulty in disassociating biological and psychosocial influences. The view taken here is that biological and psychosocial approaches reflect different levels of analysis that help us understand pain,[151,195] and so, a similar approach can be applied to sex and gender. Sex and gender can also be considered as interacting factors. It is therefore expected that a combined sex and gender approach will provide the fullest understanding of pain. One immediate implication from this position is that both sex and gender influence the experience of pain, as well as pain-related behaviours. How, and to what extent, sex and gender do this has yet to be fully determined.

This review will predominately focus on binary differences in pain between men and women because this reflects much of the research conducted to date. Where specific biological or psychosocial mechanisms are referred to, these will be clearly identified. However, average group differences can hide the overlap that occurs between men and women, as well within-group variation. There is concern that binary categories may not fully encompass the complexity of human experience and behaviour.[80,132] For example, the notion there is a typical "male brain" and "female brain" has been questioned, with a focus on the mosaic of experience that shapes brain development. Similar limitations can be applied to binary comparisons between men and women for social psychological factors. An alternative is to move away from binary group comparisons to something more sophisticated. However, the view taken here is that there is still merit in continuing to explore for differences, and similarities, in men and women's pain. It is a good starting point and certainly better than ignoring it. Furthermore, given that gender beliefs and expectations strongly reflect stereotypical binary categories, such as the "typical man" and "typical women," there is merit in exploring how these views affect how people apprise their own pain, as well as the pain of others. It is also recognised that there is a need to move beyond simple descriptive binary comparisons and towards explaining the variation that occurs in men and women's pain.

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3. Evidence for sex/gender differences in pain

3.1. Pain prevalence

Differences between men and women are found across a range of shared painful conditions, including low back pain, osteoarthritis, fibromyalgia, temporomandibular disorder, headache, and abdominal pain. These typically show that women are more likely to experience these painful conditions when compared with men.[60] Although fewer in number, there are also shared painful conditions, such as cluster headache, which show greater prevalence in men.[4,19] Epidemiological studies confirm differences in pain prevalence across a range of countries and settings.[22,32,40,66,89,162,181] For example, Tsang et al.[183] found the prevalence of pain was at 31% for men and 45% for women across 17 different countries. Similarly, Bimpong et al.[22] found pain to be at 62.3% for women and 55.5% for men across 19 European studies.

Although less commonly explored, chronic pain has been associated with mortality.[51,169] Unfortunately, few studies also consider sex and gender differences and, those that do, report mixed results.[77,160] However, there are interesting findings, which need to be followed up. For example, a study by Docking et al.[51] suggested that chronic back pain might have more of a life-limiting effect on elderly women. In a second example, using the UK Biobank cohort, a male-specific genetic association with chronic pain–related mortality was found.[133] There is also higher incidence of suicide in men, but whether chronic pain is a risk factor is currently unknown.[91]

These studies indicate women experience more pain, and show that pain has a profound impact on men.[91] Multiple factors could contribute to these differences—from greater clinical vulnerability, through to the less obvious, such as the way in which pain is assessed. For example, a recent meta-analysis of epidemiological studies not only found differences in men and women's pain, but that the method of data collection had an impact. Interviews showed a lower reporting of pain in men than in self-report measures.[172] This suggests that differences in the reporting of pain plays a role.

There are additional factors that moderate these differences in men and women's pain, such as age.[25,57,183] A pattern that emerges is that differences in men and women's pain become more obvious from adolescence, with fewer differences observed in even younger age groups.[66,105] For example, several painful clinical conditions, such as migraine and temporomandibular disorder, show a stronger prevalence difference around puberty, which then continues through the reproductive years.[60,111] There is also evidence that ethnicity impacts on pain also, although it is less clear how this might intersect with sex/gender.[57] There are a wider range of biological and social psychological factors that operate, separately and/or in combination, which might also contribute to the variation in the prevalence of men and women's pain.

3.2. Clinical and experimental pain

A second type of evidence that points to sex and gender differences in pain stems from observational and behavioural studies, conducted in both applied clinical and experimental (analogue) settings.[60,139,154] When exploring trends across different clinics, binary sex/gender differences emerge, which are consistent with the patterns reported above.[159,162] For example, when Ruau et al.[162] explored electronic patient records within a hospital setting, they found women reported more pain compared with men. Pain sensitivity has also been explored in the laboratory using experimental pain induction methods.[60,154] Evidence stems from a range of techniques, including thermal heat and cold pain, pressure pain, and others. The general pattern found is that women typically have a lower threshold and tolerance to induced pain, suggesting a greater sensitivity to pain.

However, like the prevalence studies, a variation in effects is found, which has led some to question whether there is a reliable difference between men and women.[124,130,149] The strength of effect can depend on other factors, including the type of induction method used.[154] The general pattern across these studies tends to be similar, however, with women exhibiting lower pain threshold and tolerance, suggesting this is a difference in magnitude. Smaller sample sizes might also disguise or impact on the consistency of findings. Other factors can also impact on experimental pain, such as age and ethnicity.[57,104,107,192] For example, a systematic review of experimental pain studies found greater sensitivity to pain in older-aged children than during earlier years.[26] It is unclear whether sex/gender differences in experimental pain sensitivity are stronger or weaker in older adults. Furthermore, there are general questions about the clinical relevance of experimental, laboratory-induced, pain that needs to be considered.

3.3. Biological factors

The observation that differences in men and women's pain emerge around puberty led to investigations into the role sex hormones have on pain,[60,121,166] with suggestion that oestrogen and/or progesterone increases the vulnerability to pain, whereas testosterone has protective effects.[46] To test this, explorations into whether pain and analgesia vary across the menstrual cycle have been conducted.[111,112,152,155] However, evidence is mixed. In a meta-analysis of 16 experimental studies, Riley et al.[155] concluded that, for several pain induction approaches, greater sensitivity was found during the follicular phase. However, this pattern was not found for all induction approaches, and results from subsequent studies suggest a more inconsistent pattern.[14] Even so, there are interesting findings in individual studies that point to a role for sex hormones and future investigation. For example, Ribeiro-Dasilva et al.[152] found the efficacy of analgesics also varied across the menstrual cycle. As well as the menstrual cycle, changes in pain sensitivity have been reported during pregnancy and in older age, again suggesting the sex hormones may play a role.[13,49] For example, age-related changes in testosterone have been shown to impact on pain in both men and women.[15,153]

Physiological and neural differences in men and women have also been explored and related to pain.[19,123,124,171] Sex-specific variation in pain can be moderated by genetic factors,[16,125,127] and emerging preclinical evidence implicates immune differences in male and female pain.[171] In a review of pain-related differences in human brain imaging data, Gupta et al.[71] concluded that women exhibit greater variation in sensorimotor areas, when compared with men. There also seem to be sex differences in spinal inhibition processes.[115,146] For example, a large study on 2199 adults found decreased conditioned modulation of pressure pain thresholds in women.[168] This is consistent with the conclusions of systematic review and meta-analysis of experimental studies by Popescu et al.,[146] who found that men exhibited greater inhibitory control of pain. A second meta-analytic review on 30 clinical pain studies also concluded sex has a moderating effect on conditioned modulation. Larger effect sizes were found in female-only studies, compared with mixed samples. The authors speculate that this might be due to women having more impaired conditioned modulation or that the nature of mixed groups produces greater study homogeneity.

Age might also have a moderating role, with 1 study suggesting that reduced conditioned modulation in women is more pronounced at a younger age.[128]

3.4. Psychological factors

There are also differences in cognitive-emotional and behavioural factors associated with men and women's pain.[92,93] Some studies report that depression and pain-related catastrophizing have a stronger relationship with pain in women compared with men.[50,88,103,176] For example, Sullivan et al.[176] found pain catastrophizing mediated differences between men and women in their response to an experimental pain task. A similar pattern was also reported by Keefe et al.[88] in a clinical pain study. Anxiety also shows a binary sex/gender difference, but the pattern seems to be more complex and depends on the type of anxiety being assessed. For example, anxiety sensitivity seems particularly relevant to pain in women,[95,101,180] whereas pain anxiety seems more strongly related to men's pain.[53,85] There are also conflicting results[178] and studies that do not find sex/gender differences.[130]

A relatively new approach has been to see whether binary sex/gender differences influence pain-related cognitive-emotional processing. One approach has been to explore for biases in attention and interpretation.[94,98,101] Unfortunately, there are too few studies to draw any definite conclusions, but they do suggest further exploration is warranted. Another emerging area is the potential for sex/gender differences in the interruptive and disruptive effects of pain on cognition. Self-report measures of cognitive interference suggest that women might report higher pain-related disruption.[9] However, when using objective cognitive inference tasks, more complex patterns emerge.[10,97,131]

In terms of behavioural responses, some studies suggest women report using a greater number of strategies when in pain, whereas others suggest differences in the type of strategy used.[184,185] For example, women and girls have been found to report a greater use of social support, whereas men and boys report being more likely to use avoidance and/or distraction.[100,117,161,185] Given healthcare utilization can be partially viewed as a behavioural response, it is also possible to explore for differences between men and women. Women are more likely to use healthcare services,[31,191] to use prescription and over-the-counter analgesics, and attend pain clinics.[6,44,118,141] The reported use of avoidance by men is also found in the general health behaviour literature[198] and might account for the variation in pain help-seeking as well.[91]

3.5. Responses to pain treatment

Sex and gender differences in treatment responses to pain have been considered. For example, there seem to be differences in analgesic responsiveness, including to opioids.[60,137,143,166] Niesters et al.[137] report a systematic review on experimental and clinical postoperative analgesia and found women obtained greater morphine analgesia. Differences in side effects associated with drugs, including those used for pain, have been reported,[38,144] and suggestions that reduced consumption of postoperative opioids in women might be due to an avoidance of side effects.[60] Interestingly, only a few studies have explored for differences between men and women in placebo analgesia.[138,186] Women are also more likely to use prescription opioids and have negative psychological effects,[166] whereas men may have a higher overdose risk.[87] However, in systematic review of opioid studies of pain relief, Pisanu et al.[143] found less convincing evidence for sex differences, but did report that moderators, such as age, need to be considered. Although the analgesic efficacy of cannabis has yet to be determined, there are suggestions that differences between men and women exist, including in possible side effects.[12,43,61]

Fewer studies have explored differences in the way men and women respond to interdisciplinary and/or psychosocial treatments.[29,62,79,102,134,142] In one of the first studies to explore this, Keogh et al.[102] found that both men and women showed initial improvements after an interdisciplinary treatment programme, but that the longer-term stability for some pain variables was not as good for women. Murphy et al.[134] also concluded that women did not maintain the benefits from interdisciplinary pain treatments. However, other patterns have also been reported, and unfortunately, the differences in the treatment approaches used make comparisons difficult.[79,142] Systematic reviews can help make sense of such patterns, and to date, 2 investigations, 1 on adults and the other on children/adolescents, have attempted to bring these studies together.[29,62] In a review of 17 adult studies,[62] differences across 4 outcomes after interdisciplinary treatment were explored (pain sensitivity, interference, catastrophizing, and depression) but found few differences between men and women. In a review of 40 child/adolescent studies,[29] few post-treatment differences between boys and girls were found. However, they did find that more girls than boys were recruited into these trials, and that girls had higher pre-treatment scores on some variables, such as distress. The existence of pre-treatment differences in men and women entering interdisciplinary treatment programmes has been reported elsewhere,[161] and further consideration of unintended recruitment biases is needed. For example, there is related evidence that gender-related variables differentially impact on men and women's willingness to volunteer to take part in laboratory-induced pain studies.[56]

4. Explanations for the variation in men and women's pain

The evidence for sex and gender having a role in pain is strong enough to consider the reasons why this might occur. By developing a strong conceptual approach to pain, this should provide a basis for predicting when, how, and why such differences might occur. Evolutionary perspectives suggest the variation in men and women's pain, and its expression, reflects survival adaptations.[19,173,194] For example, Berkley[19] proposed that women have a greater susceptibility to disease, especially linked to reproductive structures, and so developed heightened sensitivity. The subjective nature of pain requires effective communication methods to elicit help, as well as detect pain in others. Differences in the expression of pain might therefore be linked to differences in historical social relationships and methods of communication. For example, Vigil[187] argues that historically men interacted more with kin, whereas for women, it was more with unrelated individuals and used verbal and nonverbal methods to maintain social bonds.[90,173,187] This not only suggests a reason why women may be more willing to express pain, but also leads to predictions about the recognition of pain in others, as well as the interpersonal and relational context in which pain occurs.

The importance of social context is also a feature of social learning approaches, which have been applied, separately, to gender role development and pain.[34] From early childhood, individuals are believed to learn about gender roles through parenting, friendships, schooling, and wider media. Gender behaviours are shaped through social modelling and the reinforcing/punishing actions of others. Such approaches also

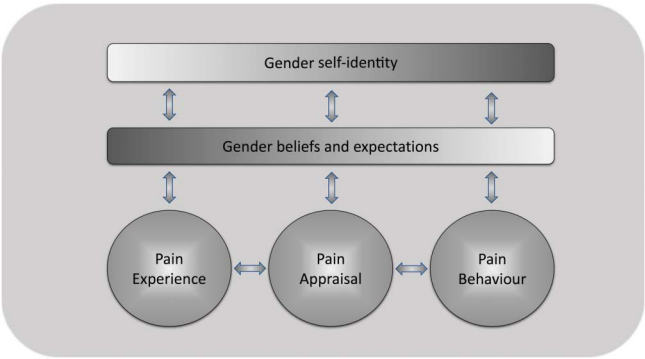

Figure 1. The relationship between gender-related constructs and pain.

highlight that broader social–cultural norms and stereotypes can impact on the way gender beliefs develop, which in turn can affect a range of behaviours including pain.[20,27,93] These themes have recently been incorporated in the gender context model of pain,[93] which includes individual concepts such as gender self-identity, the flexible and fluid nature of gender, and how gender and gender expression can be shaped by the interpersonal context. It predicts a reciprocal relationship with pain (ie, gender identity affects pain; pain affects gender identity), and that the wider (gender) context affects how men and women experience their own pain, as well as how they respond to the pain of others.

These approaches not only move us beyond descriptive comparisons, but also highlights ways to explain the variation within, as well as between men and women. They also help us look at existing evidence in new ways, such as how gender and pain can be viewed from both an individual and interpersonal level. The next section will consider this in more detail.

5. Individual gender context of pain

At an individual level, the role of gender identity, and associated beliefs and expectations, has been a primary focus for those interested in pain.[93] **Figure 1** highlights some of these gender-related constructs, such as gender identity, beliefs, and expectations, and how they might relate to the experience of, and response to, pain. This work typically explores concepts such as traditional masculinity, which is associated with stoicism, independence, and "being a man," whereas femininity is associated with sociability, caring and emotionally expressiveness, and "being a woman."[20,27,91–93,196] Both masculinity and femininity can be viewed as relatively stable trait-like characteristics and are related to pain.[3,50,120,140,182] For example, Pool et al.[145] found greater experimental pain tolerance in men identifying with traditional male roles, compared with women identifying with female roles. In an analysis of 6 studies, Alabas et al.[3] reported a small association between high masculine/lower feminine traits and higher pain threshold/tolerance. This pattern is also found in clinical studies. For example, Applegate et al.[7] found that a greater number of pain conditions was associated with higher femininity in men, but not women. Gender identity also affects how people engage with pain research. Feijó et al.[56] found men identifying with masculine, but not feminine roles, were more willing to participate in an experimental pain study.

Gender identity can also be viewed as more fluid and situationally dependent and have a reciprocal relationship with pain.[58,64,148,156] For example, experimental studies that have manipulated gender context and found it can affect pain reporting. Fowler et al.[64] found that when asked to recall feminine behaviours, men reported less pain than women. Some studies threaten gender identity to see how this affects pain.[1,18,58,120] One finding is that threats to masculine gender identity can increase pain tolerance.[18,120] However, pain can also affect gender identity. Clinical pain is reported to have a demasculinizing effect on men with strong traditional masculine beliefs, for example, being able to work, or show strength.[2,37,42] Similarly, women with strong traditional feminine beliefs reported finding chronic pain affects their ability to perform caring roles, and that this is viewed as defeminizing.[45,84,165] Such threats to identity can affect behaviour, leading some to try to reinstate their gender identity, whereas others adapt and/or change their views.[2,45,63]

Stereotypical gender beliefs and expectations about pain are also relevant.[21,96,99,197] For example, men are considered less expressive and more likely to engage in avoidance when in pain, whereas women are perceived to be more likely to catastrophize and cry. Importantly, these beliefs have been shown to impact on how pain is expressed and responded to,[156–158] including with pain medication use.[48] Gender beliefs also affect how men and women view the pain of others, and how observers respond to those in pain.[3,69,75,150,158,164] For example, Hirsh et al.[73] found that when viewing virtual patients, observers rated women as having more pain and worse at coping. Similarly, Schafer et al.[164] found that female patients were viewed more negatively, for example, less trustworthy. These findings are consistent with views that women's pain is rated more negatively and/or disbelieved.[163] Women are more likely to receive a mental health referral for pain or receive less effective pain relief.[73,163] There are also findings that suggest complex intersectional effects.[193] The concern is that such beliefs result in bias, which could affect treatment decisions.

6. Interpersonal gender context of pain

Figure 2 reflects the interpersonal context of pain and how sex and gender impact on both the person in pain and those around them. Evidence for the interpersonal gender context of pain stems from investigations into dyadic interactions around pain. For example, some have explored whether a male or female experimenter affects how men and women respond to experimental pain.[8,86,113] In one study, Kallai et al.[86] found that opposite sex-dyads resulted in lower pain reports. However, others report different patterns, and effects may depend on relational factors, such as whether and/or how people know to each other, for example, romantic partners, friends, and strangers.[24,54,55,119] Mothers and fathers seem to differ in how they respond to their child's pain,[23,68,129] whereas others find that boys and girls differ in how they respond to parents.[28,36] For example, Boerner et al.[28] found that girls were more sensitive to parental pain responses (when participating in a cold pressor task), suggesting girls are better at detecting pain in others. Spousal studies, usually with opposite sex couples, also find differences in behaviours around pain.[54,59] One study found that female partners were more likely to engage in facilitative behaviours, whereas another study found that male partners detected fewer pain situations.[135,170] Women have also been found to be closer in estimating how much pain their partner was in.[35]

Insight into the possible psychosocial mechanisms that produce these differences has focused on how men and women communicate pain. For example, the language used around pain has been considered,[81,175] including differences in the type of criticism expressed by a male or female partner.[33,110] A discourse analysis not only found women used more pain descriptors then men, but when they did talk about pain, men referred to pain relief

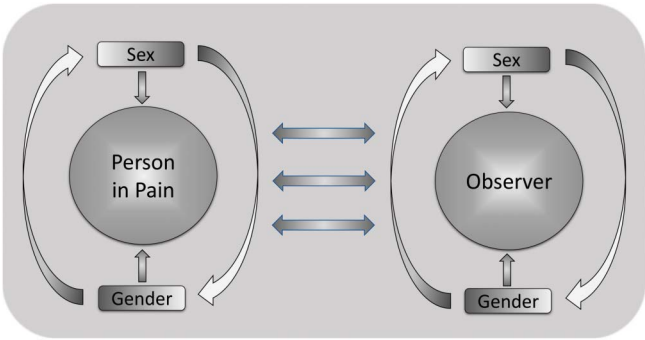

Figure 2. The interpersonal sex and gender context of pain.

and used more emotion-related language.[83] There are also nonverbal forms of pain communication. Most studies explore facial expressions, although some have also looked at vocalisations and body cues.[90,108,194] Although women seem to be generally stronger at encoding (generate) and decoding (recognise) emotional expressions, this does not seem to translate well to pain.[72] There is less consistent evidence for sex/gender differences in the encoding of pain, although some find differences in how pain is recognised.[47,106,147,167] A small number of studies suggest sex/gender-related differences in the visual attentional processes used to detect pain cues in both the face and body.[94,98,122,189,190]

7. Implications and future directions

The evidence presented here reflects over 25 years of exploration into sex, gender, and pain. This not only highlights important differences between men and women, with women showing a greater vulnerability to pain, but also points to gaps in understanding. Inconsistencies in findings, and the variation within, as well as between, men and women require explanation. These findings provoke new questions and directions for investigation.

There is a clear need to better understand the variation in pain within men and women. This has started through the identification of mechanisms at both biological (eg, genetics) and psychosocial (eg, gender identity) levels. This shows that although binary comparisons are a good starting point, the averaging of pain experience can also hide the range of human experiences.[27,93] Unfortunately, few studies have explored the variation in pain amongst those identifying as nonbinary, transgender, and/or gender-fluid. However, interesting patterns are starting to emerge.[5,114,174,188] For example, Strath et al.[174] found that gender identity had a stronger influence on experimental pain sensitivity than binary male/female comparisons.

More sophisticated conceptual and methodological approaches could be adopted and/or developed, including the interpersonal context in which pain occurs. For example, better methods of capturing gender constructs within people with pain, such as gender self-identity, are required, as well as considering ways to broaden out beyond traditional forms of masculinity and femininity.[27,93] This work has also started but needs developing.[65,179]

There is also a need to explore potential interactions between biological and psychosocial mechanisms because they arguably reflect different levels of analysis of the same phenomenon. These levels are mostly considered in isolation, and there is a need to explore how they connect and where they operate independently. This challenge is not limited to those working in pain. As well as recognising sex as a biological variable[177] and gender as a sociocultural variable,[136] perhaps, we need to consider sex and gender as interactive variables. There is also a need to consider how sex and gender differences in pain develop and change across the lifespan.[30,93] There are considerable biopsychosocial changes that occur during early childhood, which could impact on the way men and women's respond to pain in later life—how and the nature of their interdependence at different life stages is unknown. Similarly, other factors impact on pain, including ethnicity, socioeconomic status, etc.[20,57] Although this review focused on sex and gender, greater consideration of these multidimensional and intersectional elements needs to be considered.[82]

In terms of implications, an immediate consideration is to determine the extent to which biases occur in research and practice and how best to mitigate against them. In terms of research, women have been excluded from clinical trials, leading to potential inequalities in treatment options.[11,41,76] This pattern of exclusion also occurs preclinically[126] and is not limited to pain. This has led to calls for sex and gender to be routinely considered in health studies,[70,109] including for an improvement in reporting guidelines.[67,70] Building sex and gender factors into the design of clinical trials, directly considers them as moderators and mediators of treatment, including side effects, is an essential step. Systematic reviews and meta-analysis in pain could also include sex and gender as moderators.[52]

In terms of clinical practice, there are similar concerns about treatment biases. The above review highlighted the possibility for clinical decisions to be affected by sex/gender variables. There are initiatives to develop ways to reduce bias through training that could be applied to a sex and gender context.[74] There are also differences in how men and women respond to pain, including help seeking and healthcare utilization. This may also reflect structural factors, including how healthcare is set up to be accessed, and there is a need to consider whether there are health inequalities and related barriers to accessing treatment.[116,163] Unfortunately, because there are few studies that directly explore for sex and gender in pain treatment efficacy, it is too early to say how treatments could be modified. In time, it may well be possible to develop more personalised treatment approaches that take sex and gender factors into consideration.

8. Conclusion

In conclusion, this review highlights that considerable progress has been made in identifying and understanding the way in which sex and gender variables impact on pain. It also reveals gaps in knowledge and understanding. Further exploration will help us better understand the variation found in the pain experiences. Given the likely biopsychosocial mechanisms involved, this new knowledge should not only help us develop better ways to help men and women live with pain, but also better understand the nature of pain and how best to manage it.

Conflict of interest statement

The author has no conflicts of interest to declare.

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