

# Sex- and gender-responsive management of anxiety disorders: future pathways for research, education, policy and practice

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**A**nxiety disorders are the most common class of mental health disorder in Australia, affecting about 17% of people annually.<sup>1</sup> The most prevalent subtypes of anxiety disorders are specific phobias, social anxiety disorder, generalised anxiety disorder, panic disorder, and agoraphobia.<sup>2</sup> All are broadly characterised by excessive fear, worry and anxiety, coupled with avoidance of feared cues and situations.<sup>3</sup> Psychological conceptualisations posit that anxiety disorders are triggered by catastrophic, unrealistic beliefs and predictions of threat about everyday cues and situations. Avoidance of feared cues and situations maintains anxiety by preventing disconfirmation of catastrophic beliefs. The primary focus of cognitive behavioural therapy (CBT), which is the first line psychological treatment for anxiety disorders, is on reducing avoidance through graded exposure to feared cues and situations to facilitate the development of more realistic beliefs and threat appraisals.<sup>4</sup> Selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors are the first line pharmacotherapy for anxiety disorders, and should be administered in combination with CBT or guidance on graded exposure.<sup>5</sup>

This narrative review provides an overview of sex and gender influences on anxiety disorders, and the status of sex- and gender-responsive care for anxiety disorders in the Australian landscape. Literature was identified by drawing from interdisciplinary sources (spanning preclinical research to clinical trials, searching key terms “anxiety disorders”, “gender” and “sex”), practice guidelines, and grey literature, including reports from government and peak bodies and research funding guidelines.

## Relevance of sex and gender to anxiety disorders

Despite often being conflated, sex (biological characteristics) and gender (a sociocultural construct) are distinct variables (Box 1). Although anxiety disorders are experienced by people of all sexes and genders, they are not sex- or gender-neutral conditions. This is most evident in prevalence rates, with a recent analysis across 204 countries and regions finding that women experienced anxiety at 1.6 times the rate of men in 2021.<sup>7</sup> In Australia, anxiety disorders affect about 23% of Australian males, and 34% of Australian females, across the lifetime.<sup>1</sup> Anxiety disorders are also more prevalent among sex and gender minorities than cisgender people, with three in four Australian transgender (trans) and gender-diverse people reporting a diagnosis of anxiety and/or depression.<sup>8</sup> Although data on anxiety disorder rates in people born with innate variations of sex characteristics are scarce, the majority of Australians with intersex variations report their current mental health to be good or better, although rates of thoughts of or actual self-harm are high (42%), and anxiety is among the most common mental health diagnosis.<sup>9</sup> Understanding the causes

## Summary

- Anxiety disorders are the most prevalent mental illness in Australia and are more common in women relative to men, as well as transgender and gender diverse people relative to cisgender people.
- Sex and gender differences in anxiety prevalence are likely driven by a combination of factors including differential exposure to different types of stressors and trauma, gendered enculturation of different coping responses and perceived stigma of mental illness, differences in medical comorbidities, and differences in symptom presentations.
- The established impact of gonadal hormone changes on anxiety risk and symptom presentation across the female lifespan underscore the need for sex- and gender-responsive management of anxiety disorders.
- Better integration of sex and gender considerations in health and medical research, in Australian clinical practice guidelines, and in health and medical education curricula, is needed to improve the quality of care for all people with anxiety disorders.

for sex and gender differences in anxiety disorder prevalence could identify pathways to mitigate the risk for anxiety disorder development that are tailored to vulnerable populations. Some risk factors for anxiety disorders are common to people of all sexes and genders, and differential levels of exposure to these common risk factors may partly account for sex and gender differences in anxiety prevalence. In contrast, other risk factors for anxiety disorders occur uniquely in certain sex or gender groups, thereby elevating their risk profiles through distinct pathways. To illustrate, this article considers just some of the mechanisms by which anxiety risk differs as a function of a person's sex and gender.

## 1 Defining sex and gender

The Australian Bureau of Statistics 2020 *Standard for sex, gender, variations of sex characteristics and sexual orientation*<sup>6</sup> provides guidance on how these variables should be defined and measured. The Standard underwent extensive consultation and received broad approval from a wide range of stakeholder groups. According to the Standard, sex is an umbrella category in humans and non-human animals referring to a set of characteristics including chromosomes, sex organs, and gonadal hormones. Sex is typically classed as male or female based on sex characteristics observed at birth, but reported sex can change over the lifespan and may differ from that recorded at birth. A minority of the population are born with innate variations of sex characteristics (termed “intersex”) that do not fit the medical norms for male or female bodies. Gender (unique to humans) refers to a person's identity, behaviour, experiences, social norms, and power dynamics. Gender does not always align with a person's sex, is not always binary (man or woman, boy or girl), and can change over the lifespan. The societal and cultural views that influence gender change across time and place.

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## Risk factors for anxiety disorders: sex and gender differences

Stress and trauma exposure are established risk factors for anxiety that cut across sex and gender groups. Greater anxiety among marginalised populations (including trans people, gender-diverse people, or people born with innate variations in sex characteristics) may be driven by exposure to stigmatisation, stereotypes, prejudice and gendered violence in daily living; unstable housing; issues in education; bias and stigma in the medical system; and traumatic medical interventions.<sup>8-13</sup> Greater exposure to family and domestic violence, and certain types of traumas, such as sexual assault and rape, may elevate anxiety among these populations and among cisgender women.<sup>12,14,15</sup> Moreover, cortisol dysregulation as a function of trauma exposure appears to be more common in women than in men,<sup>16</sup> possibly due to the interplay between cortisol and ovarian hormones. Stress associated with gender inequities in domestic load and caring responsibilities, which also have an impact on economic and social standing, may elevate anxiety in women, and likely accounted for the observation that anxiety rates rose disproportionately in women during the COVID-19 pandemic.<sup>7,17</sup>

In addition to societal factors, relative to men, women exhibit greater levels of cognitive and behavioural risk factors that underlie anxiety disorders, including repetitive negative thinking (such as rumination and worry), and behavioural avoidance.<sup>18,19</sup> These differences could reflect innate sex differences in coping responses, but may also reflect gender differences acquired through early life learning. For instance, caregivers often encourage boys to engage in risk taking, whereas safety seeking is promoted in girls.<sup>20</sup> Relatedly, instrumentality is a trait typically associated with masculinity, yet it appears to be protective against mental illness in both males and females,<sup>21</sup> suggesting that selective fostering of instrumentality among boys may reduce their risk for anxiety disorders.

Women experience certain medical conditions (all of which are highly comorbid with anxiety disorders) to a greater degree than men,<sup>22</sup> including sleep disorders,<sup>23</sup> chronic fatigue disorders,<sup>24</sup> and chronic pain conditions.<sup>22</sup> In addition, female-specific conditions such as endometriosis and chronic pelvic pain are underdiagnosed, typically have a long duration between symptom onset and diagnosis, and lack acceptable and effective treatments.<sup>25</sup> These medical comorbidities may elevate women's anxiety rates. Moreover, negative experiences within the medical system,<sup>26</sup> including misogyny and denial and dismissal of pain, may amplify the relationship between medical comorbidities and anxiety.

Conversely, gender-related mechanisms may obscure the detection of anxiety disorders in cisgender men and falsely amplify the apparent sex imbalance in anxiety prevalence. Men who have been exposed to masculine ideals around stoicism may experience heightened stigma regarding mental illness, which may lead to under-reporting of anxious symptoms.<sup>27</sup> Sex and gender differences in the expression of anxiety symptoms may lead to underdetection of anxiety disorders (or misdiagnosis) in men. Men may express anxiety differently, perhaps due to sex differences in anxiety comorbidities; for instance, men tend to experience comorbid externalising conditions (including attention deficit hyperactivity disorder [ADHD], anger-related disorders, and substance misuse), whereas women tend to experience comorbid internalising conditions such as depression.<sup>21</sup> Therefore, the diagnostic criteria for anxiety

disorders, which focus on internalising symptoms, may be better aligned with the typical symptom profile for women than for men.

Although far from exhaustive, these examples underscore that pathways to risk mitigation for anxiety disorders differ according to one's sex and gender. Identifying the constellation of risk factors that contribute to anxiety disorders in different sex and gender groups will improve our ability to mitigate risk via personalised health care. Yet even if sex differences in anxiety disorder prevalence can be entirely accounted for and addressed through modifiable societal and cultural factors, there remains a need for sex-responsive treatment for anxiety disorders because there are clear sex-specific factors that influence the trajectory of anxiety disorders. The most robust evidence for this comes from research on hormonal impacts on anxiety disorders in females, which is discussed below.

## Relationship between sex-specific factors and the trajectory of anxiety disorders: the impact of gonadal hormones across the lifespan

Gonadal hormones oestradiol and progesterone, although primarily synthesised in the ovaries, cross the blood-brain barrier and can be synthesised *de novo* in the brain. Oestradiol and progesterone are powerful modulators of the neural circuitries that support emotion regulation, attention, learning and memory — all functions that are critical to the management of anxiety symptoms.<sup>28,29</sup> The effects of oestradiol and progesterone on the brain are mediated in part through their influence on serotonin,<sup>30</sup> which is a key neurotransmitter implicated in the aetiology and treatment of anxiety, and allopregnanolone,<sup>31</sup> which is a neurosteroid metabolite of progesterone that regulates inhibitory tone in the central nervous system through its effects on  $\gamma$ -aminobutyric acid (GABA) receptors.

Women experience substantive and dynamic changes in their hormonal milieu across the lifespan, commencing with puberty and the onset of regular hormonal fluctuations over the menstrual cycle, then, for most women, pregnancy, where levels of oestradiol and progesterone reach levels higher than the cumulative exposure to these hormones across the non-pregnant life, only to plummet postnatally, and finally perimenopause, when hormonal fluctuations become erratic and ultimately cease after the final menstrual cycle when menopause is reached. Sex differences in anxiety disorder prevalence commonly emerge at puberty<sup>32</sup> or, according to some reports, in middle childhood.<sup>33</sup> Pregnancy, the postnatal period, and perimenopause are periods of heightened risk for the development of new, or exacerbation of pre-existing anxiety disorders.<sup>34,35</sup> Similarly, for a subset of people, anxiety symptoms fluctuate across the menstrual cycle for a wide range of anxiety disorders, including generalised anxiety disorder, social anxiety disorder, panic disorder, and related conditions such as post-traumatic stress disorder and obsessive-compulsive disorder (OCD).<sup>36</sup> In many affected people, anxious symptoms worsen in the perimenstrual phase as gonadal hormones decline from peak to base levels, although others may also experience periovulatory symptom exacerbation. Perimenstrual symptom exacerbation is distinct from premenstrual dysphoric disorder and is a transdiagnostic phenomenon — it appears in other mental disorders including schizophrenia and ADHD,<sup>37</sup> as well as medical conditions such as asthma.<sup>38</sup> Dominant theories of this phenomenon purport that a subgroup of women are hormone sensitive,<sup>39</sup> wherein they experience negative psychological reactions to normative

hormonal changes, and this sensitivity increases their risk for reproductive-related anxiety and mood disorders across the lifespan.

Although hormone sensitivity represents a subgroup of women, almost all women experience some level of heightened stress around pregnancy and the postnatal period.<sup>40</sup> Over the past decade, numerous studies have revealed that the human female brain undergoes widespread and highly replicable grey matter changes in response to the massively heightened levels of hormones during pregnancy.<sup>41,42</sup> Preclinical data in female rats have demonstrated that these brain changes lead to a fundamental, and potentially permanent, transformation in the brain circuitry that regulates threat detection and fear regulation.<sup>43-46</sup> In turn, a highly common yet understudied experience among perinatal women is egodystonic intrusive thoughts of harm befalling their infant, which, for 50% of people, are thoughts about deliberate harm inflicted by the mother.<sup>47</sup> Given the near ubiquity of this experience (with most women endorsing such thoughts), it is likely that this reflects an adaptive process of pregnancy triggered by neurological changes that enables the mother to detect and overcome threat to the survival of the offspring. Nonetheless, such thoughts can be highly distressing, and negative appraisals of the meaning and implications of these thoughts (eg, “I’m a bad mother, I’m going to harm my child”) may be a key contributor to perinatal anxiety disorders and OCD.<sup>48</sup>

The normative hormonal changes that women experience over the lifespan are modified by hormonal contraception, taken by most women at some point in their lives,<sup>49</sup> and which disrupt ovarian synthesis of oestradiol and progesterone. Most research on the relationship between hormonal contraception and mental health has focused on depression, with large scale studies reporting mixed findings. Some have observed that hormonal contraceptive use is associated with greater rates of depression or antidepressant prescriptions<sup>50,51</sup> (which are also the first line pharmacotherapy for anxiety disorders), particularly when use begins in adolescence, but others have reported no relationship.<sup>52</sup> Notably, the most common reason for hormonal contraception discontinuation is side effects, including adverse effects on mood,<sup>53</sup> which suggests that a subset of people experience negative psychological effects from hormonal contraception, although this is not a ubiquitous experience. It is therefore possible that those who experience negative psychological effects from hormonal contraceptives represent a subgroup of people akin to those with hormone sensitivity, although we currently have little information about who is more likely to experience such side effects. Relatedly, a growing body of research shows that hormonal contraceptive use may interfere with the benefits of exposure therapy for anxiety disorders.<sup>54,55</sup> Although this research requires replication in a broader range of samples, taken together, this work suggests that hormonal contraceptive use should be routinely assessed and considered in the context of the patient’s symptom trajectory and response to treatment.

There is growing appreciation of the potential consequences of perimenopause for mental health. Rates of new onset anxiety disorders may increase during perimenopause among women with low pre-menopause anxiety,<sup>56</sup> but data from prospective studies are scarce, and recent reviews suggest that most people do not experience poor mental health over the menopausal transition.<sup>57</sup> As such, we require methods to identify who is at risk of perimenopausal anxiety (and other mental health conditions) so that early intervention and appropriate

management can be given to those who need it. New onset anxiety during the menopausal transition, rather than being directly related to the physiological changes of menopause, may be precipitated by the (often gendered) stressors experienced during this life stage, including simultaneously caring for younger children and ageing parents, and adapting to role transitions.<sup>57,58</sup> Candidate factors for the direct physiological effects of perimenopause on anxiety risk may be extrapolated from the literature on perimenopausal depression, on which most of the existing research has focused. These include the severity of perimenopausal vasomotor symptoms, sleep disturbance, timing and type of menopause (premature versus within the average age range, natural versus surgical), and variability in oestradiol levels and hormone sensitivity,<sup>57</sup> which are factors that may be moderated by prior trauma exposure.<sup>57,58</sup>

### Sex and gender considerations in first line treatments for anxiety

Despite clear evidence for sex and gender influences on anxiety, diagnoses and treatments are currently delivered in a sex- and gender-neutral manner. There is a paucity of research investigating potential sex and gender differences in effectiveness of CBT or pharmacological treatments. Why is this the case? For a start, in many instances, females are studied to a lesser degree than males. This is certainly the case for preclinical research on anxiety, which is the research upon which pharmacological treatments for anxiety disorders are developed and tested for safety and efficacy, and from which behavioural treatments for anxiety (including exposure therapy) are refined.<sup>59</sup> Indeed, two-thirds of preclinical research on fear, stress and anxiety published in 2021 were conducted only in males.<sup>60</sup> In clinical trials in psychiatry, although mixed-sex samples are the norm, participation among males outnumbers that of females.<sup>61</sup> To compound these issues, failure to report and analyse study outcomes disaggregated by sex and gender is rife, sex and gender data collection typically does not account for trans or non-binary participants, or people born with innate variations of sex characteristics<sup>9,62</sup> — or these groups may be excluded from trials altogether, as is also often the case with pregnant people.<sup>63</sup> In short, inadequate consideration of sex and gender in medical and psychological research has stalled the progression of sex- and gender-responsive treatments.

Partly as a consequence of sex and gender being relatively ignored in anxiety disorder research, the Australian practice guidelines for anxiety disorders<sup>5</sup> contain very little mention of sex- and gender-responsive care. Despite repeatedly noting the sex differences in prevalence, the dearth of sex- and gender-specific evidence is not noted as a limitation of the evidence. Yet, there is also a lack of information in these guidelines on what we know about sex and gender differences in anxiety. For example, pregnant people are mentioned as a “special population”, but how the presentation or triggers for anxiety during the perinatal period are different, or how treatment can be adapted, is not discussed, except to note that up-to-date information about the most appropriate pharmacotherapy for pregnant or breastfeeding people should be sought. Despite the ubiquity of intrusive thoughts about infant harm, these are not mentioned in the guidelines, and no education on intrusive thoughts is provided in standard antenatal classes, nor are they assessed as part of routine postnatal care. Moreover, the current guidelines contain no mention of perimenopausal anxiety (despite including a small section on anxiety in older adults),

nor the impact of the menstrual cycle on anxiety symptoms, nor how to diagnose or manage these issues. There is no mention of anxiety in trans or gender-diverse people.

Another major contributor to sex- and gender-neutral treatments for anxiety relates to how mental health practitioners are trained. Sex and gender literacy is not included as a core competency in primary medical programs by the Australian Medical Council,<sup>64</sup> nor by the Psychology Board, which references gender (not sex) in relation to a much broader competency around cultural responsiveness and inclusive practice.<sup>65</sup> In the absence of clear requirements to include content on sex and gender differences in medical and health curricula, it is likely that mental health practitioners are not being trained about these differences, nor about the sex and gender biases in the evidence, omissions that carry the implicit message that sex and gender are not important variables.

### Recent progress and future directions for sex- and gender-informed health care for anxiety disorders

Australia is in the midst of a paradigm shift with respect to the incorporation of sex and gender considerations into the medical research, and the health care landscape more broadly, which should filter through to the treatment of anxiety disorders. In 2024, the National Health and Medical Research Council and the Department of Health, Disability and Ageing, which implements the Medical Research Future Fund, issued their *Statement on sex, gender, variations of sex characteristics and sexual orientation*,<sup>66</sup> which strongly encourages all researchers to account for these variables throughout the research pipeline, from question setting through to data analysis, reporting and translation. This is an important step in bringing Australian research policy in line with international counterparts such as the Canadian Institutes of Health Research, the European Commission's Horizon Europe and the European Research

Executive Agency, who have mandated consideration of sex and gender for more than a decade.<sup>67</sup> Moving forward, a unified sex and gender policy across all Australian research funders, coupled with an implementation plan to assess how well sex and gender are considered in funding applications, would ensure that sex and gender are routinely considered in all Australian medical research, including that on anxiety disorders.

Improving sex and gender equity in medical research is a foundational step in ensuring that clinical practice guidelines adequately represent the unique needs of everyone according to their sex and gender. Along these lines, the National Women's Health Advisory Council commissioned a recent review to assess the incorporation of sex and gender consideration within Australian practice guidelines.<sup>68</sup> The review found large heterogeneity regarding the extent of sex and gender inclusion in guidelines and recommended that guideline development bodies should incorporate appraisals of sex- and gender-specific evidence, or at least clearly indicate where a lack of evidence exists. Given the Australian guidelines<sup>5</sup> on the treatment of anxiety disorders are due for updating, now would be an opportune time to facilitate awareness among clinicians, and changes in practice, by incorporating sex and gender considerations to a greater extent in the new iteration of these guidelines. Guidance on sex- and gender-related differences in symptom expression and comorbidity, the diagnosis and management of menstrual-related changes in symptom severity, the potential impact of hormonal contraception on anxiety, and managing anxiety across the perinatal and perimenopausal phases would be particularly helpful. At the very least, encouragement to assess the relationship between patients' hormonal status and their symptoms is warranted. Likewise, unique challenges faced by trans and gender-diverse people that may moderate anxiety risk and require adjustments to treatment approaches should be addressed in updated guidelines.

## 2 Recommended reforms among key stakeholder groups to improve sex- and gender-responsive health care for anxiety disorders

| Stakeholder                                                        | Recommendations                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|--------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Researchers                                                        | <ul style="list-style-type: none"> <li>Take accurate measurements of sex and gender (where relevant) according to the Australian Bureau of Statistics standards</li> <li>Engage in efforts to improve balanced representation of males and females in research samples, and to increase representation of sex and gender minority populations in research</li> <li>Report and analyse data disaggregated according to sex and gender</li> </ul>                                 |
| Research funders                                                   | <ul style="list-style-type: none"> <li>Develop a unified national sex and gender research policy that requires funding applicants to demonstrate integration of sex and gender considerations in all proposed health and medical research</li> </ul>                                                                                                                                                                                                                            |
| Accreditation and registration regulators (Ahpra, national Boards) | <ul style="list-style-type: none"> <li>Incorporate requirements for competencies in sex- and gender-responsive care in the following:               <ul style="list-style-type: none"> <li>accreditation standards for university medical and health programs</li> <li>registration standards for health practitioners</li> <li>continuing professional development requirements for health practitioners</li> </ul> </li> </ul>                                                |
| Health educators                                                   | <ul style="list-style-type: none"> <li>Undertake national reform of psychology and medical curricula to include content on sex and gender differences in mental illness (including anxiety disorders)</li> </ul>                                                                                                                                                                                                                                                                |
| Clinicians                                                         | <ul style="list-style-type: none"> <li>Engage in continuing professional development activities to improve understanding of sex and gender differences in anxiety risk and presentation</li> <li>Incorporate routine assessments of symptoms in relation to menstrual cycles, hormonal contraceptive use, pregnancy or perimenopause</li> </ul>                                                                                                                                 |
| Clinical guideline developers                                      | <ul style="list-style-type: none"> <li>Update clinical practice guidelines for anxiety disorders to include what is currently known about sex and gender influences on anxiety disorders (including gender differences in symptom presentation, and influences of the menstrual cycle, pregnancy, and hormonal contraception)</li> <li>Explicitly note knowledge gaps on sex and gender differences in diagnosis and treatment effectiveness due to lack of research</li> </ul> |
| Government                                                         | <ul style="list-style-type: none"> <li>Ensure that investments in women's reproductive health are adequately resourced to manage comorbid mental illness</li> <li>Conduct sex and gender assessments on all new health policies to evaluate how these policies may differentially affect different sex and gender groups</li> </ul>                                                                                                                                             |

Ahpra = Australian Health Practitioner Regulation Agency. ♦

In addition to the recent review on Australian practice guidelines, other areas of Australian state, territory and federal governments have invested in closing sex and gender gaps in health. The Centre for Sex and Gender Equity in Health and Medicine<sup>69</sup> has been commissioned by the Victorian Department of Health to review sex and gender inclusion in Victorian medical research policies and education curricula. The Centre has also been commissioned by the federal Department of Health, Disability and Ageing to review sex and gender inclusion in health and medical curricula across Australian universities, as a key output from the National Women's Health Advisory Council.<sup>69</sup> The next critical step after these reviews is to update the national accreditation and registration standards to encourage curriculum reform to incorporate sex and gender literacy as a core competency in the training of Australia's registered health practitioners. Along these lines, the Western Australian Government has invested in research to improve education and training for health care professionals working with young lesbian, gay, bisexual, transgender, queer, intersex, asexual and other non-heteronormative or non-binary sexual and gender identity (LGBTQIA+) people.<sup>70</sup> The federal government has invested in men's health charities including Movember, the Australian Men's Sheds Association, Healthy Male, and the Black Dog Institute (working on suicide prevention in men), with the aim of reducing stigma around men's mental health, promoting men's engagement with health professionals, and training health care workers to provide sex- and gender-responsive health care for men. These welcome investments should not be interpreted to mean that current mental health systems are optimised for cisgender women, for whom improvements in sex- and gender-responsive care are also needed. To this end, the recent substantive federal government investment in women's reproductive health, including new endometriosis and pelvic pain clinics, and menopause support packages, could be leveraged to improve

women's mental health by ensuring that these initiatives are resourced to manage comorbid mental health conditions such as anxiety disorders.

## Conclusion

Integration of sex and gender considerations in the management of anxiety disorders requires changes to policy and practice at multiple levels, including research, education, and health care delivery (Box 2). The implementation of these changes, many of which are now emerging in the Australian health and medical landscape, will improve the prevention and treatment of anxiety disorders for everyone through the principles of personalised health care, thereby reducing the substantive individual and societal burden of anxiety disorders.

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