Serotonin and female psychopathology

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There are sex differences in the prevalence and presentation of many psychiatric disorders. Various trends in symptomatology have emerged that are thought to be linked to periods of hormonal fluctuations such as with menses, pregnancy or menopause. With data from animal and human studies, it has become clear that there is an important interplay between the serotonergic system and gonadal hormones. The majority of the research to date has focused on the influence that estrogen has within the CNS and, in particular, how it leads to an overall increase in serotonin synthesis and availability. In reviewing this female-specific topic we hope to raise awareness to sex/gender differences in psychopathology, help identify at-risk populations and consider development of new treatment options. Future research will also need to consider the influence that progesterone and oxytocin may have on sex-specific psychopathology as well as incorporate neuroimaging and consider the influence of hormones on the serotonergic system at a genetic level.

Epidemiological studies have unequivocally established that there are differences in the prevalence of various psychiatric disorders and that these are consistent across cultures. Adult women have higher rates of depression, more anxiety disorders, eating disorders and somatic presentations compared with men, who have higher rates of substance and alcohol abuse, as well as increased antisocial personality disorder [1,201,202]. Acknowledging these differences, several regulatory authorities have mandated sex-specific analyses within clinical studies so that efficacy of treatment for the female population could be scientifically validated as opposed to extrapolated from male data [2,3]. These changes served to recognize the burden and unique experience of psychiatric illness within the female population.

Serotonin (5-HT) has been identified as an important neurotransmitter implicated in the etiology and pathophysiology of many psychiatric disorders, in particular, mood and anxiety disorders [4]. 5-HT is a monoamine neurotransmitter that is involved in regulating various functions including aggression, appetite, sleep and cognition [5]. The serotonergic neural system projects to nearly every area of the forebrain with substantial input to the hippocampus, amygdala and prefrontal cortex. These anatomical regions are involved in affective behavior, response to stress and memory formation. There are at least seven distinct families of the 5-HT receptor (5-HT1–5-HT7), each having its own subpopulation of receptors [6]. These receptors differ in their location throughout the brain and body but also in their physiological influences. 5-HT receptors are found throughout the CNS and peripherally within mast cells, platelets, enterochromaffin cells and enteric neurons of the gastrointestinal system (e.g., 5-HT4) [5].

Research from both animal and human studies has contributed to a growing body of knowledge concerning the interplay between the serotonergic system and gonadal steroids [7]. Gonadal steroid receptors are located throughout the CNS, particularly in the amygdala, hippocampus, basal forebrain, cortex, cerebellum, locus ceruleus, midbrain raphe nuclei, pituitary gland and hypothalamus [8]. More specifically, estrogen receptors are located in both the amygdala and preoptic area [9], and the ventromedial nucleus and arcuate nucleus of the hypothalamus [10]. Animal studies have shown that estrogen decreases the activity of MAO-A and MAO-B enzymes that degrade neurotransmitters, including 5-HT, to varying degrees in various brain regions [11,12] and increases the activity of tryptophan hydroxylase, the rate-limiting enzyme involved in 5-HT synthesis [13,14]. Moreover, estrogen regulates the 5-HT transporter and effects the expression of various 5-HT receptor subtypes [15,16]. Further animal studies have shown that estrogen administration can reduce 5-HT receptor density in the amygdala, hippocampus and cortex [17], and reduce receptor binding in the dorsal raphe nuclei and hypothalamus [18]. Thus, the interplay between estradiol and 5-HT leads to an overall increase in 5-HT synthesis and availability, and a decrease in 5-HT breakdown in brain regions associated with mood regulation [19,20].

There appears to be a subgroup of females who demonstrate a vulnerability to the aforementioned normal physiological changes in hormones [21]. This review will attempt to highlight research from a wide range of psychiatric disorders that provides insight

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into the unique relationship between 5-HT, estrogen and psychopathology. Notably, this review primarily focuses on mood and anxiety disorders because much of the relevant research exists within these diagnostic categories. Through the Ovid® search engine, the search databases used were EMBASE (1980–February 2012), MEDLINE (1980–February 2012) and PsycINFO (1967–February 2012). A combination of the keywords 'sex/gender difference', 'estrogen/hormone', 'serotonin' and specifics to various forms of psychopathology (e.g., 'depression/mood disorders') were used. Reference sections of relevant articles were manually searched to retrieve further studies. Our search was limited to the English language.

Psychopathology

Mood disorders

The link between gonadal hormones, 5-HT and psychopathology has been most extensively studied in mood disorders [21–25]. Rates of depression in women are approximately twice that seen in men and this sex disparity becomes apparent during the pubescent years [26,27]. While this is a period of hormonal fluctuation, it is also a transitional period that may introduce new psychosocial stressors and interpersonal difficulties that likely contribute to this disparity [28]. Individuals with a greater sensitivity to stress may be susceptible to developing a mood disorder and females show a greater postpubertal increase in stress response and recovery time compared with males [29]. Women are more likely to present with hypersomnia and hyperphagia [30], and the prototypical symptoms of depression (e.g., low mood and feelings of guilt), whereas men are more likely to present with anger or irritability [31]. Sex differences have also been noted in the presentation of bipolar disorder, with females more likely to present with a rapid cycling pattern, possibly related to fluctuations in reproductive hormones [32–36].

There is compelling evidence for a subgroup of females who experience an abnormal response to hormonal cycling within normal physiologic ranges [37]. It has been suggested that this subgroup of females experience mood fluctuations that are a biological response to hormonal fluctuations within the CNS [38]. Females who experience a depressive episode during a period of hormonal fluctuation are then at risk for subsequent depressive episodes during other times of hormonal change [39]. This sensitivity to hormonal change may be linked to estrogen receptor polymorphism with some females having a certain genetic predisposition that creates a dysphoric response to normal gonadal steroid levels [40]. Genetic studies on 5-HT transporter-linked polymorphic region (5-HTTLPR) polymorphism of the 5-HT transporter gene have shown that the short (s) allele results in decreased expression of this gene leading to decreased 5-HT uptake [41,42]. Females with the 'ss' genotype (i.e., two short alleles) show an enhanced fear response and perseveration on the emotional experience [43]. This may then put these females at risk for developing psychopathology when exposed to life stressors. Furthermore, one study showed that the 's' allele modulates the influence of lifetime and current stressors on perinatal depressive symptoms [44].

Premenstrual dysphoric disorder (PMDD) is a severe form of the premenstrual syndrome (PMS). Genetic studies have suggested that prospectively confirmed PMDD is linked to a genetic variant in the estrogen receptor-α gene [45] and PET studies have shown that female gonadal hormones and phase of the menstrual cycle influence the 5-HT receptors implicated in depression [46]. PMDD is a clinical diagnosis distinct from major depressive disorder and although both can be treated successfully with selective serotonin reuptake inhibitors (SSRIs), patients with PMDD demonstrate a rapid response to SSRIs, such that they can be used on an intermittent basis (i.e., just during the luteal phase of the menstrual cycle) with good response [47]. Although intermittent dosing is an option, a recent meta-analysis has shown that continuous dosing regimens are more effective in treating both severe PMS and PMDD [48]. The oral contraceptive pill (OCP) can help to eliminate a premenstrual breakthrough of depressive symptoms in females being treated with an SSRI [49] and OCP users experience less variability in mood across the menstrual cycle [50]. Furthermore, data indicate that the OCP can also be used effectively on a continuous basis to decrease symptoms of PMS and PMDD [51]. Thus, the rapid response to SSRIs combined with the therapeutic effect that OCPs can have on depressive symptomatology suggests a unique serotonergic pathway that has interplay with gonadal and neurosteroid systems.

The highest risk time for a depressive episode during pregnancy is during the last 3–6 weeks of gestation (when hormone levels peak) and immediately postpartum (when hormone levels decrease significantly) [52]. Women who have their first episode postpartum are then susceptible to

subsequent depressive episodes during times of hormonal fluctuation [53]. Moreover, euthymic pregnant females with a history of depression who decrease or discontinue antidepressant medication during pregnancy have a relapse rate of 75% [54], indicating that the serotonergic effects of these medications are protective during this time of hormonal variability.

The perimenopausal transition is another time of unpredictable hormonal fluctuation that leads to eventual estrogen withdrawal. This phase of life puts females at an increased risk for a depressive episode as a result of both biological and psychosocial factors [55]. Animal models have shown that estrogen enhances neurogenesis, synaptic plasticity and connectivity in hippocampal formation [56–58]. Ovarian steroids increase the cellular resilience and may prevent cellular death of 5-HT neurons in monkeys who have undergone surgical menopause [59]. Ovariectomized rats, studied as an animal model of menopause, show increased immobility (i.e., increased depressed-like behavior) in the forced swim test, which can be reversed with estradiol administration [60,61]. PET studies carried out on human subjects have shown that both estrogen and progesterone administration increases the density of 5-HT2A receptors in the right cerebral cortex [62–64]. Thus, both animal models and neuroimaging in a human population have shown that the loss of estrogen has direct effects on the serotonergic system and that hormonal replacement can partially negate these effects and subsequent risk of developing affective symptoms.

There are differences in treatment response based on menopausal status with evidence showing that SSRIs appear to be more potent in the presence of estrogen [65,66] and that postmenopausal females have similar response rates to males when compared with premenopausal females [67]. Furthermore, it has been shown that estrogen replacement therapy can cause a modest increase in plasma 5-HT levels in postmenopausal females [68] and that hormone replacement therapy leads to larger hippocampal volumes compared with nonusers and males [69,70]. Finally, interactions between the serotonergic and estrogenic systems are evident when considering that estradiol is efficacious in treating depression in perimenopausal females [71–74] and antidepressants (e.g., SSRIs) are efficacious in treating symptoms of menopause including vasomotor symptoms [75]. The possible synergistic role of estrogen in optimizing SSRI treatment has been supported by animal studies [76]. The patterns demonstrated above indicate that the serotonergic and estrogenic systems interact very closely within the CNS and that a subgroup of females are at particular risk for depressive episodes during times of hormonal fluctuation.

Anxiety disorders

Obsessive compulsive disorder

The 1-year prevalence of obsessive compulsive disorder (OCD) in Canada is 1.8%, with anxiety disorders affecting 16% of adult women in any 1-year period [203]. Qualitative differences in symptomatology exist whereby females tend to demonstrate a higher frequency of contamination obsessions or cleaning/washing compulsions. The intensity of these particular symptoms worsens in the luteal phase of the menstrual cycle as well as postpartum [77–80]. Furthermore, women with symptoms of contamination/cleaning are more likely to report the onset of their disorder during pregnancy or postpartum [81].

Much of the literature that exists on sex differences in OCD come from retrospective studies or case reports. Precipitating or exacerbating factors have been identified as times of reproductive change including menarche, premenstrually and in the ante/postpartum [82–87]. Notably, pregnancy is the only reproductive event when some females note an improvement in symptom severity. Females with OCD who demonstrate a vulnerability to hormonal fluctuations tend to also have a history of mood symptoms during those high-risk times (e.g., premenstrually). Furthermore, women with either initial-onset or exacerbation of pre-existing OCD postpartum tend to have a history of previous mood episodes and are at further risk of developing a postpartum depressive episode [84]. This cohort of women is also more likely to have had premenstrual worsening of pre-existing OCD symptoms, suggesting a particular sensitivity to hormonal fluctuations [88].

Several case reports have demonstrated both exacerbation or improvement of OCD following hormonal treatments [89–91] with some suggestion that modulating hormone systems may be a useful alternative treatment approach for OCD [89]. Although not fully understood, symptoms of OCD are influenced by both the serotonergic and dopaminergic system [92–95]. Estradiol influences the release and reuptake of dopamine and can also influence the affinity of the D2 receptors. Further research has questioned

the relationship between menarche and the onset of OCD, with hypotheses implicating oxytocin as an important neuropeptide in the pathophysiology of this psychiatric illness [96,97]. Moreover, a link between postpartum OCD and high levels of oxytocin has been suggested [98].

Post-traumatic stress disorder

Females are twice as likely to develop post-traumatic stress disorder (PTSD) than males [99]. Females more often experience sexual abuse and rape whereas males more often experience physical attacks or serious accidents [99–102]. Of note, both females and males are at risk of developing PTSD following highly noxious events (e.g., sexual abuse); however, females are more vulnerable to developing PTSD following less noxious events. When confronted with stress, the body's hypothalamic–pituitary–adrenal (HPA) axis releases the glucocorticoid cortisol to restore homeostasis. Following exposure to a trauma, cortisol levels are initially high, however, over time, a compensatory response leads to chronically low levels of cortisol [103,104]. Individuals with PTSD show decreased HPA activity and chronically low levels of cortisol [105,106].

The influence of gonadal hormones on the HPA axis has been studied in both animals and humans suggesting that estrogens enhance the HPA responsiveness to stress. From animal studies we know that estradiol influences reactivity of the HPA axis. Evidence comes from ovariectomized rodents demonstrating an attenuated HPA response and estradiol replacement inducing HPA stimulation [107]. Further studies in rhesus monkeys link the HPA axis to the serotonergic system and show that those individuals with the 5-HTTLPR 's' allele exhibit increased anxiety when faced with adversity and that these monkeys also have a decreased cortisol response to stress [105]. Studies in humans have also shown that there are sex differences in the serotonergic mediation of the HPA axis activity that leads to differences in basal cortisol secretion [108,109]. Furthermore, there is greater dysregulation of the glucocorticoid receptor in females as evidenced by greater suppression in females on the dexamethasone suppression test. Women also appear to have a greater decrease in hippocampal volumes compared with men with PTSD [110].

Few studies have linked the HPA response and cortisol levels to phases of the menstrual cycle. Females in the luteal phase have been shown to have enhanced adrenocorticotropic hormone and cortisol responses to exercise stress compared with women in the follicular phase [111,112]. Notably, a number of studies have considered the influence of the OCP on the HPA axis. Results have shown a blunted free cortisol response to psychosocial or physical stress likely related to increased production of cortisol-binding globulin, thus leading to a decreased amount of bioactive free cortisol [113]. Laboratory work on human subjects has shown that women in the luteal phase report more spontaneous intrusive recollections of emotional stimuli compared with females in the follicular state [114]. This leads to the suggestion that the phase of the menstrual cycle at the time of a trauma could influence a female's susceptibility to developing PTSD, and that future studies should attempt to control for menstrual cycle and menopausal status when studying gender-specific issues in PTSD.

Other anxiety disorders

Symptoms of social anxiety are more often found in female patients with bothersome symptoms including difficulties using public washrooms or speaking in public [115,116] and it has been suggested that symptoms may worsen in the premenstrual and postpartum period [117]. Social anxiety disorder is characterized by fear of negative evaluation by others with a biased interpretation of social cues. Oxytocin aids in modulating awareness of socially relevant emotional information. Various studies involving the use of intranasal oxytocin have shown that this neuropeptide can help improve the recognition of happy expressions, detect the accuracy of emotional stimuli and possibly even serve as an adjunct to exposure therapy in treating social anxiety by decreasing social threat perception and altering negative self-evaluation [118–120]. Furthermore, neuroimaging studies have suggested that there is possible sexual dimorphism in the neural effects of oxytocin in that this neuropeptide enhances amygdala reactivity to social and emotional stimuli in females [121]. Lastly, oxytocin release may be an important pharmacological property of SSRIs given the anxiolytic and antidepressant effects of this neuropeptide [122].

The link between panic disorder and hormonal fluctuation has not been demonstrated consistently [123]. Some studies have shown a worsening of panic symptoms premenstrually with retrospective [124] and prospective [125] ratings. However, others have shown no change premenstrually with prospective ratings [126,127].

Eating disorders

The underlying pathophysiology of eating disorders is similar to that of mood disorders

in that it is thought to be largely related to dysfunction of the serotonergic system. As a result, there is significant comorbidity between mood disorders, particularly major depressive disorder, and eating disorders. There is a documented link between low 5-HT and impulsivity; a trait that is particularly central to bulimia nervosa [128]. Both impulsive and compulsive traits have been linked to 5-HT dysfunction, as well as polymorphisms within the 5-HT transporter gene [129]. Furthermore, both 5-HT and estrogen exert a physiological influence on brain regions involved in hunger. A general trend observed in both human and animal studies is that reduced 5-HT levels are associated with increased feeding behaviors [130]. Animal models have shown that a hypoestrogenic state in ovariectomized rats leads to an increase in body weight as a result of overall food intake. Notably, supplementation with estradiol decreases food intake and body weight [131]. Further animal studies have shown that ovariectomized rats injected with ovarian hormones had smaller binge episodes and consumed less fat compared with controls [132]. Thus, the centralized effects that estrogen has on brain regions, including the hypothalamus and hindbrain, have downstream effects on hormonal systems involved in signaling hunger and satiety [133].

At puberty, females experience an increase in levels of estrogen, which then contributes to increased levels of subcutaneous fat in the context of various other psychosocial stressors, including shifts in body image. Therefore, this transitional period represents a high-risk time for developing an eating disorder. The maladaptive cycle of an eating disorder may begin with these hormonal changes that lead to phasic shifts in the menstrual cycle and the resultant interplay between the estrogenic and serotonergic system, which can lead to emotional dysregulation and behavioral disinhibition. At this point, potential for developing binge eating episodes, which, in turn, lead to compensatory strategies such as purging, overexercising and dietary restriction, arises. The subsequent dysregulation of the menstrual cycle and decrease in available estrogen leads to further exacerbation of the dysfunction within the 5-HT system [134].

Certain weight loss practices (e.g., dietary restriction) as well as increased levels of stress result in a hyperactive HPA axis and elevated levels of cortisol. Glucocorticoids serve to inhibit pituitary luteinizing hormone release and ovarian estrogen/progesterone secretion, thus leading to dysregulated menses or amenorrhea [135]. Thus, females with anorexia (AN) or bulimia nervosa are at risk for establishing a hypoestrogenic state. Patterns have been observed that show that binge eating worsens during phases of the menstrual cycle when estrogen is low and progesterone is high [136]. It has been suggested that the hypoestrogenic state of females with AN may lead to the lower rates of success when treated with SSRIs [137]. Evidently, the pathophysiology of AN and bulimia nervosa is related to interplay between the serotonergic and estrogenic systems, which affects an individual's experience with food (i.e., hunger or satiety).

Psychosis

The estrogen hypothesis suggests that this hormone may have antidopaminergic and, therefore, protective effects in the onset and course of symptoms related to psychotic illness such as schizophrenia [138]. The dopaminergic system is known to play an important role in psychotic illness. However, other neurotransmitter systems, including the serotonergic system, have also been implicated as important contributors [139,140]. 5-HT modulation is associated with a beneficial increase in striatial dopamine release. Further evidence comes from the neurobiological and pharmacological properties of the atypical antipsychotics. This group of psychotropic medications shows 5-HT antagonism, as well as dopamine modulation, which affects the negative and cognitive symptoms of schizophrenia by causing dopamine release in the prefrontal cortex [141].

Females show a delay in the onset of schizophrenia with a second onset peak after the age of 44 years once they have entered the perimenopausal stages [142,143]. Trends have been identified that show that psychotic symptoms fluctuate throughout the menstrual cycle with exacerbation during low estrogen phases [144,145]. Furthermore, studies have found that psychotic symptoms may improve during pregnancy [146], worsen during the low estrogen postpartum phase [147] and worsen with age in females only [148]. Females are at risk for an episode; this includes first episode or relapse, of puerperal psychosis as a result of the dramatic drop in hormone levels particularly in the first 2 weeks following delivery [149]. Risk of postpartum psychosis amongst women with no previous psychiatric hospitalizations appears to increase with maternal age (>35 years) [150]. Polymorphic variations in the level of expression of the 5-HT transporter gene (*5-HTT*) may play an important role in

the postpartum period, which is accompanied by a sharp reduction in brain tryptophan levels. In addition, it has been suggested that females with puerperal psychosis may have a lower than average baseline serum concentration of estradiol and may potentially respond to estrogen replacement immediately postpartum [151].

There has been some suggestion that premenopausal women may respond to lower doses of antipsychotics than their male counterparts [152]. Furthermore, some studies have shown that adding estrogen therapy to standard treatment with antipsychotics can lead to a more rapid improvement of psychotic symptoms in female and male patients [153,154]. Selective estrogen receptor modulators may have agonistic actions in the brain while limiting the potentially adverse estrogenic effects on breast and uterine tissues. Some studies have shown that adjunctive treatment with selective estrogen receptor modulators (e.g., raloxifene) may lead to more rapid improvement of both positive and negative symptoms in the postmenopausal schizophrenia population [155,156]. Thus, estrogen, and its links to the serotonergic and dopaminergic systems, likely demonstrates antipsychotic properties and/or acts as a synergistic modulator of antipsychotic medications.

Suicide

Various trends have been identified between suicide attempts or completions and the female menstrual cycle. From a methodological standpoint, this link is very difficult to accurately assess due to the suicide attempts and completions that do not come to the attention of healthcare professionals. One trend that has been replicated in various studies over the past three decades is that the probability of a suicide attempt in females appears to be highest during the menses and follicular stage of the menstrual cycle [157,158]. It appears that suicide attempts are more likely to occur when estrogen and progesterone are at their lowest.

Postmortem studies have directly examined the uterine cavity of females who completed suicide to determine trends in the stage of the menstrual cycle at the time of suicide completion. Data from various studies indicate that a greater percentage of females who died by suicide were menstruating at the time [159,160]. Moreover, a postmortem examination of brain samples demonstrated that the binding of the 5-HT transporter was lower in the ventral prefrontal cortex of individuals who completed suicides compared with nonsuicides [161]. It is possible that this lower binding represents widespread impairment of serotonergic function and this has been linked with suicidal behavior across various psychopathologies [162].

Although not yet well-defined, there does appear to be an interplay between a women's hormonal milieu, 5-HT (among other neurotransmitters) and suicidal behavior. Women with a diagnosis of PMDD are particularly sensitive to the changes in hormone levels and have been found to be over-represented in suicide attempters compared with controls [163]. Based on the information described, perhaps the stage of menstrual cycle and/or a previous diagnosis of PMDD should be included as contributing risk factors for suicide attempts.

Personality traits & aggression

Despite the dearth of published data on the interplay between hormones, 5-HT and personality disorders, there are studies from both the animal and human populations that have examined aggression. This relates to criminality in the human population and links to at least some of the personality disorders according to the Diagnostic and Statistical Manual of Mental Disorders [164], such as antisocial personality disorder (ASPD). The prevalence of ASPD in is 3% in males versus 1% in females [164], with categorical differences in symptomatology [165].

Studies on vervet monkeys have shown that there is a link between reduced serotonergic function and destructive aggression [166]. Various studies on nonhuman primates have indicated an association between low cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF-5HIAA; a 5-HT metabolite) and an increase in aggression and loss of impulse control [167–169]. Human studies have shown that low CSF 5-HIAA is also linked with impulsive tendencies found in individuals with ASPD [170,171]. One study found that elevated whole-blood 5-HT was correlated with a history of violence (measured by self-report and court convictions) in men but not in women. One hypothesis proposed by these authors is that diminished serotonergic function leads to disinhibited aggression towards oneself and others [172]. Notably, the findings of this study are consistent with others that have identified elevated blood levels of 5-HT in a conduct disorder population [173,174]. Thus, it appears that central 5-HT indicators (i.e., CSF 5-HIAA) are negatively correlated with aggression while peripheral concentration of 5-HT (i.e., whole-blood 5-HT) is positively correlated with aggression. Although paradoxical, this does

demonstrate a relationship between fluctuating 5-HT levels and impulsive or aggressive behavior.

Lastly, a recent study [175] focused on genetic testing (5-HTTLPR polymorphism) and screening for personality disorders. A significant sex difference that emerged from this work is that individuals with a short 's' allele of this polymorphism were more likely to have avoidant traits and this association was particularly strong in women. Males with the 's' allele had a lower likelihood of obsessive compulsive personality disorder traits and females with this same allele had a higher likelihood of having obsessive compulsive personality disorder traits.

Conclusion & future perspective

Research focused on sex-specific differences in psychopathology has grown significantly over the past two decades. Inclusion of women in clinical trials and analysis of data by subgroup has allowed for sex-specific trends to be identified and studied further. There is compelling evidence for a subgroup of females who experience an abnormal response to hormonal cycling within normal physiologic ranges [37]. Sex differences in psychopathology are abundant throughout the literature in clinical presentation, timing of symptoms and treatment response.

A barrier to sifting through research data related to this domain of psychiatry is the

Executive summary

Mood disorders

- There is evidence to support a distinct subgroup of females who experience an abnormal response to hormonal cycling within normal physiological ranges (premenstrual dysphoric disorder [PMDD], postpartum depression, and depression linked with peri- and post-menopause).
- From a treatment standpoint, there is crossover in treating depressive symptoms with hormone replacement (i.e., in PMDD) and to use psychotropics (e.g., selective serotonin reuptake inhibitors) to treat menopausal symptoms (e.g., vasomotor symptoms).

Anxiety disorders

- Females are more likely to have obsessions and compulsions related to contamination, with trends showing worsening of symptoms in the luteal phase.
- If the onset of obsessive compulsive disorder is postpartum, these females may be at risk for developing a subsequent episode of postpartum depression.
- Females in the luteal phase show an enhanced adrenocorticotropic hormone and cortisol response. It is possible that the position in the menstrual cycle could influence one's susceptibility to develop post-traumatic stress disorder following a trauma.
- There is limited evidence for hormonally related changes with social anxiety and panic disorder.

Eating disorders

- Both serotonin and estrogen act on brain regions (e.g., hypothalamus) that are involved in hunger, feeding behaviors and satiety.
- Trends have been noted with increased binge eating episodes premenstrually and in the mid-luteal phase.
- Although efficacious in treating both anorexia and bulimia nervosa, the hypoestrogenic state that results from disordered eating behavior may explain why selective serotonin reuptake inhibitors have a lower treatment response compared to major depressive disorder, for example.

Psychosis

- Estrogen may have a protective effect on the onset and course of psychotic illness. Evidence comes from fluctuations in symptoms across the menstrual cycle, pregnancy and menopause, with psychopathology worsening in times of low estrogen.
- Some evidence to show that treatment with hormonal modulation (i.e., with estrogen or selective estrogen receptor modulators) may lead to a more rapid response to antipsychotic medications.

Suicide

- Probability of attempting suicide was found to be highest during menses and the follicular stage. This could possibly be related to overall low levels of estrogen or a consequence of worsening of psychiatric symptomatology during the preceding luteal phase.

Personality & aggression

- From animal and human studies, central serotonin indicators (e.g. CSF 5-HIAA) have been correlated negatively with aggression, while peripheral markers (e.g., concentration of serotonin in whole blood) have been correlated positively with aggression in males but not females.

Future perspective

- There will be a focus on progesterone and oxytocin as important physiological agents that may contribute to sex discrepancies in psychopathology.
- There will be further research in the field of neuroimaging, as previous receptor binding studies have provided insight into how exogenous hormones can influence serotonin receptor density in brain regions associated with mood.
- Focus will be on the influence of estrogen and other gonadal hormones on the serotonergic system at a genetic and transcriptional level.

discrepancy within the literature between the terms sex and gender. These terms are often used in an interchangeable fashion thus complicating the task of gathering comprehensive information. It was necessary to use both terms as keywords to ensure that important publications were not excluded. Some have argued that the acceptable definition of 'sex' should refer to the biology of human and animal subjects while 'gender' should refer to self-identity and/or the social representation of an individual [176]. These definitions are in keeping with the WHO Working Definitions [204]. The standardization of these terms is important to allow for accurate inclusion of relevant research specific to sex.

Research from both animal and human studies has contributed to a growing body of knowledge concerning the interplay between the serotonergic system and gonadal steroids. Much of the research over the past two decades has focused on the relationship between the serotonergic system and estrogen, and has shown that fluctuations in estrogen likely alter transmission of 5-HT and subsequently influence psychopathology. However, future research will also need to focus on progesterone and oxytocin as these two physiological agents have been implicated as contributing to the unique differences in sex-specific psychopathology. Further research in the field of neuroimaging (particularly with PET scans) will help to provide insight into how exogenous hormones can influence 5-HT receptor density in various brain regions [62,63,177,178]. Lastly, it is important for research to also focus on how gonadal hormones affect the serotonergic system at a genetic and transcriptional level in the hopes of identifying biological markers of illness to be applied in preventive medicine.

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