Women's Mental Health

A Clinical and Evidence-Based Guide

Joel Rennó Jr.
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An Introduction to Women's Mental Health

Jeronimo Mendes-Ribeiro, Antonio Geraldo da Silva, and Joel Rennó Jr.

Women's Mental Health: A Comprehensive Approach

Are women weaker than men? We do not look for answers like that. At least not by this angle [1]. Neuroscientists and clinicians have struggled with the brain because it is such a complex organ that interacts with the whole body. Even so, over the last 30 years, an emerging body of research has achieved great improvements on the way we understand not only psychosocial and cultural aspects of sex differences, but also biological basis and how this knowledge could advance preventive, diagnostic, public policies, and therapeutic healthcare practices on mental disorders [2, 3].

Although the physiology and neurobiology of women and men are almost identical, studies on sex and gender as critical variables related to the causes and expression of medical conditions are established for a number of diseases, including selected mental disorders.

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Dysregulation of the HPA system has been associated as central to understanding the development of mood disorders. Sexual hormones promote a wide range of neuronal response and actions on hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) circuitry. Estrogen receptors are widely distributed throughout the brain – paraventricular nucleus (PVN), ventromedial nucleus (VMN), central amygdala, hippocampus, and subgenual area. Moreover, sex differences are prominent in the symptomatology and the course of mental disorders [4]. Evidence from neuroimaging and molecular research have shown the influence of genetic and epigenetic mechanisms of hormone-dependent transcriptional factors on stress response and emotion regulation circuitry [5–7].

Not only female brain anatomical structure, functioning, and disease processing – but also the way several mechanisms such as early life programming, perinatal stress, hormones (e.g., pregnancy, hormonal-based contraceptives, hormonal therapy), genetics, epigenetics, and psychosocial stressors like trauma, child abuse, and domestic violence interfere with brain activity and stress circuits are currently considered "hot topics" for a comprehensive undertanding on why prevalence of some mental disorders are higher in women than men [8–10]. Depressive disorders tied to reproductive events may partially account for this higher risk, and pathophysiological mechanisms include an increased vulnerability to fluctuations in gonadal steroids, but other neuro-

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endocrine mechanisms may play a role [11]. Women are also more exposed to emotional, physical, and sexual violence, including intimate partner violence and trauma. Sex-specific biological components may also be involved on why women get depressed more often or why they attempt suicide with more frequency since women are exposed to more high-impact trauma (e.g., sexual trauma) than men, and at a younger age [12–14].

Preclinical and clinical research have recently started to address relevant methodological confounders since results were obtained from overrepresented males subjects. Clinical studies have incorporated on their design controlling for menstrual cycle phase (follicular or luteal), either premenopause or postmenopause given the inconsistencies and heterogeneity of literature in the past [12]. Research on imaginology, molecular aspects, epigenomics, proteomics, and aspects of systems biology have been leading greater improvements and complexity to the current understanding of the underlying mechanisms of vulnerability and sex-specific differences on prevalence, onset, timing, severity of clinical presentation, and course of mental disorders [8, 15].

Hormonal milieu over reproductive years and mainly during transition periods such as premenstrual, perinatal period, and perimenopause presents challenges to some vulnerable women and may cause negative impact on mood, behavior, and coping mechanisms, which further increase the risk for mental disorders. Major depressive disorder (MDD), anxiety disorders, and bipolar disorders (BP) are some of the leading causes of disease burden worldwide, and the rate of MDD in women of reproductive age is double that of men's [14, 16]. Eating disorders, anxiety disorders, obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD) are also more prevalent in women than men [14]. Although the prevalence of bipolar disorder is similar for both sexes, the impact of hormonal fluctuation on course, severity, and clinical presentation is relevant in women [17].

Clinical conditions may also interfere with women's mental health. The association between gonadal steroids and mood was also initially recognized by endocrine disorders and then by infertility issues, mood fluctuations at late luteal phase of menstrual cycle, postpartum, and transition to menopause. Infertility, breast cancer, and other comorbid diseases have direct – interfering with physiology, interfering with treatment – and indirect impact, acting as life stressor, on mood and on prevalence of mental disorders.

Given HPA and HPG circuitry have been historically linked to changes in mood dysregulation, thought processing, and behavior, understanding the mechanisms of diseases of mental disorders is of utmost importance for development of new biological targets. Respect of such complexity enables us to discuss with patients the current clinical practices based on the best evidence available.

Relevant Topics, Inconsistent or Insufficient Data: Is "State-of-the-Art" Care Still Possible?

Some of the common frustrating topics to less experienced clinicians in this field are questions regarding uncertainty, such as "Which antidepressants and/or drugs for treatment for bipolar disorders are safe during pregnancy and lactation?", "How should I proceed with women who find out pregnancy and are on antidepressants?", or "What is the best therapeutic option for women who struggle with depressive and vasomotor symptoms during the menopausal transition?." There is no single answer for these questions. But first is worth deepening our sense of what this is about. When it comes to the perinatal period, such complexity is even magnified. Methodological and ethical barriers on conducting studies in the perinatal period and the way one should interpret results are of critical importance since even well-designed studies released on high impact factor journals might show a specific association but not cause and consequence [18].

The knowledge regarding safety issues may modify over time. The approach of clinically relevant vasomotor and depressive symptoms throughout the menopausal transition and its con-

sequences regarding safety issues on early the 2000s are also applicable argument for this theme [19]. Thus, overinterpretation of results of studies due to heterogeneity, insufficient data – sample too small or biased – recommendation based on absolute vs. relative risk, and inadequate disclosure (e.g., based on risk categories) may influence informed consent and quality of care. Indeed, misinformation regarding uncertainty in the field of women's mental health and the way we interpret observational studies may bring excessive media attention which might contribute to stigma [20]. On the other hand, risks of non-treated disorders and other relevant comorbid issues such as substance use, poor nutrition, or obesity are commonly underestimated [21–23].

The reader interested on approaching common mental disorders during the perinatal period and perimenopause will understand the proper steps of obtaining informed consent not based on risk categories but on the best evidence available [24].

Lack of Services Designed for Women's Mental Health Issues: A Still Neglected Subpopulation

In the field of women's mental health, giving a better support for women who suffer from trauma, domestic violence, and other prevalent mental disorders – such as posttraumatic stress disorder (PTSD), eating disorders, and substance use – is of remarkable importance. Even though female brain sensitivity to alcohol can cause early brain damage and dysregulation on stress-related circuitry [25, 26] and fetus exposition to alcohol and other substance during pregnancy can lead to developmental long-term negative outcomes [27, 28], most community services do not take into consideration sex differences. Cultural aspects of substance use in women are also of interest since cannabis use during pregnancy has increased over the last decade [29] and withdrawal from mental and psychosocial care in women subpopulation may cause a strong impact on public health systems worldwide [30]. Limited inpatient facilities for the care of postpartum mothers with severe mental illness called "Mother and Baby Units" – promoting treatment and attachment in a safe environment, while risks are still high – are another example of the lack of mental health services worldwide. As a consequence, development of public policies and effective services and programs built for women with severe mental disorders and alcohol and other substance use disorders is imperative.

Screening and monitoring of symptoms within the perinatal period on primary care have shown to reduce depressive symptoms in women with depression and also the prevalence of major depression [31]. A number of sex-specific screening tools are available for clinicians, some of which have also been validated for use during pregnancy. Self-administered rating scales and other sources of information including E-health-based resources have been on the focus of current and future research for increasing acceptance to highly stigmatized medical conditions. The use of psychometric instruments in clinical practice and their usefulness will be discussed – not only as screening tools but also as instruments to validate diagnosis of mental disorders (such as premenstrual dysphoric disorder (PMDD) – in which diagnosis is prospective).

Revising Standard Diagnostic Manuals and Future Directions

After decades of its recognition, premenstrual dysphoric disorder (PMDD), a recurrent and severe form of premenstrual syndrome that involves a combination of emotional and physical symptoms that result in significant functional impairment, is listed as a distinctive depressive disorder by the DSM-5 Work Group. The acknowledgment that in these circumstances it could be considered as necessary for the purpose of overdiagnosis prevention and detection and to temporarily set aside in order to obtain relevant data, political aspects must be considered as part of this issue. Although research efforts have demonstrated specific links of sex influence on mental disorders and increasing data availability from

clinical and epidemiological studies, some mental disorders are not covered by the existent standard diagnostic manuals [32]. Such has been greatly underestimated and has direct adverse effects on fetal, obstetric, and neonatal outcomes.

Regardless of consensus, DSM-5 Task Force included a specifier denominated "with peripartum onset" (from pregnancy to 4 weeks postpartum) despite evidence showing differences between pregnancy and postpartum period on etiology, risk factors, clinical presentation, and response to pharmacological and non-pharmacological interventions [33, 34]. Revising future diagnostic classification systems for terminology is critical in a means to provide increasing awareness, early identification, correct diagnosis, and appropriate management.

Final Considerations

Over the following chapters, the reader will learn key terms and concepts, including some of the emerging trends on this interdisciplinary area of women's mental health. The contributors, all leading scholars, practicing educators, and researchers in the field, bring a perspective to the theme. This book is divided into 28 chapters, and it is a definitive source of evidence-based information on women's mental health. It contains comprehensive information which is in line with DSM-5 criteria throughout.

All chapters were elaborated by experienced practitioners in the field. As such, they are intended to serve as valuable reference for clinicians, family medicine physicians, gynecologists and obstetricians, pediatricians, psychiatrists, psychologists, and other mental health providers.

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Those We Should Remember: The Pioneers of Mother-Infant Psychiatry

Ian Brockington

Introduction

Mother-infant (perinatal) psychiatry is a relatively new specialty, but has deep roots. Over the course of centuries, its knowledge base has been constructed through the work of clinicians and researchers from many nations and a multitude of disciplines. This chapter focuses on the pioneers – those who have introduced key methods of study and drawn attention to the main disorders.

Hippocrates

In the fifth century BC, he pioneered clinical description, which is the foundation of scientific medicine: the 42 brief cases in the first and third books of Epidemics [1] are among the greatest scientific achievements of ancient Greece. They include only 17 cases in women, of whom 8 suffered from severe or fatal postpartum or postabortion infections, all complicated by delirium. Since Hippocrates covered the whole of medicine and surgery, the link he noticed between psychosis and childbirth had a prominence it has never regained. This example is case 4 in the first book of Epidemics:

> In Thasos the wife of Philinus gave birth to a daughter. On day 14 she was seized with fever and a rigor. At first she suffered in the stomach and right hypochondrium, and from pains in the genitals, head, neck and loins. Six days later she had much delirium at night. On the 8th day of the illness she had another rigor and many painful convulsions with much delirium. She had no sleep. She had more convulsions on the 9th day and lucid intervals on the 10th day. On the 11th day she had a complete recovery of her memory, quickly followed by renewed delirium. Her urine contained much sediment. About the 14th day there were twitchings over all the body, and much wandering with lucid intervals followed by renewed delirium. On the 17th day she became speechless. On the 20th day she died, 34 days after delivery.

Clinical description has been woefully neglected in this area of psychiatry; in my monograph published in August this year [2], I was able to find just over 4000 childbearing psychoses, many of the descriptions brief and of poor quality. Moreover, their number is declining. In spite of the great opportunity provided by the development of mother-infant psychiatry as a speciality, and the establishment of many psychiatric mother and baby units – offering a golden opportunity to observe unusual phenomena – only 475 cases have been reported since 1975. Nevertheless, most of what we know about these psychoses is based on 'case lore', which displays their complexity, with a high proportion associated with an organic disease; as for non-organic cases, there is not one postpartum trigger, but a group of reproductive triggers that includes abortion; pregnancy; the early puerperium (from

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parturition to the 15th day), later in the first postpartum year; and weaning. There is a high relapse and recurrence rate and a link with menstruation. In the collateral study of menstrual psychosis, clinical observation alone has directed attention to a small area in the hypothalamus, containing only a few hundred cells.

The study of single cases is the basis for the classifications that simplify clinical practice and research. Nosologists, reviewing a large number of cases and examining their symptoms and course, search intuitively for homogeneous patterns, which can be proposed as disease entities and submitted for validation. The classification of mental illness related to childbearing, offered by the International Classification of Diseases and American Diagnostic and Statistical Manual, leaves much to be desired, and this offers an opportunity for progress by further observation. The role of the clinician is not just to pigeonhole patients into a local or contemporary classification, but to be inquisitive and alert to the unusual, searching for aetiological clues. A renewed recognition of the value of clinical observation will empower all clinicians. In the childbearing and menstrual psychoses, this approach has led to sharper definitions, an improved classification, a radical revision of the problems to be solved and fresh lines of enquiry.

Osiander

In 1797 this obstetrician from Tübingen described two cases of postpartum psychosis – one infective and one probably non-organic, descriptions unequalled in this literature, and, in their exemplary detail, among the classics of medical history [3]. There is a full translation of both in my monograph *What is Worth Knowing about 'Puerperal Psychosis'* [4] and of the psychiatric manifestations of the second case in *The Psychoses of Menstruation and Childbearing* [2]. This paragraph is a sample of his account:

> During these attacks this lady (a splendid singer) sang with a clear, elegant and melodic voice, and an expression of the highest enthusiasm. She sang or declaimed scenes from the time of her betrothal in self-composed verses with gestures of the finest and deepest emotion. Every movement of her facial muscles, eyes, arms, hands and fingers were the eloquent portrayal of the most ardent love under the finest veil of wistfulness. It was moving: everyone who heard her stirring songs was irresistibly moved to tears. No actress in the world, not even a Garrick, could have improved on her performance – on the fine nuances of muscular movement, on her indescribable originality, and the exaltation of her soul. But her peaceful mood would suddenly change to terror, and her tender nostalgia to fearful anger and the rage of a Medusa. She would hit out with arms of bronze, grasp whatever she could grab with an iron grip, let out heart-rending screams, bark and roar. A human being that had seemed, from her singing, to be a heavenly creature, sank to the level of a beast.

This is a graphic description of some features of puerperal mania – lability of mood and eloquence with rhyming speech or singing. Osiander was an obstetrician, and this reminds us that the first observations in our speciality were not made by psychiatrists – they preceded the establishment, by Pinel and Esquirol, of psychiatry as a discipline. The original descriptions of eclamptic psychosis [5], recurrent puerperal insanity [6], late postpartum psychosis [7] and parturient delirium [8] were all written by physicians, and the distinction between puerperal mania and infective delirium was first made by Burns [9], another obstetrician.

Osiander's work, the first clear description of one of our most important disorders, on which about 2000 works have since been published, is almost unknown: it has been cited only 15 times in 220 years; but the widespread recognition of 'puerperal insanity' dates from the beginning of the nineteenth century.

Esquirol

In his *Maladies Mentales considérées sous les Rapports Médical, Hygiénique et Médico-Légal* (1838) [10], he pioneered descriptive psychopathology, but his publications on the psychiatry of childbearing are earlier (1816–1819). He provided statistics on postpartum admissions to the Salpêtrière hospital in the 4 years 1811–1814: 92 mothers (8% of all female admissions) became

insane after childbirth, 37 of whom had onset between the 1st and 15th days. He considered the causes, which included heredity, episodes earlier in their lives, previous postpartum episodes and, especially, emotional causes. These insanities had a much higher cure rate and a much lower fatality rate than was found in other female patients. He noticed a tendency to relapse soon after recovery. His most important contribution was to pioneer long-term studies. He reported cases with 11 and 13 episodes, much more than any other author. This is his patient with 13 episodes [11]:

> A woman, whose sister suffered from puerperal psychosis, was married at the age of 25. At 26 she gave birth to her 1st child, after which she suffered from furious mania until her 2nd pregnancy, which was normal. She had 12 further pregnancies, all with hard labours, after which she was insane for 4–6 weeks. At 39 she had an attack of apoplexy followed by hemiplegia. At 47 she suffered a severe febrile illness that was followed by furious mania lasting five months. At 50 her menses ceased. At 51 her husband died and she was imprisoned. This was followed by mania from which she recovered after a month.

This research strategy has been shamefully neglected. There are numerous 'follow-up studies', but, as shown in Table 1, only 57 cases with full clinical details have been followed for more than 20 years. *The Psychoses of Menstruation and Childbearing* provides data on 73 mothers followed for at least 20 years, of whom 38 at least 30 years. It reflects no credit on psychiatry that, in 200 years of research, the majority of mothers, studied in detail and followed for over 20 years, have been collected by one clinician.

Long-term studies of cases from the literature and my series have provided much evidence of an association between the reproductive triggers: abortion and prepartum and early and late postpartum onsets seem almost interchangeable. Esquirol briefly described this case with four triggers – puerperal, seasonal, weaning and abortion [11]:

> A 26-year old gave birth to her 1st child. On day 3 she developed furious mania that lasted for two months. Every spring she showed exaltation without psychosis. At 30, when weaning her second child aged one year, she developed mania, from which she soon recovered, but a few days later relapsed. At 34 she had a 2-month miscarriage; the next day she became loquacious and developed a brief episode of mania.

The Psychoses of Menstruation and Childbearing published matrices demonstrating, in 265 recurrent cases from the literature and 118 from my own series, the high proportion with episodes starting within at least two different onset periods. This is an example from a recent German thesis [12], of a woman, followed for 20 years, who suffered from episodes related to weaning, menstruation, the early puerperium and pregnancy as well as unrelated episodes:

> At the age of 28, a woman with a strong family history of mental illness, gave birth to her 1st child, and breast-fed for 4 months. After weaning she developed insomnia and restlessness; her ideas were lively, she feared that her house was on fire and thought she was under surveillance because of her poor child-care. In hospital, she was perplexed and confused, had difficulty in distinguishing dream from reality, believed was still pregnant and misidentified people. She improved, relapsed, recovered and had several premenstrual deteriorations. Three years later she gave birth to her 2nd child. On day 3 she was unable to sleep, lost her appetite, and believed the child was starving. In hospital she was depressed and agitated, perplexed and had delusions of guilt; two months after recovery she became hypomanic, spent a lot of money and gave presents to everybody. A year later she became pregnant for the 3rd time. In the 2nd trimester she became depressed, then manic, with auditory hallucinations of neighbours discussing her; God and his angels were protecting her. In hospital, she was anxious and retarded, had memory difficulties and was under instruction by good and bad voices. She suffered a 5-month foetal death in utero, then became hypomanic. She had three unrelated episodes.

This case illustrates another finding of these long-term case studies – the variable clinical manifestations, which included delusional depression, mania and cycloid (acute polymorphic) episodes.

Table 1 Comparison of my series of puerperal psychosis with those in the literature

Category		Literature	My series
Total cases		4029	321
Prolonged observation	10–20 years	137	66
	21–30 years	43	45
	More than 30 years	14	28

There is a long-standing controversy about the nosology of puerperal insanity – whether it belongs in the bipolar spectrum or whether it is a disease in its own right, with specific features. These 'specific features' – 'confusion', bewilderment or perplexity and a mixture of symptoms from all the main syndromes (mania, depression, delusions, hallucinations, catatonia, thought disorder) – are typical of cycloid psychosis. Approaching this problem in a review of published cases and my own series of psychotic mothers, I was unsure whether the cycloids would be a separate group or linked to bipolar disorder. In the event it proved impossible to separate the bipolars (40%) from the cycloids (25%); many episodes had features of both, and many mothers had presentations typical of both at different times in their reproductive lives; thus these clinical forms appeared to be interchangeable. This mother, followed for 42 years, had two postpartum episodes, the first cycloid and the second manic:

> A 31-year old, with a history of a psychotic episode while at university, was delivered by forceps of her 1st child. After the birth, she became sleepless, euphoric and perplexed. Her perceptions became heightened and distorted. She had ideas of reference about the television, radio and newspapers – the election of the Pope, his death and another election had a special message for her. She was disorientated, and confused at what she was seeing, hearing and reading. Nothing made sense. She forgot she had a baby. She recovered after one relapse. Three years later she gave birth to her 2nd child. A week later she became hypomanic: she was sleepless, writing poetry and rearranging the bookshelves. She wanted to communicate with someone on another planet. Admitted to a mother & baby unit, she was euphoric, and talked nonstop. There was a hint of a relapsing pattern, and she recovered after 9 months. During the next 30 years she had two further episodes, and at 64 was perfectly well.

Facts cannot be established on the basis of one investigation, and there is a need to replicate this longitudinal study; here there are opportunities for all clinicians, caring for mothers in specialist services, who have the long-term care of mothers, and a span of 20 years or more in practice. With forethought they can form an alliance with their patients for long-term follow-up, clarifying the effect of reproductive events, the menopause, intercurrent medical disorders, surgical intervention and stress on the natural history of the diathesis. This is work that requires no funding, just a good standard of clinical practice. Menstrual psychosis, which usually presents in the second decade, also cries out for the longitudinal study of the effect of pregnancy, childbirth and other events.

Psychoses are not the only disorders of motherhood that lack information on prognosis and long-term effects. This is very much true of the 'bonding disorders' (emotional rejection of the infant), which are discussed below.

Marcé

In the prodigious output of his short and tragic career, this young Frenchman wrote the first monograph giving a complete account of the insanity of childbearing, as then known (mainly the psychoses) [13], and for this he is venerated all over the world, with 'Marcé Societies' established in a number of countries. He had superior powers of observation, as shown by his description of the hypnagogic and hypnopompic hallucinations that are an almost unique feature of chorea psychosis [14]:

> A 22-year old congenital syphilitic presented with a 15-day history of chorea. Her sleep was interrupted by 'dreams'. Before falling asleep she saw devils, headless corpses, ravens, bats and other terrifying objects. She believed they were going to strangle her, and found it hard to breathe. These hallucinations also occurred at the moment of waking, when she would cry out and disturb other patients. She believed her food was poisoned and heard voices telling her she was damned. She recovered after a few weeks.

He also had the intuition, often found in French physicians, to spot important clues. He considered the causes of postpartum psychosis and was among the first to draw attention to the role of menstruation. In his textbook of psychiatry [15], there is this paragraph:

> The first postpartum menses exercises, on the development of puerperal insanity, an influence that Baillarger was the first to notice, and which

> my observations confirm beyond doubt: of 44 mothers who developed puerperal psychosis, and who did not lactate, eleven became ill in the 6th week, precisely at the return of the menses. Sometimes the psychosis preceded the menses by 5–6 days, but it usually began at the onset of bleeding or during menstrual flow. I have also seen it break out when the menses were expected, but failed to appear. Mothers, who breast-feed for some months, become ill after weaning, very often at the moment the menses reappear after a long interval.

This is an important contribution that has been completely neglected by Marcé Society members, none of whom recognize these two forms of postpartum psychosis or have followed his lead on the role of menstruation. In the subsequent literature, there is much to support his ideas: among the non-organic psychoses, there are 1015 starting between day 1 and day 15 of the puerperium, 92 in the 3rd week (a sharp fall) and 447 in weeks 4–13. Eight mothers had two 4–13 week onsets and no other reproductive episodes. Surveys have found a raised admission rate in the second and third months [16, 17]. The association with the return of menstrual bleeding, which he claimed, has never been investigated, but a few mothers with early postpartum episodes have suffered repeated relapses – ten had at least five – and these have been linked to the menstrual cycle, as in this extreme example [18]:

> A 26-year old, with a strong family history of mental illness, developed a depressive psychosis after giving birth to her 1st child. After her 3rd birth she again became depressed with religious, persecutory and sexual delusions; she believed God or the Devil would arrange for her suicide, and that family members were sexually abusing her children. She recovered in two weeks, but suffered 33 identical monthly depressions, all starting in the premenstrual phase and ending three days after the menses. During her 8th episode she set fire to herself, suffering 20% burns. She eventually recovered.

v. Krafft-Ebing

It is convenient here, out of the chronological sequence, to remember the work of Baron v. Krafft-Ebing, celebrated for his *Psychopathia Sexualis* and contributions to forensic psychiatry, and also the champion of menstrual psychosis. His first publication on this subject was in 1878 [19], and in the year of his death (1902) [20], he published a monograph, *Psychosis Menstrualis* (1902), which, for 100 years, remained the most complete exposition of the subject: he had collected 68 cases, most of them from his own practice. My interest was aroused by a mother admitted with puerperal psychosis in 1981, who rapidly recovered and suddenly relapsed at the first menses. I have also collected at least 60 cases, mainly from e-mail correspondence with sufferers or their mothers, most of whom presented as teenagers. Including this series and sporadic case reports from the literature, *The Psychoses of Menstruation and Childbearing* analyses 250 cases.

These psychoses are complex: within the menstrual cycle, there are probably two triggers: about two thirds have onset during the necrotic phase and one third at the mid-cycle. Their occurrence within the life cycle is instructive. There are 26 cases with monthly episodes before the menarche. The following teenager had two episodes before the menarche and four further episodes (three psychosis and one depression) at monthly intervals between the first two menstrual bleeds, after which she remained well [21]:

> On June 24th 1888, a cheerful and good-humoured 15-year old complained of headache and insomnia, refused to eat and started to shout, sing, pray and rush about the neighbourhood. In hospital she was anxious and bewildered, restless, incoherent and disorientated. She spoke little, wept, laughed and appeared to be listening to voices. She started hammering on the doors and windows, and had to be isolated. She began to improve on July 3rd and recovered by the 8th (15 days after the onset). On August 21st she relapsed: this attack resembled the first except that anxiety and confusion were greater; she was sleepless and restless, sighed, groaned and made defensive gestures, ate little and lost 6 lb in weight. She recovered on September 2nd (after 13 days). From September 20th – 25th she had her first menstrual period, and remained well. On October 21st she relapsed –weeping, anxious, eating nothing, restless, jumping and dancing, speaking rapidly and excessively, singing, praying, smearing and hitting out; she had to be isolated. She recovered on the 27th (after six days). On November 25th, she became anxious and monosyllabic, and the next day was singing, dancing, crying, laughing

> and praying, and again had to be isolated; she recovered on the 29th (after four days). On December 18th she suffered from headache and vomiting, and complained of depression and homesickness, but recovered on the 21st. On January 22nd in the next year she relapsed – unresponsive, sleepless, restless, singing and declaiming; she had rapid mood changes – cheerful and anxious, weeping and laughing. She recovered on February 2nd (after 10 days). From February 20th – 25th she had her 2nd menstrual period, and remained well, with regular menstruation, thereafter.

Premenarchal episodes may seem incredible, but are supported by the same phenomenon in four medical disorders – diabetes, epilepsy, hypersomnia and migraine psychosis.

There are several patients who have suffered a monthly periodic illness during amenorrhoea. This young woman had six premenstrual episodes and eight during amenorrhoea [22]:

> A 20-year old, with a family history of paranoia and depression, stopped menstruating while she was working on an anti-aircraft battery in Vienna. After the war she started medical training, but became depressed and tried to hang herself. Her menses again failed. During ten months of amenorrhoea, her illness took on a regular, periodic quality, with a sudden change from confusion, restlessness and inaccessibility to complete and full recovery. A chart showed the monthly timing, with onsets August 13th, September 6th, October 4th, October 27th, November 17th (premenstrual), December 9th, January 22nd 1948 (a doubled interval), February 12th, March 7th, March 30th (premenstrual from now on), April 22nd, May 17th, June 15th and July 14th. All six episodes that occurred during regular menstruation cleared up during menstrual flow. In July 1947, she dramatically improved after an injection of blood from a woman in the 5th month of pregnancy.

Another remarkable instance of monthly periodic episodes during amenorrhoea is their occurrence in the first months of pregnancy. This is the best example, with five episodes [23]:

> A 20-year old, with a mentally ill mother and sister, became pregnant, with her last period at the beginning of March. Four weeks later she became disturbed with restlessness, pressure of speech and destructiveness; this lasted eight days. After a month she relapsed, tore her clothes and ran naked into the street, cycled off in garters and slip, hit out, bit, scratched and smashed windows, sang and spoke incoherently. In hospital she was disorientated, heard voices and said she had seen the Devil; after four days she recovered. She had three more identical relapses, then remained well. She gave birth at the end of November.

Thirteen other authors have described one or two episodes starting in the first month of pregnancy, and in my series, there are six possible cases, one of which had four episodes and much other evidence of menstrual psychosis. Menstruation-like bleeding during pregnancy occurs when the gonadorelin neuronal complex resists heavy inhibition by chorionic gonadotropic hormones. A Münster *Inaugural-Dissertation* collected 45 cases [24].

There is one example of monthly periodicity in a psychosis developing in a girl without a pituitary [25]:

> A girl of seven developed diabetes insipidus, and was found to have a large pinealoma, which was treated by irradiation. Growth and menstruation were achieved by hormone replacement. At 19 she stopped taking oestrogen and progesterone because of side-effects and became amenorrhoeic. One month after stopping the ovarian steroids, she became inactive, sleepless and deluded about a demon with a blood-red body and glittering eyes hiding behind the door. In hospital she was expressionless and gave fragmentary answers. She recovered after eight days. The following month she was again unable to sleep and gave low monosyllabic answers after a long pause. In hospital she remained silent and showed no emotion; she thought orange juice was poisoned, and tried to drink out of the toilet. She recovered in 12 days. A month later she suddenly relapsed, and refused to see her family, eat or take medicine. She claimed that her parents had been cremated, a nurse had killed her mother and poisoned the thermometer and her coffee, that staff controlled the television programs, and a firework was a sign that the murder had been successful executed. She recovered in 13 days. She had three similar episodes lasting 17, 12 and 11 days at monthly intervals. Treated with carbamazepine, she remained well.

These cases, and the possible occurrence in males, suggest a role for the hypothalamic neurones that control the pituitary.

Once again the work of this pioneer has been largely forgotten, even by German authors; since 1925 *Psychosis Menstrualis* has been cited only 12 times. Menstrual psychosis is recognized by few psychiatrists.

Tardieu

The sixth pioneer was one of three French nineteenth-century leaders of forensic pathology – Orfila, Tardieu and Brouardel. In 1868 he wrote a classic text on infanticide and in 1860 an article under the title, 'Étude médico-légale sur les sévices et mauvais traitements exercés sur des enfants' [26], in which he described injuries to 32 children who had been subjected to brutality or maltreatment, 24 of them at the hands of their parents; 5 were still breast-fed and 1 was only 15 days old. There had been earlier accounts of single cases in the German literature, including the deliberate starvation of infants; most were pathology reports without information about the mother's mental state, but in this report from Fulda [27], the death of the infant was deliberate:

> A child died at the age of 6 months. The corpse weighed 6½ lb, with no trace of fat and a completely empty gut. His mother was dominant, the father weak-willed. She completely lacked human sympathy and motherly feelings; the children were just a burden to her. She threatened to kill her eldest son (who was reared by his grandparents) because he surreptitiously tried to give his baby brother some milk. It was rumoured that earlier children had died the same way.

Tardieu knew about the parents' behaviour and mental state and wrote:

> When we consider the tender age of these poor defenceless beings, subjected daily and almost hourly to savage atrocities, unimaginable tortures and harsh privation, their lives one long martyrdom – when we face the fact that their tormenters are the very mothers who gave them life, we are confronted with one of the most appalling problems that can disturb the soul of a moralist, or the conscience of justice. This mindless and ferocious brutality can only be explained by a sort of madness.

Tardieu's discovery was ignored for nearly 100 years, until forced on the medical profession by overwhelming evidence, especially from paediatric radiology. To get this resistance into perspective, one must remember that the highest aspirations of medicine are to discover the aetiology of disease, so that it can be eliminated at source. For many diseases, the causes are legion – a summation or interaction of many factors; but child abuse is a disease with a single cause – parental assault – which is necessary and sufficient to account for everything that follows. Parental aggression itself is of complex origin, but vicious assault and callous neglect are the common pathway leading to child maltreatment. It is a disgrace that 'the battered child syndrome' was not finally accepted until 1962 [28].

Table 2 Frequency of symptoms of emotional rejection

Number of cases	Symptom
39	The desire for a transfer of infant care to another person (usually an expressed wish for relinquishment)
25	Aversion, hatred or complaints about the smell or ugliness of the baby
25	Absconding or running away from home
22	Estrangement
22	Wish for the death of the child
15	Dysphoria relieved by escaping from the child, for example, by returning to work
14	Avoidance, including gaze avoidance
13	Other ways of escape (wish that the child be stolen, abandonment, wish to escape by maternal death)

Tardieu knew that the mother-infant relationship could be severely disturbed and attributed this to mental illness. We can now identify the symptoms of this 'sort of madness': the most common symptoms in a series of 100 cases are shown in Table 2:

There are two main themes – an abnormal emotional response and a wish to escape from the crushing burden of caring for an unloved child. The following cases illustrate some of these symptoms. First there is an example of the rather common symptom of estrangement:

> A mother had an unwanted pregnancy, and asked for a termination, but too late. "All I could see was gaol bars – a prison sentence". After the birth she felt trapped. After some improvement, at 7 months, she said, "I still do not feel she is mine. I am looking after her as if for somebody else, as if I was baby-sitting".

The next mother, after recovery, wrote about her hatred of the infant and wish for a cot death:

> This mother, at the age of 32, had a planned and welcomed pregnancy, but the birth was 'barbaric'.

> She blamed her son for this, and wanted to leave the house and run away. She wished he would die a cot death – "something I knew I would not be blamed for, and nobody would know how I hated him". She repeated this phrase – "I hated him". After four months her feelings changed. "I realised he was mine and I loved him, the most precious thing in the world". For a year she was unable to tell anyone how she had been feeling. "I feel so deeply ashamed. I am frightened he might know how I felt towards him when he grows up. I can't bear to visit friends, and see them happy with tiny babies. Every time I see babies on the television, I cry because of the way I felt towards my baby – such a terrible hate."

'Inexplicable' running away from home is a characteristic symptom. In this case its significance was missed:

> A multiparous mother became depressed after the birth of her 3rd baby, and was unable to cope. She took a train to London for no clear reason. She was admitted to hospital without her baby for 3 weeks, and investigated in the usual way. She seemed quite well and was discharged without the bonding disorder being suspected. After her return home she ran away on two more occasions, and made a suicide attempt. She could not tolerate the presence of her infant. She was reluctantly persuaded to accept admission to the mother & baby unit and rapidly formed a normal relationship with her baby.

The wish for relinquishment is characteristic of severe rejection, as in this case:

> A 35-year old mother became pregnant for the first time – a planned pregnancy about which she and her husband were very happy. But, after an emergency Caesarean section, she developed no feelings for her son. She began to feel that it would be much better if he was taken away. "I have made a big mistake by having this baby; I wake in the morning and wish he had a cot death. I feel nothing for him and want him adopted"; she wanted this so much that she looked up the telephone number of social services, and considered leaving her husband, so long as he took the baby.

We now know that 25% of mothers presenting to mother-infant services have emotional rejection of some degree [29]. If a mother presents with any of these symptoms, it is essential thoroughly to explore the mother-infant relationship. An interview like the Stafford Interview [30] is helpful in modelling the tactful exploration of the mother's experience. If emotional rejection is confirmed, steps must urgently be taken to reduce the risk to the infant, because of the strong association with anger directed at the child; even the apparently mild symptom of estrangement is associated with loss of control to the point of shouting or screaming at the infant in 70% and severe abuse in 20%. These urgent steps were outlined in Chap. 6 (pages 336–360) of *Motherhood and Mental Health* [31]: they start with frank discussion with both parents about the alternatives of relinquishment and therapy. If, as in most cases, the mother wants to overcome the problem, she must (until she develops a positive relationship) be relieved of the irksome burden of child care – by her husband or relatives or (in countries that have the great asset of conjoint in-patient hospitalization) by nursing staff. She must always be supported when caring for the baby, and, if she has aggressive impulses, must never be left alone with the child. When the infant is calm and content, and the mother feels at ease, she is encouraged and helped to cuddle, talk to and play with the baby. Here techniques like baby massage and play therapy are helpful. Although there are no treatment trials in these severe disorders, and a dearth of information about outcomes, many mothers recover completely.

Just as the medical profession ignored Tardieu's work and turned a blind eye to the evidence of child abuse for a century, 'perinatal' psychiatrists have dragged their feet in recognizing that some mothers hate their infants and want to get rid of them.

In-Patient Mother and Baby Units

About 70 years ago, two British pioneers independently admitted children with their mothers to psychiatric hospitals. In 1948 *Main* admitted a toddler to the Cassel Hospital, where its mother was under in-patient treatment [32]; as a psychoanalyst he realized that this gave an unusual opportunity for studying disturbances of mothering; he wrote:

> Remarkably little has been written about mothering and its disturbances. Psychiatry needs opportunities to study severe disturbances of the mother-child relationship.

The admission of even younger children was pioneered by a young female psychiatrist, Dr. *Gwen Douglas*: she admitted six mothers with psychoses, who, after recovery, commonly relapsed when again required to care for their babies [33]. These initiatives led to the widespread development of mother and baby units in Britain, Australia and a few other countries. By concentrating mothers with all kinds of postpartum mental illness, they fostered the recognition of many milder disorders, which has helped to make childbearing, from the standpoint of psychological medicine, the most complex event in human experience [31].

The Present State of Mother-Infant Psychiatry

This specialty has developed to provide expert help to mothers afflicted by psychiatric disorders, whose sheer number, variety and range tax the knowledge of general psychiatrists. It is an area of the mental health services, which has dual responsibility – not only for the pregnant or newly delivered mother but also and equally for her child, who is vulnerable and participates in a number of syndromes. The assessment of the mother-infant relationship is a central part of the investigation, and dealing with disturbances in 'bonding' provides the best opportunity to prevent adverse effects in the children.

The scope of this specialty was recently set out in an international position paper with nearly 70 authors from 32 countries [34]. Its essence is its core knowledge, not an expensive resource such as an in-patient unit capable of admitting mothers and their infants together. It can be practised with great effect from day hospitals, and a community service is highly appropriate. Its contributions start with accurate diagnosis, which depends on the acumen of the clinicians and their grasp of the full range of disorders. It can provide clinical advice, take over the management of severe and intractable disorders and serve as a focus for medicolegal opinion, education, service development and research.

All nations should have at least one specialist mother-infant service, and large nations should have services in major cities and conurbations. At present, we are far from that minimal objective: no nation has come near to meeting the needs of mothers and their infants. An area of specialization, developed over the course of 200 years, which offers unusual opportunities for research and prevention of mental disorders in the mother and child, is still in the early stages of development.

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Epidemiology of Psychiatric Disorders in Women

Maria Carmen Viana and Rafael Bello Corassa

Introduction

Mental disorders are a serious public health problem in the world, due to their high prevalence rates, early age of onset, multiple recurrence/chronicity, and frequent association with physical conditions and disability [1–5].

It was only after the publication of the World Health Organization (WHO) Global Burden of Disease (GBD) study that mental disorders started counting as important causes of morbidity and disability [3]. The GBD disclosed that neuropsychiatric disorders are among the leading causes of disability in the world, corresponding to about 20% of the years lived with disability (YLDs), and the fifth cause of disability-adjusted life years (DALYs), approximately 7% of the total [6–8]. However, these figures are likely to be underestimated and can reach over 30% of the YLDs and 13% of the DALYs, making mental disorders the second leading cause of disability in the world [7].

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Among mental disorders, unipolar depression leads as the main cause of disability in both genders, although the burden of depression is 50% higher in women, who also suffer with a greater burden of anxiety disorders, migraines, and dementias, compared to men. Among men, alcohol and drug use disorders are the second largest cause of disability, six times higher than among women, and corresponding to approximately 30% of the total burden of mental disorders [9]. Out of the 20 leading causes of YLDs, six correspond to neuropsychiatric disorders: major depression (1st), anxiety disorders (6th), schizophrenia (11th), autism and Asperger syndrome (16th), Alzheimer's and other dementias (17th), and substance use disorders (18th) [10, 11]. Furthermore, it is estimated that diseases related to tobacco use will lead the causes of disability in developing countries by 2020 [12].

In Brazil, mental disorders are also among the main causes of disease burden, with the highest proportion of DALYs occurring in adults and among females [7, 13]. Neuropsychiatric conditions, included in the group of non-communicable diseases, are the main causes of disease burden (DALYs), accounting for 34% of the total morbidity (YLDs). Their impact, therefore, is mainly due to the consequent disability, with premature death playing a less important role [14]. For women, depression is the leading cause of DALYs (13.4%), Alzheimer's and other dementias come in sixth (3.1%), followed by bipolar affective disorder (2.9%),

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and alcohol-related disorders in 13th (1.1%). Among men, alcohol abuse/dependence is the third leading cause of DALYs (5.0%), depression comes in seventh (3.5%), bipolar affective disorder in tenth (2.7%), and Alzheimer's and other dementias in 15th (1.3%) [15]. Between 1990 and 2015, mental and substance use disorders were the third leading cause of DALYs (9.5% of the total) and greatest cause of disability (24.9%) among Brazilians. Depression is the main cause of disease burden among mental disorders (35.0%), followed by anxiety (28.0%) and alcohol use disorders (7.0%). There is still an important contribution of schizophrenia and bipolar affective disorder, each corresponding to 6.0% of disability [13].

Gender Differences in the Occurrence of Mental Disorders

Epidemiological studies have consistently identified gender differences in incidence rates and lifetime prevalence estimates of mental disorders, as well as in their psychosocial and biological determinants, course of illness, and consequences [16, 17]. In general, women present higher rates of mood, anxiety and eating disorders, and borderline personality, while men present higher rates of substance use disorders, antisocial and schizotypal personality, and impulse control, conduct, and attention deficit and hyperactivity disorders. Regarding disorders similarly affecting men and women, different age of onsets, symptom profiles, and treatment responses have also been reported [16]. Additionally, differential patterns of mental or mental/physical comorbidity have also been recognized [18]. Evidence supporting the implication of biological or hormonal causal mechanisms accounting for sex differences has not yet been demonstrated [19, 20], although numerous studies have identified triggering factors related to the reproductive cycle or to gender-specific stressors [21]. Social disadvantages associated with being a woman, including higher exposure to domestic violence, lesser educational and employment opportunities, and higher family burdens, may account to increase the risk of mental disorders [16, 21–23]. A further concern regarding gender differences in prevalence and clinical profile of mental disorders is related to questions of gender bias in diagnostic instruments, clinical assessments, and diagnostic criteria [24].

Population-based studies conducted in Western countries have showed that 35% to 45% of the general adult non-institutionalized population present some mental disorder throughout life. In Brazil, important gender differences in the prevalence of mental disorders have been identified in the Sao Paulo Megacity Mental Health Study (SP Megacity), a cross-sectional study that assessed a probabilistic sample ($N = 5037$) of the general adult population (18 years or older) resident in the São Paulo Metropolitan Area, with a response rate of 81.3% [25, 26]. The occurrence of mental disorders was assessed using the WHO Composite International Diagnostic Interview (CIDI 3.0) [27]. Lifetime prevalence estimates on the total sample and by sex are presented in Table 1. The prevalence of at least one mental disorder was 44.8% (SE 1.4), and almost a quarter presented comorbid diagnoses (23.2%; SE 0.9). The global prevalence estimate of mental disorders was 1.8 times higher for women compared to men (51.5% versus 37.7%). Women present higher rates of mood and anxiety disorders, being almost three times more likely to suffer from post-traumatic stress disorder, agoraphobia, panic, and major depression. On the other hand, men present higher prevalence estimates of substance use disorders (18.5% versus 4.7%; OR 4.4, 95% CI 3.3–5.8), with significantly higher odds ratios for alcohol abuse (4.7) and dependence (6.0) and for drug abuse (2.9) and dependence (2.5). Except for conduct disorders, which were more frequent among men (OR 2.9, 95% CI 1.8–4.5), there were no gender differences in the distribution of all other impulse control disorders investigated. Depression, specific phobias, and alcohol abuse were, individually, the most prevalent conditions, and anxiety disorders were the most prevalent class of disorders. Specific phobias and impulse control disorders presented an early onset, while mood disorders showed a later onset [26]. Regarding depressive disorders, while women have presented high prevalence

Table 1 Lifetime prevalence of DSM-VI disorders in the São Paulo Megacity Mental Health Survey total sample, by sex ($n = 5037$)

	Total		Sex				
			Male		Female		
	%	SE	%	SE	%	SE	OR (95%CI)
Anxiety disorders							
Panic disorder	1.7	0.2	0.9	0.18	2.5	0.38	2.9 (1.7–5.0)[a]
Generalized anxiety disorder	3.7	0.3	2.6	0.34	4.6	0.37	1.8 (1.3–2.4)[a]
Social phobia	5.6	0.4	4.2	0.53	6.7	0.58	1.6 (1.2–2.3)[a]
Specific phobia	12.4	0.6	7.9	0.85	16.5	0.73	2.3 (1.8–2.9)[a]
Agoraphobia without panic	2.5	0.3	1.3	0.42	3.6	0.53	2.9 (1.4–6.1)[a]
Posttraumatic stress disorder[b]	3.2	0.2	1.6	0.42	4.6	0.40	3.0 (1.6–5.7)[a]
Obsessive-compulsive disorder[b]	6.7	0.5	5.8	0.58	7.6	0.83	1.3 (0.98–1.8)
Separation anxiety disorder	7.7	0.4	6.7	0.55	8.6	0.57	1.3 (1.04–1.6)[a]
Any anxiety disorder[c]	28.1	0.9	19.5	1.29	35.8	1.45	2.3 (1.9–2.8)[a]
Mood disorders							
Major depressive disorder	16.9	0.9	10.0	0.67	23.0	1.31	2.7 (2.3–3.1)[a]
Dysthymia	1.6	0.3	0.9	0.34	2.2	0.44	2.5 (1.5–5.3)[a]
Bipolar disorder (I and II)	2.1	0.2	2.2	0.40	2.1	0.28	0.96 (0.6–1.5)
Any mood disorder	19.1	0.8	12.3	0.82	25.2	1.25	2.4 (2.0–2.9)[a]
Impulse-control disorders							
Oppositional defiant disorder	1.4	0.2	1.4	0.30	1.5	0.26	1.2 (0.7–1.9)
Conduct disorder	2.1	0.2	3.2	0.43	1.1	0.20	0.4 (0.2–0.5)[a]
Attention-deficit/hyperactivity disorder	1.7	0.2	1.9	0.28	1.5	0.29	0.8 (0.5–1.3)
Intermittent explosive disorder	4.9	0.3	4.7	0.49	5.1	0.51	1.1 (0.8–1.6)
Any impulse-control disorder	8.4	0.4	8.9	0.51	7.9	0.76	0.9 (0.7–1.2)
Substance use disorders							
Alcohol abuse	9.8	0.6	16.4	1.12	4.0	0.51	0.2 (0.2–0.3)[a]
Alcohol dependence	3.3	0.3	5.8	0.69	1.0	0.15	0.2 (0.1–0.2)[a]
Drug abuse	2.9	0.4	4.4	0.62	1.6	0.34	0.3 (0.2–0.6)[a]
Drug dependence	1.4	0.3	2.0	0.47	0.8	0.22	0.4 (0.2–0.7)[a]
Any substance use disorder	11.0	0.6	18.0	1.11	4.7	0.58	0.2 (0.2–0.3)[a]
Any disorder							
Any disorder[c]	44.8	1.4	37.3	2.08	51.5	1.83	1.8 (1.4–2.2)[a]
Two or more disorders[c]	23.2	0.9	20.3	1.56	25.8	1.24	1.4 (1.1–1.7)[a]
Three or more disorders[c]	13.4	0.7	12.7	1.17	14.0	1.02	1.1 (0.8–1.5)

Adapted from Viana and Andrade [26]
Part I sample size = 5037; Part II sample size = 2942
[a]Significant gender difference ($p \leq 0.05$)
[b]Part II disorder, estimated in the Part II sample
[c]Include Part I and Part II disorders; therefore summary measures were analysed in the full Part II sample ($n = 2942$)

rates (23% vs 10%), there were no significant sex differences in the clinical course of the disease and in symptom severity, although men reported more disability associated with depression [28]. Based on further analyses of the SP Megacity data, there were significant gender differences in current employment status: women were 5.5 times more likely to be economically inactive (95% CI: 4.38–6.90; $p < 0.01$) and had 35% more chance of being unemployed (95% CI: 1.09–1.66; $p < 0.01$), when compared to men [29]. For both genders, having 12-month mood disorders is associated with being economically inactive, but it only relates to unemployment among men, and, among women, only substance use disorders are associated with being unemployed [29].

The São Paulo Megacity is part of an international WHO initiative (World Mental Health Surveys Consortium – WMH Surveys) in collaboration with Harvard University and the Institute for Social Research of Michigan University, currently including twenty-nine countries in all

WHO areas (http://www.hcp.med.harvard.edu/wmh). In a cross-national study including 15 of theses countries, women had significantly higher lifetime risks of major depression, dysthymia, and of all anxiety disorders compared to men (Table 2). The pooled F:M odds ratios for these disorders were all statistically significant, ranging from 1.3 for social phobia to 2.6 for posttraumatic stress disorder. Opposite results were observed for most externalizing disorders and all substance use disorders, with higher prevalence rates among men compared to women, ranging from 0.2 to 0.8, with men being 5 times more likely to present alcohol abuse disorders, 3.3 times more likely to present alcohol dependence, and 1.3 times more likely to be diagnosed with oppositional defiant disorder than women [23].

The Sao Paulo Epidemiological Catchment Area Study (SP-ECA), an epidemiologic survey conducted in three neighbourhoods in São Paulo, corresponding to the catchment area of the Teaching Hospital of the Faculty of Medicine of the University of São Paulo [30], evaluated 1464 individuals, a representative sample of the general population adult residents (18 years or older). In this study, women presented higher frequencies of affective disorders (except for psychotic or manic episodes and dysthymia), anxiety disorders (except for obsessive-compulsive disorder, generalized anxiety, and social phobia), dissociative disorders (trances and loss of consciousness), and eating disorders. Men presented higher rates of harmful drug use or drug dependence, including alcohol and tobacco. Except

Table 2 Associations of gender with lifetime risk of DSM-IV mental disorders in the World Mental Health Surveys: results from 15 countries (n = 72,933)

Mental disorder	Number of subjects[a]	All-country F:M OR (95% CI)	Range	
			Min	Max
Mood disorders				
Major depression	15	1.9 (1.8–2.0)[b]	1.6	2.4
Dysthymic disorder	10	1.9 (1.6–2.2)[b]	1.3	3.8
Bipolar disorder	6	0.9 (0.6–1.0)	0.6	1.1
Any mood disorder	15	1.8 (1.5–1.8)[b]	1.5	2.5
Anxiety disorders				
Panic disorder	12	1.9 (1.7–2.2)[b]	1.2	3.4
Generalized anxiety disorder	15	1.7 (1.5–1.9)[b]	0.7	2.7
Agoraphobia	8	2.0 (1.7–2.3)[b]	1.4	4.6
Social phobia	13	1.3 (1.2–1.4)[b]	1.1	2
Specific phobia	12	2.0 (1.9–2.2)[b]	1.3	3.1
Separation anxiety disorder	4	1.6 (1.4–1.8)[b]	1.4	2
Posttraumatic stress disorder	14	2.6 (2.2–2.9)[b]	1.3	6.4
Any anxiety disorder	15	1.7 (1.6–1.8)[b]	1.2	3.2
Externalizing disorders				
Attention-deficit/hyperactivity disorder	5	0.6 (0.5–0.8)[b]	0.3	0.6
Conduct disorders	3	0.5 (0.4–0.7)[b]	0.3	0.6
Intermittent explosive disorder	6	0.7 (0.6–0.8)[b]	0.4	0.8
Oppositional defiant disorder	3	0.8 (0.6–1.0)[b]	0.5	0.8
Any externalizing disorder	12	0.7 (0.6–0.8)[b]	0.3	1.4
Substance disorders				
Alcohol abuse	15	0.2 (0.2–0.3)[b]	0.1	0.4
Alcohol dependence	11	0.3 (0.3–0.4)[b]	0.1	0.4
Drug abuse or dependence	5	0.4 (0.3–0.4)[b]	0.1	0.4
Any substance disorder	14	0.3 (0.2–0.3)[b]	0.1	0.4
Any disorder	15	1.1 (1.1–1.2)[b]	0.7	2.2

Adapted from Seedat et al. [23]
F:M female to male ratio
[a]Number of countries analysed
[b]$p < 0.05$

for tobacco dependence, the risk of suffering from a mental disorder was 1.5 times higher for women than men. Regarding alcohol consumption, men presented higher prevalence rates of alcohol abuse/dependence than women (7.8% and 3.8%, respectively), with a total lifetime prevalence of 5.5%. Considering the patterns of alcohol consumption in the sample, there were gender differences in the heavy use (defined as the consumption of five or more doses in the same event for men and four or more for women) [31]. Almost 11% of the sample reported heavy alcohol use, being 15.4% for men and 7.2% for women. Heavy drinking was significantly more frequent among young men, between 18 and 24 years of age (OR 2.9; 95% CI 1.7–4.7), while among women, this pattern reached a broader age range, with OR 4.6 (95% CI 1.8–11.9) for the 35–44 years age-group and OR 6.2 (95% CI 2.4–15.8) for the 18–24 years age-group, compared to women 45 years or older. Heavy drinking was also more frequent among separated, divorced, and widowed women (OR 4.2, 95% CI 1.8–9.5) and single women (OR 2.5, 95% CI 1.1–6.1). Heavy drinking women presented significantly higher rates of alcohol abuse and dependence throughout life and in the last year than those who were not heavy drinkers, while among men, there were no significant differences between the two groups. It was also observed that, compared to men, women reported significantly higher occurrence of death thoughts (35.2% versus 25.4%), desire to die (13.0% versus 8.4%), and suicide attempts (4.0% versus 1.9%) throughout life [32]. The presence of depressive disorders was the most important predictive factor for suicidal behaviours and cognition, regardless of gender, while alcohol and drug abuse and/or dependence was associated with a higher risk among women. The SP-ECA study also investigated the patterns in use of health services by the studied population, showing that, among respondents with some mental disorders in the 12 months prior to the interview, women sought more medical services and mental health professionals in the past 30 days, compared to men [33].

Another national study [34] investigating the patterns of alcohol consumption in a sample of 3007 individuals (2346 adults and 661 adolescents aged 14–17 years), representative of the Brazilian population (except for indigenous populations living in villages), showed that the difference in alcohol use between men and women is reducing in younger cohorts, showing a convergence between genders [35].

Kohn et al. [36] reviewed population-based epidemiological studies conducted in several Latin American countries and calculated the median prevalence of mental disorders in the region for people aged 18 years or older. The 12-month prevalence estimates of each disorder for the total sample and by gender are summarized in Table 3. The most common disorders were alcohol abuse and/or dependence and major depression, affecting about 5.5% of the sample. Anxiety and depressive disorders were more

Table 3 Twelve-month (median) prevalence estimates of mental disorders and number of people affected by sex in Latin America and the Caribbean, 2015[a]

	12-month prevalence (%)				People affected[a] (in millions)		
	Total	Men	Women	F:M	Total	Men	Women
Non-affective psychosis	0.7	0.7	1.1	1.6	2.4	1.2	1.9
Major depression	5.4	3.5	7.1	2	18.3	5.8	12.3
Dysthymia	1.7	0.9	2.6	2.9	4.1	1.3	2.2
Bipolar disorder	0.7	0.6	0.4	0.7	2.4	1.0	0.7
Generalized anxiety disorder	1.3	0.9	1.3	1.4	4.4	1.5	2.2
Panic disorder	1.1	0.5	1.4	2.8	3.7	0.8	2.4
Obsessive-compulsive disorder	1.2	1.0	1.4	1.4	4.1	1.7	2.4
Alcohol abuse/dependence	5.6	9.8	1.4	0.14	18.9	16.2	2.4
Drug abuse/dependence	0.5	1.0	0.2	0.2	1.7	1.7	0.3

Adapted from Kohn et al. [36]

[a]Projections for Latin America and the Caribbean, considering 2015 adult population of 622 million inhabitants; F:M female to male ratio

prevalent in women, while alcohol and substance use disorders were more frequent in men. Although the data may represent an underestimated magnitude of the impact of mental disorders, the authors also made projections about the number of individuals affected by various disorders in this region (Table 3). These numbers provide an estimate of the magnitude of people affected by mental disorders. For example, major depressive disorder were estimated to affect around 12.5 million people at the time of assessment, and alcohol abuse or dependence would have affected 18.9 million people in the 12 months prior to the interview. According to this survey [36], only half of affected individuals received any treatment. Although these data present serious limitations of comparability, given the different methodologies and the variety of instruments used, as well as the small number of countries studied, which do not represent the entire region, they are still informative, signalling an alert to the dimension of the social burden of mental disorders in Latin America. There is a need to restructure mental health services in these countries, since mental health assistance is usually centred in large hospitals, upgrading hospitals and expanding the network of community attention, considering the shortage of inpatient beds and ambulatory services in the region.

In an international scope, several population-based cross-sectional studies were conducted in western countries in the late 1990s and beginning of the twenty-first century, such as the National Comorbidity Survey, a nationwide study that assessed 8098 individuals 15–54 years old from a probabilistic sample of the American general population [37]; the Netherlands Mental Health Survey and Incidence Study (NEMESIS; baseline assessment), conducted in the Netherlands with a national sample of 7076 individuals aged 18–64 years [38]; the OPCS Surveys of Psychiatric Morbidity in Great Britain, conducted in England, Scotland, and Wales, evaluating 10,108 individuals aged 16–64 years residing in the community [39]; and a study conducted in Santiago, Chile, evaluating 3870 residents of the metropolitan region aged 16–64 years old [40]; and, finally, the *Encuesta Nacional de Epidemiologia Psiquiátrica*, also part of the WHO/Harvard WMHS, was conducted in Mexico, evaluating 5826 individuals [41]. In general, similar distribution patterns of psychiatric morbidities by gender have been observed in these studies, with mood and anxiety disorders affecting women more frequently than men. Sharper differences for specific phobias (animals, dark, closed places) were reported, while height and airplane phobias and phobias involving blood or medical procedures showed no differential distribution by sex. For social phobia, while prevalence rates are higher among women, treatment seeking is more frequent among men, probably due to being linked to worsened work performance.

Prospective studies also showed differences in the incidence rates of mental disorders in men and women. In the NEMESIS cohort study [42], substance use, particularly alcohol abuse, was the most frequent 12-month incident disorder among men [incidence rate (IR) 4.09/100 PYR (person years at risk)], followed by depression (IR 1.72), simple phobia (IR 1.34), and alcohol dependence (IR 0.82). Among women, depression presented the highest IR (3.9/100 PYR), followed by simple phobia (3.17). The incidence rate ratio or relative risk (adjusted by age) for any mental disorder was 1.54 times higher among women, or a 54% increased risk for women. This ratio was higher for anxiety disorders (2.6), particularly panic disorder (2.5), followed by mood disorders (2.4). The ratio was inverse for substance use disorders, with higher risk among men (3.7) [42]. In a longitudinal study following 2166 women in Goa, India, over a 12-month period, Patel and collaborators verified a higher risk of common mental disorders and use of tobacco and alcohol among poor and married (compared to single) women [22]. There was a positive association between a higher number of psychological symptoms in the initial assessment and complaints of vaginal secretion and reports of chronic physical illness [22].

In both, clinical samples as well as population-based studies, the occurrence of two or more comorbid psychiatric disorders is a common phenomenon. More recently, the denomination of double diagnosis or dual disorder has been

used when a psychiatric disorder and a psychoactive substance use disorder co-occur. In population-based studies, nearly 30% of individuals who present some psychiatric disorder in the 12 months prior to the interview have two or more associated disorders. Kessler and collaborators [43] explored the comorbidity patterns between mental and psychoactive substance use disorders in seven epidemiologic studies conducted in six countries (United States, Brazil, Canada, Mexico, Germany, and the Netherlands) that used the same diagnostic tool (CIDI). Results were consistent in various populations, showing the co-occurrence of an active mental disorder associated with substance use. Women showed higher comorbidity of depression and anxiety disorders, particularly panic disorder and simple phobias. Men showed higher comorbidity of substance use problems (mainly alcohol) and conduct disorders. The association between primary mental disorder and secondary substance use was more frequent among women (varying from 44% to 70% in the seven studies) than men (11–77%). A useful information revealed by these studies was the low rate of specialized treatment seeking, although higher use of general health services was observed.

Another interesting finding, replicated by several studies, was that, although men present lower rates of mood and anxiety disorders, they report higher levels of functional, cognitive, and social disability compared to women [18, 28, 44].

Although there is no evidence that support the implications of causal or hormonal mechanisms in explaining the higher prevalence rates of anxiety and depressive disorders among women [19, 20], it is believed that female sexual steroids, particularly oestrogen, modulate humour, what may partially explain the higher prevalence of mood and anxiety disorders among women. The fluctuations of gonadal hormones would influence the modulation of the female neuroendocrine system, from menarche to menopause. Dunn and Steiner [45] proposed a hypothesis of biological susceptibility to explain the gender differences in prevalence rates of mood disorders. According to them, women would present an imbalance in the interaction between the hypothalamus-pituitary-gonadal axis and other neuromodulators. The neuroendocrine rhythm related to female reproduction would be vulnerable to changes and highly affected by psychosocial, environmental, and physiological factors.

Otherwise, it is considered that oestrogen plays a protective role against schizophrenia, leading women to present a later age of onset and to need smaller doses of neuroleptics, besides presenting a more favourable course of the disease, more positive symptoms, and less severe symptoms than men [17, 46]. Acute psychotic episodes occur in periods of low oestradiol. There is also a positive correlation between oestrogen levels and cognitive performance [46].

Gender Differences in Mood and Anxiety Disorders

One of the most consistent findings replicated in psychiatric epidemiology is the higher prevalence of depression among women compared to men. This difference has been observed in various regions around world by means of different assessment tools and operational diagnostic criteria, but, in spite of such consistency in findings in most studies, a wide discrepancy in lifetime prevalence rates is observed, depending on countries or regions assessed [23, 26, 47]. Bromet and collaborators [47] reported the epidemiology of major depressive episodes (MDE) in 18 countries participating in the World Mental Health (WMH) Surveys Consortium, covering all WHO regions [47]. Overall lifetime mean prevalence estimates of MDE were 14.4% (SE 0.2) in high-income countries (ranging from 66.6 in Japan to 19.2% in the United States) and 11.1% (SE 0.2) in low-to-middle-income countries (ranging from 6.5% in Shenzhen, China, to 18.4% in São Paulo, Brazil). Consistent with previous epidemiological studies, women were, on average, two times more likely to have MDE than men, and the difference was significant in 15 of the 18 countries studied, although there were no significant differences in high- and low-to-middle income countries. Pooled odds ratios were 1.8 (95% CI 1.6–2.0) in high-income

countries, varying from 1.6 (CI 1.2–2.1) in Israel to 2.7 (CI 1.9–3.8) in Spain, and 2.1 (CI 1.8–2.3) in developing countries, varying from 1.9 in Colombia and India to 2.6 (CI 1.9–3.5) in Brazil [47].

Epidemiologic research involving children and adolescents demonstrated that the gender differences in incidence of major depression manifests primarily at ages 11–14 years, persisting throughout adult life [44], what may suggest a determinant role of sexual hormones, especially considering that other situations of hormonal fluctuations have been associated to depressive mood, such as premenstrual period, puerperium and menopause, use of oral contraceptives, and hormone replacement therapy. However, systematic reviews have failed to identify associations between these factors and higher rates of major depression in women [44]. Additionally, the effect of pregnancy on incidence and recurrence of depression has showed to be insignificant. The only exception seems to be the post-partum period, which is associated to a substantial increase in depression rates. Compared to recurrent cases, cases that first emerge during this period are more frequent among women with strong family history of depression.

Besides the biological differences , other theories have been explored to explain the gender differences in prevalence of depression, such as the higher persistence of depressive episodes in women, compared to men, which may be permeated by social pressure, chronic stress, and low satisfaction associated with performing traditional female roles, or by gender differences in dealing with problems and seeking for solutions. Some retrospective studies have suggested that depression presents a slower course in women than in men, but this has been refuted by methodological studies demonstrating that such higher chronicity is in fact due to differential recall bias between men and women. Indeed, there were significant sex differences in the prevalence of depression in the São Paulo metropolitan area, but once the disease was established, a similar course and severity was observed [28]. Another argument that has been widely used to explain these gender differences is that women would be able to identify their symptoms, admit the illness, and seek help more easily than men [33]. Available evidence, however, does not allow such conclusion since higher depression rates in women are observed both in studies that directly evaluated the subjects as in those based on informants; besides, systematic assessment of response patterns to psychometric tests did not show any gender differences, what also happened when the distribution of presence and severity of depressive symptoms was assessed. It has also been postulated that men in fact present the same risk of depression as women, as men would manifest irritability instead of dysphoria or anhedonia, but this hypothesis was not confirmed [48].

Exposure to stressful experiences has been associated with increasing risk for depression, such as exposure to childhood adversities, including interpersonal and family violence, neglect, trauma, social isolation, and intimate partner abuse [49–51]. Genetic researches involving the study of twins have demonstrated a strong and equivalent hereditary component in both men and women.

The comorbidity profile also seems to differ between genders, with women showing higher rates of anxiety associated to depression and men showing higher rates of psychoactive substance abuse and conduct disorders.

Atypical depression, characterized by increased appetite and weight gain and hypersomnia, seems to be more prevalent among women, indicating a sex-related differential distribution of depressive subtypes [52, 53]. In the NCS study [37], detected cases of atypical depression were compared to those of non-atypical depression (39% of all detected cases of depression). The proportion of women was higher in the atypical depression group, which also presented an earlier age of onset. The atypical depression group also had higher indices of depressive symptoms, suicidal ideation and attempts, psychiatric comorbidities (panic, social phobia, and psychoactive substance dependence), higher incapacitation, and higher use of health assets. Family history, especially parental history, of depression was more common in this subgroup, as well as history of sexual abuse or negligence during childhood. In the analysis of these data, the symptom "sensitivity to interpersonal rejection" emerged as an important aspect of the clinical profile, as well as the presence of anxious symptoms and

humour reactivity associated with irritability. Hypersomnia and weight gain remained as non-specific symptomatology.

Yonkers and collaborators [54], in a longitudinal study in which patients were assessed every 6 months for 8 years, verified that women with panic disorder presented higher indices of comorbidity with depression and agoraphobia and had three times more relapses than men, with similar findings for generalized anxiety disorder (GAD). Four epidemiological studies conducted in Brazil, the Netherlands, Canada, and the United States estimated the prevalence of GAD, which varied from 1.9% to 5.3% throughout life (combined prevalence of 3.9%) and from 1.0% to 2.9% (combined prevalence of 2.1%) in the previous year. Female-to-male prevalence ratio was approximately 2:1, and age of onset was by the end of adolescence and mid-adult life [43].

There are several explanations for these gender differences in prevalence rates of anxiety disorders. Besides factors such as higher cultural acceptance of fear and dodging behaviour in women and different adaptive patterns, men tend to use substances such as nicotine and alcohol and self-medication, what could mask primary symptomatology. According to Barlow [55], women are more susceptible to stressful events during childhood and adolescence, which, associated to the perception that their behaviours cause little impact on the environment, would cause a feeling of being out of control and the consequent development of pessimistic maladaptive patterns of evaluation of reality. These factors, associated to a genetically determined biologic vulnerability to being biologically reactive to environmental changes, would explain the higher occurrence of these disorders in women.

Regarding bipolar mood disorders (BMD), different epidemiologic studies point to the absence of difference in incidence and prevalence rates of BMD between men and women [56–58], although some studies show a higher prevalence of type II BMD among women [50].

Considering the importance of reliable and up-to-date prevalence estimates of disorders for effective health policy, planning, and evaluation, the WHO recently provided information on the proportion of the general population affected by depression and other common mental disorders (WHO 2017). It was estimated that 4.4% of the world population suffered from depression in 2015, affecting over 300 million people. Depression is considered the single largest contributor to global disability and is also the major contributor to suicide deaths, which number close to 800,000 per year in the world. Figure 1 shows the prevalence of depressive disorder by sex in all WHO regions. Depression is more common among women (5.1%) compared to men (3.6%). Prevalence distributions vary by age and sex, as shown in Fig. 2, peaking

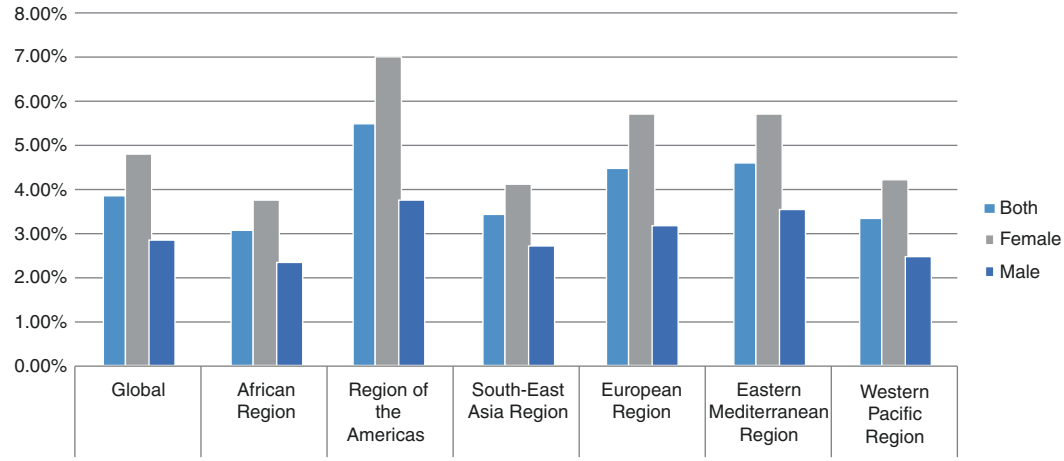

Fig. 1 Prevalence of depressive disorders, by WHO Region (%). (Source: Global Burden of Disease Study 2017 (http://ghdx.healthdata.org/gbd-results-tool))

in older adults (7.5% among women and 5.5% among men). Regarding anxiety disorders, it is estimated that 3.6% of the world population were affected in 2015 (Fig. 3) and were also more frequent among women than men (4.6% vs. 2.6%). The highest prevalence estimates are in the Region of the Americas, where 7.7% of the women had depression compared to 3.6% among men. The total estimated number of people affected in 2015 in the world is 264 million and does not vary significantly by age (Fig. 4). Finally, in all WHO regions, a higher rate of suicide deaths occurs among men (Fig. 5), accounting for 1.5% of all deaths worldwide. Suicide occurs throughout the lifespan and was the second leading cause of death among 15-29-year-olds in 2015, being among the 20 leading causes of death in 2015.

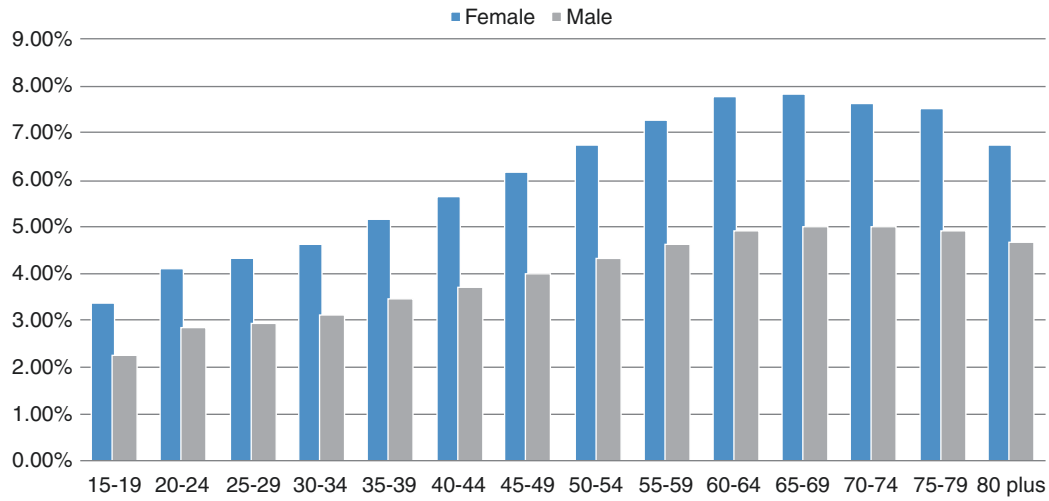

Fig. 2 Global prevalence of depressive disorders, by age and sex (%). (Source: Global Burden of Disease Study 2017 (http://ghdx.healthdata.org/gbd-results-tool))

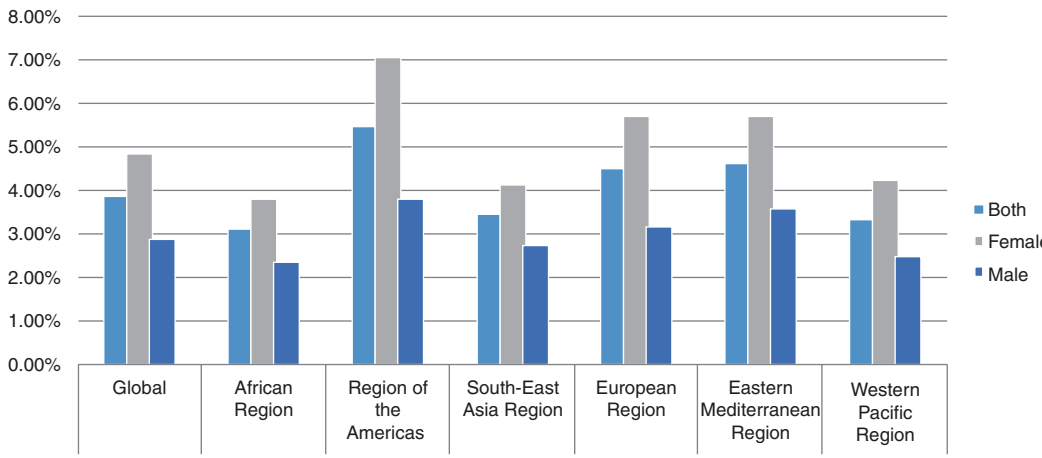

Fig. 3 Prevalence of anxiety disorders, by WHO region (%). (Source: Global Burden of Disease Study 2017 (http://ghdx.healthdata.org/gbd-results-tool))

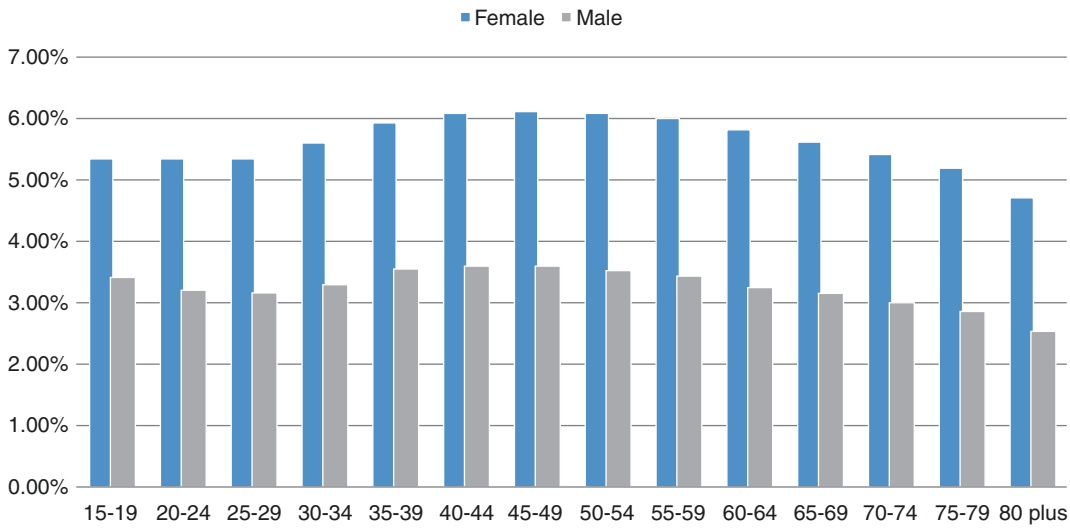

Fig. 4 Global prevalence of anxiety disorders, by age and sex (%). (Source: Global Burden of Disease Study 2017 (http://ghdx.healthdata.org/gbd-results-tool))

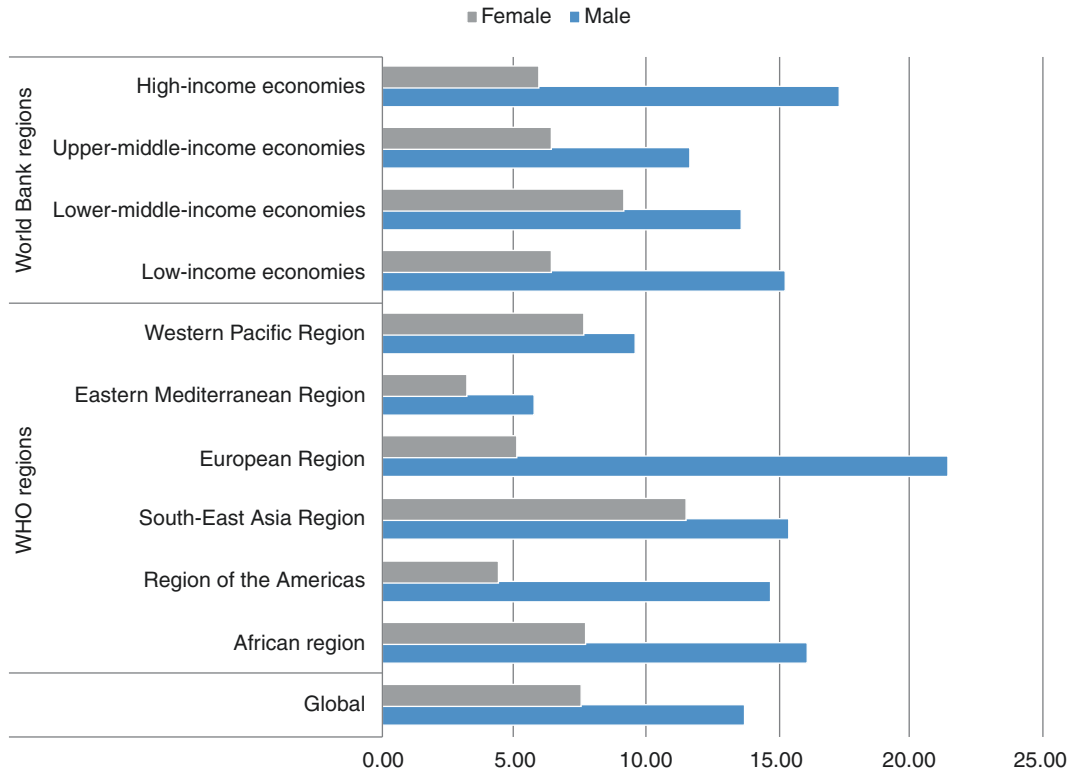

Fig. 5 Suicide rates per 100 thousand population according to the World Bank economic categories and WHO regions. (Source: WHO Global Health Estimates 2000–2016 (http://www.who.int/healthinfo/global_burden_disease))

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Psychometric Instruments and Women's Mental Health

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Rating scales are ubiquitous in mental health. They are used to assess the degree of anxiety and depression, a person's quality of life, the extent of someone's social support network, the presence of symptoms related to post-traumatic stress, and a host of other phenomena. In the clinical setting, scales can be used on an individual basis to assist in diagnosis and to track a patient's progress (or the lack thereof) over time. In research, these instruments are often the major outcome variable that determines whether an intervention has been effective or not. Their ubiquity is attested to by the fact that the latest edition of *Tests in Print* [1] lists nearly 3000 commercially available tests, and the number of scales that have been described in journal articles is roughly four times larger [2]. But not all tests are created equal. In order for them to be useful, the instruments must satisfy a number of criteria. In this chapter, we will begin by outlining the process of scale development, and following this brief introduction to psychometrics, we will review and evaluate a number of scales used in the field of women's mental health.

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Psychometrics

A Brief History

Psychometrics refers to the field of study concerned with the theory and techniques of measuring internal, subjective states, such as moods, beliefs, and attitudes, or the assessment of more objective phenomena, such as skills and educational attainment. The study of individual differences in physical attributes such as height and reaction time can be traced back to the middle of the nineteenth century with the publication of Gustav Fechner's *Elemente der Psychophysik* [3] and the collection of anthropometric data on

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approximately 10,000 individuals by Francis Galton in London [4]. Mental assessments began with the development of intelligence tests in France by Alfred Binet and Théophile Simon [5].

The mathematical foundations of psychometrics can be said to begin in 1935, with the formation of the Psychometric Society by Louis L. Thurstone and the launching of its journal, *Psychometrika* [5], which remains one of the leading journals in the field. The following year, J. P. Guilford published the first book in the area, called *Psychometric Methods* [6]. Since that time, there have been tremendous advances regarding what is now called Classical Test Theory (CTT), which has dominated scale construction for the past 80 years and still serves as the basis for the construction of new tests.

Creating Scales

In this section, we will describe the steps required to develop and evaluate a new scale. As we mentioned, this can both serve as a guide for those contemplating developing an assessment instrument and providing a template with which users can assess how well an existing scale meets their needs. We will discuss these steps in the order in which they are (or at least should be) done in real life.

Scales and Indices

Before we begin, it is necessary to discuss the difference between scales and indices [8]. As we are using the terms here, a scale is a collection of items measuring one and only one attribute, such as anxiety. This means that all of the items are correlated with one another because they all tap the same phenomenon. It also means that the items are only a sample of the universe of possible items. If we are developing a new scale of anxiety, it is not necessary to ask about every symptom; we could omit, for example, an item inquiring about rapid heart rate because whatever it measures will be picked up by the other, correlated items. All of CTT is predicated on these assumptions of a homogeneous set of items tapping a single attribute.

On the other hand, an index is closer to a checklist, consisting of items that may or may not be correlated, and is usually used to measure more heterogeneous phenomena. For example, the Apgar Scale [9] – which we would call an index – measures a neonate's heart rate, muscle tone, respiration, reflex response, and skin color. The items are correlated in healthy infants, but not in those with various disorders. If a child has a cardiac condition, for example, the scores for heart rate and skin color may be low, but the other scores would be high, whereas in cerebral palsy, reflex and muscle tone would be low and the other scores high. Indices are also used to tap sources of stress, activities of daily living, and so on, where endorsement of one item does not necessarily imply endorsement of another. Here, the choice of items defines what is being measured; change the items and the definition of the phenomenon itself changes. Feinstein called the method of constructing indices "clinimetrics" [10], but fortunately, this neologism has not been adopted outside of medicine. CTT cannot be used in constructing indices.

Bear in mind, though, that the terminology we use here is not universal, and some scales have the term "index" in their name (e.g., [11]) and, as with the Apgar, some indices refer to themselves as "scales." However, the distinction is a crucial one with regard to how a measurement tool is constructed and evaluated.

Devising the Items

Needless to say, the development of a scale begins with the construction of the items. There are many potential sources of items: previous research in the area, theory, discussions with experts in the field, and individual interviews or focus groups with patients (see reference [12] for an example of the use of these latter approaches). Also, many new scales "borrow" items from existing ones, with or without changing the wording to meet the specific needs of the new instrument. There are many reasons for this. First, there are only so many ways of asking a person, "Do you feel tense?" Second, it is likely that the items have been tested and found to work, and third, it definitely saves time. It is good practice to write three to four times the number of items that you

ultimately want on the scale because many will be weeded out in subsequent steps.

There are many potential pitfalls that can be encountered in writing items [7]. These include the following:

- Using language that is too difficult to understand. It is estimated that the average high-school graduate in North America reads at only a Grade 6 level.
- Being ambiguous. A No answer to the item "My illness prevents me from shopping" may mean that (a) the illness does not interfere with this activity or (b) the person never did this activity to begin with.
- Using jargon. For example, to most people, a "stool sample" is what is seen in a furniture store, not the result of a bowel movement.
- Having "double-barreled" questions. These are items that ask two questions at the same time, such as "I have trouble reading and concentrating." It is possible that some people have problems with one symptom but not the other, leading to confusion and inconsistency in responding.
- Using negatively worded items. These are not interpreted as the converse of positively worded ones [13] and should be avoided whenever possible.
- Having items that are too long. Items with 70–80 letters have much lower validity coefficients than those that are 10–20 letters in length [14].

The best way to check that the items are being interpreted as they were meant to be is through *cognitive interviewing* [7]. There are various formats for this, such as having the respondents rephrase the item in their own words, thinking aloud as they answer, or explaining how they decided on the answer they gave.

The next step is to assess the *content validity* of the items. This is done in two ways, each looking at a different aspect of content validity. In the first, which looks at *content relevance*, the items are sent to five to ten experts in the area (clinicians, academics, and patients) who rate them on a four-point scale: 4 = highly relevant; 3 = quite relevant or highly relevant but needs rewording; 2 = somewhat relevant; and 1 = not relevant. Based on this, a Content Validity Ratio (CVR) is calculated for each item:

$$\mathrm{CVR} = \frac{n_e - \frac{N}{2}}{N/2} \quad (1)$$

where n_e is the number of raters who deemed the item essential (a rating of 3 or 4) and N is the total number of raters. With five or six raters, items need a CVR of 0.99 to be retained; for eight raters, a value of 0.85 is required; and 0.62 for 10 or more raters [15].

Once the less relevant items have been eliminated, the remaining ones can be checked for the second aspect of content validity, which is *content coverage*. This requires that the test developer list all aspects of the phenomenon that must be tapped. For example, if the scale is meant to measure anxiety, this may include the four components of affect, behavior, cognition, and physiological changes. These are used as the headings of four columns, and the individual items are the rows. A number of content experts read each item and place a mark in the column indicating what they think the item reflects. This then indicates: (a) whether an item cannot be classified and should be dropped; (b) if it has check marks in two or more columns, showing that it should either be rewritten or eliminated; (c) whether each column has a sufficient number of items, which should be at least three; and (d) whether one column has a disproportionate number of items. Users of existing scales are encouraged to go through the same exercise, to determine whether the scale is indeed measuring what they hope it does.

Reliability

The next step is to determine the reliability of the remaining items. A reliable scale is one that (a) produces similar results if a person completes it at two different times, assuming the person has not changed in the interim (*test-retest reliability*); (b) yields similar scores if a person is evaluated by two or more independent raters (*inter-rater*

reliability); and (c) has a high degree of homogeneity among the items (*internal consistency*). The first two types are evaluated by determining the correlation between the two or more sets of scores, using either a Pearson correlation or, more commonly now, the intra-class correlation [16, 17]. Internal consistency is usually determined using Cronbach's alpha [18], but it suffers from the problem that, if the scale has more than roughly 15 items, it will be high even if the scale is heterogeneous [19].

Another way to define reliability is with the formula:

$$\text{Reliability} = \frac{\sigma_s^2}{\sigma_s^2 + \sigma_e^2} = \frac{\sigma_s^2}{\sigma_{\text{Total}}^2} \qquad (2)$$

Where O²s Is the variance of scores between people and O²e Is the measurement error. In other words, the reliability of a scale is the amount of total variance (subject variance + error variance) that is explained by differences in scores among people.

The generally accepted standards for test-retest and inter-rater reliability are that they should be a minimum of 0.70 if the scale is being used for research purposes in a new field where not much is known about the phenomenon. For established fields, the minimum is 0.80. If the instrument is used to make a decision about an individual person, then the reliability should be at least 0.90 [20]. Internal consistency should be high for homogeneous scales, but if it exceeds 0.90, this may reflect that there are unnecessary, redundant items that may actually limit the usefulness of the scale because its focus is too narrow [21].

It cannot be emphasized strongly enough that reliability is *not* a fixed property of a scale that, once established, applies in all situations. It is dependent on the instrument and the group with which it is being used. A scale that may be reliable for one group of people may not be reliable with a different group. This is a direct result of Eq. (2). If one group (e.g., the general population) has a wider range of scores than another (e.g., a clinical sample), then the reliability coefficient derived from the first group will be higher because there is greater between-person variance. The implication is that if a scale has been developed and assessed in one group, its reliability must be separately established for each new population you want to use it with.

Validity

Traditionally, validity was defined as answering the question, "Does the test measure what I think it measures?" [22]. However, current thinking would be closer to "Validation processes are not so much directed toward the integrity of tests as they are directed toward the inferences that can be made about the attributes of people who have produced those test scores" ([23], p. 1186). That is, the focus is on the scores, not the test, and what conclusions we can accurately make about people based on those scores. In order to understand the process of validation, it is necessary to understand what is meant by the term "construct" (also called a "hypothetical construct"). Most of the attributes assessed by scales are not directly observable; we infer their existence by the effects they have on phenomena we can observe. For example, we do not see depression. Rather, we see that people's sleep and appetite have changed; they are pessimistic that things will ever get better; they express thoughts of suicide; they may feel fatigued and say they have no energy; talk about being guilty or being worthless; and so forth. We hypothesize that these co-occur because they are all the outward manifestations of an underlying construct we call depression. Other attributes, such as intelligence or locus of control, and other disorders, such as schizophrenia or irritable bowel syndrome, can similarly be thought of as hypothetical constructs that are inferred on the basis of observable behaviors or symptoms.

We can develop "mini-theories" about these constructs, based on previous research, clinical observation, and a theoretical understanding of the phenomenon. For example, our knowledge of anxiety may lead us to postulate that, for example, (i) anxious people do less well on complex cognitive tasks than non-anxious individuals; (ii) anxiety should increase before an exam; (iii) those attending an anxiety disorders unit should be more anxious than people in a fracture clinic;

and (iv) anxiety levels should decrease following treatment. None of these hypotheses is world-shattering, but they indicate how scales of anxiety should perform. Based on these, we can design studies to determine whether or not a new scale of anxiety performs as it should; a process Cronbach and Meehl [24] called *construct validation*.

In the past, it was customary to talk about three different "types" of validity – content validity (do the items adequately cover the domain of interest?), criterion validity (does the new test correlate with other measures of the phenomenon?), and construct validity itself (studies based on our mini theory); and each of these was divided into many subtypes. Current thinking is that there is only one type of validity, and that is construct validity. We may speak of criterion *validation* (i.e., a method of establishing construct validity), but not criterion *validity* (i.e., a "type").

There are four points to bear in mind about validity. First, because we can always learn more about what test scores reveal about people (different groups, in different situations, and so forth), validity is a never-ending, on-going process. Second, validity is not a present/absent phenomenon, but is rather a judgment call based on an evaluation of the currently available evidence. Third, while reliability is measured with one statistic (a Pearsonian or intra-class correlation), the statistics used to establish validity can vary, depending on the nature of the study – a correlation when looking at the relationship of the new scale with an older one, an independent *t*-test or analysis of variance if the study compares groups who should have different levels of anxiety, a related *t*-test for before-after studies, and so on. Finally, and perhaps most importantly, the same caveat applies to validity as to reliability: it is not a fixed, immutable property of the scale, but depends on the nature of the group and the circumstances under which they are completing the instrument.

Constructing scales is a laborious and time-consuming process, one which can take 2 or 3 years to do well. For those who wish to delve deeper into the process, we would (self-servingly) recommend the book by Streiner, Norman, and Cairney [7].

Scales Used to Evaluate Women's Mental Health

In clinical research, scales of assessment are required to ensure that results can be interpreted and potentially generalized. They are selected based on the coverage of the relevant constructs, costs, time of administration, comprehensibility to the intended audience, and the quality of the evaluations provided. In clinical practice, one should also consider if a scale would efficiently provide information and whether it would be useful to promote a better patient-clinician communication. For both research and clinical settings, it is essential that screening tools have pronounced psychometric properties [25, 26].

Scales Used to Evaluate Psychiatric Disorders in Women

There are some peculiarities in psychiatric disorders in women. This occurs in epidemiological terms, clinical characteristics, treatment, and prognosis. Take, for instance, the mood and anxiety disorders, women are affected by them approximately twice as often as men [27], and these conditions have an increased risk for onset or worsening during reproductive events in a woman's life [28]. Nevertheless, most diagnostic instruments used for the assessment of mental disorders in clinical practice and epidemiological researches are not sex and context specific [29].

The Composite International Diagnostic Interview – Venus (CIDI-V) is a standardized clinical interview that provides core questions to assess female specificities in mental disorders, as the menstrual and contraceptive history, the perinatal history, and the use of hormone therapy in perimenopausal women. The CIDI-V was developed for epidemiological studies, but it can be a valuable tool for health-care practitioners as well [27].

Below, we describe the main tools used for screening and monitoring of female-specific conditions, such as premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD), psychiatric disorders during the perinatal period, and conditions during perimenopause. For more details regarding the psychometric properties for the tools discussed, please refer to Tables 1, 2, and 3.

Scales for Screening and Monitoring Symptoms During Premenstrual Period

More than three in four women of fertile age experience at least mild symptoms of the premenstrual syndrome that can include psychological and physical symptoms that occur in the late luteal phase of the menstrual cycle. This high prevalence suggests that premenstrual symptoms should not be regarded as something abnormal [30]. Nevertheless, 3–8% of these women suffer from PMDD, a debilitating variant of the premenstrual syndrome [26].

According to the DSM-V, an individual must have five or more of eleven symptoms present during the late luteal phase with improvement of the symptoms within a few days of the onset of the menses. A diagnostic requirement is that the symptoms should be confirmed by prospective daily ratings during at least two consecutive cycles, and if there is a discrepancy between the two menstrual cycles, a third cycle should be carried out [30, 31]. The prospective symptom rating scale is not only a key to precisely diagnose PMDD, but also to effectively manage it. The use of retrospective screening tools may be convenient before requesting a patient to prospectively record her symptoms. Moreover, it may be used to avoid delaying into treatment [26, 30].

The Menstrual Distress Questionnaire [32] was one of the first diagnostic methods for measuring cyclical premenstrual symptoms. A primary advantage of this tool is that it contributed for the development of the diagnostic scales currently used. Nevertheless, it does not align with the current diagnostic criteria for PMDD; ergo, it is not a clinically relevant tool [33].

The *Premenstrual Tension Syndrome (PMTS)* rating scale was developed in 1980 [34], using the symptom items from the Menstrual Distress Questionnaire. This tool consists of an observer (PMTS-0) and a self-report scale (PMTS-SR) used in concomitance to identify symptom severity both prospectively and retrospectively. To reflect the DSM-IV criteria, an updated version was created with a change in symptoms measured by the PMTS-O [35]. Additionally, the PMTS-SR was substituted with a Visual Analog Scale, pursuing a higher validity, reliability, and sensitivity [36, 37].

The *Premenstrual Symptoms Screening Tool (PSST)* is a 19-item retrospective tool that aligns with DSM diagnostic criteria and considers an individual's level of functioning. It is a user-friendly tool and was recently adapted into a measure of premenstrual symptoms in an adolescent population [26].

The *Daily Record of Severity of Problems (DRSP)* is one easily accessible, well-validated prospective rating scale that can be used to elucidate the pattern of symptoms. It consists of 21 items [38] and it was designed in alignment with the DSM-IV criteria for PMDD while also providing information on the severity of symptoms and level of impairment at various phases of the menstrual cycle. This tool is recommended by the British Royal College of Obstetricians and Gynecologists and is an accepted quantification technique by the International Society for Premenstrual Disorders (ISPMD) [30].

The *Carolina Premenstrual Assessment Scoring System (C-PASS)* [39] is a reliable and valid scoring system complementary to the DRSP. The C-PASS was developed to standardize and simplify the translation of the diagnosis of PMDD according to the DSM-V, aiming to define more homogeneous samples of women with PMDD in studies, therefore clarifying the understanding of the disorder.

The *Prospective Record of the Impact and Severity of Menstruation (PRISM)* [40] is a validated tool that requires punctuation on life events, concurrent medications, and menstrual bleeding. Other tools include the Premenstrual Assessment Form (PAF) [41], the 33-item Daily Assessment

Table 1 Tools for screening and monitoring symptoms during the premenstrual period

Screening tool	Number of items and scale of severity	Symptoms measured	Self-report or observer	Time to complete	Current, retrospective, or prospective	Psychometric properties	Study (year)	Ref
Menstrual Distress Questionnaire (MDQ)	47 symptoms grouped into 8 clusters. Two forms of the MDQ. Form C (cycle) and Form T (today). Repeated use of Form T is necessary to identify cyclical changes. Rated on a 6-point scale of severity	Physical and psychological	Self-report	Lengthy	Retrospective and current	Criticism regarding its reliability, validity, and instability of its factor structure	Moos Rudolf (1968)	[32]
Premenstrual Tension Syndrome (PMTS) rating scale and PMTS-updated	PMTS-observer covers 11 domains of symptoms – from (0–4) severity scale. From (0–2) in only 2 items	Physical and psychological	An observer (PMTS-0) and a self-report scale (PMTS-SR)	Brief, easy, and user-friendly	(PMTS-SR) retrospective and current. (PMTS-0) prospective	Validated, reliable, sensitive to change and severity of symptoms	Steiner et al. (1980, 2011)	[34, 37]
Premenstrual Symptoms Screening Tool (PSST)	19-item tool; 14 symptoms and 5 functional items, rated on a 4-point scale of severity	Physical and psychological, screens for PMDD and PMS	Self-report	User-friendly	Retrospective	Validated	Steiner et al. (2003)	[35]
Daily Record of Severity of Problems (DRSP)	21 symptoms within 11 domains and 3 items for impairment, rated on a 6-point scale of severity	Physical and psychological	Self-report	User-friendly	Prospective	High validity, reliability, and sensitivity	Endicott et al. (1996) and Endicott et al. (2006)	[38]
Prospective Record of the Impact and Severity of Menstruation (PRISM)	Requires punctuation on life events, concurrent medications, and menstrual bleeding – 8-point scale of severity	Physical and psychological	Self-report	One page calendar	Prospective	Validated	Reid (1983)	[40]
Premenstrual Assessment Form (PAF)	95 items, rated on a 6-point scale of severity	Physical and psychological during the last 3 cycles	Self-report	Lengthy, less user-friendly	Retrospective	Validated, reliable, high sensitivity, low specificity	Halbreich et al. (1982)	[41]
Penn Daily Symptom Report	17 items, rated on a 5-point scale of severity	Physical and psychological	Self-report	>2 min/day	Prospective	Validated, good reliability	Freeman et al. (1996)	[43]

(continued)

Table 1 (continued)

Screening tool	Number of items and scale of severity	Symptoms measured	Self-report or observer	Time to complete	Current, retrospective, or prospective	Psychometric properties	Study (year)	Ref
Daily Assessment Form	33-item checklist, rated on a 6-point scale of severity	Physical, psychological, and lifestyle of 2 cycles	Self-report	>5 min/day	Prospective	Not well validated	Rivera-Tovar and Ellen (1990)	[42]
Calendar of Premenstrual Experiences	10 physical symptoms and 12 behavioral symptoms, rated on a 4-point scale of severity	Physical and psychological	Self-report	>2 min/day	Prospective	High reliability, good predictive/ concurrent validity	Mortola et al. (1990)	[44]
Composite International Diagnostic Interview for Women (CIDI-VENUS)	A systematic and comprehensive interview for females	Female-specific questions in mental disorders and women-specific conditions, e.g., menstruation, perinatal, and menopause	Clinician administered	Lengthy	Current	Help in the epidemiological and research studies	Martini et al. (2009)	[27]
Carolina Premenstrual Assessment Scoring System (C-PASS)	A scoring system for ratings on the DRSP. It is available as a manual worksheet as well as a computerized form (Excel macro and SAS macro)	Physical and psychological. Requires ratings for 2 cycles	Self-report of the DRSP scale	Needs experience in using electronic instruments	Prospective	Not yet validated. Needs additional work to examine the validity of its diagnostic threshold	Eisenlohr-Moul et al. (2017)	[37]

Table's design adopted from Hall and Steiner [33]

Table 2 Scales for screening and monitoring symptoms during the perinatal period

Screening tool	Number of items and scale	Symptoms measured	Self-report or observer	Time to complete	Current, retrospective vs prospective	Psychometric properties	Study (year)	Ref.
Edinburgh Postnatal Depression Scale (EPDS)	4-point scale of severity	Emotional and cognitive+ one item on sleep	Self-report	<5 min	Retrospective	Moderate-to-good reliability; sensitivity 59–100%, specificity 49–100%, PPV 73%	Cox et al. (1987)	[52]
Pregnancy Risk Questionnaire	18 items that lists psychosocial risk factors for postnatal depression	Psychological, stress, social and life events	Self-report	User-friendly	Retrospective and current	In an original validation study, sensitivity was 44% with a positive predictive value of 23%	Austin et al. (2005)	[56]
Postpartum Depression Predictors Inventory (PDPI)	Clinical checklist	Psychological, stress, social supports, and marital satisfaction	Observer	User-friendly	Current	No psychometric properties	Beck (1998)	[57]
Postpartum Depression Screening Scale (PDSS)	35 items on 7 symptom subscales, scale of 1–5 for agreement or disagreement with each item (score range 35–175 with cut-off of 80 for MDD)	Physical and psychological	Self-report	5–10 min to complete, written at seventh grade level	Retrospective	Good construct/content validity, reliability; sensitivity 91–94% and specificity 72–98%; checks for inconsistent response patterns	Beck and Gable (2000)	[58]
Postpartum Specific Anxiety Scale (PSAS)	51-item measure of postpartum-specific anxiety. The optimal cut-off PSAS score for detecting clinical levels of anxiety/depression was 112	Psychological and psychosocial adjustment	Self-report	User-friendly	Retrospective and current	Recently validated, with a sensitivity and specificity of 0.75 and 0.31, respectively. Excellent stability over 6 months postpartum	Fallon et al. (2016)	[63]
Patient Health Questionnaire (PHQ-9)	Screening for mental disorders, 3-page questionnaire. A fourth page has been added that includes questions about menses, pregnancy, childbirth, and recent psychosocial stressors	Measures functional status; disability days; health-care use; and treatment/referral decisions and physical symptoms	Self-report	1–5 min	Retrospective	A useful screening tool. Kappa = 0.65; overall accuracy, 85%; sensitivity, 75%; specificity, 90%	Spitzer (1999)	[66]

(continued)

Table 2 (continued)

Screening tool	Number of items and scale	Symptoms measured	Self-report or observer	Time to complete	Current, retrospective vs prospective	Psychometric properties	Study (year)	Ref.
Generalized Anxiety Disorder Scale (GAD-7)	A 7-item self-rating scale for screening of GAD and its severity	Psychological	Self-report	<2 min	Retrospective	Valid and efficient	Terrill et al. (2015)	[66]
Mood Disorder Questionnaire (MDQ)	Is a 13-item questionnaire	Designed to screen for bipolar spectrum disorders	Self-report	Brief/single page	Retrospective	Internal consistency of 0.90 which provided a sensitivity of 0.73 and a specificity of 0.90	Hirschfeld et al. (2000)	[69]
Perinatal Obsessive-Compulsive Scale (POCS)	Has 2 scales: A severity scale: 10 questions and an interference scale: 12 questions. Scores ranges from (0–4) for each scale with a total score ranging from 0 to 48	Obsessive thoughts and behaviors during pregnancy/postpartum (2 versions)	Self-report	Brief	Current. Useful screening tool	High internal consistency, good concurrent validity, and discriminative capacity	Lord et al. (2011)	[78]

Table 3 Scales for screening and monitoring symptoms during the perimenopause

Screening tool	Number of items and scale of severity	Symptoms measured	Self-report or observer	Time to complete	Current, prospective, or retrospective	Psychometric properties	Study (year)	Ref.
Greene Climacteric Scale	21 symptoms, 4-point scale of severity	Psych., somatic, and vasomotor	Self-report	<5 min	Current	Good reliability, content/construct validity	Greene (1976)	[83]
Menopause Rating Scale (MRS I and II)	11 symptoms, 5-point scale of severity. (MRS II) updated to include anxiety symptoms	Psych., somato-vegetative, and urogenital	Self-report	User-friendly/ easy to understand	Current	Validated, highly reliable	Hauser et al. (1994) (I) and Potthoff et al. (2000)	[85, 86]
Menopause-Specific Quality of Life (MENQOL)	30-item questionnaire, 4 domains, 7-point scale of severity + quality of life	Psych. and phys. including vasomotor/sexual	Self-report	Average of 7 min to complete	Retro.	Good reliability and face/content validity	Hilditch et al. (1996)	[88]
Menopause Severity Inventory (MSSI-38)	38 items, 12 sets of symptoms, frequency and severity of symptoms measured on a 5-point scale	Psych. and phys. including vasomotor	Self-report	~5 min	Retro.	Good construct/ criterion/external validity, good reliability and sensitivity	Pimenta et al. (2012)	[91]
Midlife Women's Symptom Index (MSI)	88 dichotomous yes/no symptoms, if yes, rank on a 5-point severity scale	Psych. and phys. including vasomotor	Self-report	Lengthy questionnaire	Retro.	Good internal consistency, reliability, convergent/construct validity	I m E.O. (2006)	[89]
Everyday Complaint Checklist	16 symptoms, menopausal symptoms, yes/no response	Psych. and phys. including vasomotor	Self-report	Easy to complete, user-friendly	Retro.	Used in cross cultural comparisons	Avis et al. (1993)	[90]

Form [42], the 17-item Penn Daily Symptom Report [43], and the 22-item Calendar of Premenstrual Experiences [44]. All of these tools measure both psychological and physical symptoms.

Scales for Screening and Monitoring Symptoms During Perinatal Period

After more than two decades of research, it is now clear that the risk for affective disorders in women is at least as high, if not higher, during the perinatal period as at other times [45, 46]. The perinatal period may be associated with adverse outcomes and may have negative impacts on women's mental health, her baby, and her family. Even though only a few instruments have been developed especially for this subpopulation, there is growing body of evidence suggesting that close, continued monitoring of symptoms and of the conditions most commonly present in this period via the use of self-report questionnaires may improve decision-making and help indicate specialized treatment as early as possible whenever necessary [47].

While many researchers have hypothesized that heritability and physiological fluctuations in sex hormone milieu that occur during pregnancy and the postpartum period contribute to this vulnerability [48–49], other lines of evidence have pointed to critical roles for non-biological risk factors such as lack of social support, relationship difficulties, and stressful life events [50]. Most researchers and clinicians agree that perinatal mood changes are probably best accounted for by a combination of biological and psychosocial risk factors [51]; however, this hypothesis has yet to be empirically tested.

Although the *Edinburgh Postnatal Depression Scale (EPDS)* [52–54] was the first scale built to screen for postpartum depression, it is useful to detect depression during pregnancy [46–47] and postpartum. The EPDS is a self-report tool that contains 10 common symptom questions of depression and uses Likert-type responses. The mother chooses the answers that best describe how she has felt in the past week. At a cutoff score of 13 for identifying MDD, the sensitivity of the English-language EPDS ranges from 0.67 (95% CI, 0.18–0.96) to 1.00 (95% CI, 0.67–1.00), with most of the results between 0.75 and 0.82. The specificity of the English-language EPDS was 0.87 or greater in all studies. Sensitivity for detecting depressive disorders, including both major and minor depression, using the cutoff of 10 or greater ranged from 0.63 (95% CI, 0.44–0.79) to 0.84. At a cutoff score of 10, a study of low-income African American women reported sensitivity of 0.84 (95% CI, 0.69–0.94) and specificity of 0.81 (95% CI, 0.70–0.89) for identifying major or minor depression in pregnant and postpartum women combined. The estimates were very similar for pregnant and postpartum women [55].

The EPDS also appears to detect perinatal anxiety disorders. Three items (questions 3–5) – anxiety subscale score (EPDS-3A) – may be useful for detecting anxiety in women with a cut-off score of six [55].

The Pregnancy Risk Questionnaire is a scale of 18 items that lists psychosocial risk factors for depression post childbirth. In an original validation study, sensitivity was 44% with a positive predictive value of 23% [56]. These figures seem quite reasonable for an instrument of prediction. Another scale for the same purpose is the *Postpartum Depression Predictors Inventory*, a checklist that should ideally be completed in each of the three trimesters of pregnancy and also assesses psychosocial risk factors [57].

The *Postpartum Depression Screening Scale (PDSS)* was developed by Beck and Gable [58] for tracking postpartum depression. It is a self-assessment Likert-type scale. The instrument has 35 items that cover seven dimensions: sleep/appetite disorders, anxiety/insecurity, emotional lability, cognitive impairment, loss of self, guilt/shame, and intent to harm oneself. Each dimension is composed of five items that describe how a mother may be feeling after the birth of her baby [51]. A study was carried out comparing the PDSS Performance with the EPDS [59]. A total of 150 postpartum mothers completed the two instruments and then had a DSM-IV diagnostic interview. Eighteen of these women (12%) were

diagnosed as having major postpartum depression, 28 (19%) minor postpartum depression, and 104 (69%) had no depression. Using cut-off scores for major depression recommended in the publications of the two instruments, the PDSS achieved the best combination of sensitivity (0.94) and specificity (0.91), among the three scales. The PDSS identified 17 of the women (94%) diagnosed with postpartum depression and the EPDS, 14 of these women (78%). The observed sensitivity differential can be because PDSS addresses other components of this mood disorder.

A variety of self-report questionnaires have been developed to assess anxiety symptoms relating to the gestational period and common concerns and adjustment issues to motherhood [60–62]. These measures include constructs such as fear of childbirth, fetal health and well-being, changes in appearance, and interpersonal roles.

The *Postpartum Specific Anxiety Scale (PSAS)* [63] is a new and recently validated 51-item measure of postpartum-specific anxiety. A sample of 1282 mothers of infants up to 6 months old were enrolled online in order to preliminarily evaluate the performance of the PSAS in distinguishing between those with and without a current clinical diagnosis of anxiety/depression. The optimal cut-off PSAS score for detecting clinical levels of anxiety/depression was 112 with a sensitivity and specificity of 0.75 and 0.31, respectively. When compared to the recommended cut-off scores for the other included anxiety measures, PSAS performed marginally better than the EPDS-A, which identified 73% of cases, and better than the state form of the State-Trait Anxiety Inventory Scale (STAI-S), which detected 63% of cases. However, it did not perform as well as the trait form (STAI-T), which identified 86% of cases. Test-retest reliability of the PSAS for a subsample of participants (n = 262) who repeated the PSAS 2 weeks after the initial administration was 0.88 ($p < 0.001$), indicating excellent stability over time in the first 6 months postpartum.

An American study tested the *Beck Depression Inventory (BDI)* – a scale for general depression – during pregnancy and obtained the following result with cutoff point at 16: sensitivity of 0.83, specificity of 0.89, 0.50 positive predictive value, and 0.98 negative predictive value [64]. The study probably had a low positive predictive value because the BDI contains items of physical symptoms that were confused with a healthy pregnancy.

The *Patient Health Questionnaire (PHQ-9)* [65] and *Generalized Anxiety Disorder Scale GAD-7* [66] are self-administered instruments developed to quickly assess and monitor depressive and anxiety symptoms in adults. The psychometric properties of PHQ-9 were examined in a sample of 81 pregnant and 104 postpartum patients (n = 185) who met the criteria for major depressive disorder (MDD) based on clinician diagnoses, as compared those without any mood disorder diagnosis. Using commonly recommended cut-off scores, both measures had comparable sensitivity and specificity: sensitivity of 0.80 and 0.92 for EPDS, 0.74 and 0.89 for PHQ-9 during pregnancy and postpartum, respectively; and specificity of 0.74 and 0.53 for EPDS, 0.73 and 0.65 for PHQ-9 during pregnancy and postpartum, respectively [67]. The benefit of adopting PHQ-9 is that it may be more readily compared to results from screenings in primary care and other medical units or clinics where the PHQ-9 is used instead of perinatal-specific measures.

Psychometric properties of the *GAD-7*, a 7-item self-rating scale, were tested in a population of 240 perinatal women (n = 155 pregnant and n = 85 postpartum) referred for psychiatric consultation. The GAD-7 yielded a sensitivity of 0.61 and a specificity of 0.72 at an optimal cut-off score of 13 in this Canadian study [68]. Compared with the EPDS and the *EPDS-3A subscale*, the GAD-7 displayed greater accuracy and specificity over a greater range of cut-off scores and more accurately identified GAD in patients with comorbid MDD.

The Mood Disorder Questionnaire (MDQ) is a 13-item self-report questionnaire designed to screen for bipolar spectrum disorders using DSM-IV criteria. Each item describes a symptom or behavior characteristic of mania (e.g., racing thoughts, increased energy) and asks respondents

to indicate whether there has been a period in their lives when they have experienced these issues. A response of "yes" is scored as a positive indication of a bipolar spectrum disorder. Psychometric evaluation of the scale found an internal consistency of 0.90, which provided a sensitivity of 0.73 and a specificity of 0.90 [69].

In a subsequent study, the scale was evaluated as a measure for screening within the general population and found an internal consistency of 0.84, a sensitivity of 0.28, and a specificity of 0.97. [70]. In samples of pregnant and postpartum women, the MDQ was shown to be useful using cutoff scores of 7 or more symptoms without the supplementary questions, yielding excellent sensitivity (0.89) and specificity (0.84) [71]. Findings from two other studies also support screening with the MDQ alone or in combination with EPDS and modified MDQ scoring to maximize detection of bipolar disorder among these high-risk patients. However, this modified scoring has not yet been rigorously validated [72–73].

The Perinatal Obsessive-Compulsive Scale (POCS) was the first questionnaire developed to specifically assess obsessions and compulsions during the perinatal period. Studies indicate that women are at an increased risk of OCD onset or worsening during postpartum [74–75], and evidences suggest that up to 50% of women suffering from OCD recall onset or worsening of their symptoms during the perinatal period [76–77]. Nevertheless, while there are several existing scales to measure OCD symptoms and severity, their appropriateness has not been established during the perinatal period. The POCS is a self-report questionnaire that determines symptom severity and rates how much interference symptoms are causing in daily life [78].

Scales for Screening and Monitoring Symptoms During Perimenopause

Although the menopause is a physiological event, community-based surveys and prospective observational studies strongly suggest that the menopausal transition is a time of increased vulnerability not only for recurrence of MDD but also first onset episode of depression [79–81]. Perimenopause is usually accompanied by physical and emotional changes that can negatively affect women's quality of life, which include mood and sleep disturbance, vasomotor symptoms, and decreased sexual function. Moreover, hot flashes and night sweats are independent factors for the risk of developing a depressive episode [82]. Thus, it is critical to have screening tools available to monitor both physical and psychological symptoms during perimenopause.

The *Greene Climacteric Scale* [83] is a self-report questionnaire that provides a brief measure of a total of 21 physical and psychological symptoms associated with the menopause transition. Each symptom is rated by the respondent according to its severity using a four-point scale: not at all (0); a little (1); quite a bit (2); and extremely (3). Items 1–11 address psychological symptoms including anxiety (items 1–6) and depression (items 7–11). Examples include "difficulty in sleeping" and "feeling unhappy or depressed." Items 12–18 assess somatic symptoms, including "headaches" and "muscle and joint pains." Vasomotor symptoms (hot flushes, sweating at night) are assessed by items 19 and 20, while item 21 is a probe for loss of interest in sex. The total Greene Climacteric Score is the sum of all 21 scores. Acceptable test-retest reliability coefficients for the three subscales have been reported and ranged from 0.83 for the vasomotor scale to 0.87 for the psychological scale. The GCS can be used to screen symptoms and monitor changes during treatment [84].

The *Menopause Rating Scale (MRS)* is a health-related quality of life scale that was developed in the early 1990s aiming to measure the severity of aging symptoms and their impact on the quality of life in women. The MRS is a self-rating scale that consists of a list of 11 items comprising three independent dimensions: psychological, somato-vegetative, and urogenital symptoms. Each of the eleven symptoms contained in the scale can get 0 (no complaints) or up to 4 scoring points (severe symptoms) depending on the severity of the complaints perceived by the women completing the scale [85–86]. This is a

practical screening tool and has high reliability and applicability [87].

The *Menopause-Specific Quality of Life (MENQOL)* is a self-administered questionnaire with potential to determine differences in quality of life between menopausal women and to measure changes in their quality of life over time. This 30-item retrospective instrument includes the assessment of physical, psychological, and social changes and has a good reliability and validity [88]. Other tools include the Midlife Women's Symptom Index (MSI) [89], the Everyday Complaint Checklist [90], and the Menopause Symptoms' Severity Inventory (MSSI-38) [91].

Conclusions

In the field of women's mental health, screening tools are valuable for both clinical research and clinical practice. In general practice, scales can be used to screen female-specific conditions either by self-administered or clinician-administered instruments. They can assist the diagnosis, improve decision-making, and help indicate if specialized treatment is needed.

Screening tools may be required to some diagnoses, as PMDD, and are extremely useful to monitor quality of life, symptom severity, and treatment response. When properly constructed and in parallel with adequate psychometric properties, they can be an accurate reflection of the person's actual state, thus promoting a more efficient clinician-patient communication. Finally, screening tools are a key to help the understanding of women's mental health topics.

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Schizophrenia in Women

Mario R. Louzã and Helio Elkis

Introduction

Gender differences in schizophrenia have been described since Kraepelin in the early twentieth century. Since then, numerous studies reported that women (in general) have several differences in comparison to men, in relation to various aspects of the disorder. Many "older" reviews and books can be suggested for those interested in this theme [1–4].

In this chapter, we concentrate our review on the more recent (last 15 years) literature about the different aspects of schizophrenia in women compared to men.

Incidence and Prevalence

An overview of the incidence (per 100,000/year) of schizophrenia showed a median of 15.2/100,000 and a mean (±standard deviation) was 23.7 (±30.3). Males had a median incidence of 15.0 and a mean of 21.8 (±27.4); for females, the median and the mean were 10.0 and 21.3 (±45.1), respectively. The median lifetime prevalence (per 1,000) was 4.0 and the mean, 5.5 (±4.5). The median lifetime prevalence by gender was 3.7 and 3.8, the mean 4.9 (4.5) and 4.8 (3.8) for males and females, respectively [5].

A meta-analysis of studies of the incidence of schizophrenia in England, between 1950 and 2009, showed an overall incidence of 15.2 persons per 100,000 per year. There was a higher rate of incidence in men before 45 years old (hazard ratio: 1.99), but no difference was observed after 45 years (hazard ratio: 0.98) [6].

Van der Werf et al. [7] considered that men had a 1.15-fold higher rate of incidence of schizophrenia than women. The incidence was higher for men in the age of 20–29 years, then decreased quickly, while the incidence in women had a broader incidence curve declining slowly with age (Fig. 1).

Age of Onset

Studies in the 1980s and 1990s showed that men had an age of onset around 4 years earlier than women [4]. Nevertheless, Eranti et al. [8] in a meta-analysis of the relationship between gender and age at onset of schizophrenia concluded that males had a first admission 1.07 years earlier than females. Males also had an earlier age at first symptom (1.63 years), first positive symptom (1.43 years), and first consultation (1.22 years). This difference was observed in studies that used DSM criteria; no difference occurred when the

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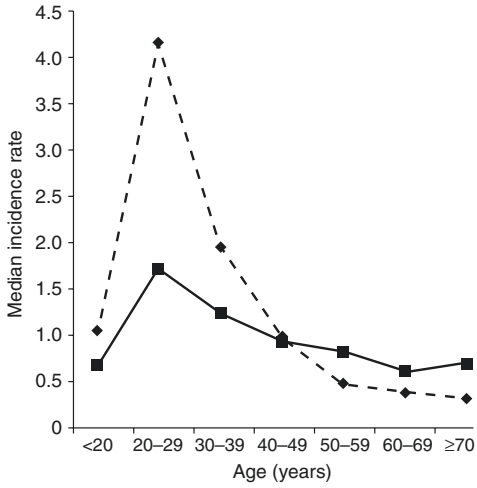

Fig. 1 Incidence rates by age of schizophrenia. (From Ref. [7]. With permission from Cambridge University Press)

studies used ICD criteria. They did not find a gender difference when comparing developed and developing countries.

Premorbid Adjustment and Ultra-High-Risk Individuals ("Prodromal Phase")

A good premorbid adjustment is usually related to a better prognosis in schizophrenia. Usually, female patients had no or few premorbid impairments in comparison to male patients. A poor premorbid adjustment is already observed during childhood in males. They may show a delay in the milestones of motor and language development; they may also have a poorer performance in school. In the adolescence, a poor academic performance may continue, and they also show social difficulties in the interaction with female peers [9].

Gender differences were also observed in individuals at ultra-high risk for the development of psychosis. The duration of untreated illness was shorter for women than men. Men had more negative symptoms than women before the manifestation of psychotic symptoms; on the other hand, females showed more affective symptoms [10]. Cotter et al. [11], in a systematic review of cross-sectional and longitudinal studies, did not find a relationship between gender and functioning in ultra-high-risk subjects in most of the studies, although one study reported that males had a poorer social and role functioning.

Cascio et al. [12], in a meta-analysis, did not find a significant gender difference in relation to the duration of untreated psychosis. In their study, the mean age of the first contact was 25.4 years for male and 27.5 years for female subjects. The mean duration of untreated psychosis was 64 weeks.

Neurobiology

Gender differences in the genetic risk of schizophrenia show inconclusive results. Molecular genetic studies reported male-specific candidate genes; on the other hand, GWAS studies reported female-specific genes [13].

Obstetric complications are more common in male than females with schizophrenia. Prenatal exposure to influenza, on the second trimester of pregnancy, was related to the development of schizophrenia in females. Sex differences in brain anatomy are reported in neuroimaging studies; males usually have a larger VBR (ventricular-brain ratio) and reduced temporal and frontal lobes in comparison to females [14]. Nevertheless, a recent meta-analysis of brain volumes in schizophrenia shows only a significant reduction of intracranial volume, more pronounced in male patients with schizophrenia, with a similar reduction in white matter volume. These observations point to a neurodevelopmental origin of schizophrenia that might have a different impact in male and female brains of future patients with schizophrenia [14, 15].

Studies of cognitive performance in schizophrenia have shown that males have some advantages, and disadvantages, in different cognitive domains in comparison to females. Some of these gender differences occur also in healthy controls so that they are gender- rather than disease-specific differences. Females (healthy or with

schizophrenia) had a better performance in verbal learning and memory; males, in visual tasks, including spatial memory and organization. Some studies demonstrated that male and female patients have different cognitive profiles specific to schizophrenia, not seen in healthy controls, while others did not find gender differences in cognitive domains in schizophrenia. These differences might be related to various aspects of the design of the studies (including the stage of the menstrual cycle, use of hormonal contraception, use of antipsychotics) [16].

Using de MATRICS battery, Zhang et al. [17] observed that male patients with chronic schizophrenia showed more cognitive impairments on reasoning and problem solving, social cognition, processing speed, and working memory than female patients with the disorder. They also had a worse performance in verbal and visual learning than females. On the other hand, reasoning and problem solving were not different between males and females with schizophrenia.

Savla et al. [18] in a meta-analysis found no gender difference in relation to various aspects of social cognition (theory of mind, social perception, social knowledge, attributional bias, emotion perception, and emotion processing) impairments in schizophrenia.

Estrogens and Schizophrenia in Women

Several characteristics of schizophrenia in women are explained by the influence of estrogens. Estrogens are considered to have a protective role in various aspects of the disorder, probably for their (weak) antidopaminergic effect. Psychosis (even in healthy individuals) can occur when for any reason estrogen levels are diminished, for example, premenstrual, postabortion, discontinuation of contraceptives, menopause, and administration of tamoxifen and other estrogen receptor antagonists [19]. Gender differences in schizophrenia seem to be less apparent in patients with an important genetic load or with significant perinatal complications so that in these cases, the presence of estrogens is less (or not) important for the development of schizophrenia.

Although less studied, there may be also a possible role of progesterone (a precursor of estradiol) in schizophrenia in women. It may also modulate neurotransmitter systems related to schizophrenia, but further research is needed to understand the interplay between progesterone and estradiol in schizophrenia [20].

There is also an important interplay between estrogens and prolactin, as hyperprolactinemia (either in drug-naïve patients or induced by antipsychotics) reduces levels of estrogens, further contributing to the emergence of psychosis [19, 21].

Clinical Features

Symptom expression may be different in male and female patients with schizophrenia in part due to the later onset of the disorder in females. In general, women have more affective and anxiety symptoms while men, more negative symptoms [3, 4].

An Australian epidemiological study of the prevalence of psychotic disorders showed differences in symptom profiles according to gender [22] (Fig. 2).

Male sex is, among others, a risk factor for suicide in schizophrenia. The difference between male and female risk is not so large as in the general population, and some studies did not show a sex difference in suicide rates in inpatients [23].

Studying the impact of defeatist performance beliefs (DPB; negative thoughts about one's ability to successfully perform a goal-directed behavior that can impair or prevent behavior initiation and engagement) on negative symptoms and functional outcome, Campellone et al. [24] observed that DPB influenced both negative symptoms and functional outcome, so that higher scores on DPB implicated in more negative symptoms and worse functional outcome. The relationship between DPB and negative symptoms was not influenced by sex; on the other hand, male sex implicated in a stronger relationship between DBP and functional outcome.

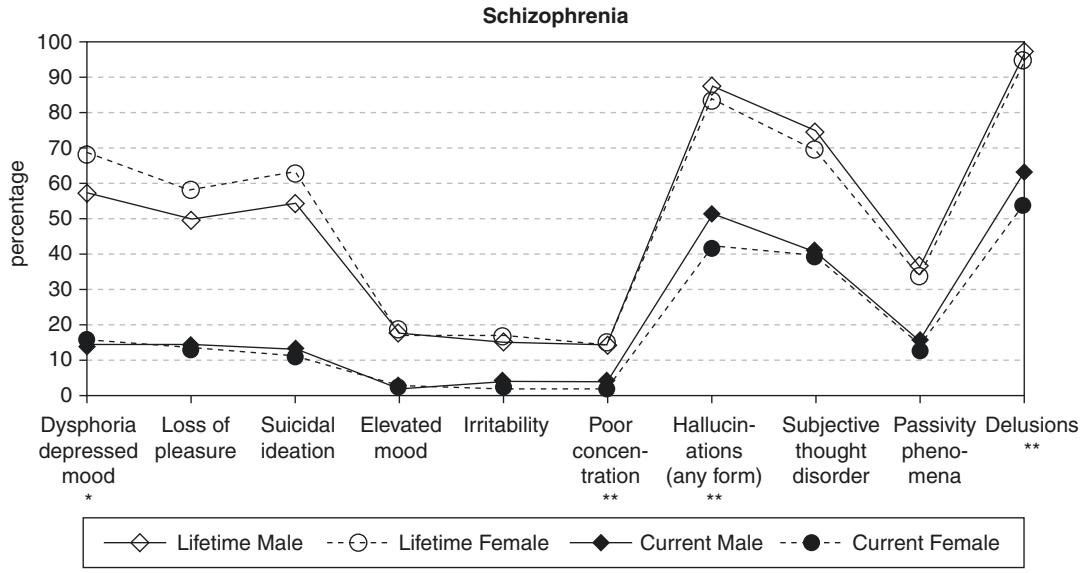

Fig. 2 Symptom profile (current and lifetime) according to gender [22]. (With permission from SAGE Publications. Legend: significant differences ($p < 0.05$); ∗lifetime, ∗∗current)

Course and Outcome

The long-term outcome of schizophrenia is heterogeneous, varying widely from full remission to severe chronic states. Lang et al. [25] reviewed studies of long-term outcome (defined as >5-year follow-up) and concluded that males had a poorer outcome than females. Other predictors of poor outcome (independently from gender) were negative symptoms, cognitive impairment, social isolation, repeated hospitalizations, and a longer duration of untreated psychosis. The rates of remission (varied definitions) in the studies ranged from 7% to 52%.

About 11–18% of the patients have their first episode psychosis before the age of 18 (so-called early-onset psychosis); this subgroup is considered to have a poor prognosis. A systematic review of early-onset psychosis (including schizophrenia, first episode psychosis, schizophrenia spectrum disorders, and psychotic bipolar disorder) did not find a consistent relationship between gender and prognosis. Although there were no differences between gender and the prognosis itself, in some studies, females had a better insight and a higher number of hospitalizations, a better global functioning, less chronic course, more frequent remission, less likelihood of taking clozapine, and less gray matter loss at follow-up. The presence of premorbid impairments, insidious onset, long duration of untreated psychosis, and negative symptoms (independently of the diagnosis) were strong predictors of poor outcome [26].

Ordóñez et al. [27] studied a sample of 133 patients with childhood-onset schizophrenia (age of onset <13 years) and found no differences between male and female patients in relation to demographic features (except a slightly younger age of onset in males), IQ, clinical aspects, premorbid functioning, and magnetic resonance imaging brain measures.

Stentebjerg-Olesen et al. [28] reviewed the literature on early-onset schizophrenia spectrum psychosis (mean age at baseline <19 years). The mean age of onset was 14.5 years (range: 7.7–16.5 years), and they found no significant effect of gender on the course and outcome (mean follow-up: 2.2 ± 1.7 years; range: 0.2–6.9 years). Even though no rates of clinical remission are reported in the study, the authors show that in the follow-up studies, both symptoms (measured by the PANSS and CGI-severity of illness scales) and functioning (measured by GAF or CGAS scales) improved significantly. The severity of positive symptoms at baseline, severity and persistence of

negative symptoms, longer duration of untreated psychosis, and poor premorbid adjustment were predictors of a worse outcome. They did not separate early-onset from childhood-onset patients.

The rates of recovery (defined as clinical remission and good social functioning, both persisting for at least 2 years) were similar for women and men (a median of 12.9% and 12.1%, respectively) [29].

Treatment

Pharmacological Treatment: General Principles

Antipsychotics represent the mainstay of treatment of schizophrenia regardless of gender differences. These agents are generally subdivided into the so-called first-generation (FGA) and second-generation antipsychotics (SGA). Table 1 depicts the most common antipsychotics used for the treatment of schizophrenia (based in part in [30]) as well as their main side effects.

FGA block dopamine receptors, particularly D_2 and D_3 receptors, while most SGA block D_2 receptors and serotonin receptors, particularly $5HT_1$ and $5HT_2$, as well as muscarinic and histaminergic receptors [31]. The dopaminergic blockage is related to its efficacy, particularly in terms of reduction of psychotic symptoms. However, the D_2 blockage is related to the appearance of extrapyramidal symptoms (EPS) and hyperprolactinemia. Blockage of 5HT receptors is related to efficacy as well as reduction of liability EPS. Weight gain is, among other mechanisms, related to receptor H_1 binding [32].

Table 1 Commonly used antipsychotics for the treatment of schizophrenia

Antipsychotic	Daily recommended doses (mg)	Main side effects
First generation		
Chlorpromazine	100–1000	Sedation, hypotension, anticholinergic side effects
Haloperidol Haloperidol decanoate (long acting injectable)	5–20 50 mg generally given intramuscular biweekly or monthly	Extrapyramidal symptoms (EPS)
Zuclopenthixol Zuclopenthixol long acting injectable	20–60 150–300 mg every 2–4 weeks	EPS
Second generation		
Amisulpride	200–600	Hyperprolactinemia
Clozapine	100–800	Serious: agranulocytosis; myocarditis/ cardiomyopathy; orthostatic hypotension; seizures. Others: fever, sinus tachycardia, neuroleptic malignant syndrome; weight gain and metabolic syndrome(MS), constipation, sedation, hypersalivation, enuresis
Risperidone (oral) Long-acting injectable risperidone	2–8 25–50 mg intramuscular biweekly	EPS, hyperprolactinemia, MS
Olanzapine	10–30	MS
Quetiapine	300–800	Sedation, MS
Ziprasidone	120–160	Sedation, QTc prolongation
Aripiprazole	10–30	EPS
Lurasidone	40–80	EPS
Paliperidone Long acting injectable paliperidone	6–12 50 mg, 75 mg, 100 mg, and 150 mg, intramuscular injection (initial dose 150 mg, after 8 days 100 mg; thereafter flexible doses every 4 weeks)	Somnolence, tachycardia, hypotension, hyperprolactinemia

Based on Ref. [30]
EPS Extrapyramidal symptoms, *MS* Metabolic syndrome, weight gain, dyslipidemia, hyperglycemia

Other important side effects related to the use of antipsychotics are the development of metabolic syndrome (MS) mainly characterized by weight gain, dyslipidemia, hyperglycemia, as well as arrhythmias with QTc prolongation, cardiovascular death, and, in the case of clozapine, seizures, blood dyscrasias, and cardiomyopathy [33].

Seeman [34] reviewed extensively the risks of secondary effects of antipsychotics in women and observed that they are much more susceptible of developing weight gain and tardive dyskinesia as well as cardiovascular arrhythmias or even death when compared with men.

Several guidelines recommend that patients should be treated in monotherapy and should start using an SGA for 4–6 weeks since these antipsychotics have a better tolerability in comparison with FGA, particularly in terms of EPS, but the use of an FGA is also recommended [35].

Responsive patients are those who achieve a substantial reduction of symptoms, particularly psychotic symptoms (e.g., severe to mild) either by clinical observation or, preferably, using standard scales such as the Brief Psychiatric Rating Scale (BPRS) or the Positive and Negative Syndrome Scale (PANSS) [36]. Patients are considered to have achieved remission when, after 6 months, symptoms reached a mild intensity with no impact on patient's behavior [37].

If the patient responds, he/she should be maintained under treatment with the antipsychotic previously used, and if not, the patient should undertake a second trial, with a different antipsychotic than the one previously used in the first treatment. This second trial should also last at least 4–6 weeks with adequate doses, and if the patient responds, he/she should be maintained with this second antipsychotic indefinitely since it well established that a patient with schizophrenia when treatment is discontinued will relapse in 3 years [38].

In the case of first-episode patients (FEP), some studies have shown that for those who achieved recovery (symptom remission plus functional recovery), supervised discontinuation could bring benefits for some patients [39, 40], but systematic reviews have shown that discontinuation of medication in FEP brings a risk of relapse and a more conservative approach (i.e., antipsychotic maintenance) is recommended [41].

Patients should be treated with monotherapy, i.e., using only one antipsychotic. However, when there is little or no response to antipsychotics, it is common to add another antipsychotic to the one which is presently use, and this procedure is denominated antipsychotic polypharmacy, which is not recommended due to the absence of evidence of efficacy as well as an increased risk of mortality [42].

In fact, almost all guidelines recommend that when patients fail to respond to 2 antipsychotics trials of 4–6 weeks of duration, with adequate doses, and show little or no improvement in terms of reduction of severity of symptoms, particularly psychotic symptoms, such patients are defined having treatment-resistant schizophrenia (TRS) [43], and, in these cases, clozapine is the drug of choice for such condition due to plenty of evidence of efficacy [44].

However, due to the risk of 1.3% of agranulocytosis, clozapine must be administered under hematological surveillance, i.e., weekly blood counts during the first 18 weeks and biweekly subsequently. Other serious risks of the use of clozapine are myocarditis or cardiomyopathy (0.02–1), orthostatic hypotension (9.0), and seizures (1.3–1.8), [33] but despite such risks, epidemiological studies have shown that clozapine is safer than other antipsychotics regarding mortality and suicide risk reduction [45, 46].

In the case of patients who lack adherence or if there are doubts about whether the patient has truly TRS, a trial with long-acting injectable antipsychotic (LAIA) is recommended [36, 47].

Particularities of Pharmacological Treatment of Schizophrenia in Women

Prolactin and Estrogens

It well established that there are differences regarding the development of schizophrenia in women since, as compared with men, they have a

later age of onset of illness and classically two peaks of incidence: 15–30 years and 45–50 years [48, 49].

This later onset is explained by the reduction of estrogen levels which provides evidence for the hypothesis that estrogen has a protective effect, which may elucidate the second peak of incidence and the development of late-onset schizophrenia, as well as the exacerbation of symptoms in women of schizophrenia when they reach menopause. Thus, during the perimenopausal period, there is an increased risk of developing psychosis for the first time an increased risk of relapse in women who already have schizophrenia [50].

Regarding treatment effects, women have lower levels of estrogen which nowadays are attributable to the use of antipsychotics, and it is well known that antipsychotics block dopamine which causes hyperprolactinemia, which increases the risk of osteoporosis and breast cancer [34, 50].

Therefore, it is recommended that, in general, women should be treated preferably with prolactin sparing antipsychotics such as aripiprazole, lurasidone, olanzapine, quetiapine, ziprasidone, or clozapine (in treatment-resistant cases) than with antipsychotics such as amisulpride, risperidone, or paliperidone, which are more prone to increase prolactin levels.

On the other hand, the estrogen protection hypothesis led attempts to such hormones as an antipsychotic augmentation strategy for antipsychotic treatment schizophrenia [51]. A meta-analysis carefully evaluated the efficacy of estrogens, as well as other sex hormones such as selective estrogen receptor modulators (SERMs) as raloxifene, testosterone, dehydroepiandrosterone (DHEA), and pregnenolone, shown to be effective on the reduction of severity of schizophrenia symptoms [52].

Additionally, a recent meta-analysis confirmed the efficacy of raloxifene on the reduction of severity of positive, negative, and total symptom in women as well as men with schizophrenia [53].

Menopause

Patients with schizophrenia generally experience worsening of symptoms of schizophrenia with menopause as well as a deterioration of their physical condition such as weight gain, dyslipidemias, osteoporosis, and increased risk of breast cancer, as happens with women without schizophrenia. However, it is necessary to bear in mind that the chronic use of antipsychotics may exacerbate such conditions and these women need even closer monitoring during this phase of life [50].

Pregnancy and Lactation

Women with schizophrenia do want to be pregnant and have children, as well women without such condition, and it is well known that during the pregnancy period, women with schizophrenia experience reduction of the severity of their psychiatric symptoms albeit a cohort study of 104 women found out that the interruption of medication leads to relapse, as generally happens with non-pregnant women of schizophrenia [50, 54, 55].

Current guidelines for the use of antipsychotic pregnancy and postpartum are not evidence-based, and it is known that the use of such substances during these periods brings the risk of teratogenic and neonatal complications, particularly in case of polytherapy, and therefore, the decision of maintaining or withdrawing these compounds during such periods is several times quite difficult [50, 56].

A meta-study of 63 quasi-randomized case-control studies identified that maternal schizophrenia remains predictive of prematurity and postpartum but, besides the use of antipsychotics, old age, smoking, and less antenatal care are also implicated [57].

The safety of antipsychotics during breastfeeding is also unknown, and clinicians must discuss and negotiate this issue with their patients since women with schizophrenia also desire to breastfeed their babies [50]. Certain guidelines, as is the case of the World Federation of Societies of Biological Psychiatry (WFSBP), recommend the use chlorpromazine or olanzapine since these antipsychotics have a low degree of excretion in the breast milk [56], and a recent systematic review of 21 different antipsychotics [58] proposed the following recommendations (Table 2).

Table 2 Recommendations for use of antipsychotics in breastfeeding patients with schizophrenia

Antipsychotics	Recommendation
Olanzapine and quetiapine	Acceptable use
Chlorpromazine, haloperidol, risperidone, and zuclopenthixol	Possible use under medical supervision
Aripiprazole, asenapine, clozapine, lurasidone, paliperidone, and ziprasidone	Not recommended

Adapted from Ref. [58]

Psychosocial Treatments

Psychosocial treatments seem to be equally effective in women and men, and the best evidence showed that the use of cognitive behavioral therapy, cognitive rehabilitation, and social skills training is very important for recovery, either for women with or without schizophrenia. Specific programs for parenting skills training are used for those mothers who have lost custody of their children [30, 50].

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Bipolar Disorder in Women: Menstrual Cycle, Perinatal Period, and Menopause Transition

Lauren F. Forrest, Mara Smith, Joao Quevedo, and Benicio N. Frey

Introduction

It is well known that differences exist between the genders as it pertains to the epidemiology, presentation, course, and management of bipolar disorder (BD). Given the fact that cases of pre-pubertal mania are exceedingly rare, it is very difficult to comment on gender differences in this population. Indeed, a 2014 review by Douglas and colleagues [1] pooled data from five studies ($n > 5000$) and reported only one case of probable mania in this population. After puberty, however, we do start to see gender differences emerge. While the prevalence, age of onset, and severity of BD are generally comparable between the genders in bipolar I disorder (BD-I) subjects, it is well known that women tend to experience more depressive and mixed episodes in addition to higher rates of bipolar II disorder (BD-II) than men [2]. Given they are more likely to present first with a depressive episode, this often results in an initial misdiagnosis of unipolar depression, subsequently delaying the diagnosis (and correct management) of bipolar disorder in women by about two years compared to men. It is also well established that women are more likely than men to be diagnosed with a BD-II and to experience rapid cycling [3]. The course of bipolar disorder also differs between the genders, with women being more likely to have a seasonal component to their illness, experiencing more depressive episodes during the autumn and winter months. Women are also more likely than men to report melancholic symptoms of depression, including hypersomnia, increased appetite, and weight gain. Indeed, more than half of women with bipolar disorder are overweight or obese, and this is known to have negative impacts on self-esteem, which may perpetuate depressive symptomatol-

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ogy. When manic, women are less likely than men to endorse hypersexuality, hyperactivity, or problem spending than their male counterparts. Furthermore, the burden of comorbidity differs between men and women, with women being more likely to suffer from eating disorders, post-traumatic stress disorder, and personality disorders than men. Gender differences are also seen with respect to medical comorbidities: double the risk of mortality from cardiovascular disease (CVD) is seen in women with BD than in the general population. This is likely due to a combination of increased risk factors for CVD (such as hypertension and dyslipidemia) but also to common comorbidities associated with increased risk for CVD such as smoking and obesity.

With respect to management considerations, women and men both appear to respond with equal rates to lithium pharmacotherapy, although women may respond to lower serum concentrations than men [2]. Drug interactions must also be considered for women, especially for those in the reproductive years. For instance, there are some significant drug-drug interactions between mood stabilizers and contraceptive agents: carbamazepine and oxcarbazepine are known to induce the metabolism of many drugs and can lower the levels of contraceptive pills, transdermal patches, progesterone-only pills, and progesterone implants, jeopardizing their efficacy. Alternatively, estrogen-based contraceptives can result in a decrease in circulating levels of valproic acid (VPA) and lamotrigine, thereby compromising their efficacy. In addition, many mood stabilizers, most notably VPA and carbamazepine, carry an increased burden for teratogenicity and therefore should ideally be avoided, or used with extreme caution, in women during the reproductive years [4].

As we will aim to delineate throughout the course of this chapter, there is evidence for an increase in BD episodes during key points in the female reproductive life cycle (e.g., during the pre-menstrual phase, pregnancy, the postpartum, and menopause). Estrogen is a key female reproductive hormone and is currently a major area of interest in BD [3]. This is evidenced nicely by the fact that four separate studies have now demonstrated that treatment with the selective estrogen receptor modulator (SERM) tamoxifen results in a significant decrease in manic symptoms compared to placebo [3]. Allopregnanolone is an endogenous neurosteroid derived from progesterone which is known to increase the activity of the inhibitory GABA-A receptor, resulting in antidepressant, anxiolytic, and sleep-promoting effects. Given that allopregnanolone levels have been found to be elevated in women with BD during euthymia compared to healthy control women and women with major depressive disorder, it has been postulated that this neurosteroid may serve as an endogenous mood stabilizer that is important in the pathophysiology (and perhaps treatment) of BD, especially in women [5]. A recent review by Frey and Dias [6] demonstrated how estrogen interacts with brain-derived neurotrophic factor (BDNF), oxidative stress, and inflammatory pathways. BDNF is a neurotrophin that has been implicated in neuronal maturation and differentiation, synaptic plasticity, and long-term potentiation in addition to learning and memory, among other things. BDNF function is known to be impaired in BD with peripheral BDNF levels being decreased during both depressed and manic phases and being negatively correlated with the severity of mood symptoms. There is evidence from animal models that estrogen can upregulate BDNF transcription. BDNF levels were found to be higher during the luteal phase and lower in the follicular phase of the menstrual cycle in healthy control women, but the opposite was found for women with the premenstrual syndrome. Estrogen-mediated effects on BDNF levels may therefore represent a kind of explanatory causal mechanism for some of the gender differences seen in the presentation and course of BD. Estrogen may also act as an antioxidant and anti-inflammatory agent, thereby improving cellular homeostasis. Notably, several reports suggest that estrogen replacement therapy may ameliorate cognitive dysfunction associated with the menopause transition [6].

In summary, women may face several challenges over the course of BD, including higher risk of mood instability during periods of hormonal fluctuations such as the premenstrual phase, pregnancy, postpartum, and menopause, as well as potential

gynecological side effects from psychotropic medications. In this chapter, we will summarize the main challenges and treatment approaches for women during these reproductive-related life events.

Bipolar Disorder and the Menstrual Cycle

Menarche marks the beginning of a woman's reproductive life and heralds the start of the monthly cyclical fluctuations in the reproductive hormones, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone, all of which are required for ovulation to occur. There is a growing body of evidence to suggest that a subgroup of women who suffer from BD may be more sensitive to the normal physiological fluctuations in hormones that occur over the course of the menstrual cycle and are therefore more prone to experiencing cyclical changes in mood in conjunction with the phases of the cycle.

There is a great deal of heterogeneity in the way that menstrual cycle phase may affect or exacerbate BD symptoms. A recent review of 25 studies on the potential effects of the menstrual cycle on BD showed that two-thirds of women with BD reported pre-menstrual exacerbation of hypomania or mania [7]. A review of 14 retrospective studies in this area reported that between 25 and 77% of women with BD experience the premenstrual syndrome (PMS), which can include an increase in somatic (e.g., breast tenderness, bloating, muscle aches) and/or psychological symptoms (e.g., mood lability, irritability, sensitivity to rejection) during the luteal phase of their menstrual cycle which improves with the onset of menses. The aforementioned retrospective studies identified and reviewed by Teatero and colleagues (2014) [7] also suggest that 15–27% of women with BD suffer from a comorbid premenstrual dysphoric disorder (PMDD), meaning their premenstrual somatic and psychological symptoms are so severe that they result in significant distress and/or functional impairment. This is a notably much higher incidence rate of PMDD than that seen in non-clinical samples of the general population, which is around 3–9% [8]. Several reports also describe increased suicidal ideation and psychotic symptoms during the premenstrual phase. The luteal phase of the menstrual cycle is known for a precipitous drop in the reproductive hormones estradiol and progesterone, which is thought to trigger the emergence of PMS and PMDD symptoms. It is hypothesized that a significant proportion of women with BD are more sensitive to this normal fluctuation in reproductive hormone levels, resulting in the precipitation or exacerbation of a mood episode.

Overall, it has been reported that menstrual cycle-related mood changes are seen in 44–65% of women with BD in studies with prospective designs. Utilizing data from the longitudinal, naturalistic Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, Dias et al. (2011) [9] found that women who reported premenstrual worsening of mood at baseline experienced a greater number of mood episodes, spent less time in a euthymic state in between mood episodes, and experienced more severe mood symptoms during a 1-year follow-up. Using a much larger sample (n = 1099) from the same STEP-BD database, Slyepchenko et al. (2017) [10] have recently shown that women who met DSM-5 provisional criteria for PMDD had an earlier illness onset, higher rates of rapid cycling, more comorbid Axis-I disorders, and a higher number of past-year hypo/manic and lifetime/past-year depressive episodes. Notably, there was a closer gap between BD onset and age of menarche in women with comorbid PMDD. These results are consistent with a large, community-based epidemiological sample (n = 1448) which found that women with PMDD are eight times more likely to also meet diagnosis of BD [11]. Thus, it is critical to properly assess women with BD for a potential comorbid PMDD or pre-menstrual exacerbation in mood symptoms as these presentations can mimic, for example, a rapid-cycling BD type II, and the treatment approach in each case would differ. In order to achieve this, it is imperative that women track their daily symptoms prospectively for a minimum of 2–3 menstrual cycles in order to accurately diagnose or rule out a comorbid PMDD.

The management of comorbid BD and PMDD can also prove challenging for the clinician, given the first line treatment for PMDD is a selective serotonin reuptake inhibitor (SSRI) or a serotonin and norepinephrine reuptake inhibitor (SNRI), both of which are known to increase the risk of manic switch in patients with BD. Smith and Frey (2016) [12] have recently outlined a clinical approach to the management of comorbid BD and PMDD: Prior to making a diagnosis of comorbid PMDD, women with BD must be relatively stable on a pharmacological regimen because unstable BD may mimic the symptoms of PMDD. Once stable from a BD standpoint, the diagnosis of PMDD can only be made through prospective daily mood charting for at least 2–3 symptomatic menstrual cycles. This is important because false positives are very high in PMDD and retrospective reports are unreliable and prone to bias (DSM-5). Once the diagnosis of comorbid PMDD is confirmed, lifestyle modifications such as sleep hygiene, diet, and exercise might be helpful. The use of calcium 600 mg BID, vitamin B6 100 mg daily, and chasteberry extract 20–40 mg daily is a relatively safe option for the management of mild-to-moderate PMDD. In more severe cases, the use of estrogen-based hormonal contraceptives might be preferred over antidepressants for women who wish for (and who do not have contraindications for) the use of estrogen-based contraceptives. While there remains a lack of evidenced-based research in this particular area, the strategy outlined above of using hormonal agents to treat comorbid PMDD in women with BD has been employed elsewhere with clinical success [13].

In addition to having a propensity toward increased sensitivity to the normal physiologic hormonal fluctuations of the menstrual cycle, women with BD are also more likely to have menstrual and reproductive abnormalities than women without BD. Indeed, a review by Kenna (2009) [14] illustrates that many of the treatments used in BD predispose women to developing hypothalamic–pituitary–gonadal (HPG) axis and metabolic abnormalities that interfere with a normal reproductive health. An early study by Rasgon and colleagues (2000) [15] found that in a sample of 22 women, menstrual abnormalities developed in all 10 who were on lithium monotherapy, in 6/10 on valproic acid (VPA) monotherapy, and in both women on lithium and VPA combination therapy. In addition, long-term treatment with the mood stabilizer VPA, in particular, is known for precipitating polycystic ovarian syndrome (PCOS), a neuroendocrine disorder characterized by hyperandrogenism, insulin resistance, obesity, hirsutism, anovulation, and infertility [15]. A cross-sectional observational study by O'Donovan et al. (2002) [16] found that 47% of a small sample of women with BD (N = 32) taking VPA had menstrual abnormalities, compared to 17% of those not taking VPA. In this sample, 41% of women with BD on VPA met criteria for PCOS, compared to 0% in a group of healthy, age-matched control women. Data from the larger, longitudinal, STEP-BD study suggests that of a sample of 86 women with BD being treated with VPA, 10.6% developed PCOS, compared to a rate of about 5% of women in the general population [17]. A follow-up study on these women revealed that menstrual cycle abnormalities remitted in 3 out of 4 women who discontinued VPA, regardless of change in body weight. VPA is also known for its teratogenicity, so may be an agent to use sparingly in women with BD during the reproductive years.

In summary, BD can interact with a woman's menstrual cycle in a myriad of ways. Not only do woman with BD have higher rates of comorbid PMS or PMDD, women with these comorbid conditions may experience pre-menstrual precipitation or exacerbation of their mood symptoms and are more likely to have a more severe course of BD. In addition, women with BD are more likely to have menstrual cycle abnormalities resulting from the psychotropic treatments used in its management, especially VPA and lithium.

Pregnancy and the Postpartum Period

Bipolar disorder tends to emerge in late adolescence or early adulthood, making reproductive considerations very important in this population

[18]. This section will cover the epidemiology and common clinical presentation of bipolar disorder in pregnancy, along with a discussion of management from preconception to the postpartum period.

While Vesga-López et al. (2008) [19] found similar prevalence rates of BD in pregnant and non-pregnant women, it has been well established that women with BD are at an increased risk of relapse in the postpartum period [20]. Notably, pregnant women who discontinue treatment are at higher risk of relapse in the postpartum period than non-pregnant women who discontinue their medication [21]. A recent meta-analysis showed that the overall risk of relapse in the postpartum period is about 23% for those who continue their medications, compared to 66% for those untreated [22]. There is also a strong association between postpartum psychosis and BD [23–26]. Postpartum psychosis is typically an episode of psychosis with rapid onset shortly after childbirth and could be an indication of mania, psychotic depression, or a mixed episode with psychotic features [27]. The onset is generally within 2 weeks of delivery, with 50% of cases occurring on postpartum days one to three [28]. Symptoms include delusions, hallucinations, confusion, perplexity, and severe mood swings. The differential diagnosis should include a substance-induced psychosis and delirium from medical causes such as eclampsia, thyroid disorders, or infection [28].

Risk factors for relapse of a mood episode include primiparity [29], medication discontinuation [21], and an acute episode within the past 6 months [30]. Risk factors for postpartum psychosis include primiparity [29, 31–33], medication discontinuation in someone with a history of mania or a psychotic disorder [34], and family history of postpartum psychosis [28]. In addition, maternal mental illness, particularly depression, has been linked with a number of adverse perinatal outcomes including obstetrical and long-term effects on offspring [35]. Women with severe mental illness (such as BD and schizophrenia) present later for antenatal care and have increased risk of smoking, use of illicit drugs or alcohol during pregnancy, pre-eclampsia, gestational diabetes, preterm birth, and NICU admission [36]. Factors such as maternal depression have been associated with epigenetic changes in the offspring glucocorticoid receptors that can mediate the child's response to stress [37]. In addition, depression impacts maternal sensitivity to infant cues and responsiveness that can have lasting impacts on the child's mental health separate from the genetic risk [38]. The interactions of these variables all contribute to increased risk, and this should be taken into account when discussing the risks and benefits of treatment vs. untreated BD in the perinatal period.

Given that bipolar disorder is one of the leading causes of disability, morbidity, and mortality [39, 40], appropriate treatment of this illness in pregnancy and the postpartum period has important consequences for mothers, infants, families, and society. The antenatal period is an opportune time for screening of BD [41], and this can be done through asking the patient about a personal or family history of BD/postpartum psychosis or through use of the mood disorders questionnaire [41–44]. Importantly, the diagnosis requires careful and thorough psychiatric assessment if a woman screens positive. Whenever possible, women with BD should be referred for specialist psychiatric assessment and care given the complexity of treatment decisions during this specific period [41].

General Treatment Considerations

Psychoeducation has been shown to be an important part of treatment of BD that prevents relapses of manic episodes as well as improves medication compliance [45–47]. Psychoeducation programs include information about the course of BD, treatments, early signs of relapse, and lifestyle management strategies [48]. With respect to pharmacotherapy, considerations should include an assessment of the likelihood of relapse based on diagnosis, illness severity, and recency of acute episodes, as well as past response to psychotropic medications [28]. Pregnancy may require increased doses of medication due the increase in blood volume, increased body fat,

increased distribution volume, and increased elimination of medication [28]. Therefore, traditional psychoeducation probably needs to be tailored to address the specific needs of this particular population.

Pre-pregnancy Counselling

It is good practice to discuss family planning and contraception with all women of childbearing age with a diagnosis of BD because a number of psychotropics can cause drug interactions that interfere with contraceptive efficacy and increase risk of unplanned pregnancy (e.g., carbamazepine, lamotrigine) [4, 28, 41, 49, 50]. Similarly, oral contraceptives can also reduce blood levels of lamotrigine, which can lead to relapse [51]. The use of valproate in pregnancy increases risk of neural tube defects including spina bifida, neuropsychological, language, and developmental challenges, as well as a higher incidence of autistic spectrum disorder [49, 52–55]. Given that 50% of pregnancies are unplanned, the use of valproate as a mood stabilizer should be ideally avoided in women of childbearing age, if possible [41]. A balanced, comprehensive discussion of potential risks of medications in pregnancy and lactation versus risks of an untreated illness is recommended.

Genetic Transmission

The risk of developing BD when there is a first-degree relative who has bipolar disorder is 5–10% compared to 2–4% in the general population [56].

Risks and Benefits of Medication Use in the Perinatal Period

A number of medications used to treat BD can lead to malformations in the neural and cardiac systems. Therefore, a careful review of medication risks in pregnancy and the postpartum period is important. The discussion may include the risks of the woman's current medication, if any, as well as the possible risks and benefits of alternatives including decreasing or discontinuing the medication, or switching to medications that have greater evidence of safety [28]. Some women may decide to discontinue maintenance therapy, and this should be done slowly, to reduce risk of relapse with abrupt discontinuation [28]. Women who decide to discontinue or lower maintenance therapy should be closely monitored for relapse into an acute mood episode [30]. Overall, available evidence suggests that lamotrigine and certain atypical antipsychotics have a relatively safer teratogenic profile compared to lithium, valproate, and carbamazepine [57].

During breastfeeding, there are several factors to consider when determining the safety of a particular medication, including pharmacokinetic factors such as drug solubility in water and lipids, protein binding, bioavailability, and volume of distribution [58, 59]. Maternal factors include the dose of the medication, the times that the medication is being taken, and the maternal plasma level [59, 60]. Infant factors include infant health (i.e., prematurity), the number of feedings, and volume of breast milk, although, in practice, some of these factors are very difficult to determine [59]. Generally, medications that are transmitted to an infant in a dose which is less than 10% of the maternal weight adjusted dose are considered relatively safe in breastfeeding [61]. Mothers who are breastfeeding while on medications should be advised to take their medication immediately after breastfeeding and not before, as well as to carefully monitor the infant for adverse effects and toxicity which are outlined below [58, 59].

Specific Pharmacotherapies

Lithium

Lithium has been associated with an increased risk of cardiac malformations, especially Ebstein's anomaly [62, 63]. A recent large study found that the overall risk for cardiac malformations was 1.65 (95% CI, 1.02 to 2.68), and the prevalence of cardiac malformations was 2.41% in infants exposed to lithium, compared to 1.15% in nonexposed infants [63]. With later pregnancy exposure, there have been case reports of associ-

ated hypotonia, cyanosis, neonatal goiter, and infant diabetes insipidus at birth [64]. Current recommendations support use of lithium during pregnancy only if alternatives (atypical antipsychotics or lamotrigine) are insufficient to achieve stability [57], or if the patient has severe BD and has been stable on lithium [64]. If lithium is used during pregnancy, lithium levels should be closely monitored, and the dose held for 48–72 hours right before the delivery to avoid neonatal toxicity. After delivery, lithium dose should be adjusted back to pre-pregnancy dose, and levels should be closely monitored [65].

Lithium has been found to pass in the breast milk at a relative infant dose ranging from 0.87% to as high as 30% [66]. Such high variability of transfer of lithium into breast milk as well as potential adverse effects on thyroid and kidney function in infants supports the recommendation that lithium should be avoided during breastfeeding [59, 67–71]. If mothers decide to breastfeed while taking lithium, infants should be closely monitored, and this includes bloodwork for lithium level, thyroid, and renal function, as well as close monitoring for drowsiness, irritability, dry mouth, excessive salivation, vomiting, constipation, hydration, urination, and tremor [66].

Lamotrigine

Lamotrigine has been inconsistently associated with an increased risk of lip/palate cleft defects when used in the first trimester [72, 73]. A large population-based case-control study found that there was no increased risk of oral cleft defects with lamotrigine use [73].

Lamotrigine has been found in breastmilk at variable concentrations; however, the research has generally shown limited serious adverse effects or negative developmental outcomes [59]. However, a recent systematic review and network meta-analysis reported that lamotrigine and oxcarbazepine were associated with higher risk for autism, although the sensitivity analysis with studies of high methodological quality on the "adequacy of follow-up" found no statistically significant results (4 studies, 283 patients, $\tau 2 = 1.01$, 95% CI 0.01 to 5.85) [74].

Valproate

Valproate use during pregnancy has a high rate of malformations (>10%), including neural tube defects, craniofacial anomalies, cardiac defects, cleft palate, and abnormal cognition and brain volumes [65]. There are also recent studies linking valproate exposure with neurodevelopmental disorders and autism spectrum disorder [75, 76]. Thus, current recommendations are to avoid the use of valproate in pregnancy and women of childbearing age; however, there may be patients who are stable on this medication with other failed medication trials in the past, and the risks and benefits must be carefully weighed. If valproate is used in women during childbearing years, high dose folate (5 mg per day) is recommended, and a detailed anatomy ultrasound should be done in the second trimester to screen for major congenital anomalies [64].

Although valproate is excreted in relatively low amounts in the breast milk, the above-mentioned systematic review and network meta-analysis reported that valproate monotherapy or combined with another anticonvulsant is associated with higher risk of a wide range of negative neurodevelopmental outcomes, including autism/dyspraxia and language, cognitive, and psychomotor developmental delay [74]. There is a reported case of thrombocytopenic purpura and anemia associated with valproate use in breastfeeding that resolved once the infants stopped breastfeeding [77]. Therefore, use of valproate should be avoided during breastfeeding due to the potential long-term negative impact on infant's neurodevelopment [64].

Carbamazepine

Carbamazepine has also been associated with an increased risk of neural tube defects, facial abnormalities, skeletal abnormalities, hypospadias, and diaphragmatic hernia at a rate of 2.2–3.3% [65]. There may also be an increased risk of neonatal hemorrhage due to its effect on the coagulation cascade [64]. Although the risk of neural tube defects is lower compared to valproate, carbamazepine should be also avoided in the first trimester.

Carbamazepine use during lactation has been shown to have transient toxic liver changes in breastfed infants [78–80]. Otherwise, no serious adverse events have been reported with carbamazepine use during breastfeeding, and there have been no serious adverse effects found on long-term cognitive outcomes [59].

Atypical Antipsychotics

Pharmacokinetic considerations must be made as pregnancy downregulates the CYP1A2 enzymes and doses of olanzapine and clozapine may need to be decreased [81]. Quetiapine, risperidone, olanzapine, and haloperidol have the lowest placental transfer of antipsychotic medications. Antipsychotics can increase the risk for gestational diabetes [81], although such risk has been recently challenged [82, 83], and increase birth weight in neonates. At the time of birth, antipsychotic medications have been noted to lead to extrapyramidal symptoms (motor restlessness, dystonia, hypertonia, tremor) in some infants [81, 84]. There has been a paucity of studies examining the association of antipsychotics with long-term neurodevelopmental outcomes, but existing data do not suggest a lasting neurodevelopmental effect of antipsychotic use [65, 85–87], except perhaps a transient neuro-motor delay at 6 months [88] Most reproductive safety data are available for olanzapine, quetiapine, risperidone, and haloperidol [57]. There might be an increased risk of birth defects with risperidone [89]. There is some evidence that there is an increased risk of premature delivery with the use of first-generation antipsychotics [90]. Clozapine is not generally recommended for use in pregnancy or breastfeeding as there is an increased risk of floppy baby syndrome [84].

All antipsychotics can be found in the breast milk to some degree [59]. Olanzapine has been studied in a number of case reports and one protective study and showed that there were low infant plasma concentrations and relative infant doses with no reported adverse events [91–98]. Quetiapine also has some data that shows a low relative infant dose from 0.09% to 0.43% with no adverse events [99, 100]. Risperidone also has low relative infant doses from 2.3% to 4.7% [101–103]. There is very limited data on aripiprazole, amisulpride, ziprasidone, and clozapine; however, amisulpride is recommended against due to its relatively high transfer found in case reports, and clozapine is not recommended due to the risk of agranulocytosis and seizures [59].

Electroconvulsive Therapy

In general, the use of electroconvulsive therapy (ECT) in pregnancy and lactation is not absolutely contraindicated but should be reserved for treatment of episodes when a woman is psychotic and resistant to treatment, or safety risks pose a threat to mother or infant (i.e., suicide, nutritional status, catatonic states) [28, 41]. Safety data from a case series showed that there are relatively low complication rates for mothers (5%) and babies (3%) and that there was only one fetal death out of 339 cases of ECT done in pregnancy [104]. Studies of long-term cognitive effects in children exposed to ECT in utero are lacking.

The Menopause Transition

Menopause marks a crucial biological, psychological, and often psychosocial transition in a women's reproductive life and is triggered by an initial dramatic fluctuation and eventual decline of gonadal hormones. Perimenopause begins when the menses first start to become irregular and generally starts between ages 45 and 50 in most women, although significant variation in perimenopausal onset does occur [105]. By definition, early perimenopause is a change in menstrual cycle length of >7 days in the length of a hitherto regular menstrual cycle; the late perimenopause starts when a woman has experienced amenorrhea between 60 and 364 days; and early post-menopausal period represents the first 3–6 years after the last menstrual cycle [106].

Prospective studies have clearly demonstrated that the menopausal transition (MT) marks a period of increased vulnerability for both new-onset and recurrent depression: women with a history of major depressive disorder (MDD) are

at a five times higher risk for relapse during the MT, and women with no history of MDD are at an approximately two to four times greater risk for a first episode of depression during this period [107]. As the MT pertains specifically to women with BD, much less is known. A recent prospective, albeit small (n = 44), study by Marsh et al. (2015) [108] found an increased rate of depressive symptoms among women in the late and post-MT compared to women in the late reproductive and early MT. Of note, the risk of depression was higher than the risk of mania in this population. Absolute levels of the reproductive hormones estradiol and follicle-stimulating hormone (FSH) did not appear to be significantly correlated with mood symptoms. A study looking at a sub-section of the STEP-BD study found that progression through pre-MT, peri-MT, and post-MT was associated with a significant decrease in euthymia and mood elevation and a significant increase in subsyndromal depressive symptoms in a population of women with BD [109]. Notably, this sample included only 13 women, who transitioned from perimenopause to postmenopause during the course of the study. Another study looking at data from STEP-BD found that women with BD between 45 and 55 years old had significantly more clinical visits with depressive symptoms and significantly fewer visits with euthymic symptoms than a pooled comparison group consisting of similarly aged men as well as younger aged men and women (30–40 years old) [110]. This further supports the claim that the MT is a time of increased risk for depressive symptomatology and depressive episodes among women with BD.

With respect to a prior history of premenstrual or postpartum mood episodes heralding a vulnerability to experience mood symptoms during the MT, results are mixed, with some that found a positive and some a negative relationship between a history of premenstrual or postpartum mood issues predisposing women with BD to develop menopause-related mood disorders [109, 111–113]. With respect to treatment strategies for women with BD during the MT, the literature is even sparser. While hormone replacement therapy has proven to be effective in the treatment of depressive disorders in women during the MT, these findings have yet to be replicated in women with BD [114].

In summary, the MT appears to be a period of increased risk for depression but not mania among women with BD. More research with regard to the role of hormonal treatment in this population is warranted.

Conclusion

This chapter has summarized important considerations for the epidemiology, natural history, and treatment of BD in various stages of a woman's reproductive life cycle. Each stage marks a time of vulnerability and presents unique considerations in selecting appropriate treatment. The information summarized here points to the importance of gender considerations when determining a treatment approach to bipolar disorder and also highlights the need for further research on alternative strategies, including hormone therapy, that may be a helpful and novel way to approach treatment of bipolar disorder in women.

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Premenstrual Dysphoric Disorder

Gabriella Francesca Mattina and Meir Steiner

Introduction

Premenstrual disorders affect women of reproductive age during the late luteal phase of the menstrual cycle. They largely consist of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD), both of which are recurrent chronic conditions that cause significant impairment in occupational or social functioning. Symptoms experienced by women with premenstrual disorders follow a cyclical and predictable pattern corresponding to the phases of their menstrual cycle. Specifically, several affective and physical symptoms emerge sometime in the 2 weeks leading up to menstruation, which then remit or become minimal within a few days of menses onset and are absent following menses. Women with PMDD experience a severe form, with more symptoms emerging in the luteal phase than those with PMS. The aetiology of these disorders is unclear, but research suggests involvement of altered neurotransmitter systems and increased sensitivity to gonadal hormone fluctuations. Due to the complexity of the disorder, there is no single treatment that is successful for all women; however, various treatments aimed at regulating neurotransmitter systems and suppressing gonadal steroids have been efficacious. This chapter will provide an up-to-date overview on the diagnosis, epidemiology, course and risk factors, aetiology, and evidence for effective treatments of PMDD.

Definition and Diagnostic Criteria

Premenstrual dysphoric disorder (PMDD), which replaced what was previously termed late luteal phase dysphoric disorder, first appeared in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) under the Appendix as a set of criteria that required further research [1]. Women meeting the suggested criteria were subsequently classified under "depressive disorder not otherwise specified", which failed to recognize its unique clinical presentation and provided no specificity towards risk factors, prevalence, and course of the proposed disorder. Following the ensuing research on the epidemiology, pathology, and treatment,

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it was concluded that PMDD was distinct from other disorders, and it became an official diagnosis under the Depression and Depressive Disorders chapter in the fifth edition of the DSM (DSM-5) [2].

To meet DSM-5 diagnostic criteria for PMDD, at least five symptoms from a list of eleven must be present in the week prior to menstruation and improve within a few days of menses onset and are negligible or absent in the week after menses [2]. Of the five required symptoms, at least one must be affective, including mood swings, anger or irritability, depressed mood, and anxiety or tension. Women must also present with one or more of the following specified symptoms: decreased interest in surroundings, difficulties in concentration, lethargy or fatigue, change in appetite, sleep difficulties, feelings of being overwhelmed or not in control, and physical symptoms (e.g. breast tenderness, joint or muscle pain, swelling of extremities, bloating, or weight gain).

The symptoms presented must have occurred during the majority of menstrual cycles of the previous year and are to be confirmed using a prospective daily ratings of at least two symptomatic menstrual cycles. A key component to diagnosing a premenstrual disorder is determining the timing of symptoms during a women's menstrual cycle. Symptoms must emerge in the luteal phase, improve within a few days of menstruation, and remit until negligible or absent following menses. Retrospective reports are often biased as patients tend to overestimate the cyclical timing of their symptoms leading to overdiagnosis [3]. When prospective ratings are not available, a provisional PMDD diagnosis may be given. In addition to their presence, the symptoms must significantly interfere with the individual's work, school, social life, and/or interpersonal relationships.

Symptoms cannot be related to the effects of a medication, other substance use, or a medical condition. Some physical conditions share overlapping symptoms with premenstrual disorders, such as migraines, anaemia, diabetes, asthma, seizure disorders, endometriosis, uterine fibroids, and hypothyroidism [4]. As a result, these conditions should be considered and assessed in order to exclude them as causal factors for the presenting symptoms.

PMS and PMDD share the same type and cyclical pattern of symptoms, but differ based on the number of symptoms required to meet criteria. Unlike PMDD, PMS does not require a minimum of five symptoms and the presence of an affective symptom is not necessary. Both diagnoses require that women present with physical and behavioural symptoms that impair functioning to a significant degree.

In addition to PMS and PMDD, several other classifications of premenstrual disorders exist and were characterized by the International Society for Premenstrual Disorders (ISPMD) [5]. These include premenstrual exacerbation, premenstrual disorder due to ovarian activity not related to ovulation, progestogen-induced premenstrual disorder following progestogen administration, and premenstrual disorder with absent menstruation following suppression of menses. PMS or PMDD may not be classified if symptoms exist exclusively as an exacerbation of another underlying psychiatric disorder, such as depressive, bipolar, or anxiety disorders. Often women may experience a worsening of symptoms of a pre-existing medical condition or other psychiatric disorder in the luteal phase of menstruation; however, this presentation does not reflect PMS or PMDD if symptoms persist throughout the entirety of the menstrual cycle with no symptom-free period. It is important to also distinguish dysmenorrhea, i.e., menstrual-related pain or cramps in the abdominal region or back that lasts several days and has an onset during menstruation [6], as a distinct condition that is not reflective of PMS or PMDD.

The inclusion of PMDD as a psychiatric disorder in the most recent DSM has been met with debate. One argument against its classification views PMS and PMDD as a culturally bound, social construct that pathologizes women's natural experience based on their reproductive state [7]. Others have criticized that a female-specific diagnosis perpetuates the notion that a woman's

distress may only be taken seriously upon being labelled as a disorder. However, such claims fail to acknowledge the prevalence of PMS/PMDD worldwide and the benefits associated with a formal diagnosis, such as the recognition, research, and treatment needed to ensure full support is given to women [8].

Self-Report Diagnostic Tools

Several rating scales were developed to assess and quantify premenstrual symptoms prospectively to identify women meeting criteria for PMS or PMDD. Of importance is the ability for these assessment tools to collect clinically relevant information in a time-efficient and straightforward manner.

The first published tool that was developed to measure premenstrual symptoms was the Moos' Menstrual Distress Questionnaires (MDQ), which is a self-report instrument that assesses 47 symptoms on a 6-point scale [9]. Its use has been criticized as some items measure symptoms not related to the menstrual cycle [10]. Less than a decade later, the first visual analogue scale (VAS) was used, which enabled individual premenstrual symptom ratings to fall on a continuous scale [11]. The VAS is an appealing measure due to its simplistic design which has participants mark a 100 mm horizontal line to display the severity of premenstrual symptoms they experience. The lines are marked at either end to represent the absence (0) and the most severe presence (100) of premenstrual symptoms. Several advantages to the VAS include its simplicity, increased compliance, and its validity and reliability for measuring change in premenstrual symptoms over time [12]. One disadvantage with paper VAS versions is the time-consuming process associated with measuring each marking by hand. Development of electronic devices that are capable of providing these results quickly from markings created on a touchscreen has eliminated that challenge [13].

In 1990, the Daily Record of Severity of Problems (DRSP) was developed and published by Endicott and Harrison [14] to collect information on the severity of symptoms and daily impairment experienced across various phases of the menstrual cycle. The DRSP includes 21 items that cover mood and behavioural and physical symptoms, as well as 3 impairment-related questions that measure impairment of work, social activities, and interpersonal relationships. The individual items are then rated from 0 to 6 (0, not at all severe, to 6, extreme severity) to allow for proper prospective diagnosing of PMS or PMDD that correspond to DSM criteria. This tool highlights the timing and nature of the problems experienced across the menstrual cycle and should be completed for at least two symptomatic cycles to confirm a PMDD diagnosis. Another prospective rating calendar that may be used is the Prospective Record of the Impact and Severity of Menstrual symptoms (PRISM), which is freely available online [15].

Another tool that was developed to help identify women with possible PMDD who are likely to benefit from treatment is the Premenstrual Symptom Screening Tool (PSST) [16]. The PSST assesses premenstrual symptoms retrospectively, thereby making it a less time-consuming tool as compared to the DRSP. A total of 14 symptoms based on the DSM-IV criteria are included that primarily focus on premenstrual mood and behaviours, with one item corresponding to physical symptoms. The participant identifies which symptoms are experienced and the degree of interference of these symptoms on various aspects of daily life using a 0–3 frequency scale ("not at all", "mild", "moderate", "severe"). A recent study on the validation of the PSST against the DRSP reported that there is high sensitivity and low specificity of the PSST for diagnosing PMS/PMDD [17], which may be due to inaccurate recall of the timing and severity of symptoms. Despite the lack of agreement between the two rating scales [17], the PSST is highly beneficial as a time-saving screening tool, and women positively identified by the PSST should be further evaluated using prospective symptom charting, such as the DRSP, to confirm a PMDD diagnosis.

Epidemiology

Approximately 80% of women will report having experienced at least one mild premenstrual symptom during the luteal phase of a menstrual cycle [18, 19]. Twelve-month prevalence rates for PMS are approximately 20–30% [20]. A recent meta-analysis reviewing epidemiological studies reported a pooled prevalence rate of 47.8% for PMS worldwide, with prevalence rates ranging from 12% to 98%, in France and Iran, respectively [21].

Due to differences in severity, PMDD is less common than PMS. Epidemiological studies over the last few decades have provided mixed results for the prevalence of PMDD, which is largely due to different diagnostic criteria used in classifying its diagnosis and different methodologies used in sampling [22, 23]. The estimated prevalence for PMDD is around 5% in menstruating women, with rates ranging between 1.1% and 6.4% observed worldwide [19, 24–30]. Due to strict PMDD criteria of a minimum of 5 symptoms, prevalence rates fail to consider the number of women experiencing severe premenstrual symptom impairment that do not meet the number of required symptoms [23]. Up to 20% of menstruating women are thought to experience clinically significant premenstrual symptoms that warrant treatment [19].

When examining symptom type, the predominant premenstrual symptom experienced globally by reproductive aged women is physical [31], whereas, for women with severe PMDD, depressed mood and irritability is often reported as the most prevalent symptom in the luteal phase [19].

Course, Morbidity, and Quality of Life

Women can develop PMS or PMDD at any time point between menarche and menopause. PMDD is well recognized as a stable disorder in which spontaneous recovery or remission is unlikely. Severity of symptoms tends to worsen over time, with peak symptoms experienced by women in their twenties to thirties, and symptoms tend to subside as ovarian activity declines and ovulation ceases with menopause [32]. Even though remission of premenstrual symptoms can be achieved through various medical treatments, symptoms often re-emerge once treatment is stopped [33]. Likewise, menopausal women can experience premenstrual symptoms when taking cyclical hormone replacement therapy [34].

Women with PMDD are estimated to suffer 3.8 years of disability adjusted life years over their reproductive lifetime [23]. The severity and chronicity of these symptoms results in impairment that extends to all aspects of daily life, with the greatest impact observed on interpersonal relationships and work productivity [32]. Indirect economic costs of burden from decreased work productivity and increased absenteeism due to PMS or PMDD are estimated around $4333 USD per patient per year [35]. Additionally, women with PMDD report increased use of healthcare services including increased number of visits to a healthcare provider and use of prescription medications [35].

Quality of life for women with PMDD in the luteal phase is comparable to those with depressive disorders [36]. Women considered at risk for PMDD based on retrospective reports experienced significantly lower quality of life on physical and mental health-related domains as compared to a US female population average, with greatest impairment observed for bodily pain and mental health [37].

Comorbidities with Other Psychiatric Disorders

Lifetime history of another psychiatric disorder is common in women with moderate to severe premenstrual symptom complaints with a previous major depressive episode most often reported as the most prevalent, followed by anxiety disorders [38, 39]. In a sample of women with prospectively confirmed PMDD, lifetime comorbidity rates were highest for major depression disorder (31.2%), followed by sub-

stance abuse (18.6%) and anxiety disorders (15.3%) [40]. Roughly 30–70% of women with prospectively diagnosed PMS or PMDD have experienced a past major depressive episode, whereas concurrent rates of PMDD comorbid with depressive disorders are between 12% and 25% [41]. Past premenstrual distress may also predict future episodes of depression, as women with a history of depressive premenstrual symptoms are more likely to experience a future depressive episode [42].

In a sample of women with prospectively confirmed premenstrual disorders, 59% reported concurrent anxiety disorders, with generalized anxiety (38%), panic disorder (25%), and social phobia (19%) described as the most common [43]. In a longitudinal study assessing obsessive-compulsive symptom change in women with obsessive-compulsive disorder (OCD) across the menstrual cycle, approximately 13% met criteria for PMDD and a greater proportion of women (48%) commonly reported premenstrual exacerbation of symptoms [44].

Large-scale studies utilize retrospective reports of PMDD in general populations worldwide to provide estimates for PMDD comorbidity prevalence. A sample examining PMDD in Korean women across all reproductive ages from the Korean Epidemiologic Catchment Area study reported that 59.3% of women with PMDD had a lifetime history of another psychiatric disorder [27]. Highest associations were reported for social phobia, post-traumatic stress disorder, somatoform disorder, major depressive disorder, specific phobia, and alcohol abuse/dependence. In this sample, PMDD was also associated with insomnia and suicidality, and women who were underweight or had a physical illness were at increased risk of PMDD [27]. In a German sample, young women with PMDD were found more likely to have at least one comorbid psychiatric disorder compared to those without PMDD [19]. Twelve-month comorbidity prevalence rates were 47.4% for anxiety disorders (mostly attributed by high prevalence rates of social phobia and specific phobia of blood or injury), followed by 29.8% for mood disorders [19].

Although comorbid PMDD and bipolar is less studied, a large-scale cohort of 1099 women who met criteria for bipolar disorder type I or II found that 45% of women had retrospectively confirmed PMDD [45]. Additional findings from this study show that women with bipolar disorder comorbid with PMDD are more likely to have additional psychiatric comorbidities (including anxiety disorders, bulimia, adult attention deficit and hyperactivity disorder, and lifetime alcohol or drug abuse) and present with a more severe illness course [45].

The experience of psychotic symptoms limited to the luteal phase of the menstrual cycle is rare but has been described in several case studies [46]. A challenge in determining PMDD comorbidity frequencies with schizophrenia is due to the difficulty in distinguishing PMDD and premenstrual exacerbation in this population. In a Chinese population of 50 women with schizophrenia, 52% met criteria for PMS, with 20% experiencing premenstrual exacerbation [47]. In a study prospectively following schizophrenia patients across one menstrual cycle, no change in psychotic symptoms were experienced across the menstrual cycle, whereas exacerbation of affective and behavioural symptoms were prominent in the premenstrual phase [48].

Large-scale study estimates of comorbidities commonly experienced with PMS or PMDD are challenging due to prospective charting needed to establish a diagnosis. As a result, many studies rely on the use of retrospective reports to assess premenstrual worsening of symptoms, which are subject to bias. Additional challenges remain in the ability to detect cyclical symptom changes in women experiencing severe symptomatic mood or anxiety disorders, which may have overlapping symptoms with PMS/PMDD.

Collectively, these results highlight a need to assess possible PMDD in women presenting with various mood and affective disorders, as morbidity and treatment can be affected. Women with psychiatric and premenstrual disorder comorbidities tend to exhibit a more severe illness course and identification of concurrent PMDD may better inform treatment considerations.

Risk Factors

Several population-based studies have been conducted examining potential risk factors for the development of premenstrual disorders.

Race Varying prevalence rates for PMDD have been reported across different racial groups. Prevalence rates for PMDD appear higher for Caucasian women than African American women in the United States [49], whereas rates in East Asia are lower than those seen in North America (1.3–2.8%) [50]. These findings may be due to cultural differences in awareness of premenstrual disorders and with attitudes regarding premenstrual mood disturbance. This possibility highlights the importance of education, especially for healthcare givers and women who may be unfamiliar with premenstrual disorder terminology and available treatments.

Age Age does not reliably predict risk; however, there seems to be an association of age with premenstrual symptom severity. Older women with PMDD who seek treatment tend to have longer duration of symptoms and are more likely to seek treatment, yet they report lower symptom severity compared to younger women [51, 23]. PMDD symptom severity appears to peak for women in their late twenties to mid-thirties [51].

Lifestyle/Diet Several lifestyle risk factors for the development of PMS have been ascertained through results of a subset of women aged 27–44 who participated in the longitudinal Nurses' Health Study II. Women who smoke cigarettes, especially those who started smoking before the age of 15, were more than 2 times likely to develop PMS [52]. After adjusting for several lifestyle factors such as smoking and physical activity, women with a body mass index (BMI) greater than 27.5 kg/m^2 were at greater risk of developing PMS [53]. Women with PMDD tend to have greater caloric intake and sweet cravings in the late luteal phase compared to the follicular phase and to control women, but no significant differences in BMI were found between PMDD and control groups [54]. Ingesting higher quantities of calcium, vitamin D, thiamine, riboflavin, and non-heme iron was associated with decreased risk for developing PMS, whereas increased potassium intake was associated with a higher risk [55–57].

Stress/Trauma Women with PMDD report a greater worsening of symptoms when accompanied by stressful life events or greater perceived levels of stress [58, 59]. A longitudinal study observing a cohort of young women found that those exposed to traumatic events were four times more likely to have PMDD compared to those experiencing no trauma [59]. Early life emotional and physical abuse increases the risk for PMS development, with an odds ratio of 2.6 and 2.1 for women reporting severe emotional and physical abuse, respectively [60]. Several studies investigating the prevalence of past sexual or physical abuse in women with PMS or PMDD have found significantly higher rates in this clinical population than women in the general population. In 174 women with PMS, 40% reported a history of sexual abuse [61]. In comparison, childhood sexual abuse rates in women in the general population have been found to be around 12.4% and 16% [62, 63]. Scores on the Childhood Trauma Questionnaire (CTQ), which measures emotional, physical, and sexual childhood abuse, were significantly greater in a sample of women from Turkey with PMDD compared to healthy controls [64]. Also noteworthy, a large majority of women (83%) who experienced sexual abuse did not disclose the abuse to any healthcare practitioner, suggesting that abuse history be screened in women presenting with premenstrual disorder symptoms [65].

Psychiatric Disorders As previously described, PMDD is often comorbid with depressive disorders. What is unclear from the literature is whether these disorders predispose risk for premenstrual disorders, or vice versa. Women with diagnosed PMDD often report past depressive episodes [41], and premenstrual distress may increase likelihood of experiencing a future depressive episode [42]. There may be an association between premen-

strual disorders and postpartum depression, as some studies report that women with PMS/PMDD are more likely to develop postpartum depression [66, 67]; however, a recent study examining women with PMDD reported low rates (11.7% of parous women) of past postpartum depression [40].

Genetic Heritability Results from family and twin studies provide mixed evidence that genetic factors contribute to the development of premenstrual disorders. First-degree female relatives in mother-daughter dyads retrospectively report similar presence or absence of PMS [68], whereas no relationship was found in symptom changes across the menstrual cycle among sisters [69]. Twin studies report retrospective premenstrual symptom heritability estimates of 35.1% [70], which was later found to be moderately stable over time in a follow-up study of the same cohort, with heritability estimates of 56% [71]. PMS concordance rates among twins have been higher for monozygotic twins, with one study reporting 0.81 vs 0.67 concordance rates for monozygotic and dizygotic twins, respectively [72]. However, one twin study determined that retrospective reports of premenstrual symptoms were associated with neuroticism personality traits, which may not reflect genetic contribution [73]. Methodological challenges associated with collecting prospective data from families to confirm PMDD diagnosis may explain why this has yet to be performed.

Menstrual Cycle Physiology

Over a century ago, women were estimated to have fewer than 100 menstrual cycles in their lifetime, owing to recurring interruptions for pregnancy and breastfeeding [74]. In today's society, women are experiencing earlier menarche, later menopause, and fewer pregnancies, leading current estimates for women to have around 400–450 menstrual cycles in their lifetime [74]. Understanding the physiology of the menstrual cycle will provide the context needed for understanding the aetiology of PMDD.

The menstrual cycle can be defined by two phases: the follicular phase (from the first day of menstruation to ovulation) and the luteal phase (from ovulation to the start of menstruation). Both phases are accompanied by the fluctuation of ovarian hormones: estradiol and progesterone. Ovarian activity and steroidogenesis occurs as a result of the hypothalamus releasing gonadotropin-releasing hormone (GnRH), which regulates the production and secretion of the pituitary gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The frequency and amplitude of GnRH pulses changes across the menstrual cycle to favour FSH or LH release and is regulated by feedback from oestrogen and progesterone levels [75].

At the start of the menstrual cycle, which is marked by menses onset, estradiol and progesterone levels are low. During this time, GnRH pulses occur approximately every 90–120 minutes, favouring the release of FSH [74]. Elevated levels of FSH are responsible for stimulating the growth of immature ovarian follicles. As the follicles begin maturating, one follicle will obtain a competitive advantage over the others making it more sensitive to FSH levels [76]. This "selected" follicle will continue to mature and release increasing amounts of oestrogen, which is then converted to estradiol. In the mid-late follicular phase, elevated estradiol levels cause a cascade of events on the hypothalamus-pituitary-gonadotropin (HPG) secretion, which results in GnRH pulses occurring once per 60 minutes, thereby favouring LH secretion and suppressing release of FSH [77]. As LH levels surge and peak, estradiol levels drop dramatically and the dominant follicle ruptures, known as ovulation [77].

Ovulation marks the transition into the luteal phase of the menstrual cycle. After ovulation, a large quantity of progesterone is produced and secreted by the corpus luteum, which is the temporary yellow hormone-secreting structure that is formed at the site of the ruptured follicle. Progesterone secreted from the corpus luteum acts on the hypothalamus to slow GnRH pulses to once every 3–5 hours [74]. The production of estradiol from the corpus luteum suppresses FSH release [77]. In the absence of fertilization, the

corpus luteum degrades, leading to decreased levels of progesterone and estradiol. The onset of menses takes place, marking the start of the next menstrual cycle. Decreased levels of these ovarian hormones release the hypothalamus and pituitary from suppression, allowing FSH secretion and the recruitment of a new cohort of follicles for the maturation process.

Aetiology

The aetiology of premenstrual disorders still remains elusive; however, PMDD is well characterized by the cyclical recurrence of symptoms that relates to fluctuations of gonadal hormones during the menstrual cycle. The temporal nature of the symptoms, which coincides with the late luteal phase of the menstrual cycle, led many to the assumption that altered hormone levels may be responsible for the clinical manifestation. However, failure to reliably detect abnormal levels of circulating ovarian hormones suggests that premenstrual disorders are not primarily caused by a simple hormone alteration [77].

Rather, the current literature supports the hypothesis that symptoms emerge in women who are more sensitive to changes in endogenous levels of hormones. Support for this theory comes from a recent study that investigated the effects of oestrogen and progesterone on women who had achieved symptom remission through ovarian suppression [78]. Ovarian suppression was accomplished with GnRH agonist administration, but due to side effects of this therapy, an add-back therapy is often implemented. The researchers found increased ratings for premenstrual tension (self-reported and rater-administered) in the first month following progesterone and oestrogen add-back therapy, whereas no change in symptoms occurred with single-blind placebo add-back [78]. Subsequent months using ovarian steroid add-back therapy led to lowered premenstrual tension scores, suggesting that the initial change in oestrogen and progesterone levels triggered symptom onset, whereas stable levels did not precipitate premenstrual symptoms. The neuromodulatory actions of oestrogen and progesterone on the central nervous system are of interest and are likely to contribute to the pathogenesis of PMDD as well.

Progesterone There is a well-established temporal association between premenstrual symptoms and ovarian steroid fluctuation with progesterone. Premenstrual symptom onset in the late luteal phase coincides with declining levels of progesterone, leading many to hypothesize that a deficiency of progesterone may be eliciting symptoms. This does not appear to be the case in PMS/PMDD, as different studies have failed to provide evidence that supports the association between low levels of progesterone and premenstrual symptoms. Investigations into plasma levels of progesterone, as well as estradiol and ovulation hormones FSH and LH, found no differences among women with PMS and controls across the menstrual cycle [79]. Additionally, premenstrual symptom severity scores were worse in cycles with higher plasma levels of estradiol and progesterone concentrations [80]. Lastly, treatment studies administering progesterone using a double-blind placebo-controlled design found no significant symptom improvement with progesterone use when compared to placebo [81].

Allopregnanolone Researchers. turned their investigations to a neuroactive steroid metabolite of progesterone: allopregnanolone (3alpha-hydroxy-5alpha-pregnan-20-one; ALLO). ALLO is synthesized in the brain and fluctuates in parallel with progesterone in the menstrual cycle [82]. ALLO is a positive modulator of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system. ALLO exerts agonistic effects on the $GABA_A$ receptor, which selectively conducts chloride anions [83]. When ALLO binds to the $GABA_A$ receptor, it enhances the effects of GABA by increasing the frequency and duration of chloride channels opening, thereby reducing neuronal excitability [83]. Typically, high concentrations of positive modulators of $GABA_A$ receptors, such as benzodiazepines and ALLO, exert anxiolytic, sedative, and anti-epileptic effects in women

[84], whereas lower concentrations induce anxiogenic effects and aggressive behaviours in animals [82]. A paradoxical effect is observed in women with PMDD, as endogenous levels of ALLO that are increased in the mid-luteal phase of the menstrual cycle are associated with an increase in negative mood symptoms [85]. An inverted U-shaped relationship between ALLO concentration and negative mood in women has been suggested and supported, with endogenous luteal levels of ALLO showing the greatest increase in negative mood, whereas low and high concentrations of ALLO have less of an effect on mood [82].

One possible mechanism by which ALLO influences $GABA_A$ receptor activity differently in women with PMDD involves increased susceptibility to abrupt changes in progesterone levels, and subsequently ALLO. levels, which triggers the emergence of premenstrual symptoms in the luteal phase. Rodent studies have demonstrated $GABA_A$ receptor subunit conformational change following fluctuations of ALLO, which returns to the usual conformation in the presence of stable hormone levels [86]. This type of conformational change could reflect short-term tolerance to the GABA-enhancing effect of ALLO in the luteal phase [87].

Further evidence supporting the role of ALLO in premenstrual disorders comes from inhibiting the rate-limiting enzyme responsible for the conversion of ALLO from progesterone, 5alpha-reductase, which led to improved mood in women with PMDD [88]. Additionally, selective serotonin reuptake inhibitors (SSRIs), which are an effective treatment option for some women with premenstrual disorders, may influence levels of ALLO. Specific SSRIs have been shown to increase levels of ALLO through influencing the activity of the second-step enzyme, 3alpha-HSD, responsible for its conversion [89]. In a treatment study for women with prospectively defined PMS, those displaying low levels of ALLO at baseline experienced a significant increase of ALLO following treatment with the SSRI sertraline, whereas the opposite was observed for women with higher baseline levels of ALLO, as they experienced a decrease in levels after treatment [90]. Furthermore, women with lower baseline levels of ALLO experienced an improvement in depression-related symptoms (feelings of depression, being out of control, and hopelessness) [90]. Taken together, there is a substantial amount of evidence supporting the involvement of ALLO-mediated $GABA_A$ receptor function. in the occurrence of negative mood symptoms in the late luteal phase.

Serotonin A monoamine neurotransmitter that has gained widespread interest among various mood disorders and is thought to play a significant role in the pathophysiology of premenstrual disorders is serotonin. Serotonergic neurons project from the raphe nucleus in the brainstem to various regions throughout the brain, and serotonergic activity regulates behaviours such emotion, mood, eating, arousal, and sleep and circadian rhythms [91]. Aberrations of the serotonergic system that result in deficiency have been associated with a myriad of mood symptoms including depression, anxiety, panic, obsessions, and compulsions [92].

Results from pharmacological studies utilizing drugs that either enhance or inhibit serotonergic transmission in women with PMS/PMDD provide the strongest implication for its involvement. Treatments that facilitate serotonergic transmission, such as through the actions of SSRIs that block the reuptake of serotonin from the synaptic cleft, reduce the symptoms of PMS [93]. In fact, SSRIs are the current first-line treatment approach for PMS/PMDD, with approximately 60% treatment response [94]. Similar observations of a reduction in premenstrual symptoms following modifications to serotonergic functioning after administering compounds that increase the amount of available or released serotonin are observed with meta-chlorophenylpiperazine (mCPP) [95], d-fenfluramine [96], and the serotonin precursor tryptophan [97], whereas drugs that counteract or decrease serotonin activity are found to worsen premenstrual symptoms, as reported with dietary tryptophan depletion studies [98] and administra-

tion of the serotonin receptor antagonist metergoline in women who achieved remission via SSRI [99]. It is of importance to note that causality cannot be inferred from pharmacological response data, as the mechanism by which each drug operates is unclear.

SSRIs are an effective treatment option for reducing premenstrual symptoms in women with severe PMS/PMDD and are commonly prescribed antidepressants for the treatment of major depression. Despite overlapping symptoms between PMDD and depression, there are marked differences in treatments for these disorders that suggest different underlying serotonergic involvement. SSRIs for the treatment of depression require continuous administration over several weeks in order to observe noticeable changes [100], whereas premenstrual symptoms, such as irritability, are reduced a few days after beginning SSRI treatment [101]. As a result, intermittent dosing of SSRIs administered in the luteal phase is a possible and feasible option for the treatment of PMDD. Further evidence supporting dissimilarities between PMS and depression come from antidepressants that non-specifically target serotonergic activity. Serotonin and norepinephrine reuptake inhibitors (SNRIs) are effective in treating depression [102], but are not as effective in treating PMS [103], which further highlights the importance and specificity of serotonin in premenstrual disorders.

Serotonergic transmission can also be measured outside the central nervous system by examining serotonin activity in blood platelets. Differences in platelet uptake of serotonin, activity of the enzyme that metabolizes serotonin (monoamine oxidase, MAO), and serotonin transporter density have been reported in women with PMS compared to healthy control subjects [104, 105]. Another method for evaluating serotonergic activity is to measure levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid. One study failed to find differences in 5-HIAA mean concentrations across the menstrual cycle and between controls and women with PMS; however, they reported that women with PMS had a lower ratio between 5-HIAA and a dopamine metabolite levels [106]. A small number of positron emission tomography (PET) studies that measure metabolic processes have been conducted to examine serotonergic functioning in vivo in women with PMDD compared to controls. A study examining the change of serotonin 1A receptor binding potential from follicular to luteal phase found that women with PMDD had a much smaller change in the raphe nucleus compared to controls [107]. Although the study was conducted on a small sample size, this pilot suggests altered density of serotonin 1A receptors in those with severe PMDD.

Oestrogen and progesterone modify serotonergic transmission by altering the amount of available serotonin at synapses through its effects on their nuclear receptors that act as gene transcription factors. Several studies examining the effects of oestrogen administration using nonhuman primates have reported increased gene transcription of the enzyme responsible for synthesizing serotonin from tryptophan (tryptophan hydroxylase, TPH) and reduced transcription of the serotonin transporter, MAO-A (subtype which selectively degrades serotonin), and the auto-receptor serotonin 1A [108]. However, the modifying effect of oestrogen on the transcription of serotonin-related genes and proteins appears to depend on several factors that include type of receptor, brain area, and duration of oestrogen treatment [109]. Progesterone also has been shown to influence serotonergic functioning through regulating several of the same serotonin genes mentioned above [108].

Taken together, all of these results suggest that a complex interaction between serotonin, sex steroids, and other neurotransmitters are likely to contribute to the pathophysiology of PMDD, but the exact pathways and mechanisms remain to be found.

Brain-Derived Neurotrophic Factor One of the most important trophic factors that has been investigated in association with PMDD and plays an important role in neuronal growth and survival, as well synaptic signalling and synaptic plasticity, is brain-derived neurotrophic factor (BDNF). BDNF expression can be influenced by

a number of internal and external factors, including neurotransmitters, sex steroids, and stress [110]. Oestrogen has been shown to increase BDNF levels [111] and BDNF may mediate progesterone's effect on cognition and mood [112]. Alterations in BDNF serum levels have been found in various psychiatric and neurodegenerative diseases [113]. In premenopausal women, BDNF serum levels are higher in the luteal phase compared to the follicular phase [114]. In patients with PMDD, higher serum levels of BDNF were reported in the luteal phase compared to the follicular phase and were significantly higher in both phases of the menstrual cycle compared to controls [115, 116].

Genetics Results from twin and family studies have implicated genetic factors in the pathogenesis of PMDD, albeit mixed evidence. Candidate gene studies have largely focused on polymorphisms within several key neurotransmitter pathways, which include genes coding for the serotonin transporter (SERT), catechol-o-methyl transferase (COMT), MAO-A (MAOA), BDNF, and oestrogen receptors alpha and beta (ESR1 and ESR2, respectively). For an in-depth summary on the genetic basis of PMDD, please see McEvoy and colleague's paper [117].

A primary polymorphism within the SERT gene that has been widely investigated among several psychiatric disorders is the serotonin transporter-linked polymorphic region (5-HTTLPR), which is comprised of a 44-bp insertion/deletion polymorphism primarily composed of two alleles: the short (S) allele and long (L) allele. Some studies found no association between 5-HTTLPR and PMDD [105, 118], whereas one study found that the S allele was associated with neuroticism personality traits in women with PMDD [119]. No associations were found for polymorphisms in genes coding for COMT [120], ESR2 [120], or BDNF [121] with PMDD. An association was detected for variations within the ESR1 gene, but only for those with a specific Val/Val genotype from the COMT polymorphism [120]. Due to the limited number of studies that have investigated the genetics underlying PMDD, it remains unclear as to whether these genes contribute increased susceptibility.

Neuroimaging A sophisticated method for observing neural structure and function in vivo is through use of neuroimaging techniques, such as magnetic resonance imaging (MRI), functional MRI (fMRI), PET, and diffusion tensor imaging (DTI), to name a few. For a review of neuroimaging studies conducted across the menstrual cycle and in women with PMDD, see Comasco and Sundström-Poromaa's review [122]. Some studies have shown abnormal grey matter volume of several structures, including the hippocampal gyrus, parahippocampal gyrus, and cerebellum in women with PMDD [123, 124]. Abnormal regional cerebral blood flow was detected in women with PMDD across different hormone conditions, where greater activity was reported in the dorsolateral prefrontal cortex, medial frontal gyrus, and the cerebellum during a working memory task, which was also consistent with activation measured using functional magnetic resonance imaging (fMRI) [125].

Several studies have been conducted analysing emotional reactivity in women with PMDD. A whole brain analysis study assessing response to emotional faces showed that patients with PMDD had reduced activation in the fronto-cingulate cortex and increased frontal and parietal activation compared to healthy women [121]. Another study using the same paradigm but with a region of interest (ROI) approach found mid-follicular increased activity at the bilateral amygdala in PMDD compared to healthy women [126]. When dealing with social stimuli, women with PMDD showed greater activation in the amygdala and insula as compared to non-social stimuli, and bilateral amygdala activity to negative social stimuli was positively correlated with progesterone levels in the luteal phase in women with PMDD [127]. Altered reactivity was also detected in women with PMDD when anticipating negative emotional stimuli such that women recruited prefrontal cortex areas more so than

healthy controls [128]. Currently, there are a limited number of neuroimaging studies that have investigated women with PMDD, which makes drawing conclusions at this stage difficult and emphasizes an area that is desperately in need of future research.

Evidence-Based Treatment

Due to the complexity of premenstrual disorders, there is no single treatment that is effective for all women with PMS or PMDD. Current treatment strategies primarily target neurotransmitter function or hormonal fluctuations through inhibiting ovarian activity. For a more detailed review on available treatments, please refer to Yonkers and Simoni's paper [129] or Reid and Soares' paper [130]. This section will provide a current review of evidence-based treatments including those that modify neurotransmitter systems or induce ovarian cycle suppression, as well psychotherapies and alternative therapies.

Selective Serotonin Reuptake Inhibitors Pharmacotherapies, especially SSRIs, are the first-line treatment option for severe PMS and PMDD. Approximately 60% of women with severe PMS or PMDD respond to SSRI treatment [94]. Many randomized controlled trials (RCTs) have been conducted using the SSRIs paroxetine, fluoxetine, sertraline, citalopram, and escitalopram in treating PMS/PMDD and are more effective than placebo in treating symptoms overall [93]. Investigations into SSRI efficacy have often used continuous administration, while some studies investigated effects with intermittent use during the luteal phase only or following symptom onset. Regardless of administration method, SSRIs in general have shown improvement of premenstrual symptoms and overall functioning in women with PMS or PMDD [93]. This cannot be said of all SSRIs, as fluvoxamine has limited evidence supporting its beneficial actions and therefore should not be considered until sufficient evidence arises demonstrating its efficacy [131].

SSRI dosages used to treat PMDD are lower than what is commonly prescribed for depression, suggesting different underlying biological mechanisms between PMDD and depression. Recommended dosages for the SSRIs in treating severe premenstrual disorders are as follows: paroxetine 5–25 mg/day, fluoxetine 10–20 mg daily, sertraline 50–100 mg daily, citalopram 10–20 mg daily, and escitalopram 10–20 mg/day [130]. Other antidepressants that do not target serotonin functioning are less effective than SSRIs, further supporting that serotoninergic dysfunction is involved in PMDD. Guidelines illustrating practical treatment algorithms to follow for administering an SSRI for women with severe PMS or PMDD can be found in Steiner and colleague's paper [132].

Premenstrual symptoms have been reported to re-emerge following SSRI discontinuation [133]; therefore some women may require long-term treatment over reproductive years to ensure premenstrual symptom alleviation. Despite its efficacy, a proportion of women fail to respond to SSRIs, and long-term use may be accompanied by several adverse side effects, including nausea, fatigue, decreased libido, headaches, sweating, and insomnia, which were found to be dose dependent [93].

Serotonin-Norepinephrine Reuptake Inhibitors In addition to SSRIs, SNRIs have also been evaluated as a possible treatment option for women with PMDD. SNRIs are a newer class of medications and block reuptake of both serotonin and norepinephrine. Results from studies of RCTs and open-label trials using SNRIs to treat PMDD have shown that venlafaxine is effective in reducing premenstrual symptoms [134, 135]. Fewer studies have investigated the efficacy of duloxetine; however, results from open-label trials suggest that duloxetine is beneficial for treating PMDD symptoms [136]. Double-blind, placebo-controlled studies are needed to confirm if duloxetine is an effective treatment option. Common side effects reported for both venlafaxine and duloxetine include nausea and insomnia [134, 136]. When directly compared, SNRIs appear to be less effective than SSRIs for the

treatment of PMS [103]. Additionally, norepinephrine-dopamine reuptake inhibitors such as bupropion are not as effective as SSRIs [137], further supporting a greater involvement of serotonergic dysfunction in PMS/PMDD.

Oral Contraceptives Due to the timing of symptoms, it is expected that treatments that regulate the cyclical change in oestrogen and progesterone that naturally occur throughout the menstrual cycle would be effective for women with PMDD. Oral contraceptive pills that are a combination of 3 mg of drospirenone and 20 μg of ethinyl estradiol and are taken for 24 days, followed by 4 days of inactive pills, have been shown to be effective in treating PMDD in clinical trials [138]. However, drospirenone-containing medicines require consideration as they may be linked to higher risk of developing blood clots. Other progestin-containing oral contraceptives or oral contraceptives used continuously show inconclusive findings for treating PMS [129]. Women with premenstrual worsening of depression taking antidepressants found that adjunct use of combination oral contraceptive pills ameliorated premenstrual depression symptoms [139]. Oral contraceptives are beneficial treatment options for women seeking contraception, but its use has also been accompanied by side effects, such as nausea, breast pain, and inter-menstrual bleeding [140].

Gonadotropin-Releasing Hormone Agonists Another form of hormonal therapy to consider for women who do not respond well to SSRI or SNRI is ovulation suppression via GnRH agonists. GnRH agonists stimulate GnRH receptors on the pituitary, which become desensitized with continuous administration and leads to reduced secretion of LH and FSH [141]. GnRH agonists replaced use of danazol, a synthetic steroid that was shown to be successful in treating PMDD at higher dosages but was also associated with adverse androgenic side effects (acne, hair growth, voice deepening) [142]. For the treatment of PMDD, GnRH agonists are 60–75% effective when compared to placebo [143]. It is important to note that GnRH agonist places the body in a state of hypoestrogenism, and long-term use is accompanied by adverse side effects such as hot flashes, bone mineral density loss, and decreased libido [143]. Hormonal add-back therapy is a strategy often used to counteract these adverse side effects and doesn't appear to influence efficacy [144].

Surgical Menopause Hysterectomy or oophorectomy can also be considered in women with severe PMDD that do not respond to other treatments; however this option is the most invasive and should only be used as a last resort. Before consideration of this treatment, confirmation that premenstrual symptoms can be alleviated and tolerated with ovulation suppression via GnRH agonist is highly recommended.

Anxiolytics Several anxiolytic medications have been tested for the treatment of premenstrual symptoms. Alprazolam, when used intermittently in the luteal phase, has been reported as being effective in some [145, 146], but not all studies [147]. Its use requires careful consideration as there is a risk for misuse and dependence. Buspirone has also been found to reduce some premenstrual symptoms, such as irritability [148], and is associated with a lower risk for medication abuse or dependence. These medications are typically considered as an adjunct for women who do not respond to SSRI or hormone regulation treatment [149].

Cognitive Behavioural Therapy Cognitive behavioural therapy (CBT) has also been tested in the treatment of PMS and PMDD. The beneficial effects of CBT appear to involve modifying negative thoughts and improve coping strategies to better handle premenstrual distress. Symptom severity following CBT was reduced in several studies, but a recent meta-analysis found small to medium effect sizes [150]. One study reported that CBT was equally as effective as the SSRI fluoxetine after 6 months of treatment, with no additive combined effects [151]. Specifically, fluoxetine induced earlier onset of symptom alleviation and had a greater impact on anxiety symptoms, while CBT was associated with the

use of more coping strategies and may be associated with greater long-term efficacy. A major limitation to use of CBT is cost and lack of available resources, as it must be delivered by a trained healthcare practitioner or psychologist.

Diet, Lifestyle Changes, and Alternative Therapies The use of complementary and alternative medicine (CAM) to alleviate premenstrual symptoms has been investigated over several decades. These approaches are non-pharmacological and reflect healthy habits. Women, especially those suffering from PMDD, are more likely to try CAM, and these options may be favoured over other medical treatments [152]. Despite the skepticism that surrounds CAM, many have been scientifically tested using RCTs. Therefore, the following will primarily focus on RCTs and systematic reviews that have investigated herbal medicine, diet, exercise, and other therapies in women with PMS/PMDD.

A systematic review of RCTs for herbal remedies in the treatment of PMS found that *Vitex agnus-castus* (also known as chasteberry) was the most well studied, and it has been consistently reported as effective in alleviating premenstrual symptoms over placebo [153, 154]. The potential mechanism by which chasteberry acts to reduce affect and physical symptoms in premenstrual disorders are unknown, but it may be through effects on the dopaminergic system [155]. *Ginkgo biloba* (also known as maidenhair tree) and *Crocus sativus* (also known as saffron crocus) were also found to be effective over placebo, but these results require replication. No beneficial effect was found for *Oenothera biennis* (also known as evening primrose) and *Hypericum perforatum* (also known as St. John's wort). It is important to note that these trials used relatively small samples, did not include severe cases of PMDD, and were not associated with any major health risks or adverse outcomes [153].

It is hypothesized that serotonin availability can be altered via diet, and a prominent theory postulates that levels of tryptophan increase following ingestion of complex carbohydrates. Two RCTs reported improvements in premenstrual symptoms following the ingestion of a carbohydrate-rich beverage compared to an isocaloric placebo drink [156, 157]. A different study administered L-tryptophan amino acid to women with PMDD found a significant effect on alleviating premenstrual mood symptoms compared to placebo [97].

Supplements, such as vitamin B6 and calcium, have also been widely studied due to their involvement in neurotransmission. Vitamin B6 is a cofactor in the tryptophan-serotonin synthesis pathway and calcium modulates neurotransmission by regulating neurotransmitter release. A systematic review reported beneficial actions of vitamin B6 (up to 100 mg/day) in treating premenstrual symptoms, but the authors cautioned their conclusions due to the low methodological quality of trials included [158]. Calcium supplements were reported effective in treating mood and somatic symptoms in women with PMS in several RCTs [159], with dosages as low as 500 mg/day [160].

From the existing literature, there is evidence that aerobic exercise intervention may help prevent or alleviate premenstrual symptoms in women who experience milder forms of PMS [161]. Exercise is often recommended by general practitioners for alleviating premenstrual symptoms, and its contribution to greater general health and well-being in all individuals is well recognized. In studies surveying treatment practices for premenstrual symptoms, women report exercise as one of the most commonly tried and effective treatments [162]. Women may also be more willing and compliant to this type of intervention over other pharmacotherapy treatments due to adverse side effects that commonly occur with pharmaceuticals; however, this treatment option may only be effective for women with milder forms of PMS.

A systematic review conducted on the effects of acupuncture treatments which contained studies with different techniques, varying number of sessions and administration periods throughout the menstrual cycle found that hand moxibustion, which involves a burning and warming stimulation of specific points on the hand, was associated with the highest improvement in overall premenstrual symptoms [163].

Other therapies that include light or sleep deprivation that are aimed at correcting circadian rhythm abnormalities in women with PMDD have also been investigated [164]. Premenstrual symptom alleviation was observed following exposure to bright white light in the evening compared to red dim light [165].

The evidence supporting use of CAM or other therapies to treat premenstrual disorders is limited. Most of the research conducted to date has focused on milder forms of PMS, lacked controls, and have yet to be tested in women with prospectively defined PMDD. However, some results are promising and demonstrate a need for replication using rigorous methodology to better determine the effectiveness of these therapies in treating PMS or PMDD.

Conclusions and Future Directions

The inclusion and recognition of PMDD in the DSM-5 was a monumental milestone for those researching or suffering from this debilitating disorder. Despite this achievement, there are still many gaps in our understanding and treatment of PMDD that require direct investigation.

SSRIs are currently considered a first-line treatment for PMDD, in addition to those that suppress ovarian hormone function; however, several factors should be considered when choosing an appropriate treatment. These factors include severity of premenstrual symptoms, prior treatment use and response, personal preferences, and future reproductive plans. It may be that different subtypes of PMDD exist based on clinical presentation that respond differently to treatment options or require different administration instructions (i.e. different dosage, longer duration, etc.). If this is the case, then research identifying homogeneous groups within PMDD is warranted and would provide great improvements to current diagnostic and treatment practices.

If ALLO sensitivity or effects on GABA-mediated neural activity play a significant role in the aetiology of PMDD, then novel treatments that target ALLO or GABA neurotransmission should be explored in the future. There is also a need for the discovery or development of other alternative therapies that may better target specific premenstrual symptoms or overall symptom complaints. In addition to finding novel treatments, future studies should aim to determine possible predictors of response to current treatment options to help determine an appropriate first-line treatment that is tailored to the patient.

Lastly, awareness and validation of premenstrual complaints are important for reducing the possible stigma attached to women's symptoms and will more effectively reduce barriers for women seeking treatment for severe premenstrual distress.

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Depressive and Cognitive Disorders in Climacteric Women

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Introduction

Perimenopause is a natural physiological event that occurs in women and is defined by the World Health Organization (WHO) as the permanent cessation of menstruation and a decrease in the levels of ovarian steroid hormones (estrogen and progesterone) due to the loss of ovarian follicular function.

The final menstrual period is retrospectively assigned after 12 consecutive months of amenorrhea in the absence of other pathological or physiological causes [1].

These changes are most pronounced in the 2 years prior to, and the 2 years after, the final menstrual period. Menstrual cycle changes may occur as early as 4–8 years prior to menopause, though the average duration of perimenopause is 4 years [2].

It generally occurs around the age of 50 years, with a range between 40 and 60 years worldwide [1, 3].

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Before 2001, the perimenopause was described as a phase with changed lengths of the menstrual cycle length compared to the established premenopausal pattern [2].

In 2001 consensus was reached with the Stages of Reproductive Aging Workshop (STRAW) criteria for defining menopausal stages. The latest consensus criteria for staging reproductive aging (STRAW+10) are based on self-reported bleeding patterns [2].

Perimenopause is defined as encompassing three stages:

- Early menopausal transition: persistent cycle irregularity, defined as ≥7 day difference in length of consecutive cycles at least twice over the previous 10 cycles
- Late menopausal transition: an interval of amenorrhea of ≥60 days in the previous 12 months
- Early postmenopause: the first year following the final menstrual period (FMP) [2]

STRAW+10 further delineates early postmenopause as encompassing the first 6 years following the FMP and late postmenopause as encompassing the remaining life span; however only the first year following the FMP is part of perimenopause [2].

During perimenopause, women might experience vaginal dryness that leads to reduced libido, dyspareunia, frequent infections in the urogenital system, urinary incontinence, and pelvic organ pro-

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lapse and other symptoms like hot flashes, night sweats, sleep disturbances, and memory complaints, osteoporosis, and metabolic changes [3–5].

Depression is a broad and heterogeneous diagnosis, with depressed mood and/or loss of pleasure in activities at the core. Severity is judged by the number and severity of symptoms as well as the degree of functional impairment [6].

Major depressive disorder (MDD) is one of the most prevalent and disabling illnesses. In 2020, MDD is expected to become the second leading cause of disability worldwide. The negative impact of this disorder on quality of life is comparable to or greater than that of other chronic medical illnesses [6].

It is one of the leading causes of disease-related disability in women, and they are nearly twice as likely, compared with men, to suffer from an episode of depression. This difference begins early in life (adolescence) and persists through the mid-50s. Therefore, it would appear that women are more at risk of depression during their reproductive years [6].

Multiple lines of evidence have implicated estrogen signaling as contributing to this sex difference. Females show an increased risk of MDD during the perimenopausal period, a reproductive stage characterized by fluctuations in estradiol. Estrogen modulates serotonergic and noradrenergic function, both of which are central to affective processing [7].

Twin and family-based studies indicate a significant genetic component to MDD, and heritability is highest with severe, recurrent, and early-onset forms of the disease [6].

Cognitive symptoms reported by women at menopause include difficulties in memory, attention, and word-finding. A study of cognitive change across the menopause transition showed that performance on a number of cognitive tasks, including recognition speed, concept integration, and psychomotor skill declined at a faster rate immediately after menopause than would have been predicted by age alone, suggesting an acceleration of decline due to loss of estradiol [8].

The regulatory effects of estrogen on choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) are particularly relevant to cognition given the key role of cholinergic transmission in learning, memory, and Alzheimer's disease [7].

Several studies suggest that cognitive function supported by the prefrontal cortex may be particularly sensitive to estrogen [2].

Perimenopausal Depression

Symptoms of depression can be psychological, physical, and/or social. Psychological symptoms may include feelings of low mood, sadness, hopelessness, low self-esteem, feelings of guilt, irritability and intolerance, a lack of motivation or interest, difficulty in making decisions, and thoughts of self-harm or suicide. Physical symptoms include changes in sleep pattern, changes in weight and appetite, unexplained aches and pains, and a lack of energy or loss of interest in sex. Social symptoms include reduced productivity at work, avoidance of social activities and friends, and difficulty with home and family life [6].

In the perimenopausal period, 20–30% of women experience depressive disorders that require treatment, and up to 90% of women show weaker mood disorders, i.e., difficulty concentrating, irritability, and emotional lability as a direct result of hormonal changes [4].

Estrogen facilitates synaptogenesis, induces growth factor production, protects against oxidative stress, and regulates neurotransmission (e.g., serotonin, norepinephrine, and acetylcholine) in brain systems associated with cognition and mood. Estrogen activity in the brain is mediated through activation of intracellular, transmembrane, and membrane-bound estrogen receptors (ERs) along with non-genomic mechanisms. There are two subtypes of estrogen receptors, ERα and ERβ. ERα and ERβ receptor subtypes are members of the superfamily of nuclear receptors that regulate transcription in target genes containing estrogen response binding elements. Both ERα and ERβ receptor subtypes are located in brain regions associated with cognitive function and emotion. The ERα receptor is predominantly expressed in the hypothalamus and amygdala, areas involved in autonomic function, emotional regulation, and associative and emo-

tional memory. The ERβ receptor is predominantly expressed in the hippocampal formation and entorhinal cortex, brain areas involved in declarative memory [7].

Patients who developed MDD have altered peripheral levels of neurotrophins, such as brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF). In addition, oxidative stress parameters such as lipoperoxidation, and inflammatory markers such as interleukin 6 (IL-6), interleukin 10 (IL-10), and tumor necrosis factor alpha (TNF-α) were also found to be altered in individuals with MDD. These data suggest that MDD may be associated with changes in neurotrophic, oxidative stress markers, and pro-inflammatory cytokines [9].

Depressive symptoms during the menopausal transition could represent the re-occurrence of preexisting disorders or reflect a general vulnerability to develop mental health problems during stressful life events [3].

Literature to date seems to suggest that not all women respond to, or experience, the transition to menopause in the same way.

There is controversy about the true incidence of disorders such as depression during the transition to menopause, with accumulating evidence that only a minority of mid-life women actually experience morbid psychological symptoms [10].

In 2006, two large cohort studies found that the menopause transition is associated with an odds ratio of 1.8–2.5 for first-onset MDD, suggesting the existence of a "window of vulnerability" during the years immediately preceding the menopause. During this period, women often suffer from hot flashes, night sweats, and difficulty sleeping, all of which have been reported to be associated with depression. In addition, concomitant changes in sex hormones, metabolism, sexuality, and lifestyle can also impact on quality of life and contribute to the development of MDD [9].

The Penn Ovarian Ageing Study provides evidence in support of these findings and describes a diagnosis of depressive disorder 2 1/2 times more likely to occur in the menopausal transition compared with when the woman was premenopausal. Within-woman change in menopausal status, increased levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and increased variability of estradiol, FSH, and LH around the woman's own mean levels were each significantly associated with high scores from the Centre for Epidemiological Studies of Depression scale (CES-D), after adjustments were made in smoking, BMI (body mass index), flushes, and other socioeconomic factors [6].

On the other hand, recent studies found no relationship between the prevalence of major depressive disorder and menopausal status. Longitudinal studies have been more consistent in finding that the menopause transition is associated with a substantial increase in vulnerability to clinically significant depressive symptoms, with odds ratios ranging from 1.33 to 1.79; this increased vulnerability is also observed in longitudinal studies in women with no history of major depression [11].

The Harvard Study of Moods and Cycles, a population-based prospective study of premenopausal women with and without a lifetime history of major depression, demonstrated a twofold increase in the risk of significant depressive symptoms in those who entered the perimenopause, compared with those women who remained premenopausal, after adjustment for age at study enrolment and history of negative life events. The increased risk for depressive symptoms was somewhat greater in women with self-reported vasomotor symptoms [6].

Kruif [12] published a review which shows that the odds for the occurrence of clinical depression are not significantly increased for women in the perimenopause compared to those in premenopause. The odds of depressive symptoms in perimenopause are doubled when compared to premenopause and similar when compared to postmenopause. Additionally, during the perimenopausal phase, women report a higher level of depressive symptom severity when compared to premenopause, but they do not report this when the comparison is to the postmenopause phase. Furthermore, there are indications of a positive relation between vasomotor complaints and depression during the perimenopause.

Etiology

The transition to menopause results from a complex interaction of internal (i.e., physiological, psychological) and external factors (i.e., social) factors [13].

There is evidence to suggest that women vulnerable to perimenopausal depression exhibit a greater "hormonal sensitivity" to the endocrine profile of the menopause transition for having both a history of premenstrual dysphoric disorder (PMDD) and a history of postpartum depression – two disorders for which reproductive hormonal flux may be pathophysiologically relevant – each of them strong predictors of perimenopausal depression [11].

While the etiology of perimenopausal depression is not well understood, most studies suggest it is not simply due to low basal hormone concentrations.

Some studies have evaluated the hormone variability hypothesis by examining naturally occurring fluctuations in ovarian hormones in relation to mood among women in the menopause transition [11].

The first of these, the Massachusetts Women's Health Study, measured serum estradiol annually for 3 years in 309 women ranging from premenopausal to postmenopausal (STRAW stages −3 to 11) and found no association between estradiol variability and CES-D score [11].

In a subset of participants in the Seattle Midlife Women's Health Study, CES-D score was not associated with a urinary metabolite of estradiol, FSH, or testosterone in 131 women in STRAW stage −3 or −2 at baseline [11].

Beginning in 1995, The Study of Women's Health Across the Nation (SWAN) tried to determine if the menopausal transition or postmenopause increases the risk for elevated depressive symptoms and/or disorder. SWAN included a standard measure of depressive symptom, estradiol or FSH levels in its baseline, and annual assessments [14].

The conclusion, over 10 years in SWAN cohort, was not associated with depressive symptoms and estradiol or FSH variability. However, regardless of the menopausal status, testosterone levels and the change (increase) in testosterone from baseline were positively associated with CES-D score. While, overall, the above studies do not support a relation between estradiol or FSH variability and mood, the absence of a positive finding may be related to the infrequent hormone sampling [14].

In contrast, considering 8 years in the Penn Ovarian Aging Study, the results showed that clinical elevations in depressive symptoms and syndromal major depressive disorder were more likely to occur at times when estradiol variability was highest. Relationship between estradiol variability and depressive symptoms continued to be significant after adjustment for increases in poor sleep, which may also accompany periods of increased hormonal flux [11].

Future research using more frequent assessments of depressed mood and ovarian hormone concentrations and isolating depression with onset during the menopause transition may therefore more definitively implicate the involvement of hormonal variability in the etiology of perimenopausal depression [11].

Another possible mechanism that explains the etiology of premenopausal depression is how reproductive steroid regulate the gamma-aminobutyric acid receptor (GABA) on the hypothalamic–pituitary–adrenal (HPA) axis [11].

Allopregnanolone (3a-hydroxy-5a- pregnan-20-one; ALLO) is a neurosteroid derived from progesterone, and it is stress responsive in animals and humans and serves as a potent, positive allosteric modulator of $GABA_A$ receptors through dose-dependent enhancement of GABA-induced chloride-ion channels [11].

GABA is the chief inhibitory neurotransmitter in the central nervous system, and its role is to regulate the HPA axis in response to stress by limiting the extent and duration of the HPA axis stress. In part, it is through ALLO's modulation of the $GABA_A$ receptor to increase GABA-ergic transmission that ALLO not only negatively modulates the HPA axis to return it to homeostasis following stress (50) but also exerts profound anxiolytic (51) and antidepressant (52) actions [11].

Two major sources of ALLO in women of reproductive age are the adrenal glands and the corpus luteum, where ALLO is converted from progesterone. Because of ovarian ALLO contributions, ALLO concentrations in premenopausal women are at its highest in the luteal phase and its lowest in the follicular phase. However, in postmenopausal women, the adrenal glands become the exclusive source of peripheral ALLO [11].

An increasing proportion of anovulatory cycles results in less frequent luteal phases and therefore overall lower levels of progesterone. Although the availability of progesterone is an important determinant of ALLO, estradiol is also likely to positively influence ALLO production through its modulation of the enzymes involved in the conversion of progesterone to ALLO, 5a-reductase and 3a-hydroxysteroid dehydrogenase [11].

ALLO fluctuation may have important implications at the $GABA_A$ receptor and could result in either too high or too low GABA-ergic inhibitory tone. So fluctuating ALLO concentrations in the menopause transition would be critical in determining overall GABA-ergic tone, mood, and, theoretically, regulation of the HPA axis [11].

To the extent that GABA-ergic dysregulation is involved in perimenopausal depression, genes coding for $GABA_A$ receptor subunits may be implicated in predisposing some individuals to respond maladaptively to ALLO fluctuations and thus be at increased risk of perimenopausal depression [11].

Risk Factors

A history of major depressive disorder is the strongest predictor of both elevated depressive symptoms and syndromal depression in the menopause transition, with odds ratios of 4–6. Also a history of premenstrual dysphoric disorder (PMDD) and postpartum depression are related to depressive symptoms and depression during the menopausal transition [11, 12].

Psychosocial stress, including unemployment, financial strain, lack of social support, and stressful life events proximate to the menopause transition also predict increased risk for both depressive symptoms and syndromal major depressive disorder. Poor sleep during the menopause transition, independent of night sweats, has been associated with an increased risk of perimenopausal depression [11].

Neuroticism plays an important role in the persistence of depression among climacteric women after 30 months. People with high levels of neuroticism tend to experience more distress. Climacteric women with high neurotic tendencies are more likely to experience psychological pain and therefore may be more predisposed to experience more depressive symptoms in the future. Individuals with high levels of neuroticism exhibit sensitivity to negative stimuli, resulting in a range of negative moods that are likely to predispose them to chronic depression [15].

Vasomotor symptoms (VMS) are also referred to as a hot flash/flush or, when they occur at night, night sweats occurring in approximately 75–80% of women. A hot flash typically begins as an abrupt onset sensation of heat beginning in the upper chest, quickly rising to the face, which can rapidly become generalized throughout the body. A hot flash is an elevation in body temperature, accompanied typically by an increase in heart rate and perspiration, usually lasting between 1 and 5 min long. Night sweats usually wake women up in a cold sweat, and their sheets and pajamas are usually soaked from the sweat. VMS can be quite disruptive, interfering with a woman's ability to work or sleep [16].

The mechanism of VMS is not completely understood; however, it is due to a changed thermoregulation set point of the hypothalamus evoked by the abruptly lowered estrogen levels during menopause. Estrogen interacts with neurotransmitters, such as norepinephrine and endogenous opioids, as well as serotonin, and thereby alters the temperature regulation set point in the hypothalamus. Postmenopausal women show a diminished serotonergic activity compared to premenopausal controls [17].

There are three categories describing the severity of hot flashes: mild, feeling hot without

perspiration; moderate, feeling hot with perspiration and without disruption of activity; and severe, feeling hot with perspiration and causing a disruption or cessation of activity [16].

Vasomotor symptoms in the menopause transition are also associated with an increased risk of elevated depressive symptoms. While the relationship between vasomotor symptoms (VMS) and depressive symptoms is multifactorial, some evidence suggests that increasingly erratic ovarian hormone fluctuation may represent a shared mediator of risk for both vasomotor symptoms and perimenopausal depression [11].

According to a recent American College of Obstetricians and Gynecologists report, previous clinical guidelines suggested that most women experience hot flashes from 6 months to 2 years, but epidemiological studies found durations between 5 and 13 years [18].

Using SWAN cohort, it was observed higher degrees of perceived stress, anxiety, depressive symptoms, and symptom sensitivity that were independently related to longer total VMS duration or longer post-final menstrual period (FMP) persistence herein extend previous findings that these psychological factors are related to VMS prevalence [18].

Women who were premenopausal or early perimenopausal when they first reported frequent VMS had the longest total VMS duration (median, >11.8 years) and post-FMP persistence (median, 9.4 years) [18].

Women who were postmenopausal at the onset of VMS had the shortest total VMS duration after the FMP (median, 3.4 year) [18].

The median total VMS duration varied significantly by race/ethnicity. African American women reported the longest total VMS duration (median, 10.1 years), and Japanese and Chinese women had the shortest total VMS durations (median, 4.8 and 5.4 years, respectively). The median total VMS durations were 6.5 years for non-Hispanic white women and 8.9 years for Hispanic women [18].

Total VMS duration was also significantly longer in those with younger age at first report of VMS, in ever smokers, and in women with greater body mass index (BMI) and higher symptom sensitivity, anxiety, perceived stress, and depressive symptoms. Total VMS duration was significantly shorter in women who were currently married or partnered, in women who had higher educational level and less financial strain, and in women who had greater social support. Neither sports physical activity nor alcohol servings per week were statistically significant [18].

Penn Ovarian Aging Study found that a more rapid rise in FSH prior to the final menstrual period predicted a decreased risk of elevated depressive symptoms after the final menstrual period, suggesting that a shorter menopause transition may protect against perimenopausal depression [11].

Guerin [13] found that better general health perceptions going into the transition to menopause showed potential for being an important protective factor against depression, as well satisfaction with body size and shape and higher self-esteem.

Indeed the various hormonal and social transformations that accompany the transition to menopause can become sources of distress, such as changes in the family structure, children leaving home, changes at work, possibly retirement, additional caregiving responsibilities, for parents or in-laws [6].

A chronical medical condition, including cardiovascular disease, musculoskeletal disorders, cancer, cognitive decline and dementia, chronic obstructive pulmonary disease, diabetes mellitus, metabolic syndrome, sleep disturbances, and migraine are predictors of a first onset of major depression during midlife [12].

Treatment

The hormone therapy (HT) – estrogen therapy (ET) with or without progestogen – is the most effective treatment of climacteric symptoms including vaginal symptoms, sexual function, urinary tract health, osteoporosis, and vasomotor symptoms [19].

However, hormone therapy is contraindicated in, or is not acceptable for use by, some post-

menopausal women or women with high risk for breast and endometrial cancer [19].

A global consensus on the use of HT was reached by The American Society for Reproductive Medicine, The Asia Pacific Menopause Federation, The Endocrine Society, The European Menopause and Andropause Society, The International Menopause Society, The International Osteoporosis Foundation, and The North American Menopause Society. They stated that HT "is the most effective treatment for vasomotor symptoms associated with menopause at any age, but benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause" [17].

The cardiovascular effects depend on the onset of use of hormone therapy. The women who initiate HT more than 10 years after menopause are at increased risk for coronary heart disease, and those women who initiate HT within 10 years of menopause tend to have a lower risk of coronary heart disease [19].

Besides HT, various antidepressant drugs (e.g., selective serotonin re-uptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)) have been studied to treat postmenopausal symptoms, and they reduce the frequency and severity of hot flashes in menopausal and postmenopausal women [19, 20].

The North American Menopause Society concluded that multiple non-hormonal therapies are appropriate considerations for menopausal and postmenopausal hot flashes.

They recommended paroxetine salt 7.5 mg/day; paroxetine or paroxetine ER 10–25 mg/day; escitalopram 10–20 mg/day; citalopram 10–20 mg/day; desvenlafaxine 50–150 mg/day; and venlafaxine XR 37.5–150 mg/ day. Patients should be started at the lowest available dose and titrated up as needed [20].

Paroxetine is only available in 7.5 mg and is currently the only drug FDA-approved for hot flashes [20].

The most common side effects reported for both SSRIs and SNRIs are nausea and constipation, with most resolving within the first week of treatment. SNRIs have been associated with increased blood pressure in some patients and should be used with caution in women with hypertension [20].

It is important to note that women with a history of breast cancer and those taking tamoxifen should avoid SSRIs. An endoxifen, an active metabolic form of tamoxifen, is formed by a CYP2D6-mediated reaction. SSRIs and, in particular, fluoxetine and paroxetine as the strongest CYP2D6 inhibitors may therefore prevent the formation of the active metabolite from inactive tamoxifen and put breast cancer patients under anti-estrogenic treatment at an increased risk of breast cancer recurrence. SNRIs are the safest drugs for this population [17].

The antidepressant use is beneficial for two reasons: first, many patients with climacteric symptoms suffer from depressive symptoms, and second, antidepressant drugs acting on synaptic serotonin concentrations may beneficially interfere with the pathophysiology of hot flashes [17].

The results of effect of HT on mood for postmenopausal women without history of depression are mixed. Some short-term trials suggested that HT improves mood, whereas others showed no change. Postmenopausal women with a history of perimenopause-related depression responsive to HT may experience a recurrence of depressive symptoms after estradiol withdrawal [21].

The Revised Global Consensus Statement on Menopausal Hormone Therapy states that "menopausal hormone therapy (MHT) may be beneficial in improving mood in early postmenopausal women with depressive and/or anxiety symptoms. MHT may also be beneficial for perimenopausal women with major depression but antidepressant therapy remains first-line treatment in this setting" [6].

Cognition

The term cognition refers to brain processes by which knowledge is acquired, stored, and used. Cognition encompasses attention and concentration, learning and memory, language, complex

perceptual and motor abilities, and also planning, judgment, and reasoning.

Cognitive abilities vary with age. In many instances, age-associated changes involve an erosion of skills. This is a process that begins insidiously in early adult life or middle age, accelerates during old age, and affects both episodic memory and executive functions [22].

The complexity in the menopause transition is marked initially by fluctuating levels of ovarian hormones and ends with an overall dearth of estrogen in the postmenopausal period [23–25]. During this transition, many women report experiencing a decline in cognitive function specifically in areas of memory and attention. Evidence on this reduction of cognitive ability is due to the decline in estrogen experienced during menopause and to memory impairment [2].

The brain is an important target organ for estrogens. The influence of estrogens on cognition could be explained from the wide distribution of two classes of intracellular estrogen receptors (ERs), α and β, that are expressed within specific areas of human brain, like the hippocampal formation (HF), amygdala, and cerebral cortex, regions that are involved in the processing of learning and memory.[26].

Other areas containing ERs are the prefrontal cortex, thalamus, basal forebrain, hypothalamus, amygdala, hippocampus, posterior cingulate, locus coeruleus, and raphe nucleus, which confirm an involvement of estrogens on cognitive functions in physiological as well as in pathological conditions [26]. Aging can impact on brain regions that are critical for the regulation of attention, learning, and memory.

Many of the biochemical, structural, and functional changes involve estrogen levels. Whereas the function of some cognitive domains, such as language and reasoning skills, is often maintained throughout the life span, age-related deficits are frequently noted in other areas including declarative memory and attentional processes [2, 25, 27].

The prefrontal cortex region of the brain has been implicated in planning complex cognitive behavior, personality expression, decision making, and moderating social behavior [28]. The basic activity of this brain region is considered to be orchestration of thoughts and actions in accordance with internal goals. Frontal cortex supports concrete rule learning. More anterior regions along the rostro-caudal axis of frontal cortex support rule learning at higher levels of abstraction [29].

The most typical term for functions carried out by the prefrontal cortex area is executive function. Executive function relates to abilities to differentiate among conflicting thoughts and determine future consequences of current activities, working toward a defined goal, prediction of outcomes, expectation based on actions, and social control (the ability to suppress urges that, if not suppressed, could lead to socially unacceptable outcomes). It also relates to the concept of working memory used by proponents mostly on the short-term maintenance of information and rather less on the manipulation or monitoring of such information or on the use of that information for decisions [30].

The executive function of the brain is the set of cognitive processes that allow the cognitive control of behavior: selecting and successfully monitoring behaviors that facilitate the attainment of chosen goals [31–33]. Executive functions include the ability to filter information and tune out irrelevant stimuli with attentional control and cognitive inhibition; the ability to process and manipulate information held in working memory; the ability to think about multiple concepts simulating information held in working memory; the ability to think about multiple concepts simultaneously and switch tasks with cognitive flexibility; the ability to inhibit impulses and prepotent responses with inhibitory control; and the ability to determine the relevance of information or appropriateness of an action [31–33]. Higher-order executive function require multiple cognitive processes including processes like planning, reasoning, and problem solving [32, 34]

The thalamus has multiple functions, generally believed to act as a relay station, major or hub, relaying information between different subcortical areas and the cerebral cortex [35]. A major role of the thalamus is support of motor

and language systems, and much of the circuitry implicates for these systems is shared. The thalamus is functionally connected to the hippocampus [36] as part of the extended hippocampal system at the thalamic anterior nuclei [37], with respect to spatial memory and spatial sensory datum they are crucial for human episodic memory and rodent event memory [38, 39].

The basal forebrain (BF) plays key roles in multiple brain functions, including sleep-wake regulation, attention, and learning/memory, but the long-range connections mediating these functions remain poorly characterized. The BF has been implicated in a variety of brain functions such as arousal, attention, and neuronal plasticity or learning [40]. To investigate further the cholinergic specificity of the effects of basal forebrain lesion, the disruption of attentional performance is induced.

The basal forebrain is a term for a group of structures that lie near the bottom of the front of the brain, including the nucleus basalis, diagonal band, medial septum, and substantia innominate. These structures are important in the production of a brain chemical called acetylcholine, which is then distributed widely throughout the brain. Acetylcholine affects the ability of brain cells to transmit information to one another and also encourages plasticity or learning. Thus, damage to the basal forebrain can reduce the amount of acetylcholine in the brain and impair learning. This may be one reason why basal forebrain damage can result in memory impairments such as amnesia and confabulation. One common cause of basal forebrain damage is aneurysm of the anterior communicating artery [41].

The hypothalamus is responsible for the regulation of certain metabolic processes and other activities of the autonomic nervous system (ANS). It synthesizes and secretes certain neurohormones, called releasing hormones or hypothalamic hormones, and these in turn stimulate or inhibit the secretion of pituitary hormones [42].

The hypothalamus controls body temperature, hunger, important aspects of parenting and attachment behaviors, thirst, fatigue, sleep, and circadian rhythms. Memory is controlled in its posterior region, area medial, and mammillary nuclei (part of mammillary bodies). Area lateral and tuberomammilary nucleus are responsible for arousal (wakefulness and attention), feeding and energy balance, learning, memory, and sleep [43].

The amygdala – shown in research to perform a primary role in the processing of memory, decision-making, and emotional reactions – are considered part of the limbic system [44]. There are functional differences between the right and left amygdala [45]. The right hemisphere is also linked to declarative memory, which consists of facts and information from previously experienced events and must be consciously recalled. It also plays a significant role in the retention of episodic memory. This type of memory does not require conscious recall. The right amygdala plays a role in the association of time and places with emotional properties. Other evidence suggests that the left amygdala plays a role in the brain's reward system. The right and left portions of the amygdala have independent memory systems, but work together to store, encode, and interpret emotion [46].

The amygdala is also involved in the modulation of memory. Following any learning event, the long-term memory for the events is not formed instantaneously. Rather, information regarding the event is slowly assimilated into long-term storage over time, possibly via long-term potentiation. Recent studies suggest that the amygdala regulates memory consolidation in other brain regions [47].

The raphe nuclei have a vast impact upon the central nervous system. Many of the neurons in the nuclei are serotoninergic and are modulated through fibrous pathways in the midbrain [48].

The rostral raphe nuclei, both the median raphe nucleus and particularly the dorsal raphe nucleus, have long been implicated in depression. Some studies have suggested that the dorsal raphe may be decreased in size in people with depression and, paradoxically, an increase cell density in those commit suicide [49–51].

The locus coeruleus is a nucleus in the pons of the brainstem involved with physiological responses to stress and panic. It is a part of the reticular activating system. The locus coeruleus

is the principal site for brain synthesis of norepinephrine (noradrenaline). The locus coeruleus and the areas of the body affected by the norepinephrine it produces are described collectively as the locus coeruleus-noradrenergic system or LC-NA system [52]. In adult humans (19–78), the locus coeruleus has 22,000–51,000 total pigmented neurons that range in size between 31,000 and 60,000 μm^3 [53].

It is related to many functions via its widespread projections. The LC-NA system modulates cortical, subcortical, cerebellar, brainstem, and spinal cord circuits. Some of the most important functions influenced by this system are [54, 55] arousal and sleep-wake cycle, attention and memory, behavioral flexibility, behavioral inhibition and stress (psychological), cognitive control, emotions, neuroplasticity, and posture and balance. The locus coeruleus is a part of the reticular activating system and is almost completely inactivated in rapid eye movement sleep [56]. Alterations in the locus coeruleus (LC) accompany dysregulation of norepinephrine function and are likely to play a key role in the pathophysiology of these neuropsychiatric disorders [57].

The hippocampus is located in the medial temporal lobe of the brain. Areas of the hippocampus are shown to be functionally and anatomically distinct. The hippocampus belongs to the limbic system and plays important roles in the consolidation of information from short-term memory to long-term memory and also in spatial memory that enables navigation. The hippocampus is located under the cerebral cortex [58].

Psychologists and neuroscientists generally agree that hippocampus plays an important role in the formation of new memories about experienced events (episodic or autobiographical memory) [59, 60]. Part of this function is hippocampal involvement in the detection of new events, places, and stimuli [61]. Some researches regard the hippocampus as part of a larger medial temporal lobe memory system responsible for general declarative memory (memories that can be explicitly verbalized – these would include, e.g., memory for facts in addition to episodic memory) [62].

Episodic memory is the memory of autobiographical events that can be explicitly state or conjured. Semantic and episodic together make up the category of declarative memory, which is one of the two major divisions of memory – the other is implicit memory [63]. The term episodic memory was coined by Endel Tulving in 1972.

Due to bilateral symmetry, the brain has a hippocampus in each cerebral hemisphere. If damage to the hippocampus occurs in only one hemisphere, leaving the structure intact in the other hemisphere, the brain can retain near-normal memory function [64]. Damage to the hippocampus does not affect some types of memory, such as the ability to learn new skills. This fact suggests that such abilities depend on different types of memory (procedural memory) and different brain regions [65].

As it has a role in spatial memory and navigation, when the hippocampus is dysfunctional, the orientation is affected, and people may have difficulty in remembering how they arrived at a location and how to proceed further [66].

Age-related conditions have a severe impact on many types of cognition, but even normal aging is associated with a gradual decline in some types of memory, including episodic memory and working memory (or short-term memory). Because the hippocampus is thought to play a central role in memory, there has been considerable interest in the possibility that age-related declines could be caused by hippocampal deterioration [67–70].

Working memory is a cognitive system with a limited capacity that is responsible for temporarily holding information available for processing. Working memory is important for reasoning and the guidance of decision making and behavior. Working memory is often used synonymously with short-term memory, but some theorists consider the two forms of memory distinct, assuming that working memory allows for the manipulation of stored information, whereas short-term memory only refers to the short-term storage of information. Working memory is a theoretical concept central to cognitive psychology, neuropsychology, and neuroscience [55, 71–73].

The posterior cingulate cortex (PCC) is the backmost part of the cingulate cortex, lying behind the anterior cingulate cortex. This is the upper part of the limbic lobe. The cingulate cortex is made up of an area around the midline of the brain. Surrounding areas include the retrosplenial cortex and the precuneus. Cytoarchitectonically the posterior cingulate cortex is associated with Brodmann areas 23 and 31.

The posterior cingulate cortex has been linked by lesion studies to spatial memory, configural learning, and maintenance of discriminative avoidance learning. The posterior cingulate cortex has also been firmly linked to emotional salience [74, 75]. Thus, it has been hypothesized that the emotional importance of autobiographical memories may contribute to the strength and consistency of activity in the posterior cingulate cortex upon successful recollection of these memories [75]. The posterior cingulate cortex is significantly bilaterally activated by emotional stimuli, independent of valence positive or negative. This is in contrast to other structures in the limbic system, such as the amygdala, which responded disproportionately to negative stimuli, or the left frontal pole, which was activated only in response to positive stimuli. These results support the hypothesis that the posterior cingulate cortex mediates interactions between emotional and memory [75, 76].

Cognitive complaints are common in women transitioning through menopause. Some researchers have suggested that declines in estrogen level may lead to deficits in the cognitive ability of postmenopausal women [77].

Other studies have shown that subtle deficits in objective cognitive performance correlated with some measures of poorer subjective memory performance [78]. Subjective memory complaints in perimenopausal women were found to be most associated with working memory and complex attention rather than verbal episodic learning or memory [79], suggesting that high effort demanding cognitive operations may lead to the perception of subjective cognitive difficulties. A study of working memory examining a subset of participants from a study by Dumas and colleagues [80] found that women with substantial postmenopausal cognitive complaints showed greater cortical activity during working memory performance than women without such complaints despite equivalent performance, suggesting that cognitive complaints may indicate increased neural effort, perhaps as a form of compensation.

Cognitive complaints after menopause may be a particularly meaningful marker for early neural dysfunction, especially as loss of estradiol at menopause has been hypothesized to contribute to the higher rates of dementia in women [8].

Neurobiological alterations concomitant with aging can impact brain regions that are critical for the regulation of attention, learning, and memory processes, such as the frontal cortex, basal forebrain, and hippocampal formation [81].

As a consequence of the aging and decline of the ovarian hormones, the neural systems are altered. Being the brain a highly plastic organ, it adapts and changes throughout the life span, constantly revising and composing information in order to adjust to an organism's ever-changing environment. Neural systems and biochemical mediators are affected by many factors that are modified with age and interactions with the environment.

A fundamental factor influencing the brain beginning early in life is sex steroid hormones. It is well established that androgens and estrogens play a key role in organizing the developing brain and set up to respond in a particular way following sexual maturity in an organism. Many of these neural systems and reproductive hormones are also associated with learning and memory processes. Neural system is critical for learning and memory processes that are concomitantly impacted by age and ovarian hormones. The effects of age may alter ovarian hormone level.

The constant neurobiological changes occur with age and impact on brain regions that are critical to complex attention rather than verbal episodic learning or memory associated with working memory [79].

Studies have confirmed these findings and shown that subjective memory complaints have predicted volume decline in gray matter, particularly in medial temporal lobe structures [82].

In addition to increased cognitive complaints during or after menopause, women also appear to be at higher risk for Alzheimer's disease (AD) particularly when they carry the ApoE€4 allele [83].

Cognitive complaints in the menopause period may be a useful index of developing cognitive and/or brain dysfunction. Also, there are structural and functional changes in the brain that may indicate developing neurodegenerative disorders [84].

Cognitive complaints after menopause may be a particularly meaningful indicator of early neural dysfunction, especially as deprivation of estradiol at menopausal has been hypothesized to contribute to the higher rates of dementia in women.

Thus, the loss of estrogen support at menopause may be more noticeable in terms of cognitive processes, particularly attention, executive function, and verbal memory [84].

The neural manifestations of early cognitive change may be apparent many years prior to the development of measurable cognitive impairment.

Conclusion

The transition to menopause results from a complex interaction of internal (i.e., physiological, psychological) and external factors (i.e., social) factors.

Not all women respond to, or experience, the transition to menopause in the same way. There is controversy about the true incidence of disorders such as depression during the transition to menopause.

Older studies defended the idea of a "window of vulnerability" during the years immediately preceding the menopause to explain the higher incidence of depression in perimenopausal women. However, recent studies have shown that a higher incidence of depressive symptoms is not due to depressive disorder.

The etiology of depression is not well understood and it is probably not simply due to low basal hormone concentrations. There are other factors involved, like neuroticism, social support, presence of vasomotor symptoms, body satisfaction, and chronical diseases.

The hormone therapy is the most effective treatment of climacteric symptoms. But it is not recommended for treatment of depression in perimenopausal women, and the antidepressants are the first recommended choice.

Various antidepressants drugs (SSRIs and SNRIs) reduce the frequency and severity of hot flashes in menopausal and postmenopausal women.

The brain is a highly plastic organ, and it is influenced early in life by fundamental factors, which are the sex steroid hormones. Throughout life span, the brain adapts and changes, constantly revising and composing information in order to adjust to an organism's ever-changing environment. Neural systems and biochemical mediators are affected by many factors that are modified with age and by the environment.

Estradiol influences cognitive function, while natural menopause or surgical (ovariectomies) cause fluctuating and decreasing estrogen levels in women.

Steroid hormones have several effects on brain development as well as on the maintenance of homeostasis throughout adulthood. Estrogen receptors have been found in the hypothalamus, pituitary gland, hippocampus, and frontal cortex, indicating that estrogen plays an important role in brain development.

It is well established that androgens and estrogens play a key role in organizing the developing brain. Many of these neural systems and molecular pathways that are impacted by age and reproductive hormones are also associated with learning and memory processes.

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Anxiety Disorders in Women

Amaury Cantilino and Carla Fonseca Zambaldi

Anxiety and fear are adaptive emotional responses when one faces a stimulus perceived as dangerous. Fear is the emotional response to a real or perceived imminent threat, while anxiety is the anticipation of future threats. Both play an important evolutionary role in the survival of the species.

A picture of intense anxiety and disproportional fear of danger is characteristic of anxiety disorders, which are among the most common mental disorders in the general population. They usually occur in comorbidity with other mental disorders and cause significant suffering and have a negative impact on quality of life. Within the group of anxiety disorders, the DSM-V brought together separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder (social phobia), panic disorder, agoraphobia, and generalized anxiety disorder [1].

In a 12-month period, the global prevalence of anxiety disorders has been estimated at 14% [2, 3]. In 2010, Wittchen et al. (2011) analyzed the prevalence of mental disorders in Europe (14 countries), in 12 months. In this study, it was observed that specific phobias occurred in 6.4% of the population, social phobia in 2.3%, agoraphobia in 2%, panic disorder in 1.8%, and generalized anxiety in 4%. It is shown that anxiety disorders are approximately twice as prevalent in women as they are in men. The differences between women and men are described in Table 1 [3]. Women, besides being more affected than men by anxiety disorders, present more symptoms, have more severe scenarios, suffer greater negative impact, and show some specificities in the clinical presentation [4]. As can be seen in this chapter, there are several biological, psychological, and social factors related to these differences.

Table 1 Prevalence of disorders, during 12 months, in Europe (14 countries) in 2010 [3]

Diagnosis	%	Gender ratio f:m
Specific phobias	6.4	2.4
Social phobia	2.3	2.0
Panic disorder	1.8	2.5
Agoraphobia	2.0	3.1
Generalized anxiety disorder	1.7–3.4	2.1

Biological Factors Related to Women's Vulnerability to Anxiety Disorders

There are several mechanisms related to the neuropathophysiology of anxiety disorders, such as genetic factors, the hypothalamic-pituitary-adrenal (HPA) axis, activation of the limbic system, the

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serotonergic and the monoamine systems, gamma-aminobutyric acid (GABA), glutamate and oxytocin, and the immune system [5].

The fight or flight response, regulated by the HPA axis, is one of the basic mechanisms of anxiety. In the presence of a stress stimulus, or stressor, the HPA axis produces a neuroendocrine response. A chain of events occurs in the paraventricular nucleus of the hypothalamus, causing the production of corticotropin and vasopressin. These two hormones stimulate the production of the adrenocorticotropic hormone (ACTH) in the pituitary gland and the subsequent synthesis and secretion of glucocorticoid by the adrenal cortex.

Men and women secrete different levels of these hormones in response to similar stimuli. Women, in response to stress, have a faster and more intense HPA response [6]. Studies on rodents observed that, in response to stressors, females secrete higher concentrations of corticosteroids than do males and the levels remain higher for a longer period of time [6].

The gender-related biological factors involved in stress response are complex and entail many regions of the nervous system. The gonadal hormones exert much influence on the HPA axis, by way of gene expression, protein synthesis and cellular excitability [6]. The gonadal hormones influence the intrauterine development of the brain morphology, as well as greatly influencing the HPA axis, starting at puberty and in the different phases of the woman's life cycle. There are ovarian hormone receptors in several regions of the brain that directly or indirectly regulate the activation and negative feedback of the HPA axis. Furthermore, gonadal hormones modulate various learning and memory processes and interfere in the fear circuit and in stress sensitivity [7].

Li and Graham (2016) determined that the sex hormones interfere in one's susceptibility to anxiety through downregulation of the neurobiological systems of stress regulation and by facilitating the continuation of anxiety after it is established [8]. Sex hormones seem to be largely responsible for the vulnerability of women to anxiety disorders. Besides the HPA axis, gonadal hormones interfere in neurogenesis [9, 10], in the serotonergic circuit and in the neuroimmune response [11, 12].

Psychosocial Factors Related to Women's Vulnerability to Anxiety Disorders

Besides being of the female gender, other risk factors for anxiety disorders are family history, negative interpersonal relationship with parents, inhibited or shy temperament, and experiencing sexual abuse and traumatic events [5].

Women suffer trauma less often than men do. However, they are victims of potentially more traumatic events, such as sexual abuse and domestic violence [13]. Many women have a history of past sexual abuse. Child sexual abuse is a serious trauma that causes long-lasting changes in the brain circuits. The HPA axis suffers the effect of chronic stress, where cortisol levels and ACTH are initially high then later drop to low levels. Child sexual abuse is associated with several repercussions in physical and mental health; one of these is the chance of having anxiety disorders increasing 2.5–3 times [12, 14, 15].

Sexual abuse and other forms of violence also occur in the life of an adult woman. Violence against women is a public health problem, as yet under-identified and the cause of great stigma. Sexual abuse is considered to be an endemic condition, and it is estimated that 35% of women worldwide have been victims of some type of violence from their partner, or of some form of sexual violence from a non-partner [16]. In 2010, it was determined that 7.2% of women older than 15 years, worldwide, had been victims of sexual violence from a non-partner [17]. This data may be underestimated due to the large stigma associated with this topic and the difficulty women have in reporting such issues. Sexual abuse and domestic violence, be it physical, sexual, or psychological aggression from a partner, are factors associated with the occurrence of anxiety disorders. Experiencing domestic violence increases the chance of suffering from some anxiety disorder by four times [18].

Specific to women is the trauma associated with childbirth. There are situations experienced during the delivery that are understandably traumatic, due to the real risk of death and threat to life. In addition, childbirth can be traumatic even for women

who have had a delivery with no complications or risks. This occurs when women experience this or assault on her life, or on her or her baby's physical well-being, feeling afraid, a sense of horror, helplessness, frustration, or hurt dignity [19]. Many women, during a traumatic childbirth, go through dissociative experiences, where time may be perceived in an altered manner, as if it were going by too fast or in slow motion; there can be periods of amnesia where she is unable to remember certain episodes; or she might have an out-of-body experience or feel as if she is in a dream [20]. Traumatic childbirth is associated with having posttraumatic stress disorder, depression, and also anxiety symptoms [21].

Social expectations placed upon women, the stereotypical behavior they are raised to match, and some culturally reinforced behaviors are not always beneficial to their mental health. For example, boys are more encouraged to face their fears than girls. It is more acceptable for girls to be shy, inhibited, fearful, worried, or attached to their families. Shy behavior in boys is less socially tolerated, prompting parents to seek treatment and not to reinforce this behavior in their sons [22]. Also in adult life, it is more tolerated for women to lead a more reclusive life, where they avoid whatever causes them fear and discomfort.

Some characteristics of women may favor the vulnerability to anxiety disorders. Women take more notice of danger, overestimate more often the possibility of danger, foresee danger and are preemptive, likely due to evolutionary factors to protect their offspring. In a study with rodents, females had a quicker response to fear and avoidance, as well as greater inflexibility in their response to fear [23]. Women have more concerns and deliberations, feel less capable of dealing with feared situations, and are prone to avoid such circumstances [24].

Life Cycle Factors

Women go through huge transformations over the course of their life cycle, in psychosocial aspects as well as in physiological and hormonal ones. During these periods great hormone oscillations occur, such as in premenarche, pregnancy, postpartum period, and perimenopause, and they are considered windows of vulnerability. These are times of greater susceptibility to the exacerbation of preexisting psychiatric illnesses or to the emergence of new conditions.

Pregnancy is a time of great modifications in gonadal hormone levels, which impact the neurobiological system. Besides other functions, the placenta causes hormone changes of estrogen and progesterone, with the purpose of maintaining the pregnancy. The maternal HPA axis increases in size, due to estrogen stimulus. Cortisol increases 2–3 times, and there is an increase in ACTH by way of production in the pituitary gland and in the placenta throughout pregnancy and even more so during labor [25].

Pregnancy is considered a crisis period, where flexibility is necessary, as well as the use of mental resources, in order to adjust to the new reality. The woman needs to adapt to her new physical condition and body image. The way she relates to her partner and family changes and her role at work or her productive life may require restructuring. There is a complete overhaul to her routine, free time, tasks, and responsibilities, besides changes in her priorities, habits, and interests. Adjustment may be even more difficult in an unplanned or unwanted pregnancy.

Postpartum is a time of critical hormone changes. At the end of pregnancy and after childbirth, oxytocin levels increase, favoring uterine contractions, lactation, control over anxiety, and mother-baby attachment. With the elimination of the placenta, the high levels of estrogen and progesterone, which were increased during gestation, suffer an abrupt drop. Moreover, this is a time of great demand for mental adjustment.

There is the expectation that women will be radiant with the baby's arrival, but actually, it is a time of stress. The first days with the baby are quite intense and demand much dedication on the part of the puerperal woman. She is placed in a situation of much responsibility when caring for a dependent and fragile infant. Many times, the puerperal mother faces the routine of caring for her child while still feeling pain or recovering physically. Generally, breastfeeding is not as easy

as expected and sleep deprivation is notable. She must adapt to a new identity and to a new role.

Aging also brings a series of psychosocial changes to a woman's life, and some of these changes may be characterized as stressors, leading to quality of life impairment and the development of mental disorders.

Menopause is an important milestone in the woman's aging process. Menopausal transition is a time of change in the endocrine and reproductive system, when there are drops in the levels of estrogen and progesterone due to ovarian failure. Women face a series of losses, such as the end of fertility, joviality, clinical health, and their status after retirement. Some women experience stressful life events, such as taking on the role of a sick relative's caregiver, losing their partner, taking on multiple responsibilities like caring for grandchildren or parents. Furthermore, there is a decline in social support as children leave home. Thus, this time is a source of considerable stress, which contributes to a woman's vulnerability to anxiety disorders [26–28].

Separation Anxiety

Separation anxiety, although often occurring during childhood, may be present in adolescence and adult life. The onset of separation anxiety disorder may occur at any time during childhood, and more rarely during adolescence. Generally, there are periods of exacerbation and remission. The condition is marked by anxiety related to a possible separation and the avoidance of situations involving separation from one's home or family nucleus (e.g., going to college, moving away from attachment figures) [1].

Women with separation anxiety present fear or excessive anxiety involving separation from home or attachment figures. During gestation, a woman may fear being alone, constantly demanding the presence of her partner or relatives and, when required to be separated from close family or friends, reacting with anxiety and insecurity.

In the postpartum period, a woman with separation anxiety may develop separation anxiety with regard to her child. She responds with fear, anxiety, excessive worries, and guilt in situations where she has to be separated from her child. The woman believes that the child will not be well taken care of, be safe, or feel all right with another person. She worries excessively if the child gets hurt, becomes ill, or is in discomfort. Separation anxiety during postpartum is often accompanied by depression or another anxiety disorder. This clinical condition may impact the mother's life and cause significant suffering as well as produce negative repercussions on the child's emotional development. Excessive worries may gravely impair the capability of these mothers to encourage a feeling of confidence in their children, fostering a risk factor for anxiety states [29].

Specific Phobia

In specific phobia, fear or anxiety occurs, confined to the presence of a situation or specific object, which may be called phobic stimulus. Intense fear or anxiety ensues with the proximity of the feared object or situation, or by anticipating that presence, or in the actual presence of said object or situation. Moreover, fear or anxiety may take on the form of a panic attack [1].

Specific phobias can be classified in types: animals (e.g., insects, snakes, dogs), natural environments (e.g., darkness, thunder), situational (e.g., closed spaces, elevators, flying), blood-injection injuries (e.g., seeing blood, having an injection), or others (e.g., clowns, loud noises). In total, 21.2% of women and 10.9% of men met the criteria for any single specific phobia. Multiple phobias were reported by 5.4% of the females and 1.5% of the males. Animal phobia had a prevalence of 12.1% in women and 3.3% in men. Point prevalence of situational phobia was 17.4% in women and 8.5% in men. For mutilation phobia no gender difference was observed, being presented in 3.2% of the women and 2.7% of the men [30].

The exact prevalence or impact of specific phobias in the peripartum period is not known, but there is a specific phobia at this time, namely, tocophobia or fear of childbirth [31]. Being afraid of childbirth is normal during gestation, but preg-

nant women who have tocophobia have an intense and disproportional fear of dying at the time of delivery, of feeling pain, of being afflicted with a perineal lesion, of not having adequate support, of losing control or panicking during childbirth, and/or of complications or losing her baby [32]. This phobia is accompanied by persistent anxiety, nightmares, and physical symptoms [32]. Fear of childbirth occurs in 14% of pregnant women, being more common in primiparas or in women who have had a previous, traumatic delivery [33]. Tocophobia is associated with a history of physical or sexual abuse, traumatic gynecological exams, or myths surrounding childbirth. Tocophobic pregnant women have a higher incidence of elective delivery by Caesarean section [34].

Social Anxiety Disorder (Social Phobia)

Clinical Vignette 1: Clinical Case Lúcia (Fictitious Name)

Lúcia, 24 years old, was a very shy child and it was hard for her to make friends at school, as she was so withdrawn. When at college, she showed much difficulty in interacting with more people, especially if they were strangers or in some position of authority. She was incapable of addressing the professors. If asked to answer a question in class or to orally present some project, she was unable to talk and had tachycardia, cold sweat, and tremors. On days of oral presentations she started skipping class and in due course was unable to attend classes any longer. She does not go to parties and hardly ever leaves the house, and her relationships are restricted to her family sphere.

She married a man 12 years her senior who is rude to her in several ways, but Lúcia is unable to demand better treatment. She is in the postpartum period and her baby is 1 month old. She is terribly embarrassed at having to care for her child in front of visitors, people she does not know well, and her mother-in-law. The latter often criticizes the way she cares for the baby, which leaves her feeling more insecure. Subsequently, Lúcia began presenting depressive symptoms, such as crying easily, distress, anhedonia, and changes in her appetite.

Social phobia is characterized by persistent and disproportional fear in social situations or performance activities. People suffering from this disorder fear being negatively assessed, showing anxiety, being inadequate, or offending others, associated with anticipatory fear and avoidance. Fear may be triggered in social situations, such as being introduced to other people, meeting people in authority, eating or drinking in public places, participating in groups, arriving at a party, or being examined. Other triggers may be performance situations, such as speaking in public, writing in front of others, playing a musical instrument in public, giving news publicly, and expressing displeasure [35].

This disorder generally starts during infancy or adolescence and can be precipitated by any stressful or humiliating event. There are several factors involved in the development of social phobia, such as genetic factors, life events, and one's temperament. Inhibited temperament, marked by the tendency to fear non-familiar social situations, is linked to social phobia [22]. In general, girls who already show inhibited temperament during infancy develop social phobia in adolescence or adulthood, as shown in Clinical Vignette 1.

The prevalence rate of social phobia, 6.5% in women and 4.8% in men, was observed in a 12-month period [24]. Besides having a greater chance of manifesting social phobia, women demonstrate a higher number of feared social situations, more comorbidity with a depressive condition and the desire to die, compared to men [24]. Women have more fears that are related to interaction with authority figures, speaking in public, working while being watched, entering a room where other people are already seated,

being the center of attention, expressing disapproval, reporting to a group of people, and going to parties. With regard to men, they show more fear of urinating in public or returning a purchase at a store. Women show more fear than men do in professional situations, such as being interviewed, talking with an authority figure, and speaking in a meeting, and their fear has a greater negative impact on their professional lives [36]. Social phobia has repercussions on social functioning, on one's professional life, and on other areas of life. Women with social phobia tend to drop out of school earlier and present a lower level of education and professional training.

Panic Disorder

Panic disorder is characterized by recurrent unexpected panic attacks, a sudden surge of fear or intense discomfort that spikes in minutes, during which a series of physical and cognitive symptoms occur [1]. This condition is associated with worries about panic attacks or their consequences, such as having a heart attack, a convulsion, "going crazy," or losing control. Generally, there are changes in the person's behavior, in the attempt to minimize or avoid the panic attacks or their consequences. Examples of this include avoiding physical effort, reorganizing daily life to guarantee there will be help available in the case of a panic attack, restriction of habitual daily activities, and avoiding agoraphobic situations, such as leaving the house, using public transportation, or going shopping. If agoraphobia is present, an additional diagnosis of agoraphobia is established (DSM).

Female patients with panic disorder had significantly higher levels of agoraphobia, and The Health-Related Quality of Life scores of female patients with panic disorder (PD) were significantly lower than those of male patients [37]. In terms of its course, panic disorder is more chronic among women than among men and is associated with higher rates of comorbidity with GAD, somatization disorder, and agoraphobia [13].

Panic disorder is present in 0.2–5.2% of pregnant women [38–42]. Although some studies show differing results, it is indicated that preexisting symptoms of panic disorder are exacerbated in one-third of women during pregnancy [43, 44]. It was once believed that pregnancy was a protective factor for panic disorder. However, the observation is that panic disorder may persist, worsen, or begin during gestation. Anxiety during gestation is related to the increased resistance of the uterine artery, which may cause delayed intrauterine growth and a low-weight newborn or premature birth. Furthermore, it shows an association with behavioral and emotional changes in the child [45–50].

During the postpartum period, an exacerbation of preexisting symptoms of the disorder is seen, as well as a high rate of first-time appearance of symptoms. In a study with 64 women suffering from panic disorder, it was observed that 10.9% had a symptom onset in the first 12 weeks of postpartum. This rate is considerably higher, around 0.92%, than what is expected for any other 12-week period [17]. There is a negative impact on quality of life in women with panic disorder during postpartum, as well as on their day-to-day functionality and on the mother-baby relationship [51].

The mother-baby relationship begins still during pregnancy, but it becomes even more intense at the time of childbirth and during the mother-child interaction in the postpartum period. The attentive and constant maternal care in response to the baby's demands and necessities and the loving stimulus through gazing, physical contact, and vocalizing are crucial for the cognitive, motor, and emotional development of the child. Not only postpartum depression but also anxiety states may bring harm to this relationship, as exemplified in Clinical Vignette 2.

Clinical Vignette 2: Case Ana (Fictitious Name)

Ana is 32 years old and had her first child 2 months ago. Her pregnancy and delivery had no complications, but she complained of feeling very tense and worried while pregnant. For more than 1 month she has felt sad, distressed, and wanting to cry. She has been unable to care for the baby; she thinks she "doesn't have the strength" or that "she can't manage." She complains of periods of tachycardia, cold sweats, faint-

ing sensation, and waves of hot and cold, followed by the feeling that she is going to die or lose control. She has not slept, has lost a lot of weight, and has had no appetite. She has needed help taking care of the baby, for she fears being alone with the child. She fears leaving the house alone, believing that the episodes may occur and there will be no one nearby to help her.

Agoraphobia

The fundamental characteristic of agoraphobia is accentuated fear or anxiety triggered by real or foreseen exposure to a variety of situations. It can occur when the person uses public transportation, remains in open or closed spaces, is in line or in a large crowd, or goes out alone. Generally, agoraphobics believe that escaping from these places may be difficult or that help may not be available when symptoms from a panic attack, or other embarrassing or debilitating symptoms, plague them [1].

Compared to patients without agoraphobia, a significantly higher number of the patients with agoraphobia were female. Compared to patients without agoraphobia, those with this disorder had a more severe panic disorder had a higher prevalence of comorbidities, a higher suicide risk, more hypomanic episodes, and more frequent episodes of social phobia. In addition, patients with agoraphobia had a higher level of neuroticism, sensitivity to anxiety, and trait anxiety [52].

Generalized Anxiety Disorder (GAD)

Clinical Vignette 3: Case Joana (Fictitious Name)

Joana, 55 years old, civil servant, complains of constantly feeling muscle tension, not being able to relax, and not concentrating at work. She is tired during the day and cannot sleep at night. She notices that her mind does not stop worrying. She feels too much pressure at work and constantly worries about meeting deadlines; despite this, she is so nervous that she cannot be productive. She worries continually about her adolescent daughter. She fears urban violence and that her daughter might be assaulted or kidnapped. When her daughter goes out, Joana cannot relax and calls her many times, unable to put the phone down as she waits for text messages. She complains of aches and pains and detects muscle tension. She is sad and does not know how to break free from this situation.

Generalized anxiety disorder (GAD) is characterized by excessive and hard-to-control worrying and anxiety. This apprehension takes up time and energy and is accompanied by unease, frayed nerves, fatigue, difficulty concentrating or feeling like your mind has gone blank, irritability, muscle tension, and sleep disturbances [1].

GAD may begin in infancy or at any time during adulthood. Average age of onset is 30 years. GAD tends to be chronic, with several recurring episodes over the years [1]. Genetic factors, temperament, exposure to stress, and confrontation style are all involved in the etiology of GAD. It seems to be associated with a negative temperament and neuroticism, with fear of the unknown and what is not familiar, intolerance of uncertainties, and inhibited temperament [13]. There is not much information on gender-related differences as to specificity in the presentation and course of GAD. During peripartum, the occurrence of GAD may bring about important implications.

Showing concern during pregnancy is a frequent condition. Many pregnant women are afraid and worry about losing their baby and fetal abnormalities and have fear of childbirth and death or of feeling pain or having complications during the delivery such as hemorrhaging or mutilations [53]. When these worries are exaggerated, recurrent, and persistent, they could be manifestations of GAD.

Approximately 20% of pregnant women show some symptom of anxiety [54]. GAD showed a prevalence of 4.1% during pregnancy,

with 5.3% in the first trimester of gestation, 0.3% in the second trimester, and 4.1% in the third trimester [55]. Anxiety during pregnancy may cause repercussions for the fetus and obstetric outcome. The presence of GAD during pregnancy is associated with preeclampsia, nausea and more frequent vomiting, higher number of visits to the obstetrician, premature delivery, low weight at birth, low APGAR score, and difficulties in breastfeeding [56–60].

Usually, if GAD is present during gestation, it persists in postpartum. The postpartum period is also a time of much concern over financial issues, doing housework, physical appearance, and the baby's health. GAD has a prevalence rate of 6.7% at 5–12 weeks of postpartum [55]. In a study conducted in Recife (a capital city in northeastern Brazil), with 400 puerperal women, 30% showed anxiety symptoms and 16.5% had a diagnosis of GAD [61]. Most of the cases began in the perinatal period. GAD during postpartum causes a negative impact on quality of life and on the mother-baby relationship.

Women in the menopause transition and the postmenopausal period are affected by vasomotor symptoms, urogenital atrophy, sexual dysfunction, somatic symptoms, cognitive difficulty, sleep disturbance, and psychological problems. Compared with depression, anxiety symptoms and disorders have generated far less attention in studies of midlife women despite the prevalence of anxiety and their association with distress, impaired quality of life, and vasomotor symptoms (VMS). The prevalence of anxiety symptoms in midlife women is substantial, with estimates as high as 51% of women 40–55 years old reporting any tension/nervousness or irritability [62]. Compared with premenopausal women, perimenopausal women are at a greater risk for symptoms of anxiety [61].

Treatment

Anxiety disorders are still underdiagnosed and undertreated. It is estimated that approximately 40% of the cases go untreated [63]. When facing a condition of anxiety, one should proceed with a differential diagnosis with other possible causes for the symptoms, such as effects of substances (e.g., drug abuse or medication) or medical conditions (e.g., hyperthyroidism, cardiopulmonary disorder, traumatic brain injury), or another mental disorder. Furthermore, it is important to identify comorbidities and the presence of other clinical issues [1].

The treatment of anxiety disorders involves the use of psychotherapy resources as well as medication. Cognitive-behavioral therapy proves to be efficacious in treating anxiety disorders [63]. Mindfulness-based cognitive therapy has also shown to be an effective option in controlling stress and anxiety [64].

The medications used in treating anxiety disorders include serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and reversible inhibitors of monoamine oxidase A (RIMAs), anticonvulsants, and atypical antipsychotics [63].

The pharmacokinetics and pharmacodynamics of drugs differ between women and men. This is due to the physiological differences such as body weight, plasmatic volume, gastric filling and acid production, levels of plasma proteins, enzyme activity, and drug transport and clearance rate. Several studies have shown differences in the pharmacokinetics and pharmacodynamics of antidepressants in women compared to men. For example, women weigh less and have a smaller liver and a higher fat percentage, and these factors are related to drug absorption and distribution. Moreover, it has been verified that women present reduced P-gp activity. P-gp is a P-glycoprotein that transports substances, present in the absorption and distribution of antidepressants. Women also have a different cytochrome P450 expression. The drug-metabolizing enzymes (DMEs), known as cytochrome (CYP) P450 enzymes, play a fundamental role in metabolizing antidepressants. The most important CYPs in antidepressant metabolism are CYP2D6, and CYP2C, CYP3A, and the CYP1A families, which are expressed in the liver

but also in other organs, including the brain. CYP3A4 activity is higher in women than in men, which may be due to an increased expression of the gene encoding the enzyme. Despite these findings, the clinical implications of these differences are still unclear [65].

Although many studies have investigated the gender-related differences as to the efficacy of antidepressants, there is no consensus on the subject. Some studies have suggested that while men respond better to TCAs, women show a superior response to SSRIs. In a retrospective analysis of 235 men and 400 women randomly assigned to receive the SSRI sertraline or the TCA imipramine, women responded preferentially to sertraline and men showed a better response to imipramine [66]. Differently, in a large reanalysis of nine different studies of TCAs, MAOIs, fluoxetine, or placebo, Quitkin et al. (2002) reported no difference in efficacy in men and women [67]. Similarly, a later study by Hildebrandt, Steyerberg, Stage, Passchier, and Kragh-Soerensen (2003), comparing the efficacy of clomipramine, citalopram, paroxetine, and moclobemide, showed no effect of gender on response [68]. More studies are necessary in order to clarify whether or not the findings have any clinical implications [69]. In a similar manner, studies related to antidepressant tolerance showed discrepancies in the results and a consensus was not reached [65]. Women are at greater risk of having side effects from psychotropic drugs; however, in the same way, the findings on the matter have not produced information having clinical implications for the use of these drugs [70, 71].

Peripartum has repercussions on the pharmacokinetics and pharmacodynamics of the drugs. Moreover, treating mental disorders during gestation and puerperium requires care in order to protect the fetus or child. Non-pharmacological treatments should be preferred. In choosing drugs to be administered during gestation, one must observe the risk of teratogenicity, risk for the fetus, and risk for the obstetric outcome. During postpartum, drugs with a short half-life should be preferred, ones with a lower plasma/milk index, having low risk of repercussions on the child's health. A woman in peripartum should be well oriented on the risk/benefits of drug use and should participate in the therapy decision.

Menopause is also a time that shows repercussions on the use of antidepressants. There are studies that show lower efficacy of SSRIs in menopause, when compared to the reproductive period. Nonetheless, there are also studies with discrepant results, causing the matter to bring no practical implications in choosing the treatment of anxiety disorders, medication dosage, and usage time [69].

Generally, in the treatment of anxiety disorders, SSRIs and SNRIs are usually preferred as initial treatments, since they are generally safer and better tolerated than TCAs or MAOIs. Benzodiazepines may be useful as adjunctive therapy early in treatment, particularly for acute anxiety or agitation, to help patients in times of acute crises, or while waiting for onset of adequate efficacy of SSRIs or other antidepressants. Due to concerns about possible dependency, sedation, cognitive impairment, and other side effects, benzodiazepines should usually be restricted to short-term use and generally dosed regularly rather than as needed. Several anticonvulsants and atypical antipsychotics have demonstrated efficacy in some anxiety and related disorders, but are generally recommended as second-line, third-line, or adjunctive therapies. The choice of medication should take into consideration the evidence for its efficacy and safety/tolerability for the treatment of the specific anxiety and related disorder, as well as for any comorbid conditions the patient might have, in both acute and long-term use [63].

Conclusion

There are sex-related differences in anxiety disorder. Women are more affected than men by anxiety disorders, present more symptoms, have more severe clinical presentation, and suffer greater negative impact. Anxiety disorders in perinatal are risk factors for adverse outcomes for mothers and children. Improve assessment, recognition, and diagnosis of anxiety disorders in

women are needed. The treatment of anxiety disorders involves the use of psychotherapy and psychotropic medication. Sex differences in response to treatment are still unclear.

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Obsessive-Compulsive Disorder in Women

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Sex Differences in the Prevalence of OCD in Nonclinical Populations

The lifetime prevalence of obsessive-compulsive disorder (OCD) in the general population worldwide ranges from 2% to 3% in most studies, whereas current or 1-month estimations are around 1% [1, 2]. Most community-based surveys involving adult populations have shown either a similar distribution between sexes [3, 4] or a slight female preponderance among individuals with OCD [5–11]. This pattern differs from most anxiety disorders (e.g., generalized anxiety disorder, specific phobias, panic disorder, agoraphobia), which are considerably more frequent among women. OCD was classified among the anxiety disorders in DSM-IV but is described in a separate group of "OCD and related disorders" in the DSM-5 [12].

Due to the dimensional nature of OCD symptomatology, more recent epidemiological studies have also investigated the prevalence of less severe (i.e., subclinical or subthreshold) symptoms. Interestingly, OCD was significantly more prevalent among females, whereas subclinical symptoms were more prevalent among males in a study of 591 adult subjects in Switzerland [13]. Grabe et al. [14] also described a male predominance of subthreshold OCD symptoms among 4075 adults in Germany.

Among nonclinical children and adolescents, a male predominance is usually reported. For example, the current prevalence of OCD was significantly higher in male adolescents in India, compared with females (1.1% vs. 0.5%) [15]. Similar rates in boys and girls were reported among 10,438 youngsters aged 5–15 years in the UK [16]. Interestingly, while no significant differences were observed between genders in OCD prevalence in a sample of 1514 school children in Spain, more males than females presented subclinical symptoms [17]. Similarly, in Greece, 3.3% of 5784 college students fulfilled ICD-10 criteria for OCD, with no gender differences, but the prevalence of subthreshold symptoms was significantly higher among males: 9.9% vs. 7.7% [18]. In contrast, a female preponderance was observed for subclinical symptoms among 2427 late adolescents in Greece, as well as a similar though not significant trend for clinical OCD [19]. Likewise, among 2323 adolescents in Brazil [20], girls were significantly

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more likely than boys to present subclinical symptoms (24.8% vs. 14.4%) and clinical OCD (4.9% vs. 1.4%) in the previous month. In another Brazilian study, however, no differences in sex distribution were determined among 2512 6–12-year-old children for both full diagnosis and subclinical OCD [21].

In summary, major epidemiological studies report either a slight female predominance or a similar prevalence of OCD in adults from the general population. However, the sex-related epidemiological findings for children and adolescents and for subclinical symptoms are, thus far, inconclusive (see Table 1 for summary results).

Table 1 Sex differences in the prevalence of OCD and subclinical OCD (summary findings of community-based studies)

Source	Sample	Tools/ period	Overall prevalence	Females	Males	*p*
Politis et al. Greece [19]	2427 high school adolescents (16–18 years old)	CIS-R (previous week)	OCD: 1.39% Subclinical OCD: 2.77%	OCD: 3.2% Subclinical OCD: 7.7%	OCD: 1.01% Subclinical: 2.08%	OCD: $p = 0.06$ Subclinical: $p =$ **0.03**
Jaisoorya et al. India [18]	5784 college students (18–25 years old)	CIS-R (previous week)	OCD: 3.3% Subclinical OCD: 8.5%	OCD: 3.2% Subclinical OCD: 7.7%	OCD: 3.5% Subclinical OCD: 9.9%	$p = 0.56$ (ns) ***p* = 0.02**
Jaisoorya et al. India [15]	7560 adolescents (12–18 years old)	CIDI CIS-R	OCD: 0.8%	OCD: 0.5%	OCD: 1.1%	***p* = 0.005**
Alvarenga et al. Brazil [21]	2512 children (6–12 years old)	DAWBA	OCD: 3.1% OCS: 19.4%			$p = 0.57$ (ns)
Vivan et al. Brazil [20]	2323 high school students (14–17 years old)	OCI-R (previous month)	OCD: 3.3% OCS (score > 20): 18.3%	OCD: 4.9% OCS: 24.8%	OCD: 1.4% OCS: 14.4%	***p* < 0.001** ***p* < 0.001**
Canals et al. Spain [17]	1514 children	MINI-kid	OCD: 1.8% Subclinical OCD: 5.5% OC symptoms: 4.7%	OCD: 1.9% Subclinical OCD: 3.8% OC symptoms: 4.7%	OCD: 1.6% Subclinical OCD: 7.6% OC symptoms: 4.8%	ns ns ns
Viana and Andrade São Paulo city, Brazil [11]	2942 adults (>17 years old)	CIDI (lifetime)	OCD: 6.7%	OCD: 7.6%	OCD: 5.8%	Female OR: 1.3 (95% CI 0.98–1.8) – ns
Fineberg et al. Switzerland [10]	591 (cohort study; 30-year follow-up period)	SPIKE (previous year)	OCD: 3.5% OCS: 9.7% OC symptoms: 11.2%	OCD: 5.3% OCS: 9.3% OC symptoms: 8.8%	OCD: 1.7% OCS: 10.1% OC symptoms: 13.7%	
Douglass et al. [5]	930 participants (18 years old)	DIS (previous year)	OCD: 4%			Male/female ratio: 0.7:1
Kolada et al. Canada [4]	3258 adults	DIS (lifetime and 6- month)	OCD: 2.9% (lifetime) 1.6% (6-month)	OCD: 3.1% (lifetime) 1.6% (6-month)	OCD: 2.8% (lifetime) 1.6% (6-month)	ns

OCD obsessive-compulsive disorder, *OC* obsessive-compulsive, *CIS-R* Clinical *Interview* Schedule – Revised Version, *DAWBA Development and Well-Being Assessment*, *OCI-R Obsessive-Compulsive Inventory-Revised*, *MINI* Mini International Neuropsychiatric Interview, *CIDI* Composite International Diagnostic Interview, *SPIKE Structured psychopathology interview and rating* of the social consequences of psychic disturbances for epidemiology, *DIS* Diagnostic Interview Schedule

This could be due to intrinsic differences or to methodological differences related to assessment instruments, diagnostic criteria, and the age range of participants (males are usually younger than females at onset of OCD symptoms – see below).

Sex Differences in Age of Onset, Clinical Course, and Severity and Negative Impact of OCD Symptoms

Regarding OCD clinical course, the most consistent finding in the literature is that women tend to present a later age of onset of symptoms compared with men [13, 22–35]. Later interference of OCD symptoms in functioning and older age at clinical assessment were also reported among women in one study [32]. Moreover, females were more represented among geriatric outpatients with OCD in a recent multicenter clinical study of 416 participants [36]. In the National Comorbidity Survey Replication study [33], significantly different age-of-onset curves were observed for males and females: the global mean age of OCD onset was 19.5 years old, but males made up the majority of very early-onset cases (before age 10), while females showed a higher slope during adolescence, i.e., a much more rapid accumulation of new cases after age 10. Therefore, early-onset OCD is predominantly associated with the male sex. While some studies [28, 32] described similar OC symptom global severity in men and women, Fontenelle et al. [27] reported lower number of obsessions and compulsions, lower symptom severity, and better global functioning among women. Lower severity of obsessions and higher frequency of abrupt onset and of episodic course were described among women [26]. A lower rate of unemployment was reported by Lochner et al. [28] in women with OCD, compared with men (3.7% vs. 11.7%, $p = 0.025$). Nevertheless, compared with boys or men, in some studies girls or women with OCD presented higher scores on scales measuring the severity of depressive [20, 27, 32] and anxiety symptoms [32]. Higher suicidal risk was observed among women in a study of 545 Indian patients [35].

Among 220 OCD patients, sexual abuse during childhood was more frequently reported by females than males [28]. In addition, women were more likely than men to report at least one stressful life event (SLE) before OCD onset in several studies [34, 37–39]. Goldberg et al. [38] investigated factors possibly related to chronicity, including familial loading, exposure to SLEs before OCD onset, and gender in 449 Spanish patients. Interestingly, only the combination of female gender and no previous exposure to SLEs increased the odds of chronic course at higher levels of family loading. In other words, gender and SLEs modified the association between familiarity and OCD chronicity. Likewise, high family risk strongly predicted chronic course of the disorder among female patients without environmental insults among twins [40]. A recent meta-analytic study [41] reported that past trauma exposure was associated with higher severity of OCD symptoms, but this association was stronger for females. Therefore, OCD course seems to be influenced by several interacting factors, including gender.

Moreover, a recent study has shown that some aspects related to maternal care (i.e., poor care, overprotection, and overcontrol) were associated with higher odds of presenting hoarding symptoms, but only among females with OCD [42].

No significant differences between sexes were observed regarding level of insight [28] and family loading of OCS/OCD [32, 38]. Concerning impairment in functioning, several studies described that women with OCD are more likely than men to be married and/or to have children [24–26, 31, 32, 35, 43–46], suggesting a better prognosis. In a Japanese study [45], females presented less impairment in social and occupational functioning than men, but were more likely to involve others in their OCD symptoms (e.g., reassurance-seeking behaviors). However, in a review on quality of life (QoL) in OCD [47], an unexpected negative relation was observed between global QoL outcomes and female gender. As possible explanations for this finding, the authors mention higher severity of depressive

symptoms and higher frequencies of contamination symptoms and SLEs among women.

In summary, a sexually dysmorphic pattern of susceptibility to OCD may be present [28], concerning both genetic and environmental factors. For example, perinatal factors and early brain injury may be particularly important etiological factors among males with OCD [48]. Other authors [26, 44] have indicated that men could be more vulnerable to biological lesions or constitutional aspects relevant to OCD etiology, whereas environmental factors, including stressful or traumatic experiences, could have greater influence in women.

Onset or Aggravation of OCD Symptoms Among Women According to the Reproductive Cycle (Premenstrual Period, Pregnancy, Postpartum, and Menopause)

The symptomatology of OCD can present several variations during the lifetime of some women, especially in relation to their reproductive events. The age of onset of OCD in women has a bimodal distribution with the first peak incidence occurring between 13 and 16 years of age and the second between 22 and 32 years of age, which are common ages of puberty and pregnancy, respectively [49, 50]. Exacerbation of OCD symptoms in the menstrual period and onset or exacerbation during pregnancy and postpartum have been recognized for many years, yet these symptoms often go undetected and untreated [51]. Aggravation of OCD in pregnancy and in the postpartum period is of particular concern, as it involves potential adverse consequences for the patient, her family, and the newborn. Nevertheless, it has received limited prospective investigation, in contrast to depressive and psychotic disorders, which have been widely studied in these periods [52].

In a study comparing postpartum women with OCD and healthy postpartum counterparts [53], the former had a heightened self-reported and endocrine response to psychosocial stress, associated with a distinct brain activation pattern involving the orbitofrontal and temporal cortices. Data in this field suggest that there is a "hormone-related" subtype of OCD in women, in whom hormonal or other biological changes related to reproductive events could contribute to the onset or aggravation of the disorder. The role of sex hormones has been extensively investigated, suggesting that estrogen has multiple neuromodulating effects and mediates numerous neurotransmitter systems in the central nervous system, including the serotoninergic and dopaminergic systems, and the orbitofrontal cortex, all implicated in the pathophysiology of OCD [54, 55]. Estrogen increases dopamine release in the caudate-putamen and nucleus accumbens and alters the binding of dopamine in the striatum [56]. The serotoninergic system is thought to be dysregulated in OCD, and this can be accentuated by ovarian steroid fluctuations, which could be involved in the pathophysiology of OCD, postpartum depression, and premenstrual syndrome [57, 58]. Estrogen can also change postsynaptic receptor affinity of serotonin receptors and increase their density. Progesterone and other steroid hormones act through genomic (classical) and non-genomic mechanisms, which induce delayed and immediate effects, respectively [54].

Menarche-related onset was described by Guglielmi et al. [59] in 13.0% of women with OCD, while in two studies by Labad et al. [60, 61], OCD onset occurred in the same year of menarche in 21–22% of the female participants. Of note, patients with hoarding symptoms were more likely to report OCD onset at menarche [61]. In a study by Vulink et al. [56], approximately half of the 101 patients reported exacerbation of OCD symptoms during the menstrual period. Likewise, Moreira et al. [62] described that 49.7% of 455 women with OCD had experienced premenstrual worsening of obsessive-compulsive and depressive symptoms and a higher frequency of sexual/religious obsessions. In an international collaborative study, 37.6% of women with OCD experienced symptom exacerbation a week prior to menses [59]. Forray et al. [63] affirmed that women who had onset or worsening of OCD during pregnancy were also

more likely to present premenstrual worsening, compared with never pregnant women with OCD (65.5% vs. 39.3%), reinforcing a possible linkage between the reproductive cycle and OCD course in a subset of women. Concerning menopause, Guglielmi et al. [59] described OCD onset in this period in 3.8% of the sample and worsening of preexisting OCD in 32.7%. In a study of 269 postmenopausal women attended at a gynecology outpatient clinic [64], the prevalence of OCD was 7.1%, but only 0.7% reported onset in that period. The most common obsessions were contamination and symmetry/exactness, whereas the most common compulsions were cleaning/washing and checking [64]. In the study by Vulink et al. [56], 47.0% of the sample reported OCD worsening during menopause, as opposed to 6.0% reporting symptom improvement.

During the perinatal period, hormonal variations are not the only influence on OCD course. The birth of a child and infant care can be sources of considerable psychological stress, which can contribute to worsening of previous symptoms or even to OCD onset. Moreover, OCD onset or exacerbation during pregnancy and/or postpartum can be a traumatic experience for some women and impact the planning for a future pregnancy [59]. Importantly, women may be reluctant to admit and disclose these symptoms, due to the stigma and to long-standing cultural norms of the "perfect," "loving," and "selfless" mother. Therefore, there is a pressing need for psychoeducation on OCD for both perinatal women and healthcare professionals, as OCD symptoms may go undiagnosed and untreated for a considerable period of time [65, 66].

Among 78 women with preexisting OCD [63], 15.4% described onset during pregnancy and 14.1% in the postpartum, whereas 34.1% and 22.0% of pregnancies involved exacerbation and improvement of symptoms, respectively. In an international collaborative study [59], 5.1% of women reported OCD onset during pregnancy and 4.7% in postpartum, while worsening of preexisting OCD was reported by 33.0% during pregnancy and 46.6% in postpartum. Moreover, exacerbation in the first pregnancy and first postpartum was associated with exacerbation in the second pregnancy (OR 10.82, 95%CI 4.48–26.16) and in the second postpartum (OR = 6.86, 95%CI 3.27–14.36) [59]. In a study of 434 women in the third trimester of pregnancy [67], the prevalence of OCD was 3.5%, but only 0.5% reported onset during pregnancy. Among 52 women with preexisting OCD, 32.7% reported symptoms worsening during pregnancy, whereas 13.5% reported improvement in symptoms [68]. In another study of 52 women [56], 33% and 48% described OCD worsening during pregnancy and after childbirth, respectively. In a Brazilian community-based study of 400 postpartum women, 9.0% met the criteria for OCD and 2.3% reported postpartum onset [69]. In a Canadian sample of pregnant women [70], the prevalence of OCD was 3.9%, and the onset occurred in the (current or prior) pregnancy and postpartum in 1.0% and 2.9%, respectively. In the Alberta Pregnancy Outcomes and Nutrition (APrON) study, a longitudinal perinatal cohort study of 1575 women in the prenatal period and 1481 in the postnatal period, prevalence was 12.0% and 10.9%, respectively [71]. In a meta-analysis of OCD among women [72], the prevalence estimates were 1.1% in the general population, 2.1% during pregnancy, and 2.4% in the postpartum period, reinforcing that the perinatal period involves a greater risk, despite several methodological differences across studies.

During the first postpartum weeks, both mothers and fathers tend to be very preoccupied by caregiving thoughts about their infants, but these thoughts decline by the third postpartum month [73]. Nevertheless, mothers usually report higher levels of preoccupation than fathers, and first-time parents, more intense preoccupations than experienced parents [73]. Pregnancy and childbirth can trigger the onset or exacerbation of OCD in a substantial number of women to a far greater extent than in their male partners [74]. Moreover, the early and rapid onset after childbirth, with OCS arising within the first 3–4 weeks of delivery, differs from the gradual onset of typical OCD [74–76].

In fact, intrusive thoughts during pregnancy and puerperium is a common phenomenon, some studies showing that 49–69% of women are

affected [51, 77]. In a sample of postpartum women who screened negative for OCD, 42.3% experienced obsessions and compulsions [78], mainly of aggressive content involving accidental or deliberate harm toward their babies. Evolutionary theories propose that these intrusive thoughts are adaptive, leading parents to make considerable efforts to protect their infant's safety [79]. Interestingly, females developing symptoms during pregnancy tend to report more contamination obsessions and cleaning rituals, whereas those with symptoms beginning in the postpartum period tend to report more obsessional thoughts of harming the infant, checking rituals, and avoidant behaviors [51]. Uguz et al. [68] demonstrated that contamination and symmetry obsessions, as well as cleaning/washing and ordering/arranging compulsions, were more frequent among those women whose symptoms exacerbated during pregnancy. In the study by Labad et al. [61], women with symptoms from the contamination/cleaning dimension were nine times more likely to report OCD onset during pregnancy or postpartum. In a retrospective study comparing perinatal-related and nonperinatal-related subgroups [63], contamination obsessions were more frequent in the former, whereas obsessions regarding harming the infant in the postpartum period did not differ significantly (approximately 20% of the total sample). In the study by Uguz et al. [67] on women in the third trimester of pregnancy, the most common obsessions were contamination and symmetry/exactness, and the most common compulsions were cleaning/washing and checking. Of note, a self-report instrument (the Perinatal Obsessive-Compulsive Scale, POCS) was developed and validated to help clinicians detect obsessions and compulsions in this important period [53].

Regarding treatment, women with perinatal OCD can be managed according to standard approaches [80, 81], as there is no evidence that they respond differently to pharmacological agents usually prescribed in OCD treatment [50]. Obviously, the safety profile of these agents during pregnancy and breastfeeding should be considered. An intensive cognitive behavioral therapy (CBT) intervention delivered to six women with postnatal OCD [82] demonstrated improvement for all participants on all measures, both at post-intervention and during follow-up. Likewise, a controlled trial of time-intensive CBT was successful in ameliorating maternal symptoms, suggesting that it is as an effective intervention for postpartum OCD [83]. Therefore, active treatments can attenuate the potential negative effects of pregnancy and the postpartum period on preexisting OCD [84].

Further prospective investigations on the role of hormones on OCD course during the perinatal period could contribute to the development of more effective treatments for those women whose symptoms began or worsened during reproductive events.

Table 2 summarizes the findings of OCD course among women, according to the reproductive cycle.

Table 2 OCD course during the reproductive cycle (summary findings)

OCD onset at menarche	
Labad et al. [60]	22.0%
Labad et al. [61]	21.1%
Guglielmi et al. [59]	13.0% (12.3% US; 14.3% Dutch)
Premenstrual worsening of OCD	
Vulink et al. [56]	49.0%
Forray et al. [63]	Related to OCD worsening in pregnancy
Moreira et al. [62]	49.7% – higher frequency of sexual/religious obsessions
Guglielmi et al. [59]	37.6% (40.6% US; 32.0% Dutch)
OCD onset at menopause	
Uguz et al. [64]	0.7% (10.5% in OCD group)
Guglielmi et al. [59]	3.7% (3.8% US; 3.6% Dutch)
OCD worsening at menopause	
Vulink et al. [56]	47.0%
Uguz et al. [64]	29.4%
Guglielmi et al. [59]	32.7% (38% US; 21.6% Dutch)
OCD onset in pregnancy	
Labad et al. [60]	2.0%
Uguz et al. [67]	0.5%
Forray et al. [63]	15.4%
Gugliemi et al. [59]	5.1% (5.7% US; 3.7% Dutch)
Fairbrother et al. [70]	1.0%
OCD worsening in pregnancy	
Labad et al. [60]	8.0%
Vulink et al. [56]	33.0%

Table 2 (continued)

Forray et al. [63]	34.1%
Uguz et al. [68]	32.7%
Gugliemi et al. [59]	33.0% (35.3% US; 26.5% Dutch)
OCD onset in postpartum	
Labad et al. [60]	7.0%
Zambaldi et al. [69]	2.3%
Forray et al. [63]	14.1%
Gugliemi et al. [59]	4.7% (4.6% US; 4.9% Dutch)
Fairbrother et al. [70]	2.9%
OCD worsening in postpartum	
Labad et al. [60]	50.0%
Vulink et al. [56]	48.0%
Gugliemi et al. [59]	46.6% (45.7% US; 49.2% Dutch)

Sex Differences in OCD Symptoms or Dimensions

Concerning OCD symptoms, several studies from different countries have reported that women are more likely to present contamination obsessions and/or cleaning rituals [23, 26, 29, 31, 34, 35, 44, 46, 85–91], whereas men have a greater likelihood of presenting sexual and/or religious obsessions and related compulsions [25, 26, 29, 31, 32, 34, 35, 43, 85, 88, 90, 92] and symmetry/ordering symptoms [31, 32, 88, 89, 91–93]. In a multicenter study of 858 patients with OCD from several sites in Brazil [46], the sexual/religious dimension was more frequent and also more severe among men.

Higher frequency of contamination and cleaning symptoms among female patients is an almost universal finding in OCD phenomenological studies, probably involving biological, psychological, and sociocultural aspects related to the female role in different societies. In a functional neuroimaging study during a provocation task of cleaning symptoms, Mataix-Cols et al. [94] described a greater activation of areas, such as the ventromedial prefrontal regions, medium temporal gyrus, right caudate nucleus, medium frontal gyrus, and left cingulus antero-dorsal gyrus in OCD patients, compared with normal controls. A study on adults without psychiatric diagnoses indicated that the same brain areas present a large number of sexual hormone receptors, with these structures presenting greater volume among women [95]. Alonso et al. [96] examined the role of estrogen receptor genes in the genetic susceptibility to OCD and verified that a five single-nucleotide polymorphism (SNP) haplotype, located at the 50 end of intron 1 of estrogen receptor gene (ESR1), was associated with the presence of contamination obsessions and cleaning compulsions. This finding could partially explain the greater proportion of women with these symptoms. An association between SLEs and contamination/cleaning symptoms has also been demonstrated [39, 90], and SLE preceding OCD is more frequent among women [26, 34, 37–39].

Studies are controversial regarding gender predominance of aggressive obsessions [97]. However, some authors study them together with sexual/religious obsessions [89, 92], which are more common among male patients. While some authors reported higher frequency of aggressive obsessions among women [25, 46], others described the opposite [29, 87, 92]. As discussed above, the fear of aggressive impulses toward the baby is frequently reported by women with OCD onset during the postpartum period [51].

The symmetry-ordering dimension has been associated with sexual obsessions and early onset and comorbidity with tic disorders, all aspects associated with the male gender [98]. While some studies reported a higher frequency of these symptoms among men [31, 32, 88, 91–93], others described similar rates in both genders [26, 29, 34, 35, 46, 86].

Regarding hoarding symptoms, some studies reported no significant gender differences [26, 29, 32, 35, 90, 99], whereas others described a higher prevalence among men [89, 100, 101]. In contrast, one study [46] described an association between hoarding dimension and female sex. As previously cited, perceived poor maternal care, maternal overprotection, and maternal overcontrol were associated with hoarding only in women with OCD [42].

Table 3 summarizes the findings of sex differences in OCD symptoms or dimensions.

Table 3 Sex differences in OCD symptoms or dimensions (summary findings)

Author, year (country)	Sample size (M/F) [age range]	Males	Females
Minichiello et al. (USA) [23]	138 (67; 71) [6–68]	Obsessions alone	Cleaning
Noshirvani et al. (UK) [44]	307 (137; 170) [16–67]	Checking	Cleaning
Hantouche et al. (France) [92]	646 (261; 385)	Ordering/symmetry Sexual/religious/aggressive	
Lensi et al. (Italy) [25]	263 (112; 151) [11–71]	Sexual[a/b] symmetry/exactness Odd rituals[a/b]	Aggressive[a] cleaning[b]
Bogetto et al. (Italy) [26]	160 (76, 84) [> 18]	Sexual Repeating rituals	Contamination Cleaning/washing
Sobin et al. (US) [43]	100 (44; 56) [adults]	Sexual	
Lochner et al. (South Africa) [28]	220 (107; 113) [18–75]	Aggressive	
Tükel et al. (Turkey) [29]	169 (73; 96) [16–60]	Sexual Aggressive	Contamination
Karadag et al. (Turkey) [88]	141 (41; 100) [16–73]	Sexual Symmetry obsessions Checking rituals	Contamination Washing
Labad et al. (Spain) [90]	186 (114; 72)	Sexual/religious	Contamination/cleaning
Jaisoorya et al. (India) [31]	231 (166; 65)	Religious Symmetry	Cleaning
Li et al. (China) [91]	139	Symmetry/ordering	
Torresan et al. (Brazil) [32]	330 (182; 148) [10–72]	Sexual Religious Symmetry obsessions Mental rituals	
Albert et al. (Italy) [34]	415 (217; 298) [>18]	Sexual Repeating rituals	Contamination Cleaning Ordering
Torresan et al. (Brazil) [46]	858 (354; 504) [18–77]	Sexual/religious	Aggression Contamination/cleaning Hoarding
Cherian et al. (India) [35]	545 (332; 213)	Sexual, religious, doubt Repeating rituals Counting rituals	Contamination Washing/cleaning Checking

[a]At OCD onset
[b]At index evaluation

Sex Differences in OCD Comorbidity with Other Psychiatric Disorders

Comorbidity rates in OCD are very high, reaching up to 92% of patients, as reported in a large multicenter study [102]. Overall, females who are diagnosed with one mental disorder are more likely than males to have three or more comorbid disorders [103]. Some sex differences were reported in comorbidity of anxiety disorders before the separation of OCD from the anxiety disorders group, in the DSM-5. Across different anxiety disorders, comorbidity with affective disorders, eating disorders, impulse-control disorders, self-injurious behavior, and other anxiety disorders are more likely to appear in females than in males [28, 97, 104]. In contrast, males are more likely to report comorbid ADHD, intermittent explosive disorder,

substance use disorders [8, 26, 44, 105], hypersexual disorder, and pyromania [28, 97, 104]. Particularly in OCD, comorbidity with Tourette syndrome and tics are much more pronounced in males, compared with females [31, 32, 106–108].

In a large study from India using structured interviews, a comorbid axis I disorder was present in 60% of subjects with OCD, with social phobia being overrepresented among men and major depression among women [35].

Social phobia [26, 29, 31], hypomania [25, 26], and depersonalization [26] have been more frequently reported in comorbidity with OCD in males. In contrast, a greater occurrence of comorbid depression [25, 31, 44], eating disorders [26, 32, 44], and impulse-control disorders – particularly trichotillomania [31], compulsive buying [92], and skin-picking [32] – has been reported in women with OCD.

Of note, sex differences regarding comorbidity with major depressive disorder (MDD) in OCD vary among studies. Some studies report that female patients are more likely than males to report MDD [24, 43, 44, 88, 90], whereas others reported no sex differences [25, 29, 31, 32]. In a large Brazilian multicenter study, Torresan et al. [46] observed a high overall comorbidity of OCD and MDD, but no significant differences between males and females.

Concerning personality disorders (PDs), cluster A PDs (particularly schizotypal PD) were more prevalent among males, whereas borderline and dependent PDs were more prevalent in female patients in a study by Matsunaga et al. [45].

The observed sex differences in the rates and types of comorbidity could be related to the association between the exposure to different stressors and the development of anxiety disorders. For example, one study identified that the type of childhood trauma in OCD patients differed between genders, with sexual abuse being more common in females and emotional neglect in males [28]. It is likely that these sex differences in prior traumatic events in clinical samples merely represent sex differences in the general exposure to such events. Alternatively, childhood trauma and severe biological stressors may play a stronger role in the development of OCD according to sex. For example, it has been suggested that early brain trauma may be particularly involved in the early development of OCD in males [28, 97], whereas other stressful events are more likely to precipitate OCD in females [28]. Further evidences suggest that sex differences exist in the associations between specific or general stressful and traumatic events and the development of different anxiety disorders. In addition to the possibility that different traumatic or stressful events can precipitate anxiety in males and females, it is possible that the degree to which anxiety is associated with hereditary or environmental factors differs according to sex. The evidence available so far indicates that additional research is needed to better clarify these associations.

Table 4 summarizes the findings of sex differences in OCD comorbidity with other psychiatric disorders.

Table 4 Sex differences in comorbidity of OCD with other psychiatric disorders (summary findings)

Females	Males
Simple phobias (Torresan et al.; Torresan et al.) [32, 46]	Social phobia (Assunção et al.; Torresan et al.; Cherian et al.) [35, 46, 120] Posttraumatic stress disorder – PTSD (Torresan et al.) [32]
Eating disorders (Albert et al.) [34] Eating disorders – anorexia nervosa (Torresan et al.) [32]; anorexia nervosa and bulimia (Torresan et al.) [46]	Attention deficit and hyperactivity disorder – ADHD (Jasoorya et al.; Cherian et al.) [31, 35]
Compulsive buying and skin-picking (Torresan et al.) [32] Compulsive buying, skin-picking, and trichotillomania (Torresan et al.) [46] Trichotillomania (Jasoorya et al.) [31]	Tic disorders (Lochner et al.; Torresan et al.; Torresan et al.; Vivan et al.) [20, 28, 32, 46] Alcohol use disorders (Gentil et al.; Torresan et al.) [46, 105]
Depression (Cherian et al.) [35] Minor depression (Albert et al.) [34]	Bipolar disorder (Albert et al.) [34]

Treatment

With regard to treatment seeking, the evidence suggests that males are generally less likely to seek and receive mental health treatments compared with females [109], and females suffering from anxiety disorders have a significantly higher healthcare usage, compared with their male counterparts [104]. One study that examined help-seeking behaviors across the life span in males and females with different anxiety and mood disorders verified that females were more likely than males to seek help for all anxiety disorders, including OCD [109]. One must consider, though, that part of the increased help-seeking behavior may be due to the higher prevalence of certain comorbid disorders among females.

In addition, sex differences in anxiety have the potential to influence treatment outcomes. For example, males and females differ in the physiological stress response involving both the HPA axis and the serotonergic system [110, 111]. Such differences may affect treatment outcomes, including response to psychotropic medication. In turn, variables that are moderated by sex in their effects on anxiety may be targeted in therapy aimed specifically at male or female patients.

Bekker and Mens-Verhulst [112] conducted a literature search for empirical studies reporting the influence of sex on outcomes in treatment studies. They identified 1 meta-analysis that divided 33 treatment studies into studies based primarily on male or female populations and reported no significant differences in treatment effectiveness between the two groups. More specifically, evidence addressing the role of gender in predicting response to serotonin reuptake inhibitors (SRIs) in OCD suggests that gender has no effect [113]. In contrast, Steiner et al. [110] affirmed that male gender was associated with a better treatment response, whereas Mundo et al. [114] reported that females with OCD presented a better response to SRIs, particularly clomipramine and fluvoxamine. However, due to small sample size and high dropout rates (equal in males and females), it is unclear whether these differences were equal for the two drugs and whether interactions between treatment and response to a prior symptom-provoking agent differed in males and females [114]. In another study of 69 OCD patients (37 females) treated with clomipramine and venlafaxine, no significant differences between males and females were verified regarding treatment response [115]. Although it is relevant to examine whether potential sex differences in treatment effects are caused by a higher degree of comorbidity in females, such associations should be examined in mediation and moderation analyses. Unfortunately, the exclusion of individuals with comorbidity is very common in treatment studies, thus preventing this type of analysis.

Males and females can also differ in how they respond to psychotherapy. Possibly because of the effects of estrogen, sex differences have been reported in both fear conditioning and extinction [116]. Since exposure therapy is commonly used to treat anxiety disorders, it is likely that sex differences may exist in the effectiveness of such therapies. Nevertheless, one study of CBT combined with acceptance and commitment therapy (ACT) reported that the treatment was equally effective in males and females presenting different anxiety disorders [117]. Another study examined the effects of intensive behavioral therapy in severely affected treatment-resistant OCD patients and reported greater symptom decrease in females than in males, even after controlling for initial OCD severity and psychosocial functioning [118].

From a review by Christiansen [119], we learn that, overall, females are more likely than males to seek and receive mental health treatments. In addition, it is rare to find sex- and gender-specific analyses of treatment outcomes, although we might expect that sex differences in gonadal hormones, metabolism, fear conditioning, and extinction lead males and females to present different responses to both pharmacotherapy and psychotherapy. There is some evidence from research on depression that females respond better to SRIs and CBT (particularly exposure) than males, whereas males respond better to tricyclic and tetracyclic antidepressants. Finally, the author highlights that sex differences in second-

ary outcomes can be found independent of sex differences in the primary outcome [119].

In summary, many questions remain unanswered at this point and should be explored in the future, such as sex differences in treatment tolerance, side effects, compliance, and dropout rates, as well as the effects of female use of oral contraceptives, hormone replacement therapies, reproductive status, and menstrual cycle on treatment outcomes.

Conclusions

Several interacting mechanisms are probably responsible for mediating the effects of sex/gender in biological and psychosocial risk factors for OCD [48]. Despite some fairly consistent specific sex-related differences in OCD phenotype and clinical course, it is still unclear whether it is valid to subtype OCD according to sex [34, 97]. Nevertheless, sex-specific differences in etiologic pathways for OCD general and specific manifestations are very likely [42].

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Trauma and Stressor-Related Disorders in Women

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Introduction

The diagnosis of posttraumatic stress disorder (PTSD) was created by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-3rd Edition in 1980, finally updating instruments from psychopathology for traumatic conditions and providing clinical and research guidelines. PTSD practically replaced the two previous diagnoses widely used for traumatic experiences: adjustment reactions and war neurosis. Thus, war veterans were finally provided scientific studies and a more suitable clinical approach [1].

Although statistics indicate that world violence is declining, in several locations – whether endemic or subjective – populations perceive themselves vulnerable to violent threats. We may be more concerned and vigilant for safer and quieter environments. With the increased speed with which we know of terrorist attacks and small-armed conflicts, our sense of insecurity has increased. In the specific field of violence against women, Brazil ranks fifth in the world rates of femicide [2].

One of the greatest findings in the field of psychiatry is that violence can cause mental illness. Perhaps this is the great challenge for the psychiatrist: to establish the diagnosis and treatment for these patients in all the particular characteristics [3].

As a basis for PTSD, two elementary concepts contained in the picture description merit a closer examination: stress and trauma. It is now known that the pathological effects of stress and trauma are part of a complex circuit involving neuroendocrinology, genetics, neurotransmission, neuromodulation, and immunology.

In his note on stress, the long-time researcher Hans Selye concluded that the body adapts to external stressors via physiological responses that seek to maintain or restore the balance known as homeostasis. Selye describes what he calls the "general adaptation syndrome" and how we deal with it. The syndrome is composed of active strategies of confrontation, fight and flight usually triggered by the presence of a stressor or a controllable threat or possibility of escape. There are also passive strategies, usually of immobility, activated if the stressor is uncontrollable or there is no possibility of escape. Female rape victims may have a state of paralysis known as tonic immobility during this form of violence. This prevents the active resistance response against the aggressor and points to more severe posttraumatic pathologic conditions [4].

The definition of stress for the psychiatric clinic is fundamental for the definition of acute conditions called acute stress disorders (ASD) [5]; both for Selye and Robert Sapolsky, there is no life without pressure. The alarm triggered by

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stress generates responses that can be translated into learning and adjustment. But when this adaptive system fails, the pathological aspect of stress erupts, requiring immediate adjustments and other, finer, longer-lasting adjustments.

Long neglected by nosography codes, ASD has become more studied after the creation of the PTSD diagnosis. The importance of dissociative phenomena appears in the diagnosis and also in the prognosis of both ASD and PTSD. The dissociative reactions that occur during the trauma and its immediate period have been considered a risk factor for developing late and more severe psychopathological conditions [6].

This type of traumatic dissociation would have a predominantly maladaptive character.

One of the greatest challenges for the field of PTSD is defining the concept of trauma in mental health. For the psychiatric clinic, trauma could be conceived as the expression of the effect of violence on the psyche, especially in memory.

Studies by Eric Kandel indicate that the physiological pathway involving the acquisition, maintenance, and erasure of memory may perform an adaptive function of forgetting the negative stimuli we label here as violence [7].

The main characteristic of PTSD in clinical experience is the impossibility of forgetting the traumatic event. For the psychiatric clinic, the concept of violence brings up the idea of trauma. This would be the expression of the effect of violence on the mind. The blackout caused by the traumatic event forces the individual to a constant update of the unpleasant negative experience.

Thus, trauma could be understood as an adaptive dysfunction after a disruptive event with risk of death, the basis of which is memory impairment, but with repercussions on thinking and emotions. This is perceived by the psyche as a memory of the threat of extinction.

Psychopathology

The presence of a traumatic event is not sufficient for the development of PTSD because most people exposed to extreme violence will not develop a pathological reaction. Pre-trauma factors are relevant and some people appear to be more resilient than others; there are risk factors correlated with the disorder. However, the trauma per se is fundamental to PTSD and a requirement for the diagnosis.

Despite subjective experiences, some events are more severe than others. Sexual abuse, rape, and combat experiences have the higher conditional risk for PTSD development. Almost 50% of the subjects who went through these experiences will develop PTSD [8].

The DSM-5 restricted the characteristics of the traumatic event only to those that endangered the individual's integrity and life [9]. This approach reinforces the idea that PTSD is a disorder related to a disrupted survival response. Initial hypothesis of underlying mechanisms in PTSD relied on pathological fear responses and impaired learned conditioning. An impressive and prolific experimental literature, using animal models, emphasized interventions using behavioral approaches, like exposure and desensitization, which is the golden standard for PTSD therapy [10].

Recently, other systems and aspects on human trauma responses have been studied, such as context discrimination, attachment, and interpersonal relationships, leading to new proposals for understanding and treating PTSD [10].

Although PTSD patients have common core symptoms related to its diagnostic criteria, some individuals display very different clinical scenarios. Intrusive images or thoughts typically invaded the minds of PTSD patients, characterizing a classical clinical presentation. However, sometimes the images are not visual but olfactory or acoustic, always related to the traumatic event. These symptoms are vivid, experienced emotionally and physically as an actual revival. Eventually, the experiences are associated with dissociative states, leading to flashbacks, when images are external, objective, with an impaired test of reality.

These symptoms are extremely uncomfortable, causing the patient to avoid triggers that could elicit the reviviscence. Some triggers are external like situations, places, or people; others are internal triggers like sensations, feelings, or

thoughts related to the traumatic event. These avoidance symptoms lead PTSD patients to severe social and functional impairment. Often patients need to be accompanied to medical or psychological consultations by their family or friends. Many of them are unable to work or study, usually staying at home and avoiding social contact.

As they are terrified of new adverse experiences, PTSD patients may become hypervigilant, looking out for possibly dangerous situations or people. The hypervigilance causes irritability, suspicion, and sleep disorders.

Patients become pessimistic about the future and feel very negative about themselves and their abilities to face adversity. They also complain of being emotionally anesthetized even toward loved ones. Memory problems are pervasive, like total or partial trauma-related amnesias.

PTSD patients are distrustful and frightened, always living on alert. They do not believe in their ability to react to threat, feeling incapable: they are afraid of not enduring, becoming paralyzed, or having catastrophic reactions when facing a new violent event. This misperception of their capacity to react to an anticipated aggression is linked to cognition of an impaired ability to act, which is related to impaired self-cognition. This impairment is a disturbance of the essence of self-conscience.

PTSD patients have an impaired reality testing leading them to think, constantly, that a new traumatic event is imminent. Such psychopathological symptom is a signal of severe mental disturbance, affecting complex psychological functions that individual takes years to acquire during the long process of human psychological development.

Diagnostic Criteria

The diagnoses of ASD and PTSD are necessarily related to a traumatic event; the A criterion for the diagnosis of both disorders is that the person, or someone closely related, is exposed to actual or threatened death, serious injury, or sexual assault – also witnessing or being exposed to repeated details of traumatic events can trigger the symptoms (e.g., firefighters, police officers).

The diagnostic criteria of the DSM-5 restricted the traumatic event to those cited above, while the International Classification of Diseases (ICD-10) still includes a broader spectrum of events as the criterion A. ICD-10 included, in the chapter of Stress-Related Disorders, the adjustment disorder and two unspecified diagnoses following traumatic events, including distressing symptoms after stress that does not fulfil criteria for PTSD [11]. Meanwhile, the chapter of Trauma and Stressor-Related Disorders in DSM-5 includes only adjustment disorder, and some others only related to children.

This chapter will follow the DSM-5 launched in 2013 and it will focus on ASD and PTSD [12].

The symptoms of ASD are the same as PTSD; during the acute phase, dissociative symptoms are very frequent. ASD is diagnosed if the following symptoms are present after 3 days and during 1 month after the traumatic event. After this period, if symptoms persist, a diagnosis of PTSD is given [13].

Besides criterion A, at least nine symptoms from the following four categories (B + C + D + E) are necessary to fulfil the diagnostic criteria:

Criterion B – Intrusions (at least one): Repetitive distressing memories of the event; nightmares related to the event; flashbacks, sometimes during the episodes the person acts like the event is occurring in the present moment.

Criterion C (at least one): Avoidance of thoughts, situations, people, and places related to the event.

Criterion D – Negative mood (at least two): Lost of interest in daily activities; negative beliefs, fear, guilty, shame; inability to experience positive emotions; distorted cognitions; lack of memory related to the event; numbness.

Criterion E – Arousal (at least two): Constant state of alertness; increased startled response; insomnia; impaired concentration; feelings of irritability and anger; self-destructive behavior.

Criterion F – Symptoms last more than 1 month.

Criterion G – Distress and impaired functioning.
Criterion H – Not due to substance use, medical condition, or other illnesses.

The next two specifications are also possible:

- Dissociative type: Depersonalization and derealization in response to reminders of the traumatic event
- Delayed symptomatology: Beginning of symptoms after 6 months of the event

Physiopathology

There is much evidence of biological abnormalities associated with PTSD. An imbalance between the sympathetic and parasympathetic branches of the nervous system (with increased activity of the former and decreasing of the latter) is probably much more a consequence than a risk factor [14]. Alterations in HPA-axis function are also described as a blunted rhythm and a failure to produce extreme variation on HPA cycle [15].

The amygdala is a structure responsible for acquisition and modulation of memories related to fear. Amygdala activity is dependent on concurrent activation of glucocorticoids and adrenergic mechanisms [16]. Patients with PTSD have increased amygdala activation.

The prefrontal cortex (PFC), an important area responsible for executive functioning, working memory, attention, decision-making, planning, and organization, has reciprocal connections with the amygdala. One hypothesis associated with PTSD pathogenesis correlates an impaired prefrontal cortex and a hyperactive amygdala to an exaggerated emotional responsiveness. Findings of a smaller volume and a decreased activity of the PFC could be associated with impaired fear extinction. Emotionally loaded images probably are related with PFC-amygdala dysfunction. Medial PFC takes a behavior and neurochemical control over stressor. An imbalanced PFC-amygdala promotes more primitive areas [17–20].

The hippocampus is another fundamental structure in the brain associated with PTSD pathogeneses; evidence strongly suggested that its dysfunction is a risk factor for the development of PTSD symptoms. The hippocampus is correlated with intelligence quotient (IQ) and coping skill. Alterations in this structure were found in subjects who suffered from early trauma [21–23]. Researchers hypothesized that PTSD patients have an impaired ability to recognize safe contexts and the impairment is associated with smaller volume and decreased activity of the hippocampus. Based on the present evidence, we can say that the hippocampus is vulnerable to stress and is implicated on traumatic memories.

Acute stress promoted by a highly violent event can impair hippocampus functioning, which is a fundamental structure to generate contextual memory from fear experiences. Individuals with a preexisting impaired functioning of the hippocampus likely have difficulties in creating contextual memories, which worsens with acute stress events. Chronic stress, a characteristic of PTSD patients, will promote more damages to hippocampus plasticity and efficiency perpetuating the impairment of fear conditioning [24–27].

Translating all these biological findings to clinical settings (from bench to bed), we can interpret some clinical observations as a model for a comprehensive neurophysiopathology of psychiatric symptoms. Patients with PTSD are not able to distinguish safe from dangerous contexts. Such impairment is related to a state of hyper-arousal, probably related to a dysfunction of the amygdala, and an imbalance of sympathetic and parasympathetic nervous system, causing all stimuli to be considered threatening. Traumatic memories that were not contextualized invade the reality testing.

Impaired neurodevelopment process before the traumatic event, decreased activity of the prefrontal cortex, hyperactivity of the hippocampus, and hyperactivity of the HPA axis may play a role in the physio-pathogenesis of this disorder.

Women have two times more risk of developing PTSD compared to men, having also more intense intrusive thoughts. The emotional memories are more severe if the traumatic event happened during the luteal phase. On the other hand,

estradiol increases women's ability to terminate these emotional memories [28]. These results suggest a hormonal factor behind the higher risk for women to develop PTSD.

Most Frequent Types of Trauma Related to PTSD in Women

As said before, women are more likely to develop PTSD than men, and the most frequent events reported in surveys to be related to the start of symptomatology are sexual abuse (before the age of 18) and intimate partner violence. Epidemiological studies show that sexual abuse is more frequent in girls than boys and, although partner violence occurs in both directions, when the man is the aggressor, the severity of physical harm is worse, leading to life-threatening situations that can cause PTSD [29, 30].

One important risk factor for the development of PTSD is maltreatment during childhood; maltreatment includes several types of abuse and negligence. Women who suffered sexual abuse during childhood have an increased risk of developing mental illness in adult life, including depression, anxiety disorders, and PTSD [31].

Specifically related to PTSD and sexual assault, Ullman and cols proposed that girls who suffered sexual abuse have difficulty to discriminate threatening situations and repeatedly put themselves in risk during adulthood. Very frequently with young girls, the abuser is a person living in intimate relation with the child (e.g., father, uncle, grandfather, neighbor) in a protector role, who, instead, becomes an aggressor. Experiencing this type of dysfunctional attachment style since childhood, the girl loses the ability to recognize intentions of other men and puts herself at risk, becoming prone to sexual revictimization. Besides this misperception of the environment, neurobiological changes in stress response systems occur during this important period of development, and the vulnerability to develop PTSD is established [32, 33].

Rape is strongly related to the development of PTSD; studies show rates around 40–50% of women developing PTSD after sexual assault, only comparable to rates of PTSD post combat situations. Interpersonal violence, including intimate partner violence, have higher conditional risk for PTSD than non-intentional violence [34].

Ferrari and cols reported an increasing risk of developing anxiety and PTSD symptoms as severity of intimate violence increased. In the studied sample of 260 women from the United Kingdom, more than three quarters reported PTSD symptoms above the clinical threshold [35]. In South Africa, a sample of 511 women had 11.6% PTSD diagnosis rates if exposed to intimate violence [36]. In China, an evaluation of 1015 women showed that the ones who suffered psychological or physical violence at home were 5.06 times more likely to have PTSD [37].

Given the fact that women usually look for treatment in general practitioner's services and/or gynecological-related services, it is extremely important that the professionals working at these settings learn to recognize PTSD symptomatology and refer these women to proper treatment. Social assistance is necessary because they usually have difficulties leaving the aggressive environment, an effect related to PTSD symptomatology.

Traumas Specifically Related to PTSD in Women

Breast Cancer

Since life-threatening illness was included as potentially traumatic event in DSM-IV, a growing body of research has investigated cancer-related PTSD, predominantly in breast cancer (BC) populations. Patients with cancer are exposed to aversive and potentially traumatic events such as surgical treatments, side effects of chemotherapy, and recurrence. Some susceptible subjects develop PTSD. PTSD in patients with BC is primarily linked to cancer diagnosis. Chemotherapy and mastectomy were not found to significantly contribute to PTSD symptoms. Comorbidity with anxiety and depression symptoms may hamper diagnosis of this disorder. Receiving a breast cancer

diagnosis can be a significantly traumatic experience, and many women experience persistent cancer-related posttraumatic stress symptoms: PTSS. The literature shows considerable between-study variation in the prevalence of PTSS. Predictors of severe PTSS are related to low social status, previous physical and mental illness, axillary lymph node involvement, and reduced physical functioning. In studies that used clinical interviews based on DSM-IV criteria, rates of PTSD related to BC varied between 2.4% and 6% [38, 39].

PTSS were prevalent in a sample of Brazilian women recently diagnosed with breast cancer. A total of 81% of women presented at least one symptom, 17.9% were diagnosed with PTSD, and 24.5% with subsyndromal PTSD. We identified high comorbidity among PTSD, anxiety, and depression. Scores on domains of the quality of life scale were significantly lower in women with PTSD and subsyndromal PTSD [40].

The concept of traumatic response to stress may prove a useful and precise basis for the assessment of the psychic responses of women with breast cancer by healthcare teams. Distress and other diffuse psychological phenomena that do not meet threshold for a diagnosis may be viewed within a spectrum of posttraumatic stress responses, presumably as subsyndromal PTSD or PTSD-like symptoms. Indeed, arguments have been advanced that symptoms of anxiety and depression among patients with cancer should be viewed as posttraumatic stress responses.

Traumatic Delivery

There is increasing recognition by clinicians and researchers that a proportion of women may be traumatized by giving birth – some of them severely enough to develop PTSD as a result. Traumatic delivery is defined when, during labor or delivery, the mother presents intense fear of her own death or that of her child, besides feelings of impotence, helplessness, and horror. Traumatic delivery is associated with painful delivery, emergency obstetric procedures, and inadequate care during labor [41]. The study of postnatal PTSD is still in its early stages, and there are conceptual issues that need to be taken into consideration when looking at research evidence. For example, labeling traumatic responses to birth as "posttraumatic stress disorder" assumes some equivalence between childbirth and other traumatic stressors, such as rape or natural disasters. However, delivery differs from other traumatic events in that it is predictable and can be a positive experience for many women. Even when experiencing a traumatic delivery, a woman may see her baby as a positive outcome that makes the experience "worth it." Some authors have been proposed for postnatal PTSD other criteria, as partus stress reaction or postnatal stress disorder [42].

Approximately one third of women appraise childbirth as traumatic. However, only 10% have a severe traumatic stress response in the initial weeks after birth, and this reduces to 2.4% at 6 months. Finally, the prevalence of postpartum PTSD has been estimated between 1.3% and 5.9%. However, the research was mostly cross-sectional clouding the conclusion of whether women with postnatal PTSD also had PTSD before delivery. It is possible that the proportion of women with postnatal PTSD includes women with either ongoing PTSD (where delivery exacerbates symptoms from previous event or transfers the focus of symptoms onto birth) or recurrent PTSD (where delivery reactivates symptoms that were previously resolved). Women who presented dissociative symptoms or negative emotions during delivery or a history of traumatic events, depression in pregnancy, poor social support, and a perception of a staff less supportive proved more vulnerable to postpartum PTSD [42]. The limited research available suggests that a history of psychiatric problems, mode of delivery, and low support during labor put women at increased risk of postnatal PTSD, though a simple relationship between mode of delivery and traumatic stress responses is unlikely. Health teams charged with caring for women during the peripartum period should be aware of this condition to allow identification and prevention [41].

Treatment

Treatment of PTSD and ASD has been profoundly researched and developed over the past two decades. There are several practical guidelines for clinicians, but overall the efficacy of proposed interventions is still limited. There are a few discrepancies among evidence-based publications, but, overall, psychotherapy is the modality of treatment that yields the best results and shows greater tolerability. Nevertheless, the lack of head-to-head comparison studies between psychotherapy and pharmacology makes it hard to stratify treatment types [43]. In addition, patient preference, response to prior treatments, comorbidities, availability of different modalities, and clinical judgment are important issues to be taken into account when planning treatment.

Trauma-focused cognitive behavioral therapy receives the strongest recommendation. Therapies that include either exposure or cognitive restructuring, such as prolonged exposure, cognitive therapy, cognitive-processing therapy, and stress-inoculation therapy (a combination of techniques used to strengthen the coping skills of PTSD patients), show solid evidence of efficacy, as well as eye movement desensitization and reprocessing (EMDR) [44, 45]. Other psychotherapies that do not use exposure have been developed to fulfill the need of patients who either do not improve with or do not tolerate exposure treatment. Interpersonal psychotherapy is already well established for the treatment of depression and has been adapted for the treatment of PTSD, showing similar response rates and lower attrition when compared to exposure [46].

When pharmacological options are considered, antidepressants are first-line agents, particularly sertraline, paroxetine, fluoxetine, and venlafaxine. Second-line recommendations are phenelzine, nefazodone (not commercialized in many countries due to liver toxicity), or imipramine [44]. There is some evidence to recommend mirtazapine and tricyclic antidepressants; the evidence is mixed for anticonvulsants, and benzodiazepines are contraindicated for the treatment of PTSD [47]. A recent review found evidence supporting the use of fluoxetine, sertraline, paroxetine, and mirtazapine; imipramine also showed large effect sizes, but the higher dropout rates might be related to worst tolerability [48]. Effective daily dosage of antidepressants has been in the same range as those used for depression. PTSD symptomatology scores usually start to decline in 2–4 weeks after beginning of treatment, and full response is seen in up to 12 weeks, but only 30% achieve remission [45]. Atypical antipsychotics, particularly risperidone, showed some efficacy in treating female patients with PSTD than males, but the evidence is preliminary [49]. This class of drugs might be more useful for patients with severe dissociation or psychotic symptoms related to PTSD, as an augmentation strategy, or when comorbidities such as bipolar disorder are present. The alfa-1-adrenergic agonist prazosin has shown efficacy for the treatment of sleep disturbances in PTSD, particularly nightmares [50]. Overall, the limited efficacy and side effects, plus risk of relapse after discontinuation, make specific psychotherapies the treatment of choice when available.

Trauma and stressor-related disorders display a unique opportunity for prevention, since we can readily identify victims of traumatic events that might lead the disorders before their onset. Trauma-focused psychotherapy for prevention of PTSD has been recommended for patients with ASD, with either a component of exposure or cognitive restructuring [44]. An intervention review from Cochrane Library shows that hydrocortisone might be an option for the prevention of PTSD after exposure to a traumatic event and might reduce symptoms once PTSD is already established as well [51]. A few strategies that were frequently used after acute trauma are now not recommended: psychological debriefing immediately after an exposure to a traumatic event has been proved not useful and possibly harmful to the victim [52]. Use of benzodiazepines after exposure to traumatic events might increase the risk of developing PTSD; therefore it should be avoided – nevertheless, this is still a common practice in emergency settings [53].

There is little information on gender differences regarding treatment response. The course of illness in women tends to be longer, and

chronicity might imply in more aggressive treatment needs [54]. Non-pharmacologic interventions seem to be effective regardless of gender, but some particularities might be present. One study found that, after a 6-month follow-up, men submitted to exposure therapy alone presented reduced maintenance of improvement compared with women treated by the same method or compared with men submitted to exposure therapy combined with cognitive restructuring [55]. They hypothesized that men needed the cognitive restructuring aspect of therapy to reduce dysfunctional cognitions, whereas women were able to do so with exposure alone, possibly because of a greater capacity to retain and process emotions.

There is some evidence that women might respond better to serotonergic agents, particularly when pre-menopausal [54]. It is also important to consider hormonal fluctuations and use of hormonal contraceptives when medication is used in women, as well as gender-related metabolic changes in the cytochrome P450 enzymes, altering plasma concentrations. Pregnancy and lactation in particular pose challenge for pharmacological treatment, and psychotherapy is the modality of choice. When medication is necessary, SSRIs are preferred – fluoxetine seems to be the drug with more evidence of safety. There is controversial evidence on the link of paroxetine and cardiac defects. All psychotropic medications enter breast milk, and among the SSRIs the ones that appear to be safer during breastfeeding are sertraline, paroxetine, and fluvoxamine.

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Sexual Dysfunctions and Gender Dysphoria in Women

Carmita H. N. Abdo

Female Sexual Dysfunction

Introduction

The human sexual response is a complex—and as yet not fully understood—process that involves the interaction of physiological, psychosocial, emotional, and cognitive factors. These factors can vary between individuals and even within the same individual depending on the time, setting, circumstances, and cultures [1–3].

Different models have been used to describe the human sexual response cycle. Masters and Johnson introduced a model of the sexual response cycle, unified for both men and women, defined as the linear progression of four physiologic phases, including excitement, plateau, orgasm, and resolution [4]. In the 1970s, Kaplan modified this to a three-phase model (desire, arousal, and orgasm) [5]. In both of these genitally focused models, orgasm was considered essential for sexual fulfillment, and the importance of intimacy and the emotional aspects of sexuality were not addressed [6].

In the 2000s, Basson [7] drastically modified this linear model of female sexual response. She proposed a circular model incorporating sexual stimuli, emotional intimacy, and relationship satisfaction. This model also emphasizes the importance of emotional satisfaction during sexual activity and recognizes that female sexual functioning is more complex and is less linear than male sexual functioning [7].

Definition and Classification

Sexual dysfunctions are a heterogeneous group of disorders that are typically characterized by a clinically significant disturbance in a person's ability to respond sexually or to experience sexual pleasure [3]. In addition, persistent and distressing change in any of the stages of the sexual response cycle results in sexual dysfunction [8].

Female sexual dysfunction is a multifactorial problem that has detrimental effects on the quality of life of women and has negative impacts on psychological, interpersonal, and intrapersonal aspects [9].

Table 1 summarizes the classification of female sexual dysfunction adopted by *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [3].

It was recently published 11th edition of the International Classification of Diseases (ICD-11) [10], including sexual dysfunctions in Chap. 6 Mental, Behavioral or Neurodevelopmental Disorders. In this edition sexual dysfunctions are defined as "syndromes that comprise the various ways in which adult people may have difficulty experiencing personally satisfying, non-coercive

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Table 1 Classification of female sexual dysfunction according to the DSM-5 [3]

302.72 Female sexual interest/arousal disorder
302.73 Female orgasmic disorder
302.76 Genito-pelvic pain/penetration disorder
302.79 Other specified sexual dysfunctions
302.70 Unspecified sexual dysfunction
Substance/medication-induced sexual dysfunction

sexual activities. In order to be considered a sexual dysfunction, the dysfunction must: (1) occur frequently, although it may be absent on some occasions; (2) have been present for at least several months; and (3) be associated with clinically significant distress." The new classification of female sexual dysfunctions is shown in Table 2 [10].

Table 2 Classification of female sexual dysfunctions according to the ICD-11 [10]

Sexual dysfunctions
HA00 Hypoactive sexual desire dysfunction
HA00.0 Hypoactive sexual desire dysfunction, lifelong, generalized
HA00.1 Hypoactive sexual desire dysfunction, lifelong, situational
HA00.2 Hypoactive sexual desire dysfunction, acquired, generalized
HA00.3 Hypoactive sexual desire dysfunction, acquired, situational
HA00.Z Hypoactive sexual desire dysfunction, unspecified
HA01 Sexual arousal dysfunctions
HA01.0 Female sexual arousal dysfunction
HA01.00 Female sexual arousal dysfunction, lifelong, generalized
HA01.01 Female sexual arousal dysfunction, lifelong, situational
HA01.02 Female sexual arousal dysfunction, acquired, generalized
HA01.03 Female sexual arousal dysfunction, acquired, situational
HA01.0Z Female sexual arousal dysfunction, unspecified
HA01.Y Other specified sexual arousal dysfunctions
HA01.Z Sexual arousal dysfunctions, unspecified
HA02 Orgasmic dysfunctions
HA02.0 Anorgasmia
HA02.Y Other specified orgasmic dysfunctions
HA02.Z Orgasmic dysfunctions, unspecified
GC42 Sexual dysfunction associated with pelvic organ prolapse
HA0Y Other specified sexual dysfunctions
HA0Z Sexual dysfunctions, unspecified
Sexual pain disorders
HA20 Sexual pain-penetration disorder
HA20.0 Sexual pain-penetration disorder, lifelong, generalized
HA20.1 Sexual pain-penetration disorder, lifelong, situational
HA20.2 Sexual pain-penetration disorder, acquired, generalized
HA20.3 Sexual pain-penetration disorder, acquired, situational
HA20.Z Sexual pain-penetration disorder, unspecified
GA12 Dyspareunia
HA2Y Other specified sexual pain disorders
HA2Z Sexual pain disorders, unspecified
HA40 Etiological considerations in sexual dysfunctions and sexual pain disorders
HA40.0 Associated with a medical condition, injury, or the effects of surgery or radiation treatment
HA40.1 Associated with psychological or behavioral factors, including mental disorders
HA40.2 Associated with use of psychoactive substance or medication
HA40.3 Associated with lack of knowledge or experience
HA40.4 Associated with relationship factors
HA40.5 Associated with cultural factors
HA40.Y Other specified etiological considerations in sexual dysfunctions and sexual pain disorders

Etiology

Multiple factors must be taken into consideration when attempting to identify a causative agent for sexual dysfunction. Medical and surgical conditions with the potential to cause sexual dysfunction can range from anatomic processes to pelvic floor disorders, lower urinary tract problems, metabolic disorders (diabetes), cardiovascular problems, inflammatory diseases, neurologic conditions, and gynecological cancer. Moreover, there are a multitude of secondary problems that can lead to sexual dysfunction, such as hormonal imbalance, childbirth, breastfeeding, and menopause [11, 12].

Psychiatric disorders, such as depression and anxiety, are also possible causes, as are associated treatments/medications, such as antidepressants, antipsychotics, and hormonal methods of contraception [13, 14].

Other factors include previous history of sexual abuse, negative attitudes toward sex, body image issues, type of sexual practices, loss of intimacy, and conflicted relationship [11].

Table 3 summarizes the main psychiatric factors associated with female sexual dysfunction.

In many cases of female sexual dysfunction, it is not possible to recognize the precise pathogenesis of the dysfunction since there may be an interplay among psychological, interpersonal, and organic factors [15]. In addition, some of the disorders of female sexual functioning overlap [16]. By way of illustration, vulvovaginal atrophy may be associated with dryness and dyspareunia at menopause, and this sexual pain affects other domains of the sexual response (desire, arousal, orgasm) and the frequency of sexual activity [17].

The partner's role as a precipitating or maintaining factor of female sexual dysfunction has been overshadowed by focusing on individual medical, psychological, or interpersonal factors of sexual function. There is a dynamic and reciprocal relationship of one partner's sexual function, sexual satisfaction, and physical and mental health to the other partner's sexual health and satisfaction [18].

Table 3 Psychiatric factors affecting sexual function of women

Psychiatric disorders
Depression
Anxiety
Bipolar affective disorder
Obsessive-compulsive disorder
Schizophrenia
Eating disorders
Personality disorders
Other psychiatric conditions
Lifestyle
Alcohol consumption
Smoking
Lack of physical activity
Drug abuse
Other factors
Sexual abuse
Use of medications that interfere with sexual function
Negative sexual attitude
Negative body image
Sex practice (penile-vaginal intercourse, anal sex, oral sex, and masturbation)
Domestic violence
Loss of intimacy
Conflicted relationship

Adapted from Khajehei et al. [11], Basson and Schultz [12], Graziottin et al. [13], and Labbate [14]

Epidemiology

The available data of incidence and prevalence of female sexual dysfunction is scarce. These data also differ considerably because of variations in the definitions of sexual dysfunction, different diagnostic tools used, methods of data collection, criteria for composition of sample populations, and influence of cultural factors [19]. Added to this if that there is no presence of personal distress due to sexual difficulty does not consider "real" sexual dysfunction [3]. Therefore, the incidence of female sexual dysfunction has been estimated to range from 25.8% to 91.0% depending on the source [19].

A 5-year incidence of 40% of sexual dysfunction in women was found in a Swedish study from the 1990s [20]. One study from the United Kingdom found that 5.8% of women reported symptoms of sexual dysfunction and 15.5% reported lifelong

sexual dysfunction. Hypoactive sexual desire disorder was the most prevalent recent and lifelong sexual complaint. The generalizability of this study is limited (sample of volunteers and the response rate was 50%) [21]. In an Australian study, 36% of women reported at least one new sexual disorder during the previous 12 months. Lacking interest in having sex had the highest incidence, followed by taking too long to orgasm. Women between 20 and 30 years were just as likely as older women to develop two new sexual disorders in the 12-month study period, namely, lack of interest in having sex and not finding sexual pleasurable [22]. Dyspareunia due to lack of lubrication was reported by 5–25% of younger women with marked cultural differences leading to resulting sexual distress [23]. Lack of orgasm despite high arousal is of uncertain prevalence because studies generally include women with low arousal alongside their lack of orgasm [24].

A decrease in sexual activity during pregnancy [25], especially during the third trimester, and postpartum [26] is due to many psychological and physiological factors and is logical and not indicative of ongoing sexual disorders [25].

The Brazilian Sexual Life Study (BSLS) showed that, on average, 26.6% of the women complain of difficulty in arousal, 26.2% report anorgasmia, 17.8% have pain at sexual intercourse [27], and 9.5% have hypoactive sexual desire, and these prevalence vary according to age [28]. The difficulty of arousal, for example, occurs in 28.0% of women between 18 and 25 years old, compared to 38.1% of Brazilian women over 60 years of age and 24.4% of those between 41 and 50 years [27]. These rates coincide with those of population studies in other countries [29, 30]. This study did not access personal distress related to sexual difficulty and therefore is not necessarily sexual dysfunction [27].

A large-scale study of American women aged 18–102 years (mean 49 years) found that prevalence of any sexual problem was 44.2% (hypoactive desire disorder, 38.7%; arousal difficulties, 26.1%; and anorgasmia, 20.5%), whereas sexually related personal distress was observed in only 22.8% of respondents. There is a sharp age-dependent increase in the prevalence of all three sexual problems, with only 27.2% of women aged 18–44 years reporting any of the three problems, compared with 44.6% of women aged 45–64 years and 80.1% of elderly women (65 years or older). In contrast, sexually related personal distress are lowest in elderly women (12.6%), compared with 25.5% and 24.4% of middle-aged and younger women, respectively [31].

It is fair to say that most female sexual dysfunction increases with age. Across a variety of assessment methods, the prevalence of women's sexual disorders regardless of age is on the order of 40–50% [32]. In the same direction, postmenopausal vaginal dryness and associated dyspareunia was found to affect some 15–30% of women with marked cultural differences to the extent that this leads to bothersome sexual difficulties [23]. On the other hand, there are postmenopausal women who maintain sexual satisfaction, in spite of a decline in sexual function and activity, because of the protective psychosocial factors associated with being in a long-term very satisfied relationship [17].

Clinical Presentation and Diagnosis

There are three main criteria for diagnosing a female sexual dysfunction: symptoms need to have persisted for a minimum of 6 months, be experienced in all or almost all (75–100%) sexual encounters or have been persistent/recurrent, and have caused clinically significant distress [3]. Table 4 illustrates the symptoms that should be observed to make the diagnosis of sexual dysfunction according to DSM-5.

For each sexual dysfunction, one should specify whether the dysfunction is lifelong (the disturbance has been present since the individual became sexually active) or acquired (the disturbance began after a period of relatively normal sexual function); generalized (not limited to certain types of stimulation, situations, or partners) or situational (occurs only with certain types of stimulation, situations, or partners); and mild, moderate, or severe in distress over symptoms in

Table 4 Diagnostic criteria for female sexual dysfunction according to DSM-5 [3]

Female sexual interest/arousal disorder
Lack of sexual interest/arousal for a minimum duration of 6 months as manifested by at least three of the following indicators: 1. Absent/reduced frequency or intensity of interest in sexual activity 2. Absent/reduced frequency or intensity of sexual/erotic thoughts or fantasies 3. Absence or reduced frequency of initiation of sexual activity and is typically unreceptive to a partner's attempts to initiate 4. Absent/reduced frequency or intensity of sexual excitement/pleasure during sexual activity on all or almost all (approximately 75%) sexual encounters 5. Sexual interest/arousal is absent or infrequently elicited by any internal or external sexual/erotic cues (e.g., written, verbal, visual, etc.) 6. Absent/reduced frequency or intensity of genital and/or nongenital sensations during sexual activity on all or almost all (approximately 75%) sexual encounters
Female orgasmic disorder
At least one of the two following symptoms where the symptom(s) must have been present for a minimum duration of approximately 6 months and be experienced on all or almost all (approximately 75%) occasions of sexual activity: 1. Marked delay in, marked infrequency, or absence of, orgasm 2. Markedly reduced intensity of orgasmic sensation
Genito-pelvic pain/penetration disorder
Persistent or recurrent difficulties for a minimum duration of approximately 6 months with one or more of the following: 1. Marked difficulty having vaginal intercourse/penetration 2. Marked vulvovaginal or pelvic pain during vaginal intercourse/penetration attempts 3. Marked fear or anxiety either about vulvovaginal or pelvic pain on vaginal penetration 4. Marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration

criterion A (a description of the distinguishing features of the dysfunction) [3].

In addition to the specific criteria for each sexual dysfunction, DSM-5 also contemplates five associated factors for the diagnostic formulation: (1) partner factors (e.g., partner sexual problem; partner health status); (2) relationship factors (e.g., poor communication, discrepancies in desire for sexual activity); (3) individual vulnerability factors (e.g., poor body image; history of sexual or emotional abuse), psychiatric comorbidity (e.g., depression; anxiety), or stressors (e.g., job loss; bereavement); (4) cultural or religious factors (e.g., inhibitions related to prohibitions against sexual activity or pleasure; attitudes toward sexuality); and (5) medical factors relevant to prognosis, course, or treatment [3].

Obtaining Sexual, Health, and Psychosexual History for Diagnosis

The sexual history should include medical, sexual, reproductive, psychiatric, use of medicines, surgical, and social information [33]. Important content would include a past medical history, current health status, reproductive history, endocrine profile, and psychiatric condition [34].

Validated questionnaires play an important role in the diagnosis and treatment of female sexual dysfunctions. They are used to (1) identify/diagnose women with a specific dysfunction, (2) assess the severity of the dysfunction, (3) assess the distress caused by the dysfunction, (4) evaluate the impact of the dysfunction on the women's quality of life (e.g., sexual confidence, relationship satisfaction, mood), (5) examine the impact of the dysfunction on the partner quality of life, and (6) measure improvement or satisfaction with treatment [33, 34].

There are several instruments with good reliability and specificity: Female Sexual Function Index (FSFI) [35], Changes in Sexual Functioning Questionnaire – Female (CSFQ-F) [36], Arizona Sexual Experience Scale (ASEX) [37], Female Sexual Distress Scale-Revised (FSDS-R) [38], Sexual Interest and Desire Inventory–Female (SIDI–F) [39], and Female Sexual Quotient (FSQ) [40]. As an illustrative example, the description and questions of the Female Sexual Quotient (FSQ), a measure of the sexual function and dysfunction of the woman, developed by us, are presented below.

The FSQ was elaborated and validated by Abdo (2006) [40] and includes all questions about desire and sexual interest (questions 1, 2, and 8), foreplay (question 3), arousing of the woman and sexual interaction with partner (questions 4 and 5), comfort in sexual intercourse (questions 6 and 7), and orgasm and sex-

Table 5 Female Sexual Quotient (FSQ) [40]

Answer this questionnaire truthfully considering the last 6 months of your sex life by the following score: 0 = never 1 = rarely 2 = sometimes 3 = near than 50% of the times 4 = the majority of the time 5 = always
1. Do you often think spontaneously in the sex or remember in the sex or imagine yourself doingsex? ( ) 0 ( ) 1 ( ) 2 ( ) 3 ( ) 4 ( ) 5
2. Does your interest in sex is enough for you to participate in sexual intercourse with will? ( ) 0 ( ) 1 ( ) 2 ( ) 3 ( ) 4 ( ) 5
3. Do the preliminaries (caresses, kisses, hugs, cuddles, etc.) stimulate further relationship? ( ) 0 ( ) 1 ( ) 2 ( ) 3 ( ) 4 ( ) 5
4. Do you often get lubricated (wet) during sexual intercourse? ( ) 0 ( ) 1 ( ) 2 ( ) 3 ( ) 4 ( ) 5
5. During the sexual intercourse, as the excitement of your partner increases, do you also feel more stimulated for sex? ( ) 0 ( ) 1 ( ) 2 ( ) 3 ( ) 4 ( ) 5
6. During the intercourse, do you relax the vagina enough to facilitate penetration of the penis? ( ) 0 ( ) 1 ( ) 2 ( ) 3 ( ) 4 ( ) 5
7. Do you often feel pain during sexual intercourse when the penis penetrates your vagina? ( ) 0 ( ) 1 ( ) 2 ( ) 3 ( ) 4 ( ) 5
8. Can you get involved without being distracted (without losing concentration) during intercourse? ( ) 0 ( ) 1 ( ) 2 ( ) 3 ( ) 4 ( ) 5
9. Can you reach orgasm (maximum pleasure) in sexual relations that you get? ( ) 0 ( ) 1 ( ) 2 ( ) 3 ( ) 4 ( ) 5
10. Do the degree of satisfaction that you get from intercourse give you desire to have sex at other times, on other days? ( ) 0 ( ) 1 ( ) 2 ( ) 3 ( ) 4 ( ) 5
Sexual performance score 0–20 points – null to poor 22–40 points – poor to unfavorable 42–60 points – unfavorable to regular 62–80 points – regular to good 82–100 points – good to excellent

ual satisfaction (questions 9 and 10). It consists of 10 questions with answers ranging from 0 (never) to 5 (always). Score ≤2 in single question suggests dysfunction in respective sexual domain (Table 5). Higher total score indicates a better performance/sexual satisfaction. A cutoff of 60 was established as a way of screening for female sexual dysfunction; therefore, scores ≥62 indicate better sexual function. The FSQ score is obtained by the sum of 10 questions multiplied by 2 to obtain the weight average of 100. In question 7 for the FSQ, the score was already fixed, i.e., 5. The score was calculated as follows: 5 minus the value given by the patient. In the FSQ , the following reference ranges and respective interpretative comments were observed: 0–20 points, null to poor; 22–40 points, poor to unfavorable; 42–60 points, unfavorable to regular; 62–80 points, regular to good; and 82–100 points, good to excellent. This instrument has a high internal consistency (Cronbach's alpha 0.98) [40].

A patient's history and questionnaires may not be sufficient to assess sexual function, and laboratory and imaging investigations are dictated by the woman's medical history and physical examination findings. These tests can assess or identify specific etiologies or assess the role of comorbid conditions. Referral to a specialist in sexual medicine may be considered if a more specialized physical examination, testing, or treatment is needed [41].

Female Sexual Dysfunction and Psychiatric Disorders

Depressive symptoms are strongly associated with sexual dysfunction and dissatisfaction, and screening for depression has been recommended in women with sexual dysfunction and chronic illness [42, 43]. Conversely, depressed patients should be screened for sexual dysfunction [44].

A recent systematic review and meta-analysis confirms for the first time a bidirectional association between sexual dysfunction and depression. The existing literature is sufficient and shows that depression predicts sexual dysfunction and, conversely, sexual dysfunction predicts depression. Etiological mechanisms for the apparent bidirectional association are unclear and likely complex given the heterogeneous nature of depression and sexual function domains, their overlapping nosology, and potential mediating and/or confounding effect of comorbid diseases [44].

A large body of research has shown that severity of sexual dysfunction corresponds to the overall severity of the mood disorder [45] and that depression can have a scarring effect on female sexual functioning even after remission of affective symptoms [46].

Depression diminishes sexual incentives and reduces emotional intimacy that is a major sexual incentive for women. Sexual information processing in the brain is severely compromised by nonerotic thoughts and emotions and poor concentration leading to minimal arousal and no triggered desire [24]. Studies which control for current mood (as well as for medications, marital state, and substance abuse) confirm a history of recurrent depression to be associated with reduced sexual arousal and reduced sexual pleasure [42].

Negative mood (even in the absence of a clinical depression) has been found to impair sexual function [47], while negative or positive sexual experiences were found to modulate mood the day after the sexual encounter [48, 49]. Chronic dyspareunia is three times more common in women with a premorbid diagnosis of depression [50]. The anhedonia of depression has been shown to be associated with inhibition of desire and response as well as with the risk of sexual pain [51].

Studies show that anxiety disorders are risk factors for low sexual desire and arousal [52–56], orgasmic difficulties [57], and dyspareunia [50]. Both sexual and nonsexual worries can be strong distractors when women with anxiety disorders are attempting to be sexual, inhibiting their arousal [58].

"Anxious arousal" has been shown to be linked to women's reduced subjective arousal, impaired lubrication, and sexual pain [48]. Internal stressors may modulate pain circuitry and be involved in central sensitization of the nervous system [59]. Damage to self-image and sexual self-confidence and the increased burden of guilt and responsibility for deterioration of relationships from the inability to have penetrative sex only add to the woman's stress and maintain the vicious cycle [60–62]. Some personality traits also appear to be risk factors to female sexual dysfunction. These include fear of negative evaluation by others, introversion, not being open to new experiences, emotional instability, hypervigilance to pain (significantly correlated with pain intensity during intercourse), and utilization of negative coping strategies [63, 64].

Comparative studies show that obsessive-compulsive disorder is more detrimental to sexual function than social anxiety or generalized anxiety disorder [54, 65].

A variety of sexual dysfunctions, including impaired arousal, delayed or absent orgasm, low frequency of sexual activity, and decreased sexual satisfaction, are present in women with psychotic illness [66–68]. Effects of antipsychotic medications, positive and negative symptoms of psychosis, stigmatization, sexual trauma, somatic concerns, institutionalization, and interpersonal difficulties also contribute to sexual dysfunctions [69].

The potential link between sexual dysfunction and sexual trauma in women with psychotic illness needs more studies. Childhood sexual abuse and intimate partner violence are more likely in women with psychotic illness than in general population [70, 71].

Women with bipolar disorder have casual partners, engage in nonmonogamous sexual partnerships, and had sex with partners with unknown HIV condition more frequently than healthy women [72].

Table 6 Drugs, mechanisms of action, and risk of antidepressant-induced sexual dysfunction

Drug	Mechanisms of action	RAISD	Comments
SSRIs [73]	Block 5-HT reuptake	High	Risk similar (meta-analyses) Comparative studies of SSRIs have not consistently shown any statistical difference in their potential to cause sexual side effects [69] Case reports of increased desire, spontaneous orgasms, and orgasms provoked by exercise from fluoxetine [72]
SNRIs [74]	Block 5-HT reuptake, noradrenergic	Medium	Desvenlafaxine and duloxetine? Low risk Reports are conflicting, some consensus that there are fewer sexually negative effects from SNRIs than from SSRIs, particularly in the case of duloxetine [73]
MAOIs [75]	Dopaminergic, noradrenergic but serotoninergic	Medium	Transdermal selegiline? Low risk A recent formulation of transdermal selegiline is reported to be comparable to placebo in terms of sexual side effects [74]
Quetiapine [76]	Antagonizes D_1, D_2, 5-HT_2, 5-HT_{1A}	Medium	Dose lower than for schizophrenia
Mirtazapine [77]	Noradrenergic, serotoninergic but blocks 5-HT_2, dopaminergic	Low	Weight gain
Bupropion [78]	Dopaminergic, noradrenergic	Very low	Caution with contraindications
Trazodone [79]	5-HT_{2A}/5-HT_{2C} antagonism, weakly blocks 5-HT reuptake	Very low	
Moclobemide [80]	Reversible MAOI	Very low	
Vilazodone [81]	Combined SSRI and HT_{1A} partial agonist	Negligible	More studies are needed
Vortioxetine [82]	Inhibits serotonin transporter, agonist 5-$HT_{1A;}$ multimodal	Negligible	More studies are needed
Aripiprazole [83]	Partial agonist D_2, 5-HT_{1A}, antagonist 5-HT_{2A}, spares prolactin	Negligible	More studies are needed
Lithium [84]	Unclear	Medium	More studies are needed

MAOI monoamine oxidase inhibitor, *RAISD* risk of antidepressant-induced sexual dysfunction, *SNRI* serotonin-norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor
Adapted from Basson and Gilks [24]

Antidepressant-Induced Sexual Dysfunction

It has proven difficult to accurately identify the incidence of treatment-emergent sexual dysfunction (encompassing both the worsening of preexisting problems and the development of new sexual difficulties in previously untroubled patients) during antidepressant treatment [69]. In addition, the frequency of sexual dysfunction due to antidepressant medications is difficult to assess, given that the adverse sexual effects of anxiety and depression are comparable to the side effects of antidepressant medications [24].

Presumed mechanism of interference with sexual function with different classes of antidepressants and approximate risk of drug-induced sexual dysfunction are shown in Table 6 [73–84].

Antipsychotic-Induced Sexual Dysfunction

Sexual function impairment is frequent during treatment with antipsychotics and is associated with a significant impact on patients' quality of life [69]. Depending on the measurement method, it affects between 38% and 86% of

patients [85–88], including remitted ones and those experiencing a first episode of schizophrenia [89, 90].

The mechanisms by which antipsychotic drugs may cause sexual dysfunction are as follows: dopamine receptor antagonism, dopamine D2 receptor antagonism, histamine receptor antagonism, cholinergic receptor antagonism, and alpha-adrenergic alpha receptor antagonism [91, 92].

To date, there are few studies dealing with the impact of metabolic syndrome on female sexual function. Despite this, it is already known that both antipsychotic medications and psychotic illness contribute to impaired sexual function [93, 94]. Several studies indicate that some antipsychotics are associated with serious adverse effects such as metabolic syndrome, which includes increased visceral adiposity, hyperglycemia, hypertension, and dyslipidemia induced by these medications, and are more frequent in females. Additionally, there is some evidence that female sexual dysfunction is associated with high prolactin levels [95].

Management of Female Sexual Dysfunction

Patient Education

Most patients have relatively little knowledge and low level of access to information on healthy sexuality. Effective patient education requires time, communication skills, and didactic resources that facilitate positive sexual behavioral changes. It is a process that continues until the patient's follow-up [96].

Education may be structured in three steps: (1) provide information on normal sexual functioning that may include a description of spontaneous and responsive sexual desire, the role of motivation in sexual desire, the importance of adequate sexual stimulation, the impact of pleasurable experiences on sexual function, and the influence of age and relationship duration [97–99]; (2) educate the patient about factors that are derived from the sexual and medical history that may disrupt sexual function (e.g., mood disorders, medications that impair libido, relationship satisfaction, self-esteem, body image) [100]; and (3) assess motivation for treatment and discuss treatment options [100, 101]. If the patient has a partner, involving the partner in treatment may sometimes be helpful [41].

Office-based counseling may also be useful to reevaluate and alter interfering, misconceptions, taboos, and myths that contribute to women's sexual difficulties [102].

Psychotherapy and Sex Therapy

Psychological therapies access a myriad of topics related to sexual function and satisfaction, such as distracting or negative thoughts, cognitive restructuring of problematic beliefs, perception of sexual arousal, performance anxiety, communication skills training, sexual self-esteem, and body image concerns. Both cognitive behavioral therapy (CBT) and mindfulness-based cognitive therapy have proven benefit and are basic to the treatment for women's sexual dysfunctions of desire, arousal, and orgasm [2, 41].

Mindfulness-based cognitive therapy, which cultivates active awareness of the body and its sensations in a present-centered, nonjudgmental manner, has recently been implicated as potentially beneficial for women with sexual interest/arousal disorder [103, 104]. Mindfulness may affect sexual function through improved interoceptive awareness and increased attention to sexually relevant physiological cues [105]. By focusing on the physical sensations of sexual activity instead of being preoccupied with sexual performance or with current level of desire or arousal, couples can learn to be present and respond to their partner during the sexual situation [106].

Sensate focus exercises usually are present in sex therapy [107, 108]. Focusing away from intercourse can alleviate anxiety and decrease self-monitoring and cognitive distractions considered to promote women's sexual dysfunction [109]. Encouragement of exploration of erotica is often a component of sex therapy as are skills to improve couple communication [108].

Table 7 Psychological factors that impair the female sexual function and therapeutic approaches

Psychological factor	Therapeutic approach
Depression and/or anxiety	Pharmacotherapy/cognitive behavioral therapy
Fear of sexual pain	Psychotherapy
Stress or distraction	Cognitive behavioral therapy
History of abuse (physical, sexual, emotional)	Psychotherapy
Poor self-esteem/body image	Psychotherapy
Relationship factors	Office-based counseling or refer for individual/couples therapy
Self-imposed pressure for sex	Office-based counseling or refer for cognitive behavioral therapy
Lifestyle factors (e.g., fatigue, sleep deprivation)	Office-based counseling
Substance abuse	Psychotherapy
Sexual factors (e.g., inadequate stimulation)	Office-based counseling
Religious, personal, cultural, or family values, beliefs, and taboos	Office-based counseling or refer for cognitive behavioral therapy

Adapted from Clayton et al. [41]

Several psychological factors can impair the female sexual arousal and desire. Table 7 summarizes these factors and the main recommended therapeutic approaches [41].

The treatment of dyspareunia ideally requires a multidisciplinary approach involving physician, physiotherapist, and psychotherapist. Treatment focuses on learning techniques to reduce or cope with the pain, as well as dealing with catastrophic thoughts, anticipation of pain, and avoidance of all sexual exchange [110].

Women with psychotic illness may not be able to participate in CBT or sex therapy for their sexual dysfunction, requiring instead a more supportive therapeutic approach [24].

Management of Treatment-Induced Sexual Dysfunction in Depressed Patients

Depression, anxiety, and psychosis are recognized as the major risk factors for women's sexual dysfunction. Therefore, the initial step is to ensure remission of these psychiatric conditions [24].

The frequency of patients receiving antidepressant treatment who report sexual dysfunction when directly questioned by physicians is substantially higher than those who spontaneously report sexual dysfunction to their physician [111, 112].

Antidepressant-induced sexual dysfunction has been reported in up to 70% of patients treated with SSRIs or SNRIs [77, 113, 114]. Neurotransmitters, such as serotonin, dopamine, and norepinephrine, are involved in the physiology of sexual functioning as well as in regulating mood. Antidepressants may increase or decrease the function of these neurotransmitters in various end organs. Dopamine is related to motivated behaviors, including sexual behaviors, whereas norepinephrine stimulates sexual arousal and vasocongestion. Activation of serotonin systems results in suspension vasocongestion, thus diminishing arousal mechanisms in genital organs. The action of 5-hydroxytryptophan may also decrease nitric oxide function and genital sensation. The balance of effects of various antidepressants on these neurotransmitters regulates their effects on sexual function [115–117].

In contrast, several antidepressants have been associated with lower incidences of sexual dysfunction compared with the SSRIs. Some have even been used in the treatment of SSRI-induced sexual dysfunction, including bupropion, mirtazapine, nefazodone, and vilazodone [116].

It should also consider that while a substantial proportion of patients experience treatment-emergent sexual dysfunction while taking antidepressants [77, 114], the reduction of depressive symptoms through successful antidepressant treatment can also be accompanied by reported improvements in sexual desire and satisfaction [118–120].

In order to reduce the negative effect of antidepressants on sexual function, several strategies have been developed. One or more of the following interventions can be chosen:

1. Watchful waiting involves continuing therapy at the same dosage to determine whether tolerance will develop [116].
2. Switch to another antidepressant from the same class (or one that exerts a similar effect) with a lower incidence of sexual dysfunction (e.g., bupropion, vortioxetine, vilazodone, moclobemide, desvenlafaxine, nefazodone, or mirtazapine) [24, 121].
3. Dosage reduction of antidepressant: especially useful in patients who are experiencing other side effects as well. It should be attempted only in patients who have responded well to the medication, and the clinician and patient should be watchful for any signs of relapse or discontinuation symptoms [121].
4. Drug holidays, in which a patient is advised to skip her antidepressant treatment for a 1 or 2 alternate days, can be effective but can also undermine treatment compliance [121].
5. Use "antidotes" or other psychotropic agents to counteract sexual dysfunction or alleviate its symptoms [24]. This strategy also encourages patients to maintain adherence to effective antidepressant treatment regimens [122, 123]. Adding bupropion can reverse SSRI-induced dysfunction [124], as can the addition of aripiprazole [125]. Vortioxetine has been shown to improve sexual dysfunction from SSRIs in patients in remission from depression [126].

Transdermal testosterone for loss of sexual desire in postmenopausal women showed some benefit [127]. However, this hormonal therapy is controversial given the need for supplementing estrogen also, the lack of benefit in premenopausal women, of long-term safety data, and of any formulation for women [24]. In Brazil, testosterone prescription for desire, arousal, and orgasm dysfunction is only approved for postmenopausal women under estrogen use [128].

Physical exercise immediately prior to sexual activity significantly improves sexual desire in women taking antidepressants. Scheduling regular sexual activity significantly improved orgasm function, but exercise did not increase this benefit. Physical exercise (to increase sympathetic nervous system) drive might combat the sexual side effects of serotonergic antidepressants given serotonin has an inhibitory effect on noradrenaline and women's genital sexual arousal is sympathetically driven. However, no effects on subjective arousal were demonstrated [129].

In addition to the abovementioned strategies, the overall stance is often to accept the sexual side effects and use evidence-based psychotherapy. Both CBT and mindfulness-based cognitive therapy are effective for women with sexual dysfunction caused at least in part by antidepressants [130, 131].

Physiotherapy

Pelvic-floor-related sexual dysfunction comprises dyspareunia, vaginism, and chronic pelvic pain (CPP). There is a recent tendency to more frequently involve physiotherapists in the multidisciplinary assessment and treatment of female sexual dysfunction and pain management [132]. Several studies emphasize the efficacy of pelvic physiotherapy as part of the multidisciplinary approach for CPP and sexual dysfunction [133–136].

Gender Dysphoria/Gender Incongruence in Women

Introduction

One of the concepts of gender identity was coined in the middle 1960s, describing one's persistent inner sense of belonging to either the male or female gender category [137]. However, some authors argue that gender identity is not a forced dichotomous choice (male or female) and that 'complete maleness or complete femaleness' represents the extreme ends of a spectrum of body types [138]. The American Psychological Association described gender identity as the person's basic sense of being male, of being female, or of indeterminate sex [139]. In turn, the American Psychiatric Association defines gender identity as a category of social identity which refers to an individual's identification as male, female, or, occasionally, some category other than male or female [3].

The term "gender dysphoria" was first introduced by Fisk (1974) to describe individuals who experience sufficient discomfort with their biological sex to form the wish for sex reassignment [140]. In the DSM-5, gender dysphoria is defined as an individual's affective/cognitive discontent with the assigned gender (usually at birth and referred to as natal gender) [3].

The DSM-5 uses the term gender dysphoria to refer an individual's affective/cognitive discontent with the assigned gender, highlighting that it is a specific definition when used as a diagnostic category. Thus, gender dysphoria refers to the distress that may accompany the incongruence between one's experienced or expressed gender and one's assigned gender. Gender dysphoria is not the same as gender nonconformity, which refers to behaviors not matching the gender norms or stereotypes of the gender assigned at birth. The term transgender refers to the broad spectrum of individuals who transiently or persistently identify with a gender different from their natal gender. Transsexual denotes an individual who seeks, or has undergone, a social transition from male to female (MtF) or female to male (FtM), which in many, but not all, cases also involves a somatic transition by cross-sex hormone treatment and sex reassignment surgery [3].

Apart from gender dysphoria, there are many other terms, such as gender nonconforming, gender variant, gender fluid, bigender, third gender, gender queer, gender neutral, agender, and nonbinary, along with "trans," transsexual, and transgender [141].

Each sociocultural group has its own set of gender categories that are the basis of the individual's social identity in relation to other members of that group [142]. In many cultures, social stigma toward gender nonconformity is widespread, and gender roles are highly prescriptive. Gender-nonconforming people in these settings are forced to be hidden and, therefore, may lack opportunities for adequate health care [143].

Etiology

There are several biological hypotheses that attempt to explain gender dysphoria, ranging from genetic factors and prenatal alterations to hormone levels and external factors like stress [144].

It is hypothesized that feelings of gender incongruence may arise from atypical sexual differentiation of the brain under the influence of prenatal hormones [145]. Time windows for prenatal development of genitals and the brain are believed to differ; thus, exposure to atypical levels of prenatal hormones during a certain gestational period may have an effect on the brain but not the body [144].

Prevalence

Population-based data from European countries provided the best estimates of the prevalence of gender dysphoria in Western societies. In Belgium, for example, the prevalence of transsexuality, defined as having undergone sex reassignment, was 1:12,900 for adult males and 1:33,800 for adult females; data from the Netherlands were similar: 1:11,900 adult males and 1:30,400 adult females.[1414]

A literature review that included ten studies, involving eight countries, found that the prevalence range from 1:11,900 to 1:45,000 for MtF and 1:30,400 to 1:200,000 for FtM [146].

According to the DSM-5, for natal adult males, prevalence ranges from 0.005% to 0.014%, and for natal females, from 0.002% to 0.003%. Since not all adults seeking hormone treatment and surgery attend specialty clinics, these rates are likely modest underestimates. Data from specialty clinics vary by age group. In children, sex ratios of natal boys to girls range from 2:1 to 4.5:1. In adolescents, the sex ratio is close to parity; in adults, the sex ratio favors natal males, with ratios ranging from 1:1 to 6.1:1 [3].

Diagnosis

As research about gender incongruence/gender dysphoria increased, the terminology and diagnosis criteria were reviewed in successive versions of the DSM and ICD. Changes in various aspects of the diagnosis and etiological factors,

Table 8 Diagnostic criteria for gender dysphoria in children, adolescents, and adults [3]

Criteria for gender dysphoria in children
A. *A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following (one of which must be Criterion A1):*
1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender) 2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing 3. A strong preference for cross-gender roles in make-believe play or fantasy play 4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender 5. A strong preference for playmates of the other gender 6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities 7. A strong dislike of one's sexual anatomy 8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender
B. *The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning*
Specify if: with a disorder of sex development
Criteria for gender dysphoria in adolescents and adults
A. *A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:*
1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics) 2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics) 3. A strong desire for the primary and/or secondary sex characteristics of the other gender 4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender) 5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender) 6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender)
B. *The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning*
Specify if: with a disorder of sex development Specify if: posttransition, the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen—namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).

however, were not only based on research. Social and political factors contributed to the conceptualization of gender incongruence/gender dysphoria as well [147]. It is important to emphasize that both DSM-5 and ICD-11 depathologizes gender identity and considers other gender expressions besides the male/female dichotomy, focusing instead on dysphoria [3, 10].

In DSM-5, diagnostic criteria are divided into gender dysphoria in children and gender dysphoria in adolescents and adults. In children this condition is defined as a strong inconsistency between the sex one feels or expresses and the one assigned, with duration of at least 6 months, which manifest in at least six of characteristics presented in Table 8. In gender dysphoria in adolescents and adults, there is also a strong inconsistency between the sex the individual feels and expresses and the one assigned, with a duration of at least 6 months, manifested by at least two characteristics listed in Table 8. The dysphoria should be associated with a clinically significant distress or deterioration in social, work, and/or other areas important to functioning [3].

Preschool-age children are less likely than older children, adolescents, and adults to express extreme and persistent anatomic dysphoria. In adolescents and adults, incongruence between

experienced gender and somatic sex is a central feature of the diagnosis [3].

Some women with gender dysphoria will recall a childhood pattern of sex-typed behavior that corresponds to the behavioral indicators of gender dysphoria in childhood (early-onset gender dysphoria), which might be present in the absence of an explicit desire to be of the other gender [148]. For other adults, there is no clear evidence of childhood cross-gender identification; rather, the indicators of gender dysphoria emerge at puberty (late-onset gender dysphoria). Some researchers consider early onset to be any time prior to puberty, whereas other researchers consider early onset to be during the toddler and preschool years, the developmental period in which both gender identity and gender role behaviors are first expressed [149].

The ICD-11 working group recommended (1) retaining gender diagnoses in ICD-11 to preserve access to care but (2) moving these categories out of the ICD-11 chapter "Mental and Behavioral Disorders" [144]. In fact, the ICD-11 adopted the nomenclature "gender incongruence," characterized by a marked and persistent incongruence between an individual's experienced gender and the assigned sex. Gender variant behavior and preferences alone are not a basis for assigning the diagnoses in this group. In addition, the term "transsexualism" was excluded. This condition was included in a new chapter called "Conditions Related to Sexual Health" [10]. The ICD-11 classification of gender incongruence is presented in Table 9.

The main differential diagnoses of gender dysphoria should be made with nonconformity to gender roles, transvestic disorder, body dysmorphic disorder, and schizophrenia and other delusional disorders, bipolar, dissociative, and personality disorders [3].

Table 9 ICD-11 classification of gender incongruence [10]

HA60 Gender incongruence of adolescence or adulthood Gender incongruence of adolescence and adulthood is characterized by a marked and persistent incongruence between an individual's experienced gender and the assigned sex, as manifested by at least two of the following: (1) a strong dislike or discomfort with the one's primary or secondary sex characteristics (in adolescents, anticipated secondary sex characteristics) due to their incongruity with the experienced gender; (2) a strong desire to be rid of some or all of one's primary and/or secondary sex characteristics (in adolescents, anticipated secondary sex characteristics) due to their incongruity with the experienced gender; (3) a strong desire to have the primary and/or secondary sex characteristics of the experienced gender. The individual experiences a strong desire to be treated (to live and be accepted) as a person of the experienced gender. The experienced gender incongruence must have been continuously present for at least several months. The diagnosis cannot be assigned prior the onset of puberty. Gender variant behavior and preferences alone are not a basis for assigning the diagnosis
HA61 Gender incongruence of childhood Gender incongruence of childhood is characterized by a marked incongruence between an individual's experienced/expressed gender and the assigned sex in prepubertal children. It includes a strong desire to be a different gender than the assigned sex; a strong dislike on the child's part of his or her sexual anatomy or anticipated secondary sex characteristics and/or a strong desire for the primary and/or anticipated secondary sex characteristics that match the experienced gender; and make-believe or fantasy play, toys, games, or activities, and playmates that are typical of the experienced gender rather than the assigned sex. The incongruence must have persisted for about 2 years. Gender variant behavior and preferences alone are not a basis for assigning the diagnosis
HA6Z Gender incongruence, unspecified This category is an *unspecified* residual category

Transgender Clinical Care

The general health and well-being of transgender women should be attended to within the primary care setting, without differentiation from services offered to cisgender (non-transgender) people [150].

Health professionals can assist gender dysphoric individuals with affirming their gender identity, exploring different options for expression of that identity, and making decisions about medical treatment options for alleviating gender dysphoria [151].

An international, multidisciplinary professional association, World Professional Association for Transgender Health (WPATH),

promotes evidence-based education, care, research, advocacy, public policy, and respect in transsexual and transgender health care. WPATH standards of care recommend a therapeutic triad (psychological, hormonal, and surgical); the number and type of interventions applied and the order in which these take place may differ from person to person [151, 152]. WPATH recognizes and validates expressions of gender that may not necessitate hormonal or surgical procedures. As the prevalence of nonbinary gender presentations is increasing, provision of information to patients and health-care providers about multiplicity of gender identity/expression and medical interventions is essential [150, 151].

Mental Health Care

Several studies have shown increased rates of depression in transgender populations [153–155]. Studies with transgender women found 61% of depression [156] and 40% of anxiety disorders [157].

The responsibilities related to mental health-care assessment and referral are as follows: accurately diagnose the patient's gender dysphoria; diagnosis and discussion of treatment options for coexisting mental health concerns; inform the patient regarding the available treatments and their consequences; provide psychotherapy; evaluate the patient's eligibility and suitability for hormone therapy and surgical procedures; make formal referrals to other professionals (e.g., endocrinologists, surgeons); make oneself available to the patients for follow-up treatments; and educate relatives, employers, and institutions about gender dysphoria [144, 150, 151].

Comorbid psychopathology is significantly more prevalent in women with gender dysphoria than in the general population. Mood and anxiety disorders are especially likely to occur in association with gender dysphoria [144, 158]. Both hormone therapy and gender-affirming surgery can alleviate the distress caused by gender dysphoria [159–161].

Screening for conditions related to the oppression and stigmatization that transgender women experience should be done. These include high-risk sexual behavior, substance abuse, suicide attempt, and being victims of violence [150].

Physical Health Care

Hormonal therapy is a necessity for most transgender women undergoing a medical transition. Drugs are used to suppress the natal hormones, typically gonadotropin-releasing hormone (GnRH) analogues or agonists. If these drugs are not available or occasionally when they cause side effects, progestin, cyproterone acetate, and spironolactone are alternatives [162–164].

Feminizing and masculinizing hormone therapy will induce physical changes that are more congruent with a patient's gender identity. In FtM patients, the following physical changes are expected to occur: clitoral enlargement, growth in facial and body hair, cessation of menses, atrophy of breast tissue, increased libido, deepened voice, and decreased percentage of body fat compared to muscle mass. In MtF patients, the following physical changes are expected to occur: breast growth, decreased testicular size, decreased libido and erections, and increased percentage of body fat compared to muscle mass [151].

For transgender women, natural estrogen (17β-estradiol) is recommended, rather than synthetic ethinyl estradiol or conjugated estrogens, because 17β-estradiol can be measured and monitored in plasma, and it appears to be less associated with the risk of thromboembolism. The clinician must discuss the risks with the patient and obtain informed consent. Being treated for HIV poses additional complexities in clinical decision-making for hormone therapy, including interactions of certain antiretroviral drugs with hormones. Feminizing hormones are prescribed usually lifelong [151].

Patient consent must be requested to decisions about gamete storage. Where genital reconstructive surgery definitely results in sterility, hormone therapy on the other hand also has an important, but partially reversible, impact on fertility. The current fertility preservation options for FtM transgender are embryo cryopreservation, oocyte cryopreservation, and ovarian tissue cryopreservation; for MtF, sperm cryopreserva-

tion, surgical sperm extraction, and testicular tissue cryopreservation [165].

In the majority of children with cross-gender behavior, it does not persist into late puberty [166, 167]. For adolescents with persistent gender dysphoria, the use of GnRH analogues is emerging as standard practice. The treatment blocks the expected maturation of secondary sex characteristics (e.g., breast development, voice deepening, and facial hair growth). It allows that the adolescent proceed with restricted pubertal growth, while experiencing a change in gender role during younghood [150, 168]. In all cases involving endocrine therapy, follow-up is crucial.

Removal of facial hair is essential for individuals transitioning to a female role. Some transgender women may seek further removal of body hair, particularly of that on the chest, abdomen, and limbs. Several hair removal techniques can be used, with laser hair removal reserved particularly for individuals with dark colored hair. Electrolysis and pulse wave light therapy are alternative treatments, but no treatments are acknowledged as being able to completely remove new hair growth [150].

Transgender women might seek the assistance of a voice and communication specialist to develop vocal characteristics (e.g., pitch, intonation, resonance, speech rate, phrasing patterns) and nonverbal communication patterns (e.g., gestures, posture/movement, facial expressions) that facilitate comfort with their gender identity [151]. Voice and communication therapy may help to alleviate gender dysphoria and be a positive and motivating step toward achieving one's goals for gender role expression [169].

Gender-affirming surgery (both genital and nongenital) is a medically necessary intervention for many patients with gender dysphoria. Genital and breast/chest surgeries are to be undertaken only after assessment of the patient by qualified mental health professionals [151].

Transgender women must be well informed about surgical implications (especially since some procedures are irreversible), limitations, and cost. Realistic expectations of surgical results must be given. Surgical intervention can help to resolve a self-perceived mismatch between the body and self-identity. Genital reconstruction surgery is typically the last stage in transition for those who cannot otherwise accept their gender dysphoria. A transgender person may seek nongenital surgery to change their physical appearance and to better assimilate societally within their reassigned gender [150].

For the MtF patient, surgical procedures may include breast/chest surgery (augmentation mammoplasty), genital surgery (penectomy, orchiectomy, vaginoplasty, clitoroplasty, vulvoplasty), and nongenital, non-breast surgical interventions (facial feminization surgery, liposuction, lipofilling, voice surgery, thyroid cartilage reduction, gluteal augmentation, hair reconstruction, and aesthetic procedures) [151, 170, 171].

For the FtM patient, surgical procedures may include breast/chest surgery (subcutaneous mastectomy, creation of a male chest), genital surgery (hysterectomy/ovariectomy, reconstruction of the fixed part of the urethra, which can be combined with a metoidioplasty or with a phalloplasty, vaginectomy, scrotoplasty, and implantation of erection and/or testicular prostheses), and nongenital, non-breast surgical interventions (voice surgery, liposuction, lipofilling, pectoral implants, and various aesthetic procedures) [151]. These patients usually prioritize mastectomy to promote a more masculine body image [172].

By following surgical procedures, mental health professionals, surgeons, and patients share responsibility for the decision to make irreversible changes to the body [151].

Surgery and hormonal therapy alleviate gender dysphoria. Transgender women, after sex reassignment, have considerably higher risks for mortality, suicidal behavior, and psychiatric morbidity than the general population. Sex reassignment surgery may not suffice as treatment for gender dysphoria and should inspire improved psychiatric and somatic care after sex reassignment for these patients [158].

Transgender women who have concomitant physical or psychiatric illnesses should be given the same degree of care, and access to care, as non-transgender individuals [150].

Conclusion

The expectations of individuals and of society for the health care of transgender women are evolving. The evolution of the standards of care allows for a flexible pathway of support from health professionals who provide care during transition and follow-up. Nevertheless, the fundamental challenge remains as to how the standards of care will be negotiated, approved, and implemented by the public and private health authorities of various countries, in the context of broader sociopolitical issues [150].

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Eating Disorders and Personality Disorders in Women

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Introduction

Eating disorders (EDs) are characterized by inadequacies in consumption, by eating patterns and behavior, as well as by a variety of mistaken beliefs about food, leading to progressive worsening of nutritional and psychopathological aspects.

These disorders are determined by a multifactorial etiology, while cultural aspects (such as concerns with weight and body shape, standards of beauty), psychological aspects (individual and family), use of restrictive diets (which may initiate a cascade of biological changes), and biological vulnerability (genetic and family history of eating disorder) play an important role in the triggering, the maintenance, and the perpetuation of the respective symptoms [1].

The EDs are most commonly observed in developed and industrialized countries, with the greatest incidence in young women between 18 and 30 years of age (3.2%). Although less common in men, the severity is the same, while homosexual men have a higher predisposition than heterosexual men. Risk factors include gender, ethnicity, childhood eating problems, weight and body concerns, negative self-rating, history of sexual abuse, and/or psychiatric disorders [1].

Eating disorders cause intense emotional distress, morbidity, and psychosocial impairment [2]. The mortality of patients diagnosed with eating disorders is high both for clinical complications and for suicide, as this shows the need for improvement in the diagnosis, treatment, and multidisciplinary approach of the healthcare teams in order to avoid negative outcomes [3].

Statistics from the National Eating Disorder Association suggest a monthly cost of US$30,000.00 for inpatient treatment, while patients in intensive outpatient treatment cost US$500 to US$ 2000 per day [4].

Comorbidity among EDs is more a rule than an exception. Original articles and a variety of reviews have been pointing to associations between personality and EDs while proposing many different theories on the understanding of this association and its significance in terms of etiology, expression of symptoms, adherence to treatments, and evolution of the clinical condition [5].

Updates to the DSM 5

Improvements in the diagnostic criteria in the Diagnostic and Statistical Manual of the American Psychiatric Association, 5th edition (DSM 5) contributed to more accurate diagnostics,

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significantly reducing the number of patients who fit into the residual category of atypical eating disorders [6].

The Eating Disorders chapter of the DSM 5 includes the following categories along with the respective modifications for AN, BN, and BED [7].

Anorexia Nervosa (AN)

Characterized by self-inflicted weight loss, voluntary loss of weight, and distortion of body image, accompanied by fear or refusal to gain weight; the need for amenorrhea was abolished in DSM 5 since it was observed that many individuals had all the characteristics for AN, but with some menstrual activity. In addition, this criterion could not be used in prepubescent girls, women using hormonal contraceptives, or postmenopausal women nor men. A temporal reference was also included for the classification of the subtypes, defined as restrictive subtype (AN-R) (in the last 3 months, there was no episode of compulsion or purgative practice) and purgative subtype (AN-P) (in the last 3 months, there have been episodes of compulsion and/or purging). DSM 5 uses the individual's BMI as the severity specifier.

Bulimia Nervosa (BN)

Characterized by episodes of binge eating, i.e., intake of large quantities of food in a short period with a sense of loss of control, and use of compensatory methods inappropriate for weight control, such as self-induced vomiting, compensatory diets, use of medications (laxatives, diuretics, appetite suppressants), and exaggerated physical exercises. Excessive concern with weight and body shape is observed. DSM 5 includes as a minimum diagnostic criterion, one compulsion episode, once a week, in the last 3 months. As a severity specifier, the frequency of inappropriate compensatory behaviors practiced by the patient is used.

Binge Eating Disorder (BED)

Characterized by recurrent episodes of binge eating in the absence of compensatory behaviors to promote loss or avoid weight gain. Increasing evidence indicating that BED is a specific condition led to it being inserted into DSM 5 as a diagnostic category in the chapter on eating disorders, instead of only mentioning it in the appendix. It also includes, as severity specifiers, the frequency of binge eating episodes.

At the end of this chapter, we present the new DSM 5 diagnostic criteria for the three main EDs.

Gender-Related Considerations

Over the past two decades, study results have highlighted the relevance and specificity of female mental health. The evidence covers several areas of interest and confirms gender differences in relation to biological factors; risk factors and protective factors; trauma, violence, and social stressors; etiopathogenesis, onset, course, and prognosis of mental disorders; and identification, treatment, and intervention. In addition, it is proven that work disability due to mental health conditions in women is significantly higher than in men, while depression in women accounts for 42% of the causes of neuropsychiatric disability compared to 29.3% in men, and rates are even higher – reaching up to 65% – if women of reproductive age (16–55 years) are considered. Despite the influence of gender on the onset and development of mental disorders, mental health diagnostic manuals do not yet have a gender-specific approach. To date, there is no specific assessment tool that provides detailed information on the psychopathology of mental disorders related to pregnancy, postpartum, menstrual cycle, perimenopause, and postmenopause. Epidemiological studies show that at the onset of a woman's reproductive age (menarche), mood disorders are up to twice as common in women as in men, in addition to anxiety, eating disorders, and somatoform disorders. There are also differences in the type and size of the comorbidities [8].

Recent studies suggest that the testosterone circulating in boys and the absence of it in girls, while still in intrauterine life, would have primary effects on the CNS and, consequently, on the behavioral differentiation. In adolescence, again, circulating sex hormones are part of the reorganization of the CNS and emergence of female and male secondary characteristics, and this phase would be related to the etiology of eating disorder: testosterone as a protective factor in men and estrogen and progesterone as a risk factor [9].

Gender differences are also reflected in eating behavior. Women demonstrate a greater preference for food with high sugar and carbohydrate content when compared with men; as the changes in serum levels of ovarian hormones seem to have a relationship with this intake, being that, in the post-ovulation phase, where there is a peak of estrogen and progesterone, there is a higher frequency of episodes of compulsion and "emotional eating" (i.e., reactive to negative emotions), and, in the pre-ovulation phase, this frequency decreases. Again high testosterone levels may contribute significantly as a protective factor, as high levels of this hormone in the postpubertal phase in boys were associated with fewer episodes of binge eating [9].

Caroleo et al. classified 201 obese individuals into 2 different clusters. The objective is to outline the differences between psychopathology, personality traits, cognitive patterns, and genes. Recognizing different patterns of obesity contributes to a greater understanding of the disease and to the development of individualized treatments. Again the influence of gender can be observed. Two different patterns were observed in the individuals studied [10]:

- Cluster 1: had a higher percentage of male gender and higher rates of social eating and prandial hyperphagia, higher percentage of lean mass, and a higher frequency of the long allele of the 5-HTTLPR gene.
- Cluster 2: had a higher percentage of female gender and higher rates of emotional eating, compulsive eating, craving for carbohydrates, nocturnal eating, snacking pattern, and a worse metabolic and inflammatory profile. In this cluster there were impaired scores in all psychopathological schools (BES, BDI, STAI, BIS), higher rate of psychiatric comorbidities, higher BMI, higher proportion of BED, higher percentage of fat mass, more affective symptoms and dysfunctional personality traits (greater avoidance of harm and less self-direction), worse decision-making, and greater cognitive impairment (flexibility). In relation to the genetic profile, there is a higher frequency of the short (S) allele of the 5-HTTLPR gene.

The short (S) allele of the 5-HTTLPR gene has already been related to various psychiatric conditions and eating disorders. This allele was related to a higher propensity for major depressive episodes due to stressors; less transcriptional activity and less efficiency in the reuptake of serotonin (which may explain greater presence of psychiatric comorbidities); higher impulsivity, higher rates of BN, anxiety, and depression; higher levels of anxiety and impulsivity in women diagnosed with ED; and greater emotional instability and severity of psychopathological symptoms [10].

Finally, women diagnosed with AN present higher probability of low weight gain in pregnancy and higher rates of spontaneous abortions, cesarean delivery, lower birth weight of newborns, and premature birth. In addition, women diagnosed with BN present higher rates of spontaneous abortions, hyperemesis gravidarum, and postpartum depression [11].

Comorbidities

The psychiatric comorbidity among EDs is very common and is of great interest since it is part of the treatment aim. Some of these comorbidities present very early onset in childhood and adolescence, sometimes even earlier and, in others, arising concurrently with EDs. The early emergence and frequent chronification of many of these conditions make it possible to "separate the chaff from the wheat" (i.e., to determine what the

comorbidity is, what the main disease is, and what is the personality of the individual) a difficult task.

The diagnosis of the comorbidity assists with the treatment and the implementation of the suitable therapy for the respective clinical picture [12].

Anorexia Nervosa

The purgative subtype of anorexia nervosa (AN-P) has a higher prevalence of psychiatric comorbidities, suicide attempts, and self-mutilation than the restrictive subtype (AN-R) [13]. The severity of the psychopathological condition of the eating disorder influences the psychiatric comorbidity and is associated with higher rates of suicidal ideation [14].

AN has long been related to depression, which is the most prevalent comorbidity in anorexic patients, with an approximate rate of 40% in those with the restrictive subtype and 82% in those with the purgative subtype. Some of the alterations found, such as fatigue, irritability, dysphoric mood, loss of libido, insomnia, and difficulty concentrating, may be due to an altered nutritional status. With weight gain, the symptomatology would tend to disappear in the absence of a real comorbidity [15].

Secondly, anxiety disorders appear, at a rate of 24% for patients with AN-R and 71% for those with AN-P. In third place, we have obsessive-compulsive disorder (OCD), for which the lifetime prevalence in women with AN ranges from 10% to 62% [15]. Finally, alcohol and drug dependence affects up to 25% of patients with EDs [16].

Rates of psychiatric comorbidity and suicidal ideation are lower in adolescents than in adult women; this suggests that early and effective intervention may prevent the development of more severe psychiatric comorbidities. It is known that prolonged fasting in these patients leads to brain dysfunctions (metabolic and hormonal changes, leading to neurotransmitter dysfunction) and may predispose to psychiatric comorbidities. In addition, AN leads to educational and vocational impairments, while compromising social relationships, which is also predisposing to psychiatric comorbidities such as anxiety and depression. The mortality rate varies from 5% to 20%, and the main cause is suicide. Approximately 50% of adult patients report suicidal ideation and up to 26% attempt suicide [14].

Bulimia Nervosa

The most observed comorbidity in BN is depression, with a lifetime prevalence varying from 50% to 65% [17]. Second most common comorbidity are disorders of abusive use of psychoactive substances whose prevalence varies from 30% to 60% being that the prevalence of alcohol dependence is 26%, and the eating disorder precedes alcohol abuse in 68% of cases [16].

Higher than expected rates of bipolar disorder have also been found in patients with BN, reaching about 14.3% [18, 19]. Prevalence rates for generalized anxiety disorder range from 8% to 12%; for panic disorder, the rate is approximately 11%; for social phobia, it is 17%; and it is about 40% for OCD. Certain studies have shown that posttraumatic stress disorder (PTSD) is significantly more common in BN patients.

Binge Eating Disorder

Binge eating disorder is associated with rates of significant psychiatric comorbidities comparable to bulimia nervosa and anorexia nervosa. The most common comorbid disorders are depressive disorder, bipolar affective disorder, anxiety disorders (30–60%), and, to a lesser extent, disorders due to alcohol and drug use (approximate 23%) [15, 16].

Personality and Eating Disorders

Studies have compared the traits and the diagnosis of personality disorders (PDs) in patients with EDs. One of the most frequent findings is the high prevalence of PDs in patients with EDs compared to normal controls, in addition to

marked differences between the different subtypes of EDs. It is noteworthy that the vast majority of the studies were conducted in the previous decade, using the DSM-IV and DSM-IV-TR diagnostic criteria, with there being certain differences in relation to the current diagnostic criteria. In addition, it is important to note that the different methodologies in the articles reviewed contributed to variable rates of epidemiology for personality disorders in eating disorders. The studies use different inclusion and exclusion criteria, and the samples are heterogeneous in relation to the demographic aspects and stages of the eating disorder. Finally, another important aspect is that the studies use different scales for the personality assessment and some are self-reporting, which can contribute to a result bias due to the distortion and denial of the disease by the individual assessed. The diagnosis of the comorbidity assists with the treatment and the implementation of the suitable therapy for the respective clinical picture [12].

Although it is common to describe personality traits that precede and contribute to the onset of EDs, it should be understood that this association can interact in several ways: by predisposing, being a risk factor, having a common genetic basis, deriving from self-imposed eating restriction, or being the result of neuropsychological alterations that perpetuate with the chronification [5, 12].

Personality and Anorexia Nervosa

Lavender et al. assessed the personality of 116 women with typical AN or partial disorders. They propose a clinical assessment model with three personality subtypes: low emotional regulation (n = 55), high emotional regulation (n = 17), and having low psychopathology (n = 44), characterized by a normal personality tendency. The personality subtype with low emotional regulation is characterized by self-mutilation, great demand for new stimuli, oppositional behavior, and a greater presence of symptoms of EDs. On the other hand, the subtype with high emotional regulation presents compulsions and low demand for new stimuli, with a trend toward comorbidity with OCD throughout life and a high degree of perfectionism. The third subtype has a low level of psychopathologies, presenting the lowest levels of symptoms of EDs and low comorbidity with other psychiatric disorders. The diagnosis of the comorbidity assists with the treatment and the implementation of the suitable therapy for the respective clinical picture [20].

Another study, performed with adolescent patients with AN, divided them into three subgroups according to the personality characteristics observed. The first subgroup was called a perfectionist with a high degree of functioning, in which the patients have the resources to deal with reality in a healthy way and without significant identity disorders, but tend to be perfectionists and very self-critical. The second subgroup is emotionally unstable, characterized by dysphoria, unhappiness, fear of rejection, and frequent feelings of inferiority. The third subgroup is the contained/controller, in which the patients who present difficulties in expressing their emotions, think in specific terms, often do not understand metaphors and are inhibited [21].

Categorical studies suggest that between 25% and 69% of anorexic and bulimic patients have at least one PD. The most described disorders in patients with AN-R are the avoidant PD, obsessive-compulsive PD, and dependent PD. Among patients with AN-P, the most described PD is the *borderline* type [22].

Personality and Bulimia Nervosa

Nagata et al. showed that patients with BN presented more impulsive traits (manifested by alcohol and drug use and abuse, self-mutilation, and suicide attempts) than those with AN. The authors argue that this impulsivity may be the expression of the individual's basic personality, the expression of the psychopathological abnormalities of the disease, or a biological consequence of a chaotic eating behavior [23].

The PDs most found in BN patients are *borderline* PD (between 14% and 83%), histrionic

PD (up to 20%), dependent PD (up to 21%), and avoidant PD (up to 19%), although these numbers reflect extremely heterogeneous diagnostic criteria [22].

Personality and BED

The association between BED and obesity is common. It is known that adults with personality disorder are at greater risk of obesity and less successful with conservative weight loss treatment programs. The increase in the severity of obesity is accompanied by an increase in the prevalence of PDs, reaching 23.4% in grade 3 obesity [24].

A study by Becker and Grilo assessed comorbidities in 347 individuals with ED in 4 subtypes: those with mood disorders (MD), those with substance use disorder (SUD), those with both (MSD), and those without any of these comorbidities (wMSDc). The results showed an approximate prevalence of 37% for MD, 10% for SUD, 17% for MSD, and 36% for wMSDc. These groups differed in terms of PD characteristics, as those with MD and MSD have the highest frequency of PD comorbidity. The most common comorbid PDs were avoidant (23%), obsessive-compulsive (19%), paranoid (7%), and borderline (6%) [23].

There are few studies that assess BED and PD comorbidity. Older studies, comparing obese individuals with and without BED, reveal that those with comorbid BED have high prevalence of comorbid PD, particularly with the avoidant, histrionic, and borderline subtypes. However, comparing BED with general samples of psychiatric patients, the high prevalence of comorbidities with both avoidant and obsessive-compulsive disorder is evident [25].

Personality Traits, Personality Disorders, and Eating Disorders

The following are the main characteristics related to personality traits and personality disorders in eating disorders. There is insufficient data for women-specific characterization, whereby the results, for the most part, do not distinguish gender.

Personality Traits, Assessment Tools, and Eating Disorders

Several instruments for personality assessment identify traits often found in patients with EDs.

Perfectionism is one of the most observed traits, being characterized by the establishment of high and unrealistic standards about oneself, despite the adverse consequences. Most instruments have a one-dimensional approach to assessing perfectionism; however, two instruments present a multidimensional approach to this trait: the Multidimensional Perfectionism Scale, which assesses self-oriented, other-oriented, and socially prescribed perfectionism; and the Frost Multidimensional Perfectionism Scale, which assesses five components, concern for mistakes, parental criticism, personal norms, and doubts about actions and organization [26].

People with AN, BN, BED, and unspecified eating disorder (UFED) tend to present higher scores in the one-dimensional assessment of perfectionism when compared to those without ED [27]. When assessed by the Frost Multidimensional Perfectionism Scale, patients with AN and BN present excessive concern regarding errors and doubts regarding the quality of their actions. Most studies, when comparing individuals with AN, BN, and UFED, suggest similar scores for perfectionism [28]. Individuals with AN present high levels of personal standards, whereas BN presents higher rates for parental criticism. The use of inappropriate compensatory mechanisms is associated with high rates of concern for errors, parental criticism, and doubts regarding actions [29]. These features related to perfectionism do not tend to improve with treatment [12, 30].

Impulsiveness, an important characteristic of patients with ED, is understood as a construct composed of five different facets: negative urgency (tendency to engage in impulsive

behavior when faced with strong negative emotions), positive urgency (tendency to engage in impulsive behavior when faced with strong positive emotions), lack of planning (inability to consider the consequences of certain behaviors), search for sensations (desire for exciting emotions and sensations), and lack of persistence (inability to persist in a certain activity when bored or tired) [12].

Individuals seeking treatment for weight loss and obese individuals with and without BED present similar negative urgency results, suggesting that this may be elevated in obese individuals regardless of the presence of binge eating. When comparing the different diagnoses of EDs, those with AN and UFED have similar negative urgency scores, those with BN tend to have higher scores than those with AN, and those with AN-P tend to present higher scores than in AN-R [31, 32].

Positive urgency appears to be elevated in individuals with AN-P, BN, and UFED, although it has been poorly studied in individuals with EDs [33].

When assessing the lack of planning through the Barratt Impulsiveness Scale (BIS) – motor subtest for the assessment of the lack of planning – individuals with ED, in general, present higher scores than those of control groups. Among the ED subtypes, individuals with BN present higher scores than patients with AN; there is a difference in the results of individuals with AN-P, which present significantly higher results when compared to AN-R [25, 32].

In the search for sensations, the results tend to vary according to the type of diagnosis. When comparing the EDs, individuals with BN present higher scores than those with AN, similar to those with BED. However, few studies have found a relationship between the search for sensations and the behaviors observed in individuals with EDs, such as binge eating and compensatory behaviors [34, 35].

The relationship between lack of persistence and EDs also tends to vary according to the diagnosis, as individuals with AN present lower scores and individuals with BN present similar results when compared to their controls. In addition, individuals with BN have higher scores than those with AN which lack persistence [5, 12].

When assessing the characteristics of impulsivity and compulsion, which are commonly understood as being characteristic of BN, it is noticed that the intensity of symptoms is related to relevant clinical characteristics. Bulimic patients who present lower results in the characteristics of impulsivity and compulsion exhibit a personality with less pathological characteristics, symptoms of EDs, and depression; patients with high levels of impulsivity and compulsion present a personality with more pathological characteristics, self-mutilation, and greater severity of eating and depressive symptoms [36].

The "motivation to approach" refers to the tendency to approach gratifying situations, and the "motivation to avoid" indicates a tendency to move away or avoid situations associated with punishment. In the assessment of the motivation to approach, two scales are used: the Sensitivity to Reward Scale of the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) and the Behavioral Activation System (BAS), reward and punishment response scales. Individuals with EDs have divergent results on both scales, where those with AN, BN, and BED show higher scores than controls in the SPSRQ than in the BAS, which can be explained by the fact that the SPSRQ assesses situations and social rewards and the BAS assesses generic situations [37].

In the motivation for avoidance, that is, the tendency to depart or avoid situations associated with punishment, the results are high in individuals with AN, BN, BED, and UFED when compared to controls. The presence of this characteristic has been associated with episodes of compulsion, laxative abuse, use of diet pills, restrictive diet, and emotional eating [5, 37].

Eating Disorders and Broadband Personality Scales

Broadband personality scales aim to characterize normal personality dimensions. The instruments most used are the following.

NEO Personality Inventory (NEO-PI-R) Its theoretical basis is based on the five personality factors model, which presupposes that the personality is composed of five major domains: neuroticism, extroversion, openness to experience, kindness, and condescension. Individuals with AN and BN, when assessed with NEO-PI-R, present higher levels of neuroticism and lower extroversion levels than controls without PDs. These findings correspond to a difficulty with emotional regulation and common interpersonal problems among individuals with EDs. Individuals with BED also appear in the few existing studies, with higher levels of neuroticism compared to normal controls [12].

A study comparing AN subtypes identified that people with AN-R had levels of condescension similar to those of the controls, whereas those with AN-P and those with BN had lower levels of condescension. Individuals with ARs, on the whole, had lower results for conscientiousness than controls. However, those with AN-R presented similar results to controls and higher levels of conscientiousness than those with BN and AN-P [12].

Multidimensional Personality Questionnaire (MPQ) This is a self-report scale that assesses personality traits in a normal range, in 3 major factors and 11 primary scales. Used in individuals with EDs, the following results were described: in BN there is a significantly higher presence of negative emotions and lower positive emotional results when compared with normal controls; in individuals with BED, the results are significantly lower in positive emotions, but the results in BN are more expressive, demonstrating the high degree of neuroticism. According to Peterson et al., when the Beck Depression Inventory was introduced as a covariant, the difference between the groups disappears. Thus, the presence of mood alterations (mood swings) may complicate the assessment of higher-order personality dimensions, such as positive and negative emotions, and it may be difficult to differentiate whether the negative affect is a dependent state or indicative of a longer-lasting trait. Individuals with AN-P and BN tend to report higher negative emotions than those with AN-R and BED [12, 25].

Freiburg Personality Inventory-Revised (FPI-R) A study using this instrument reports that young women with EDs present low levels of life satisfaction and concern with health and high levels of social orientation, inhibition, irritability, tension, somatic complaints, and emotionality when compared to controls. According to this study, women with AN-R, AN-P, and BN without purging present worse outcomes than controls in the extroversion domain. Those with AN show lower scores in the areas of weakness and extroversion than those with BN, while presenting higher results in inhibition and concern for health. In addition, those with AN-R present worse results in the area of aggressiveness than those with BN and worse in the emotional state than those with AN-P or BN [12].

Temperament and Character Inventory (TCI): Cloninger Model Another instrument was validated and used in Brazil for the assessment of personality traits. The TCI is a self-completion questionnaire consisting of 240 items of the "True" or "False" type. The model by Cloninger and collaborators is based on the division of the personality into two components: temperament (traits genetically inherited) and character (individual differences regarding concepts about oneself and perception of one's objectives and values). This model is composed of seven factors and interprets the development of the personality as an interactive epigenetic process, in which the factors of temperament (search for novelty, avoidance of damage, dependence on reward, and persistence) initially motivate the development of character factors (self-directive, cooperative, and self-transcendent), which modify the meaning and saliency of the perceived stimuli to which the person responds. Thus, temperament contributes to the development of character and vice versa [5].

Research carried out over the last decade has found consistent results in which individu-

als with EDs score lower when compared to controls. Persistence has greater association with AN-R, while search for novelties has a greater association with BN. Binge eating, purging, and emotional eating tend to be negatively associated with scores for self-direction, avoidance of harm, and search for novelty (e.g., AN-P, BN) [5, 35].

Individuals recovering from AN present improvements in the search for novelty and avoidance of harm scores suggesting an improvement in social interaction and anxiety with treatment. Most of the studies also revealed that the scores related to cooperative, self-transcendence, and dependence on gratification are not associated with EDs [5].

Comprehensive Measures of Pathological Personality

Studies on PD in patients with ED have also used self-assessment tools for psychopathological aspects of the personality, such as the Dimensional Assessment of Personality Pathology-Basic Questionnaire (DAPP-BQ), Karolinska Scale of Personality (KPS), and Minnesota Multiphasic Personality Inventory 2 (MMPI-2) [12].

The DAPP-BQ is a scale with 18 subscales that seeks to delineate 4 dimensions of personality (emotionally unstable, dissociated behavior, inhibition, and compulsiveness). KPS is composed of 15 subscales which were designed to assess psychopathological vulnerability from a neuropsychological perspective [12].

Evidence was found in the DAPP-BQ of affective instability and anxiety for the EDs. Affective instability refers to the tendency to experience frequent fluctuations in intensity or types of emotions, and it is suggested that this characteristic would increase vulnerability to maintaining negative emotional states and maladaptive behaviors [12].

The affective lability is also related to episodes of binge eating in BN, and women with BN who present greater affective lability present greater severity of symptoms and more frequent compulsions. Likewise, patients with AN-P tend to have greater affective lability than those with AN-R [12].

Anxiety is also associated with EDs. The DAPP-BQ and KPS scales indicate a propensity toward the anxiety measurements. When the KPS is used, patients with BPs present higher scores than controls for anxiety, somatic, and physical symptoms. Similar results are observed in clinical and subclinical individuals with AN, who exhibit anxiety symptoms in the DAPP-BQ. Using KPS, patients with AN present lower levels in somatic and physical anxiety symptoms than those with BN [12].

In general, research carried out over the last decade suggests that affective instability is associated with EDs, being prevalent in those individuals who present episodes of binge eating (AN-P and BN), and that anxiety levels are higher in patients with EDs when compared to controls. However, depressive and anxious symptoms may mediate or moderate the relationship between BN and affective instability. In addition, patients with BN tend to have higher scores on scales that assess personality traits in relation to cluster B patients – personality disorders, such as affective instability, identity problems, and aggressions – when compared to their sisters and patients with AN [5].

MMPI-2 has been widely used to assess personality in EDs. It contains 10 clinical scales, 15 content scales, and 15 complementary scales. MMPI-2 presents clinical profiles for the pathologies. For example, AN-R, AN-P, BN, and UFED often have a type 2–7 profile, characterized by a mixture of depression and anxiety symptoms. In this study, all the TAs presented higher scores in the six scales, indicating a similar profile for psychopathology and anxiety, characterized by somatic concerns, as the person tends to focus on the physical symptoms as a tactic to avoid stress, anger, paranoia, anxiety, and social alienation. Individuals with AN-P, BN, and UFED presented higher rates on the scale, suggesting somatic concern (somatization) in those with ED when engaged in a compulsive or purging episode. When compared to control groups, individuals with AN-P had higher depressive symptoms than those with AN-R. Individuals with BN presented

higher scores on the 9th scale than those with AN-R, AN-P, and UFED, suggesting a greater tendency for impulsive behaviors. In general, individuals with AN-R presented lower symptomatology compared to the other groups, indicating greater symptomatology among the groups with BP that presented purging or compulsion. In another study, women with binge eating disorder, who underwent intensive treatment, presented similar and elevated results in MMPI-2 scales 1, 2, 4, 6, 7, and 8, indicating a profile characterized by somatization, anxiety, paranoia, and social isolation [5].

There are few studies on middle-aged women with EDs. However, in a recent study using MMPI-2 in patients with EDs (64% restrictive and 36% compulsive), it was observed that, in total, they presented lower levels of anxiety and greater denial of the disorder among middle-aged women. They also suggest higher levels of depression, feeling of insistence, lack of insight, somatic denial, emotional overcontrol, and dependency problems [5].

Treatment

Anorexia Nervosa

AN treatment requires professionals from different areas. The minimum team consists of nutritionist, psychologist, and psychiatrist [1].

Psychotherapeutic treatment should address a variety of factors such as cognitive, volitional, and affective recovery, morbid fear of gaining weight, dissatisfaction with body image, promoting functional recovery, and self-esteem in addition to developing the patient's responsibility for the treatment. Both cognitive-behavioral and psychodynamic psychotherapy have been used, and there is no evidence of superiority of one model over the other. Changes in the family dynamics are important maintainers of the AN, with the family therapy being the treatment of choice when considering children and adolescents [38, 39].

The treatment of pure AN (about 16% of cases) is re-nutrition [1, 40].

Fluoxetine may improve the prognosis of AN patients after achieving adequate weight, preventing relapse and promoting attenuation of dysphoric mood and obsessive thoughts. Olanzapine has shown efficacy in decreasing anxiety and improving psychopathological aspects and seems to contribute to weight gain in acute phase. When using antidepressants to treat comorbidities, selective serotonin reuptake inhibitors (SSRIs) are preferred because of their good efficacy, while being associated with low risk of cardio/neurotoxicity [40–43].

Bulimia Nervosa

The treatment of BN, as well as AN, must be performed by a multidisciplinary team with psychiatric, nutritional, and psychological care. The objectives include, firstly, regularization of the eating pattern, suspension of purging, and restriction, in addition to nutritional guidance [1].

Psychotherapy with a cognitive-behavioral approach has shown the best results. The best response in the treatment of BN comes from the combination of cognitive-behavioral therapy (CBT) with the use of psychotropic drugs [17, 43].

Pharmacotherapy has been widely researched. The use of antidepressants, particularly SSRIs (in particular fluoxetine – recommended at higher doses than those used in the treatment of depression – from 60 to 80 mg/d) and selective serotonin and noradrenaline reuptake inhibitors (SNRIs), has shown moderate efficacy in the treatment of BN, for reducing compulsions, self-induced vomiting, and possible depressive symptoms. The use of topiramate has been showing positive efficacy results as well [40, 42, 43].

Binge Eating Disorder

The treatment of choice for ED without comorbidities is psychotherapy, with cognitive-behavioral therapy being the gold standard [43].

When choosing treatment for BED, psychiatric and clinical comorbidities should be consid-

ered. Comorbidity with obesity, diabetes mellitus, and/or systemic arterial hypertension should be considered when choosing and planning the therapy, as it increases the morbidity and mortality [40, 43].

Pharmacological treatment aims to control food impulsivity while essentially including the following drugs: the selective serotonin reuptake inhibitor antidepressants, the best known of which is fluoxetine and appears to be the first choice of treatment, in addition to sertraline and fluvoxamine; bupropion, dopaminergic antidepressant; sibutramine, a serotonergic and noradrenergic action satiety-promoting agent which appears to be the option of choice in the presence of comorbid obesity; topiramate and lamotrigine, anticonvulsive agents and mood stabilizers, which seem to favor the control of episodes of binge eating; and lisdexamfetamine, FDA-approved as the first on-label drug for the treatment of BED; however, it is not yet approved by ANVISA in Brazil for BED treatment (use should be considered with caution in patients with a personal or family history of depressive disorder, bipolar disorder, or psychosis). The benefits of the medications do not appear to be long-lasting after discontinuation [19, 40, 42–44].

Eating Disorders and Personality Disorders

When the ED is accompanied by a PD, the prognosis is generally unfavorable, although there is no consensus on the matter. These individuals, in addition to needing longer periods of hospitalization, present a more frequent tendency to chronification, more suicide attempts, and self-mutilation and mobilize other patients and the team in a massive way, arousing varying feelings in the respective members. Disruptive personality traits may result in increased emotional distress, increased risk of suicide, increased family dysfunction, and frequent hospitalizations. They may also be related to major depressive symptoms, impaired overall functioning, use of laxatives, increased body dissatisfaction, avoidance of increased harm, and decreased self-direction [26].

In cases of comorbid borderline PD, there is no consensus; pharmacological therapies can directly improve impulsivity and reduce marked mood swings and anxiety. Medications include atypical antipsychotics, serotonin reuptake inhibitors (SRIs), selective serotonin and noradrenaline reuptake inhibitors (SSNRIs), and mood stabilizers. Lithium salts, widely used in bipolar disorder, pose a risk to patients with BP. Weight loss, dehydration, and excessive exercise can lead to severe intoxication from this medication. Valproate, because of the significant risk of inducing weight gain, should be avoided when possible. Anticonvulsants such as lamotrigine and topiramate may be alternatives to mood stabilizers, considering gradual adjustment of administrations and care of the significant side effects (reduction of contraceptive effect and cognitive impairment due to topiramate and severe pharmacodermia secondary to lamotrigine use). The risk of addiction and substance abuse indicates avoiding the use of benzodiazepines and hypnotic benzodiazepine receptors [30, 40, 42, 43].

In comorbidity with borderline PD, psychotherapy is a fundamental part of the treatment, focusing on improving self-regulation in general (including symptomatology of the ED), reducing self-destructive behavior, improving interpersonal relationships, and alleviating affective instability [45].

Final Considerations

Certain personality traits are more frequent in eating disorders when compared to control groups. High levels of perfectionism, neuroticism, negative urgency, avoidance, search for social reward and self-direction, as well as low extroversion are found.

Among eating disorders, the most prevalent personality disorders are that of avoidant and obsessive-compulsive.

As perfectionism and obsessive-compulsive traits share certain characteristics such as rigidity, need for control, and methodical behavior, it is not surprising that obsessive-compulsive disorder

is common among eating disorders. In addition, avoidant PD is characterized by fear of criticism, rejection, and embarrassment and feelings of imperfection, which trace the intense search for social reward and avoidance also present in eating disorders.

Borderline PD and paranoid PD are most observed in AN-P and BN. These results are consistent with the psychopathological findings of these EDs that report higher levels of emotional dysregulation, anxiety, aggression, self-referral, and distrust of others.

Differences in the personality among EDs are also evidenced as, for example, greater impulsivity in BN, when compared to AN and BED.

Evidence suggests that personality traits may be more related to specific symptoms of EDs than the specific diagnosis, e.g., binge eating and purging behaviors are more likely to avoid harm, negative urgency, self-directive, affective lability, somatic concern, depression, and emotional instability and seek novelties in addition to negative emotions.

With the advancement of research in recent decades, it is more evident that the dimensions that involve the personality influence several important areas of functioning of the EDs, such as the assessment, symptoms, and treatment.

The contribution of these studies favors the choice of a more personalized and suitable treatment.

The study of personality contributes to the better understanding of EDs and its related symptoms. Certain personality traits, such as affective lability, have been associated with a greater tendency to engage in impulsive behaviors, such as self-mutilation and risky sexual behavior in BN, and mutually act with high levels of compulsion, predisposing to intense physical activity. In addition, perfectionism has been associated with more severe symptomatology in EDs, and evidence suggests that this trait persists even after treatment. Studies involving EDs and PDs are a promising way to understand the profiles of patients with EDs and to provide more effective diagnostic criteria and prevention of relapse.

Diagnostic Criteria According to DSM 5

Anorexia nervosa: diagnostic criteria
A. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. *Significantly low weight* is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.
B. Intense fear of gaining weight or of becoming fat or persistent behavior that interferes with weight gain, even though at a significantly low weight.
C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.
Specify whether: *Restricting type*: During the last 3 months, the individual has not engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise. *Binge eating/purging type*: During the last 3 months, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).
Specify if*:* *In partial remission*: After full criteria for anorexia nervosa were previously met. Criterion A (low body weight) has not been met for a sustained period, but either Criterion B (intense fear of gaining weight or becoming fat or behavior that interferes with weight gain) or Criterion C (disturbances in self-perception of weight and shape) is still met. *In full remission*: After full criteria for anorexia nervosa were previously met, none of the criteria have been met for a sustained period of time.
Specify current severity: The minimum level of severity is based, for adults, on current body mass index (BMI) (see below) or, for children and adolescents, on BMI percentile. The ranges below are derived from World Health Organization categories for thinness in adults; for children and adolescents, corresponding BMI percentiles should be used. The level of severity may be increased to reflect clinical symptoms, the degree of functional disability, and the need for supervision. Mild: BMI > 17 kg/m^2 Moderate: BMI 116–16.99 kg/m^2 Severe: BMI 115–15.99 kg/m^2 Extreme: BMI < 15 kg/m^2

Bulimia nervosa: diagnostic criteria
A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following: 1. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than what most individuals would eat in a similar period of time under similar circumstances 2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)
B. Recurrent inappropriate compensatory behaviors in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise.
C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 months.
D. Self-evaluation is unduly influenced by body shape and weight.
E. The disturbance does not occur exclusively during episodes of anorexia nervosa.
Specify if: In partial remission: After full criteria for bulimia nervosa were previously met, some, but not all, of the criteria have been met for a sustained period of time. In full remission: After full criteria for bulimia nervosa were previously met, none of the criteria have been met for a sustained period of time.
Specify current severity: The minimum level of severity is based on the frequency of inappropriate compensatory behaviors (see below). The level of severity may be increased to reflect other symptoms and the degree of functional disability. Mild: An average of 1–3 episodes of inappropriate compensatory behaviors per week Moderate: An average of 4–7 episodes of inappropriate compensatory behaviors per week Severe: An average of 8–13 episodes of inappropriate compensatory behaviors per week Extreme: An average of 14 or more episodes of inappropriate compensatory behaviors per week

Binge eating disorder: diagnostic criteria
A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following: 1. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than what most people would eat in a similar period of time under similar circumstances 2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)
B. The binge eating episodes are associated with three (or more) of the following: 1. Eating much more rapidly than normal 2. Eating until feeling uncomfortably full 3. Eating large amounts of food when not feeling physically hungry 4. Eating alone because of feeling embarrassed by how much one is eating 5. Feeling disgusted with oneself, depressed, or very guilty afterward
C. Marked distress regarding binge eating is present.
D. The binge eating occurs, on average, at least once a week for 3 months.
E. The binge eating is not associated with the recurrent use of inappropriate compensatory behavior as in bulimia nervosa and does not occur exclusively during the course of bulimia nervosa or anorexia nervosa.
Specify if: In partial remission: After full criteria for binge eating disorder were previously met, binge eating occurs at an average frequency of less than one episode per week for a sustained period of time. In full remission: After full criteria for binge eating disorder were previously met, none of the criteria have been met for a sustained period of time.
Specify current severity: The minimum level of severity is based on the frequency of episodes of binge eating (see below). The level of severity may be increased to reflect other symptoms and the degree of functional disability. Mild: 1–3 binge eating episodes per week Moderate: 4–7 binge eating episodes per week Severe: 8–13 binge eating episodes per week Extreme: 14 or more binge eating episodes per week

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Alcohol and Substance Use Disorders in Women

Silvia Brasiliano, Adriana Trejger Kachani, Fabio Carezzato, and Patricia Brunfentrinker Hochgraf

Introduction

Until recently, substance use disorder was considered a male problem. An androcentric view, insensitive to gender issues, was therefore prevalent on the subject [1]. It was only in 1995 that the National Institute on Drug Abuse (NIDA) formally established a program to study the differences between genders and the specific aspects of drug addiction in women, and it was not until 2014 that the National Institutes of Health (NIH) determined that both sexes be represented in in vitro and animal model studies as a prerequisite for disbursement of funds [2].

Despite the general prejudice toward any addiction to psychoactive substances, women are still more stigmatized than men. As far back as the code of Hammurabi, which dates to 1762 BC, we find claims such as "a wife who drinks wine… may be abandoned at any time" [1]. Stereotypes of greater aggressiveness, tendency to promiscuity, and failure to fulfill family duties are more commonly associated with addicted women than men [3]. In spite of the changes in male and female social roles, it is not difficult to observe that this prejudice persists and obstructs women's access to treatment. As a result, they are generally underrepresented in the health centers. It is estimated that 23% of men and 15% of women with alcohol use disorders seek treatment [4, 5]. Given this scenario, it is not difficult to imagine why addicted women have, for decades, been considered more severe cases than men, and why an array of myths have been created around them as, for example, of women being less engaged in treatment, presenting unfavorable clinical course and having worse prognosis than men [6]. In 1987, Edwards (1987), criticizing psychiatric studies on female alcoholism, united them under the title "An Assortment of Unfounded Beliefs" [7]. Especially in this century, an increase in research with women and their progressive differentiation from the male population made it possible to identify characteristics and necessities that, when considered appropriately, favor the course and prognosis of psychoactive substance dependence in women.

Diagnosis

The concept of psychoactive substance dependence has evolved since the last century. There are many diagnostic criteria around the world, yet the Diagnostic and Statistical Manual of Mental Disorders is the most widely used classification. It is currently in its fifth edition: the DSM-5 [8]. For these criteria, the quantity or frequency of use is not relevant; rather, the main

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aspect is the degree of dysfunctionality presented by the individual. For substance use disorder diagnosis, there must be a pattern of substance use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

The substance is often taken in larger amounts or over a longer period than was intended.

1. *There is a persistent desire or unsuccessful efforts to cut down or control substance use.*
2. *A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.*
3. *Craving, or a strong desire or urge to use the substance.*
4. *Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home.*
5. *Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.*
6. *Important social, occupational, or recreational activities are given up or reduced because of substance use.*
7. *Recurrent substance use in situations in which it is physically hazardous.*
8. *Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.*
9. *Tolerance, as defined by either of the following:*
   (a) *A need for markedly increased amounts of the substance to achieve intoxication or desired effect.*
   (b) *A markedly diminished effect with continued use of the same amount of the substance.*
10. *Withdrawal, as manifested by either of the following:*
    (a) *The characteristic withdrawal syndrome for the substance.*
    (b) *The substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.*

Despite the criteria for psychoactive substance dependence being identical for both genders, there is still resistance in diagnosing women, mainly due to the social stigma. The strong social stigma prevalent in the general population and, in particular, among substance-abusing women themselves, is also manifested in the attitudes of the health care providers, who generally have difficulty diagnosing dependence in women [9]. A study performed at the John Hopkins Hospital showed alcoholism diagnosis was ignored in 34–93% of female patients, especially in those from higher social classes [10]. In another research, Sallaup et al. (2016) observed that even in psychiatric services, substance abuse and related disorders in women are underdiagnosed [11]. Although toxicological tests showed no differences between genders, only half of the women received the diagnosis of psychoactive substance use disorder.

Therefore, what we see is a combination of mutually reinforcing problems. Female patients show more embarrassment than men [12], seeking help indirectly, expressing vague complaints about their physical and/or psychic health, generally to nonspecialized physicians, resulting in underdiagnoses [13]. In the rare occasions when they are diagnosed, they are referred to non-gender-specific treatment services for psychoactive substance dependents, where men and their needs predominate [12–14].

Epidemiology

According to Slade et al. (2016), "prevalence of alcohol use and its related problems has been historically between 2 and 12 times greater among men than women. But there is evidence that this difference is becoming smaller, especially among the younger generations" [15]. In fact, all the epidemiological studies, in Brazil and throughout the world, suggest that for most substances abuse is predominant among males, except for psychotropic medication in some regions (e.g.,

benzodiazepines). The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC I), an ample study performed in the United States between 2001 and 2002 with 43,093 individuals aged 18 and older, found a 17.4% prevalence of alcohol dependence among men and 8% among women, resulting in a ratio of 2.6 men to each woman. The same study found, in its last year, a prevalence of alcohol use disorders in general of 12.4% for men and 4.9% for women [16].

Recent data from NESARC III, conducted between 2012 and 2013, found a prevalence of alcohol use disorders of 17.6% for men and 10.4% for women [17]. Dawson (2015) observes that when we consider the monthly heavy episodic drinking in the two periods, the increase was almost two times greater among women than men. In relation to other drugs, excluding alcohol and nicotine, we found a prevalence of drug dependence of 3.3% among men and 2% among women, resulting in a ratio of 1.9 men to each woman [18–20]. But, when considering drug use disorders in the last year of NESARC I, we find 2.8% of men and 1.2% of women [16]. On NESARC III, we find 4.9% of men and 3% of women, showing once more a decrease in the difference between the sexes [17]. Corroborating these data, the National Survey on Drug Use and Health – SAMHSA shows a prevalence of substance abuse in individuals aged 12 years or older of more than 10.8% for men and 5.8% for women, in a ratio of 1.8 men to each woman [21]. In Brazil, the 2nd National Survey of Alcohol and Drugs – LENAD – that interviewed 4607 individuals aged 14 and older in 2012, found a prevalence of alcoholism of 10.5% for men and 3.6% for women (2.9 men to each woman). The same group previously found, in 2006, a prevalence of alcoholism of 13.6% among men and 3.4% among women (4 men to each woman). Therefore, evidence suggests that in Brazil, while alcohol abuse decreased in men, it increased in women, reducing the discrepancy between the sexes. With respect to drugs, this same study describes a use three times greater among men than women [22].

Genetics

The first controlled studies on the genetics of alcoholism in humans suggested a higher genetic influence in men than in women. However, more recent studies did not confirm these findings. These studies were performed with a larger overall and specifically female population. Prescott et al. (1999) studied 9295 twins in Virginia between 1934 and 1974, with 5091 men and 4168 women. They found evidence of substantial genetic influence both in men and women, with a genetic estimate slightly higher in women (55–66% against 51–56% in men) [23, 24]. Also, the UCSF Family Study found a higher genetic influence on female drinking and suggests that environmental influences are responsible for the beginning of regular alcohol use, whereas the genetic influences are responsible for the development of alcoholism itself [25].

A recent meta-analysis of 13 twin studies and 5 adoption studies found a 49% heritability for alcohol abuse–related disorders. They also found these rates to be similar in both sexes. This value suggests that alcohol dependence heritability is higher than depression heritability but lower than schizophrenia's [26]. An Australian study with 5993 twins investigated the high prevalence of alcoholism in women that reported binge eating or compensatory behavior in comparison with women diagnosed with other eating disorders and with healthy women [25]. They indicate shared genetic traits for both disorders. Another study suggests the existence of a common genetic influence for addiction to any substance, but it also indicates specific genetic variants that increase the risk of addiction to each substance. In this sample of young adult male and female twins, we can conceptualize the lifetime comorbidity among alcohol, tobacco, and cannabis as alternative manifestations of a heritable latent trait. Further, gender differences in the relative influence of genetic and environmental factors on each substance are likely to arise from substance-specific effects [27].

Onset and Evolution

Men and women present multiple differences with regard to psychoactive substance dependence, based on a complex combination of social, genetic, hormonal, neurophysiological, and environmental factors [2, 28, 29]. Women claim specific reasons for using psychoactive substances: weight control, coping with stress and exhaustion, and self-medicating emotional and psychological problems [30]. Concerning the motivation for initiating alcohol consumption, women tend to mention significant life events, e.g., divorce or death of a spouse, whereas men generally report no special triggering event [31]. Considering substance use onset properly, women begin consumption of alcohol and other drugs at a later time than men, and report a faster progression in the development of the same symptoms, and also shorter intervals between the first use and dependence [31, 32]. This phenomenon is frequently called *telescoping effect* in the literature. Initially described for alcohol abuse, many recent studies observe the same effect for opioids, marijuana, and crack [29, 33, 34]. Considering still consumption pattern, women tend to drink less amounts of alcohol than men. With respect to frequency, while some studies show it is lower in women, others observe no differences in relation to men. It is also known that men generally present combined abuse of multiple substances, whereas women tend to abuse only one substance [35]. Recent studies with young cohorts failed to find evidence of the telescoping effect, probably due to changes in women's consumption pattern, approximating them to the male pattern. Several studies show that in the past few years women have started to drink earlier and ingest greater quantities of alcohol than the preceding generations [36–38].

In relation to onset risk factors, men are generally pushed by their peers, and women by their spouses. These data are consensual among different authors and reveal that the drug user spouse not only introduces and reinforces the woman's consumption but also plays an important role in the maintenance of her behavior [1]. Although, in general, women use substances for shorter periods of time before entering treatment, they appear to seek treatment when issues are more serious [39]. Women are more worried about the use of marijuana than men. In general, as is the case with other drugs, they have a partner who also uses it, whereas men typically consume the substance with their social network. There is a greater correlation between the daily consumed amount of marijuana and the impact on women's quality of life. They also present worse craving symptoms, such as headaches, heats, irritable temper, and emotional lability, which lead them to frequent relapses. Women are more vulnerable than men to the anxiogenic, reinforcing, and sedative effects of marijuana [34].

Physical Aspects

There are important gender differences in the physiological response to psychoactive substances. Most of these singularities are determined by three factors. First, women have a smaller blood volume than men, when adjusted by weight. Also, women have more body fat than men. These differences impact in the blood concentration and storage of the used substance in women [40]. They tend to have higher substance blood concentrations than men when using the same amount of drug, when adjusted by weight. The third general reason for gender differences found in the response to substance use and abuse is sex hormones and its variability in women. Anker and Carrol (2010) observe that estrogen and progesterone interact with the hypothalamic–pituitary–adrenal axis (HPA axis), GABAergic system, and mesolimbic dopamine system, modulating the sensitivity to substance reward effects in general [41]. This would be the basis for gender differences in substance abuse disorders. The authors also indicate the role of sex hormones to be considered in the development of gender-specific prevention and treatment programs.

Women tend to drink lower alcohol volume than men in quantity. However, as discussed previously, serum concentration after ingestion of one unit of alcohol will be higher in women than men, adjusted by weight [42]. Also, women body

composition increases their risk for developing organic problems related to alcohol consumption. Women tend to present earlier and more serious diseases, either acute issues or chronic diseases [40, 43]. Body composition and blood volume are also reasons for this higher risk. Women also have other characteristics that increase their vulnerability for alcohol-related diseases. Another reason for a higher alcohol concentration in their blood is the lower level of alcohol dehydrogenase (ADH) in the gastric tissue, compared to men. The ADH is a primary enzyme involved in alcohol metabolism [40, 44]. Women's alcohol metabolization is estimated to be one-fourth of a men's and the ingested/absorbed ratio is close to 1:1 [43]. These factors help to understand the 1.5–2 times higher morbidity among them.

It has been observed that women with drinking disorders have higher risk of developing liver injuries and cirrhosis than men in the same condition [40, 45, 46]. The lower concentration of ADH in the stomach leads to higher amounts of alcohol reaching the liver. Also, women's metabolization of the alcohol is faster than men's, increasing the concentration of toxic metabolites as acetaldehyde in the organ. Furthermore, alcohol degrading enzymes and cytochromes seem to be affected by estrogen levels, which would lead to higher free radical concentration after alcohol consumption [47–49]. It is noteworthy that the risk for cirrhosis is positively related to the body mass index (BMI) in heavy drinkers [50]. Like men, women seem to benefit from alcohol cardiovascular protective effects. However, the ideal dose and the dose in which this effect is no longer observed are lower than men's, probably because of the higher bioavailability as mentioned. For the same reason, women tend to have more cardiomyopathy and other alcohol-related heart diseases [51, 52]. Also, the risk for atrial fibrillation and hypertension increases with the increase of alcohol consumption in women [50].

Alcohol consumption, even if moderate, seems to increase the risk for breast cancer. Several studies observed an increase of risk directly proportional to the amount of alcohol ingested. A 10-year study that followed 38,000 women in the USA showed a statically significant increase of relative risk for developing invasive breast cancer in women who reported alcohol use in the beginning of the study. This risk was greater in women who reported an average daily consumption of 30 g of alcohol [53].

Both men and women showed a decrease in brain volume and cognitive and learning impairment with chronic alcohol consumption. Although changes were similar in both groups, the women participating in these studies had less years of alcohol drinking, which would also suggest a higher vulnerability to alcohol [54]. A more recent study did not find any gender differences in alcohol-induced brain damage [55].

Women tend to have less symptoms when remaining abstinent of alcohol when compared to men. This is not true for cocaine and amphetamines abuse. Women tend to suffer more cravings than men, being more at risk for relapse as well [56]. Data are controversial concerning variation in cocaine effects in different phases of the menstrual cycle. Some studies indicate stronger cardiovascular and subjective effects on the follicular phase compared with the luteal phase [57]. An increase of stimulant effects mediated by the estrogen and attenuation of these effects by progesterone would explain the observed differences. Also, a possible variation in peak serum concentration during the different phases of the menstrual cycle could explain these findings [58]. On the other hand, several other studies did not find any differences either in gender or menstrual cycle regarding the effects of cocaine [59]. Some studies showed lower peak cocaine plasma levels in women compared to men [58, 60], whereas others did not find any differences [59]. Gender differences in cocaine cardiovascular effects also display controversial results. While some studies found women to have less variation in blood pressure and different response in heart rate [60, 61], others failed to observe any differences [58, 59, 62]. Although women show a higher brain perfusion [63] and smaller alterations in EEG [64], studies suggest that they have more risk for CNS injuries and gray matter volume decrease [65].

Regarding the MDMA, the most common and clinically relevant side effects are the

hyperthermia and hyponatremia [66–68]. The hyponatremia is caused by excessive water consumption and inappropriate secretion of antidiuretic hormone [69]. Hyperthermia is induced by psychomotor activation and MDMA direct action in the brain [67, 70]. Both the excess of movement and the high temperature can induce rhabdomyolysis and consequently renal injuries [71, 72]. Women are more susceptible to MDMA-induced hyponatremia [69, 73]. One study found that women are more sensitive to the substance's CNS action that leads to the release of vasopressin [74]. On the other hand, men are more vulnerable to hyperthermia and rhabdomyolysis caused by MDMA ingestion. This is the result of estrogen's protective effect in the CNS.

Overall, women with substance abuse disorders have a higher mortality rate than men with this condition. A study from Stockholm with a hospitalized population found that men and women with drinking disorders are respectively three times more likely to die and are five times more likely to die than the general population [75]. Also, McCrady et al. (2009) suggest a 50–100% higher mortality in women than men with alcohol-related disorders [5]. A recent meta-analysis of 81 studies by Roerecke and Rehn (2013) shows a higher mortality rate in women when compared to men with drinking disorders. Epidemiologic studies found a 1.5 higher rate in women (2.98 × 4.64). In clinical samples, men showed a 40% lower rate than women (2.38 × 4.57). Mortality risk also varied according to age, both for men and women. In women 40 years old or younger, that risk was 13 times higher compared to the general population, whereas men had a 9 times higher risk. This indicator declined after 40 years of age but increased again after 60 years of age [76].

Nutritional Aspects

The nutritional consequences of alcohol and substance abuse vary according to the type, amount, frequency, and time of use of each drug, since each substance relates differently to health damages (Table 1) [77]. Thus, psychoactive substances may compromise women's nutritional state, since they influence food and water intake, as well as metabolism and weight [78]. Many factors may cause nutritional deficiency in drug abusers: the increase in nutritional needs in order to detoxify or metabolize the drug; inactivation of the enzymes and coenzymes needed for energy metabolism; liver damage, leading to inadequate storage of nutrients; or even bad absorption or poor use of nutrients, when there is dieresis or diarrhea [79]. Furthermore, during detoxification and abstinence, drug dependents may present diverse physical perturbations, such as nausea, vomit, and diarrhea, which contribute to caloric and electrolytic unbalance [79].

Studies on nutrition and alcohol dependence have advanced. As a drug that contains calories, it substitutes food in the diet of severe dependents; the alcoholic patient is generally described as undernourished, once alcohol substitutes adequate calories and nutrients. When consumption is moderate, alcohol intake is usually a source of additional energy to the patient's regular diet. This type of calorie source is known as "empty calories," lacking essential nutrients such as proteins, vitamins, or minerals, in spite of its high energy value. The composition of alcoholic food items, which is generally rich in fats, is another relevant factor. This, together with alcohol metabolism, would explain the high frequency of

Table 1 Nutritional consequences of drug dependence [88]

Drug	Nutritional aspects
Alcohol	Hypertension, peripheral insulin resistance and/or diabetes mellitus, dyslipidemia, poor vitamin and mineral absorption, lactose intolerance, decreased immunity, deficiency in complex B vitamins and iron
Marijuana	The "munchies" – consumption of food with poor nutritional value, similar to binge eating
Cocaine and crack	Appetite suppression, altered food habits, malnutrition
Amphetamines	Loss of appetite, xerostomia, dehydration, constipation, vomit, diarrhea
Opioids	Decreased appetite, xerostomia, constipation, hyperkalemia, anemia

overweight and obesity generally found among alcohol-dependent patients, combined with associated conditions [80–83]. Concomitantly, the cellular aggression caused by alcohol decreases immunity as well as nutrient absorption, since it causes pancreatic insufficiency and affects intestinal brush border enzymes, such as lactase [80]. Poor absorption of fat-soluble vitamins A, D, and E can cause respectively pellagra and lipid peroxidation of hepatocytes and mucous membranes, among other diseases [84, 85]. Water-soluble vitamin deficiency is also frequently described in the literature; lack of vitamins such as thiamine, riboflavin, niacin, pyridoxine, folic acid, and vitamin B12 may cause serious problems for the drinker. Ethanol metabolites such as acetaldehyde can cause increased degradation of the active form of pyridoxine, or interfere in the formation and liberation of the active form of folate. Hyper-homocysteinemia is consequently also common in alcohol abuse, since the related metabolic pathway is strongly associated with the ingestion and absorption of vitamins B6, B12, and folate. Hyper-homocysteinemia is considered an additional risk factor for cerebral or peripheral coronary vascular disease, as well as for thrombosis [86].

Psychoactive substance dependence interferes in food habits. Diet is usually irregular and has poor nutritional value [87]. Substance abuse furthermore has an important influence on the dependent's eating behavior: lack of regular habits and chaotic feeding, which frequently mirror their lives as a whole [88]. Individuals usually alternate between meal restriction when under the influence of drugs and hyper-caloric meals in periods of abstinence. Diagnosis of disordered eating is not uncommon. The behavior has been understood as a sub-clinical eating disorder that may develop into a full-blown eating disorder. A study performed with 55 patients entering a treatment program for women with drinking problems observed that 54.5% of the patients presented chaotic eating behavior: 45.5% failed to eat three main meals a day (breakfast, lunch, and dinner) and 60% reported not feeding adequately due to substance use [89]. Considering that disordered eating is a significant risk factor for eating disorders, this finding is alarming. It is known that 50% of women in treatment groups for substance abuse usually present eating disorders [90]. The same sample population usually presents a greater prevalence of bulimia nervosa (37%), in which impulsivity is an important predictor and leads to poor prognosis. This is because substance dependence is related to compulsion and impulsivity which, during abstinence, may be directed to food [91]. This is why the prevalence of binge eating disorder is high in women participating in substance abuse treatment groups [90]. In a study performed in a reference outpatient substance abuse health center for women, a 33.75% prevalence of eating disorders was verified among patients, and binge eating disorder was the most frequent [92]. Another study performed exclusively with women with drinking problems observed that among those who were able to remain abstinent for a period of 3 months, chocolate consumption was 33.3% higher than among those who continued drinking [93]. It is known that many drugs lead to an important weight loss, not rarely recovered that this weight is regained after treatment. For the alcohol- and drug-dependent woman, who normally suffers from low self-esteem, recovering the lost weight or gaining more than before can have an influence on the risk of relapse [94–96]. Identifying and addressing the issue of women's dissatisfaction with their bodies is thus a critical aspect for treatment success and low relapse rates [94].

When looking at co-occurring drug dependency and eating disorders among women, we find that there has been an increase in the number of women who initiate drug use motivated by weight loss. Eating disorders in women who also abuse an anorexigenic drug thus deserve particular attention [94, 97, 98]. A study with incarcerated drug-dependent women showed a mean weight gain of 9 kg in the first 2 years of prison time, a rate superior to that of nondependent inmates, suggesting that dependent women used food to alleviate the symptoms of abstinence in prison [99]. Compensatory behaviors, such as self-induced vomit (5%), use of laxatives (9%), and fasting (17%), are common in this environment [95].

Gynecologic Aspects

Chronic use of cocaine is also associated with menstrual cycle dysfunction, increased rates of amenorrhea, and hyperprolactinemia [100, 101]. Gender differences have been little explored in relation to other drugs. It is known that heroin interferes in the menstrual cycle and that opioid-dependent women may present secondary amenorrhea [102]. Alcohol use and its relation to sexual dysfunctions, although vastly known with regard to men, is not fully clear in dependent women [103]. While alcoholism is associated with impotence and diminished sexual interest in men, sexual dysfunction in women can be caused by alcohol abuse or, inversely, sexual dissatisfaction may motivate consumption. Regarding cocaine, both men and women report increased libido after consumption. Elevated levels of luteinizing hormone (LH) seem to be connected to sexual arousal [104]. Alcohol and drug use increase the probability of women contracting sexually transmitted diseases, especially HIV, even if the drug is not injectable. This is due to the high-risk sexual behavior women engage in under these circumstances, such as an elevated frequency of unprotected sexual relations and, frequently, exchange of sexual favors for money or drugs [105]. Increased high-risk behavior (more sexual partners, unprotected sex, sexually transmitted diseases, among others) are also related to crack use [106].

Obstetric Aspects

Preterm births and low weight gain, neurobehavioral impairment, alterations in brain structure, and neonatal abstinence syndrome are the clinical conditions most commonly associated with alcohol and drug use during pregnancy. It is worth noting, however, the great discrepancy between different studies. In a recent review, Jansson and Velez (2011) point out that research on the effects of mother's drug use over the baby and child is a complex challenge given the high numbers of biological and psychosocial factors that might cause or influence the observed phenomena [107]. The authors suggest that discrepant results may be due to the neglect of psychosocial protection in the analyzed studies. They also highlight the failure in estimating the weight of presumed biological mechanisms relative to other risk factors. Besides those, some studies may have failed to adequately consider other factors frequently associated with substance abuse by pregnant women, such as poverty, stress, lack of social support, physical abuse, psychiatric comorbidities, nutritional deficiencies, STDs, other infectious diseases, and lack of adequate medical care [107].

The greatest problem concerning different drug abuse conditions, in Brazil as well as in the rest of the world, is the fetal alcohol syndrome (FAS). In the USA, it is estimated that there are 1–3 cases per 1000 newborns [43]. It is considered the third highest frequent cause of infant mental retardation. This syndrome consists of a combination of any of the following issues: low body weight relative to gestational stage, facial structure malformation (small palpebral fissures, flat nasal bridge, absence of philtrum), malformation of the heart ventricular septum, hands and feet malformation (especially syndactyly), besides mental retardation (from mild to moderate). Behavioral and learning disabilities may persist at least during childhood [108]. Fetal alcohol syndrome is considered an extreme manifestation in a continuum of abnormalities grouped under the term "fetal alcohol syndrome disorders" (FASD) [109]. Published evidence suggests that drinking in the first gestational trimester increases 12 times the risk of FASD. Drinking throughout the second and third trimesters increases 61 times this risk. Considering all the pregnancy period, the observed increase is by 65 times. Drinking only in the first trimester is five times less risky than drinking throughout pregnancy [110]. Since the relation between alcohol use frequency and amounts with that syndrome is unknown, as well as the role of nutritional deficits secondary to alcoholism, it is recommended that pregnant women refrain from drinking during this period. Even in the Old Testament, there are references

to the negative effects that drinking could have during pregnancy: "… but he assured me: you will become pregnant and will give birth to a son. However, do not drink wine or other fermented beverages" [111].

There are few studies about the long-term consequences of fetal exposure to drugs. Although some published evidence suggests that these children's physical and psychological development may be compromised, it is unclear whether these negative effects are direct or indirect. Jansson and Velez (2011) point out that the consequences of drug use over child development vary according to consumed doses, gestational period, medical complications due to premature delivery, low newborn body weight, quality of care, and the newborn's environment [107]. In any case, such methodologically limited studies shared with no criteria produced misunderstanding. According to Terplan and Wright (2011), "the persistence of the serious damage hypothesis in the medical literature has supported a higher discredit of women who consumed cocaine during pregnancy. The implication that these women unqualified for maternity is judging them as undeserving of motherhood" [112].

Since drug use during pregnancy is an important motivator for seeking treatment, adopting adequate approaches to both mother and baby may prevent future risks to physical and mental health. The few studies about the relationship between motherhood and drugs in Brazil show that these mothers feel qualified for motherhood and actually show it, although they are conscious of the negative effect of substance abuse on their children [113]. Evidence shows that pregnant women who abuse drugs, particularly those addicted to crack, suffer important social discrimination even in health care facilities. This attitude leads them to avoid prenatal care, fearing reproach from health care professionals and also fearing loss of parental rights. Considering that, it is important, on the one hand, to instruct health care professionals about how to handle this population and, on the other hand, to actively seek these pregnant women to offer treatment [114].

Social and Psychological Aspects

Even in rats, not all variation among the sexes is due to biological processes; they are, rather, the result of a combination of genetic, epigenetic, socio-cultural, and environmental factors that mediate the expression of specific traits, such as those involved in relapse and the maintenance of abstinence, among others [115]. Drug use among women is influenced by their social context [102]. At first, a spouse who is generally also dependent reinforces her behavior, either because he supplies the drug or the money to obtain it, because she fears losing the relationship if she ceases to use the drug, or because the partner minimizes the risks involved in the substance use [31, 115]. Different from men, who report having problems with their wives due to drug use and claim that they are the greatest supporters to their treatment, women not only lack the support from their spouses, they frequently must handle the spouse's active opposition to their seeking treatment [115]. A 2016 Swedish study showed that the inverse relation between marriage and alcohol use disorders was stronger in women than men, and that the relation between the risk of developing an alcohol use disorder and the spouse's history of drug use problems was stronger in women than men [116].

The lack of a social support pattern frequently repeats itself with family and friends. While men's family and friends encourage them to stop using drugs, women report feeling they have little support, since drug use is frequently the cause of conflict that distances the family or even disrupts relationships. Even when a more drastic separation does not happen, families seem to provide little support for women, since they generally feel embarrassed by their behavior or, yet, tend to deny the dependency [115]. In Brazil, Guimarães (2009) compared 30 women with alcohol-related disorders to a control group of 32 nondrinking women and suggested that "families of women with drinking disorder are more dysfunctional in many aspects, and many of these dysfunctional patterns are transmitted throughout the generations" [117]. Furthermore, it is noteworthy that a clear relationship between alcohol and domestic violence still exists.

Several studies demonstrate that domestic violence toward women is much more common among those who abuse or are dependent on alcohol. In the same way, the frequency and amount of alcohol intake are positively related to the incidence of violence. However, when domestic violence is involved, it is not clear to what extent it is the cause, the effect, or both [106, 118]. The most important consequence of this situation is that the majority of women with substance-related disorders suffer from social isolation and present deep feelings of rejection and loneliness. Thus, different from men, whose withdrawal from conviviality with their peers favors abstinence, to women, a fundamental therapeutic strategy is the (re)construction of interpersonal relations. This reconstruction is connected not only to the possibility of gaining distance from one other but mainly to the recovery of self-esteem. Drug abusing women, like any other women in Western society, typically define their identity and many of their roles in terms of their relations with others, that is, as sisters, friends, companions, daughters, mothers, colleagues, or even victims. These relationships are vital in the development of their self-image, which means, on one hand, that disunion, separation, and ruptures with others contribute significantly to their low self-esteem and, on the other hand, that relationships are a powerful factor in their motivation to recover from dependence [5, 119, 120].

Another relevant factor with respect to social context is that women generally have greater family responsibilities than men, especially in relation to childcare, since, even if they are married, this responsibility is primarily theirs. Although maternity is in itself an important motivator for seeking treatment, childcare may constitute a barrier, since structural economic difficulties faced by these women may make it difficult to attend the treatment center with regularity, or, yet, block the possibility of a longer hospitalization period [121]. Considering the general issue, while dependent men have more legal problems, involving illicit activities, greater number of warnings and incarceration, women show more medical problems, social and family difficulties (facing prejudice, dealing with the partner, with maternity), and psychological symptoms, frequently reporting low self-esteem, self-destructive behavior, and elevated levels of anxiety and depression. Although both men and women report professional problems, women show more financial difficulties and unemployment [122]. According to Barcinski (2009), studies that report the role of women in drug traffic in Brazil show that they perform less prestigious activities, or more risky ones. These studies also show that maternity contributes to recovery from drug traffic. However, it is important to note that most studies on violence and drug traffic are based on male behavior [123].

A specific aspect of drug addiction in women, which has been vastly explored in the literature, is the relation between physical and sexual abuse in childhood as well as adult life and alcohol and other drug dependence. Some estimates suggest that approximately 70% of women who seek treatment for drug-related problems were victims of physical or sexual abuse during childhood and that the prevalence of incest varies from 12% to 31% [124]. In the intent of exploring the predictive value of child sexual abuse in substance use–related disorders and in other psychiatric disorders, Kendler et al. (2000) conducted a large investigation with 1.411 twin females and concluded that child sexual abuse is a crucial causal factor related to increased risk of psychiatric disorders, being greater the more severe the type of abuse was. However, despite the greater probability for alcohol and other drug dependency, there is no evidence for specific risk related to a determinate pathology [125].

Psychiatric Comorbidities

With respect to psychoactive substance use disorders, until the recent publication of the Epidemiological Catchment Area Study (ECA) (1991), most of the literature on associated psychiatric comorbidities was based on clinical samples. The results of the ECA suggest, on one hand, that the observed relation in this type of sample was not always representative of those in the general population. On the other hand the

data collected from the ECA enabled one of the first studies with a general population sample, showing high rates of comorbidity among alcoholics, who presented a 3 times greater probability of having other psychiatric disorders, when compared to the general population [126]. This increased prevalence was also observed in other drug addictcs, since 53% of them presented some other associated disorder [127]. With respect to gender, alcoholic women have more comorbidity than men (65% of women versus 44% of men) as well as women in the general population (31% of alcoholics versus 5% of other women) [128].

Data from the National Comorbidity Survey (1994), another large investigation with the American population, showed that for alcohol abuse related disorders the most frequent associations were, for both men and women: other drug abuse; conduct disorder and antisocial personality; and anxiety and depression disorders [128]. In this study, comorbidity was also more frequent in women than in men. Women had a 2 to 3 times higher probability of presenting anxious and affective disorders than men, while men were 2 times more likely to present other drug dependence, conduct disorder, and antisocial personality [129]. For addiction to other drugs, the epidemiological studies verified that they had a 7 times higher chance of having depression throughout their lives. In general, probabilities were greater for men than women for all types of drugs, except marijuana and cocaine [128]. A recent study shows women that abuse marijuana have more comorbidity anxiety and depression disorders than men which, if not addressed, worsens the prognosis of the treatment (Sherman et al., 2017).

A study with 629 illicit drug users, recruited from different treatment and non-treatment settings, shows high prevalence of cooccurrence of mainly mood and psychiatric disorders. Being female, recruited from an out-of-treatment setting and the number of substance use disorders (SUD) are risk factors for substance-induced disorders [130].

Other researches with greater diversity of diagnoses of the Axis I showed, for women with problematic use of both alcohol and other drugs, in population and clinical samples, high rates of comorbidity with post-traumatic stress disorder and eating disorders. In an investigation on the associated factors to psychoactive substance use with 140 women, Tucci [131] observed women who were alcoholic or dependent on other drugs had the same rates of comorbidities (82,9%), and the most prevalent disorders in both cases were generalized anxiety, post-traumatic stress disorder (PTSD), and depression.

Olsson and Fridell [132] showed that comorbidity between substance abuse and psychiatric disorders is common in the general population, but is yet more common in the population undergoing treatment. Studying patients in Sweden, they verified that women who remained in compulsory care are a very vulnerable group: most have psychiatric comorbidity, high rates of personality disorder, and make more use of health care facilities. In this study 10% of women died prematurely (mean 34,5 years of age), an average of 5 years after the first compulsory treatment.

Women with PTSD in the last six months have twice the risk of having alcohol-related problems than others, and the relation seems to be to stressful experiences more than to PTSD directly [50]. The prevalence of SUD in patients with PTSD varies between 34% and 52%, depending on the studied population. Looking in detail at the type of drug used by the PTSD patients, we find that marijuana seems to be used to provide relief for traumatic memories and improve sleep, while cocaine is used to reduce avoidance behavior and numbing symptoms. Several hypotheses were postulated as to this relation: self-medication, a lifestyle that favors both disorders, shared vulnerability (cognitive, affective, and neurobiological factors common to both disorders). In any way, the data show that the association of SUD, PTSD, and frequently alcohol use disorders is a risk factor for poor response to treatment [133, 134]. Together more than separately, these disorders present more chronic physical health problems, impaired social functioning, high rates of suicide attempts, and more problems with law enforcement.

In a sample of the general population, Goldstein et al. [135] found, among the alcohol-

dependent patients, the following significant differences: 38% of men and 61,6% of women with comorbidity of some mood disorder (OR 0,4); 15,6% of men and 8,3% of women with comorbidity with antisocial personality disorder (OR 2,0); 36,9% of men and 62,5% of women with comorbidity of any anxiety disorder (OR 0,7). However, when these data were adjusted for the sociodemographic characteristics, no significant differences were observed in relation to sex for the co-occurrence of additional psychiatric diagnoses.

In relation to other drugs abuse and related disorders, the same study showed 60,7% of men and 77,8% of women (OR 0,4) with some mood disorder; 55,7% of men and 73,6% of women (OR 0,5) with some anxiety disorder; 74,2% of men and 62,3% of women (OR 2,3) with alcohol dependence; and 33,7% of men and 25,2% of women (OR 1,2) with antisocial personality. However, once more, after adjustments the differences were very small, being the greatest comorbidity of drug abuse in women who abused alcohol; comorbidity of alcohol abuse in women who abused drugs; comorbidity of dependent personality disorder in drug dependent men [135].

The data showed, for the disorders of Axis II, that women also have greater comorbidity than men. It was verified that 20% to 40% of women with alcohol use disorder have one or more associated personality disorders, such as borderline personality disorder (BPD) and dependent personality disorder [136].

In any way, the high prevalence in the general population suggests there may be specific differences in these associations and that the form the comorbidities relate might be sex-specific. Another issue raised is that women would seek treatment due to the comorbidities more than to alcohol or drug use disorders, and this data would interfere when samples are clinical [135].

To Goldstein et al. [135], the multifaceted characteristics of the substance use disorder patients' morbidity indicate the importance of a careful evaluation of the mental disorders and of the substance use disorders themselves, regardless of the health care environment the patient enters.

In a meta-analysis with 41 studies performed between 1985 and 2006, intended to verify the comorbidity of eating disorders (ED) and alcohol use problems, Gadalla and Piran [137] found only four studies that mentioned a negative association between ED and alcohol use problems. The other investigations presented a positive correlation, but the magnitude of this correlation varied greatly, probably due to the heterogeneity of the samples and diagnostic differences, among others. For alcohol use, this positive correlation was with bulimia nervosa, binge eating disorders, and nonspecified eating disorders. No correlation was found with anorexia nervosa. Another study points out that among women who seek treatment for alcohol abuse/dependence, 36% claimed eating compulsively and 26% had some eating disorder. Conversely, women with some form of purgative eating disorder presented 22% to 35% of alcohol abuse, while among anorexics of the restrictive subtype only 9% presented this condition [25].

We must consider that just as drugs, highly palatable foods have reinforcing properties that may alter dopaminergic function increasing the reward motivational drive and decreasing inhibitory control in the limbic system, leading the brain to reward deficiencies. In women with ED, drug use may be due to hypersensibility acquired by the reward system. Indeed, drugs in general and some eating behaviors are used to handle negative emotions [138, 139].

Recent studies showed that, similar to exogenous opioids, chronic use of palatable foods may downregulate endogenous opioid function. Thus, opioids and palatable foods could be used in abstinence periods [139].

As in PTSD, women have more comorbidity with other psychiatric conditions when ED and substance abuse-related disorders are concomitant than when they are present separately. These women also present personality disorders, more emotional instability, and greater impulsiveness [140].

There are several models to explain the association between ED and psychoactive substance use disorders: addiction model (similitude of symptoms), genetic/family model, biological model (involvement of the dopaminergic, endogenous opioid, serotoninergic, and gamma-aminobutyric systems), personality model, development trajectory model, among others, all of which still require more empirical research [141].

In short, a new patient profile emerges from this association of ED and substance use disorders. This group is multi-impulsive and has twice the risk and vulnerability of a dangerous nature, as well as high mortality rates [140, 141]. Women have twice the probability of having comorbidity of SUD and major depressive disorder (MDE) than men, and they realize better that their needs are not addressed at the existing treatment centers [142].

Kolla et al. [143] observed that some symptoms of attention-deficit hyperactivity disorder (ADHD) are predictors of problematic alcohol and drug use in both men and women. Symptoms of hyperactivity associate with problematic use of alcohol in both men and women, but marijuana does so only in men. Hyperactivity, impulsive, and conduct disorder symptoms all predicted problematic alcohol and cannabis use in males. Among the three symptoms previously described, hyperactivity showed the strongest relation with problematic alcohol use in females. There seems to be a sex-specific association of inattentive symptomatology with alcohol and cannabis misuse that was present only in women. Possibly, in the general adult population, the ADHD symptom domain of inattentiveness is more relevant to expression of risky alcohol and cannabis use in women in comparison to men. "Associations between ADHD symptom expression and hazardous substance use manifested differently in males and females, suggesting that sex effects are critical to understanding these relationships" [143].

The relation between alcohol consumption and suicide is greater in women than in men. A mean 34% to 56% suicides had relation to problems related to alcohol use. A study conducted in the European Union with youth aged between 15 and 29 years found that, while boys are influenced by violence-related stress, girls are strongly influenced by heavy drinking [144].

The high comorbidity rates strongly suggest psychiatric disorders and psychoactive substance use-related disorders are associated by means of shared neurobiological and behavioral abnormalities. Despite acceptance of this approach among many researchers, the nature of the causal relation and its factors remain obscure.

Treatment

Assertions that treatment results were worse in women than in men persisted in the literature until the end of the last century: women supposedly had less treatment adherence and presented worse clinical course [6]. Nowadays, we know that these assertions are based more on myths and prejudices than in research data. Bravo et al. (2013), in a 20-year longitudinal follow-up with men and women treated for alcoholism, concluded that women have greater treatment adherence and better long-term clinical course [38]. Important differences among men and women in psychoactive substance dependence suggest the necessity of gender-oriented treatment, mainly for women, who often declare preference for exclusively feminine treatment programs [145]. Many studies show that women benefit more when treated in these programs, since they allow an integral commitment to treatment [146, 147]. On the other hand, mixed-gender treatment programs often fail to attend to women's needs, since men's issues are prevalent in these groups, making it harder, if not impossible, to address women's specific issues. Construction of a personal identity, improvement of self-esteem, development of positive interpersonal relations, mother-child interaction, and vocational training are generally central issues in the recovery of women with drug problems. These issues are hardly addressed in mixed-gender groups, which tend to be centered in men's issues like abstinence and its maintenance [147].

These are some reasons for the proposal and development of specifically feminine treatment programs. Although different meanings are attributed to the expression "women's exclusive program," all authors tend to agree that it does not mean simply "transforming into exclusively female" a program designed for men, developed from a male-oriented philosophy. Therefore, there is consensus that, in order to develop and implement exclusively feminine programs, the fundamental principle, beyond attending to this specific population, is to be sensitive to gender issues, i.e., to make use of strategies particularly responsive to the issues that are characteristic of women with drug-related problems. Ideally, in order to attend these goals, the programs should be structured in a way to preserve the relationship of women with their children, who should also be involved in the treatment [25, 146]. Moreover, gender sensitivity should include other factors, already mentioned in the literature, such as follows [148]:

- Support to overcome barriers that can be structural (e.g., childcare and legal counseling), attitude-related (such as shame of discussing the issue, lack of hope with respect to the program's results), personal (as unemployment, family duties), and social (such as the spouse's or family's opposition to treatment) [149].
- Integration with services of clinical and mental health, including prenatal care [148].
- The need for the team of health care providers to recognize, empathize, and handle the particularities of women's drug abuse.
- Training of the team for addressing specifically feminine issues, directly or indirectly related to the use of alcohol and other drugs.

This means that there is need for a treatment program with multidisciplinary teams, including, in an integrated manner: (a) social services, mainly in the form of childcare support and social reinsertion; (b) legal counseling, to clarify women's and mother's legal rights; (c) counseling for couples and families; (d) sexual and maternity education, and family planning; (e) professionals working on issues related to self-esteem and the body, as occupational therapists and nutritionists; (f) exclusively feminine group psychotherapy, where affective and interpersonal issues can be dealt with, not only those related to alcohol and drugs; and (g) support from the team, as well as frequent and continuous contact, would be more attractive to women with substance-related disorders and more effective in the fulfillment of their needs [119, 146, 150].

In other words, as Davis (1994) claims, exclusively feminine treatment programs should be more concerned with the fact that their patients are women than with the fact that they are addicted to psychoactive substances. Although these circumstances are progressively getting clearer to specialists, the evaluation of the effectiveness of these programs has only just begun and, still, there are few studies concerned with these issues. One of the first variables to be analyzed in treatment programs is the motivation of the users to join the programs. A study by Grosso et al. (2013) showed that women have more internal motivations: concern with drinking progression (61.1%), physical health (43.4%), mental health (38.9%), and family relations (38.3%), whereas men's motivations are predominantly external. An interesting data in this study is that the motivation to seek for treatment is negatively associated with the result and the length of stay in treatment [149, 151, 152].

Women with co-occurring disorders are generally more likely to choose mental health rather than substance abuse treatment services, but these facilities may not be well equipped enough to address co-occurring substance use problems [133]. Another important variable is the length of stay in substance abuse treatment, since it is well established that adherence is one of the most important factors in predicting the case evolution, and it is positively correlated with post-treatment withdrawal. Greenfield et al. [147] claim that gender itself is not a significant factor in retention or response to treatment. However, evidence shows that there are significant factors for adherence. Some of them are gender specific and can vary in different kinds of programs [153]. In a study with 637 women in 16 residential treatment programs, Grella et al. (2000) demonstrated that the variation in adherence and evolution rates

after 12 months were associated both with the characteristics of the clients and with the characteristics of the programs. Regardless of the program, women with a history of treatment had a tendency to present worse results, both in adherence and in post-treatment withdrawal [154]. On the other hand, although pregnant patients and those with dependent children had lower rates of retention than other women (49% × 58%, respectively), in programs with a greater concentration of patients in similar situations their permanence in treatment was significantly superior (from 98.6 days to 124.1 days). However, in relation to the case evolution, measured by abstinence in a period of 12 months, they did not differ from the other patients. Given the large diversity in the rates of abstinence found in the programs – from 11.1% to 88.9%, with a mean 44% – and taking into account the greater diversity of services offered in the programs with higher concentrations of pregnant women and/or women with dependent children in comparison to those with less women in this situation, the same study then aimed to verify if the patients treated in these programs had higher rates of abstinence. The results showed, however, that abstinence was not correlated with any characteristic of the programs and that, for these women as well as for the others, the only association found was in relation to retention: the patients who remained in treatment for 90 days or longer had four times the probability of being abstinent in the follow-up period than those who stayed less than 90 days. The authors concluded that, in post-treatment evolution, the characteristics of the programs probably have an indirect effect, i.e., one mediated by retention.

While gender itself has not been predictive of retention, issues traditionally associated with gender, such as childcare, employment, and trauma, are related to the variation found in retention by gender. Thus, in women, higher retention was associated with being married, having a higher income, having lower psychiatric severity, and being unemployed. Furthermore, women with depression were also more likely to remain in treatment longer than women without mood disorders. The Drug Dependent Woman's Treatment Center (PROMUD) of the Institute of Psychiatry, at the Hospital das Clínicas of the Medical School of the University of São Paulo (USP), has conducted throughout the years some comparative studies on permanence in treatment. The first research comparing retention rates in this service with a traditional gender-mixed program showed that while alcoholic women presented significantly superior rates of permanence in the exclusive program for women in 6 months (57% × 34.8% in mixed treatment), no significant differences were verified for those with other drug dependences (43.9% × 46.3%) [155].

Among the different hypotheses for explaining these results, there were two main ones. The first concerned the gender of the group psychotherapists. While for women with drinking problems their feelings of shame, the stigma, and the guilt were eased with the presence of a therapist of the same sex, facilitating approach and intimacy, the same did not happen with women with other drug abuse [156]. These patients, younger, less guilty of their behavior, and accustomed to drug consumption with a group of male and female friends, had as their greatest issue the absence of care from the parental couple and/or the absence of a father figure. These differences suggested that, possibly, group counseling with a pair of therapists (a man and a woman) could further extend the support they needed, and also provide a positive model of care [155].

The other hypothesis was related to the great concern with body issues and its linear association with self-esteem, which caused any intervention (either with a drug or the cessation of a drug) that could affect the shape, size, or aspect of their body to be immediately rejected, frequently with abandonment of the treatment. Is this sense, it seemed that a nutritional approach could be of fundamental value to support, educate, and intervene on these issues. These changes had a significant impact on the rates of retention. In the posterior studies, we observed that after a 6-month period, it increased from 43.9% in a mixed sample to 65.17% in PROMUD, and, after a year, regardless of the drug used, retention was 50%, in comparison to 20% of traditional gender-mixed treatments [157]. If this first line of investigation, in spite of its briefness, clarified that

women feel more attracted, engage more, and remain longer in specialized services for women, the issue of its effectiveness in the case evolution is still less studied. This is clear in two review and meta-analysis studies [147, 150, 152]. In the first, Orwin et al. (2001) performed an extensive review of the treatments offered to women in order to conduct a meta-analysis on their effectiveness and concluded that, in comparison to gender-mixed services, programs only for women obtain additional beneficial results and are more effective, especially when they have intensified approaches, directed specifically to the needs of their target population [158]. In the other review, Ashley et al. (2003) found similar results examining the components of therapeutic approaches in 38 evolution studies, with 7 randomized clinical samples and 31 nonrandomized samples [146]. The authors observed significantly superior results, such as higher retention rates; decrease in substance use; reduction in the high-risk behaviors for HIV; and improvement in self-esteem, depression, and prenatal and neonatal care, such as daycare, prenatal follow-up, women-exclusive admission, workshops on female issues, strategies for mental health care, and intensified programs. In the discussion of the results, the authors point out a series of reasons to justify the increased efficacy of the intensified programs exclusive for women, in relation to the standard programs. They suggest that some components of the first approach, as the existence of daycare, could reduce the barriers to treatment access. Other components, such as prenatal follow-up and strategies for mental health care, can attract and retain more women in different life situations (e.g., homosexuals or victims of abuse), since they would ensure that these women's specific problems be addressed.

In a research with a therapeutic group exclusive for women, "The Women's Recovery Group," Greenfield et al. [147] found that, during the 12 weeks of treatment, this therapy and the mixed-gender counseling group were equally effective in decreasing substance use [153]. However, the exclusively feminine group significantly showed great improvement in reducing alcohol and drug use during the 6-month post-treatment follow-up phase. Women furthermore felt much more satisfied in the exclusively feminine treatment groups. On a wider range version of this study, Greenfield et al. (2014) failed to confirm these results [150]. In this Stage II, both the exclusively feminine psychotherapy group (Women's Recovery Group) and the mixed-gender group had significant reductions in days of substance use during the group therapy. The authors suggest that the differences between Phases I and II may be due to the open format of the groups in Stage II; they had a low mean number of patients per group and lack of participation stability. These factors may have affected the women's experience of mutual support, which was the most important component related to the effectiveness of the exclusively feminine therapy group. A study by Sugarman et al. (2016) showed that women-only groups for recovery from drug use disorders were significantly more cohesive and had higher attendance rates than the mixed-gender groups [145]. Women feel more welcome and safe in these groups, and verbal support seems to be central to retain them in treatment. In a research with drug-dependent mothers, Evans et al. (2013) claimed that, 10 years after treatment, 48% of the women had successful results – they were alive, were not involved with illicit substances, nor with the criminal justice [152]. In comparison to the gender-mixed group, the exclusively feminine treatment group had greater association with success in the follow-up period. According to these authors, this association was mediated by the number of incarcerations during the 10-year follow-up, and showed that the exclusively feminine treatment group was related to a smaller number of incarcerations which, in turn, was associated with better results.

With respect to case evolution, another research study in a Brazilian treatment center exclusive for women comprising 74 alcohol addicts and 49 women addicted on other drugs showed that after 6 months, 50% of the alcohol group and 46.9% of the other drug addicts were not consuming drugs, and another approximately 30% in both groups had reduced consumption. These numbers also repeated when improvement in general functioning was considered, an index that includes, besides consumption, family and occupational relations and leisure [159].

Considered together, these investigations highlight that the efficacy of treatment for women is a complex issue, and future research in a broad range of subjects is needed to determine which intervention is effective, for which women, and in which environment. Along these lines, McMahon and Luthar (2000) already pointed out in the beginning of this century that a change of perspective in research is necessary. For these authors, studies should currently be directed more toward knowledge of the differences between women than to comparing their characteristics with men's [160].

Thus, one of the reasons that has been mentioned for the difficulty in establishing programs for women with recognized efficacy relates to the fact that they probably do not constitute a homogeneous group. In their comparative study of gender-mixed and exclusively feminine programs, Copeland et al. suggested, already in 1993, that the less favorable results in their sample population of women undergoing treatment might have been influenced by the fact that exclusively feminine programs, in comparison to the gender-mixed ones, attracted more women who were homosexual, had children, with a history of abuse, and with history of maternal alcoholism, that is, patients with more severe issues and more difficulties.

Niv and Hser [161] found a similar result almost 15 years later. Women who were treated in women-exclusive approaches obtained better results with respect to drug use and legal issues, but had greater probability of hospitalization and used more psychiatric and drug and alcohol treatment facilities in the follow-up period than the women in the mixed-gender treatments. This difference in the profile of women referred to exclusively feminine programs is common to several other researches, suggesting that even in a subgroup of women there are distinct characteristics that may be related to different responses to treatment.

In relation to delimitating specific subgroups, research on the comorbidity of psychoactive substance abuse and other psychiatric disorders has been considered a particularly useful tool, since it allows characterizing sources of heterogeneity within groups. A comorbid psychiatric disorder furthermore influences the presentation, permanence, and evolution of substance dependent patients in treatment.

Concerning addicted women, there is no consensus on the direction of the influence of comorbid psychiatric disorder in treatment [147]. While some studies suggest association with the majority of symptoms or psychiatric disorders is a predictor of a worse evolution, others failed to find this correlation, and even pointed out an inverse relation.

An investigation conducted in an exclusively feminine program verified that women with substance-related disorders who presented another psychiatric disorder remained for significantly longer periods in outpatient treatment than the patients with no comorbid disorder regardless of the substance used. The disorder that most significantly affected the permanence in treatment was mood disorder. On the other hand, comorbidity with eating disorders was significantly associated to early abandonment (in up to 3 months) of the treatment program [162].

In another research at the same center, which verified the influence of hospitalization in the retention to treatment during a period of 36 months, the obtained results were basically similar with respect to the presence of some comorbidity and mood disorders, that is, a significant increase in permanence time. For the eating disorders, on the other hand, there were no significant rates of abandonment, suggesting that hospitalization could favor the patient's retention and continuity in treatment [163].

There is little research on the repercussions of the association between eating disorders and substance use-related disorders. Despite this, however, since it occurs frequently in the clinical practice, on the one hand, and since data suggests it may indicate greater severity of psychiatric and clinical disturbances in patients, on the other hand, its careful study is not only important, but also fundamental for therapeutic planning, either in substance abuse programs or eating disorder programs [147, 164].

Studying 80 alcohol and other drug dependent women, Brasiliano (2005) verified that 27 (33.75%) of them had clinical eating disorders, 17 (21.25%) had subclinical eating pathology,

and 36 (45%) did not present this comorbidity. With respect to their characteristics, the group with clinical eating disorder was significantly younger, showed more severe alcohol use, and tendency to more severe use of drugs. The subclinical group differed from the other two in that they presented a worse occupational situation.

After 1 year of treatment, significant changes were verified in behavior and eating habits in the subclinical group, and in body image in the clinical eating disorder group. No differences were observed between the three groups in relation to permanence in treatment, and all improved significantly in relation to substance use in 12 months. The patients in the group with clinical eating disorders, however, had a slower evolution. These data fail to support the hypothesis that the association with eating disorders affects the clinical course with dependent women, suggesting that an integrated approach, one that answers to the needs in a personal and individualized manner, has, in general, more chance of success.

Treatment programs that receive only dependent women or only women with ED must be attentive to comorbidities in both groups, and especially must: be careful when prescribing psychotropic medication, be careful when prescribing diet and exercise, actively search for abuse/trauma history, remember that treating one disorder may trigger another, and monitor comorbidity during treatment [141]. It is noteworthy that interventions which include training ability to handle negative emotions help to interrupt the cycle of self-medication for both food and alcohol/drugs [139]. The nutritional follow-up in treatment programs for substance use disorders is also fundamental to prevent and treat EDs.

According to Compton et al. [165], finding clear correlations between comorbidity with specific psychiatric disorders and, for example, an altered risk of relapse for individuals in treatment programs for dependence could have important implications both in the reduction of the risk, by means of therapeutic approaches adequate for the comorbid disorder, and as a predictor in the case evolution.

With respect to the treatment, another noteworthy aspect is that the integrated programs (in which psychiatric disorders and substance abuse are approached simultaneously by the same person, team, or service) have been suggested as the most effective [39, 166]. Some authors also highlight that worse prognosis in dependent patients with comorbidity may be attributed, to a great extent, to the traditional approach, that treats substance abuse in one health service and the associated psychiatric disorder in another [56].

According to [167], this effectiveness would be connected to the change in perspective by the healthcare providers, who would stop focusing on the particularities of each of the disorders and amplify their view to see that, when substance abuse coexists with a psychiatric disorder, the disturbance is greater than the sum of its parts, so that inevitably they exacerbate each other

Conclusion

Although the detection of psychoactive substance-dependent women is increasing, there is still little research to clarify their true needs, in order to develop both treatment and prevention programs. However, there remains no doubt that they constitute a group with characteristics so diverse from men's that it becomes impossible to generalize results from one group to the other. Furthermore, despite the rare studies on their effectiveness, the exclusively feminine treatment programs with an integrated approach that attends to women's specificities are, to the present moment, the ones who offer the best chances of success in the treatment of female dependence. Among the different aspects for future investigation, the present research indicates the need to verify subgroups of dependent women who would benefit additionally from specific approaches.

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Attention-Deficit/Hyperactivity Disorder and Women

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Introduction

Attention-deficit hyperactivity disorder (ADHD) is a heterogeneous disorder with a complex etiology. It is characterized by a range of symptoms related to control of attention, impulses, and activity. ADHD is one of the most widely studied disorders [1] and is estimated to affect 3–5% of school-age children [2]. A study conducted by Polanczyk et al. found a worldwide prevalence of 5.29%, varying mainly due to methodological differences between studies [1]. ADHD has been associated with high risks of academic failure, unemployment, comorbidities, and substance abuse [3]. A study conducted by Biederman et al. (1999) found that girls with ADHD experience more conduct, mood, and anxiety disorders [2].

In this chapter, we discuss gender differences in the prevalence and nature of ADHD, the difficulty of diagnosis both in childhood and in adulthood in women, conflicts between symptoms and gender norms, and, finally, the impact of ADHD in women. We also discuss the stigma associated with ADHD in women.

ADHD in Women

Although the prevalence of ADHD is higher in boys, it remains a major cause of psychiatric disability in girls [2]. The male-to-female ratio is approximately 3:1. When diagnosed in childhood, the disorder persists into adolescence in about 50–80% of cases, and into adulthood in 30–50% [4]. In adulthood, the male-to-female ratio is roughly 1:1. This suggests that ADHD may be underdiagnosed in girls or that girls are more likely to exhibit the inattentive form, which tends to persist over the life course [5]. Although symptoms develop in childhood, a significant proportion of women with ADHD are only diagnosed as adults [6]. This gap in diagnosis may be partly explained because the symptoms found in women, such as forgetfulness, disorganization, low self-esteem, and anxiety, are considered less obvious than the disruptive behaviors often exhibited by men.

When ADHD remains undiagnosed, the possibility of understanding one's own problems and accessing appropriate treatment options is lost [7]. Over time, self-esteem and self-image can suffer as a result of repeated experiences of failure, alienation, and inadequacy. This increases the risk of comorbidities. Women who are not

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diagnosed with ADHD before adulthood are more likely to experience symptoms of depression and anxiety, sleep disorders, eating disorders, substance abuse, and low self-esteem [8].

Data from the nationally representative Canadian Community Health Survey-Mental Health (2012) were analyzed, comparing 107 women aged 20–39 years (inclusive) with ADHD to 3801 without ADHD. Women with ADHD had twofold the prevalence of substance abuse, current smoking, depressive disorders, severe poverty, and childhood physical abuse, and triple the prevalence of insomnia, chronic pain, suicidal ideation, childhood sexual abuse, and generalized anxiety disorder in comparison with women without ADHD. Following adjustments for age, race, education, and income, women with ADHD remain with superior risk to several health issues, pointing that women with ADHD are at risk for early adversities, health and mental health problems [9]. In another study, 458 males and 452 females with ADHD were drafted at a tertiary referral center. All probands underwent a four-step procedure for diagnosing ADHD, involving the Structured Clinical Interview of Diagnostic and Statistical Manual of Mental Disorders Axis I disorders to determine comorbidity. Women show higher rates of mood (61% vs. 49%), anxiety (32% vs. 22%), and eating disorders (16% vs. 1%) [10].

A case-control study with 206 participants investigated suicidal ideation in patients with adult ADHD and its association with gender and psychopathology. Suicide ideation was assessed by the Beck-I Depression-Inventory, and Conners' Adult ADHD Rating Scale was used to characterize the ADHD symptom domains. The likelihood of suicide ideation was significantly higher in females with ADHD, compared with controls; the difference was not significant in males. "Problems with Self-Concept" scores on the CAARS showed the closest association with suicide ideation in females; in males it was "Impulsivity" scores. The outcomes emphasize the relevance of a strategy for risk evaluation and prevention in women. The important connection of Problems with Self-Concept with suicidal ideation may be prominent for women with ADHD, because it provides information for the early recognition of those who are at risk of suicide. It is also relevant for prevention as there is evidence that, although untreated ADHD is associated with poorer long-term self-esteem, a beneficial response to pharmacological or nonpharmacological therapy can be elicited for the majority of self-esteem outcomes. Hence, it is appropriate that future research targets on the evaluation of therapy directed to women self-esteem [11].

ADHD is repeatedly mentioned as a risk factor for misconduct. Nevertheless, several studies do not consider other criminogenic variables into account when describing such link. It is even less clear whether models that include ADHD as a potential risk factor for criminality consider the importance of sex differences. For women subjects, only conduct disorder symptoms and problematic cannabis use demonstrate a connection with crime. In other words, ADHD did not anticipate a history of arrest, and when contrasting females and males, conduct disorder symptoms and cannabis misuse put forth stronger effects on the history of arrest for females than males [12].

If diagnosed late or not at all, ADHD is associated with lower levels of life satisfaction. This, in turn, is associated with long-term medical problems, peer rejection, and difficulties at work and in relationships [13]. Undiagnosed women are less able to be consistent mothers and to cope with work and family demands and have higher divorce rates [7]. Compared with their peers, girls with ADHD report increased anxiety, distress, depressive symptoms, and external locus of control. They also tend to exhibit self-harm, social impairment, suicidal ideation, and suicide [3], and are at higher risk of psychological impairment. Female adolescents with ADHD are more likely to experience attentional and organizational difficulties than boys do but are less likely to be disruptive.

Because they do not mobilize attention to themselves, they are more likely to be left out in the classroom [7].

In a nationwide survey conducted by Harris International (2002), 14% of female adolescents

with ADHD were prescribed antidepressants before being treated for ADHD, compared with only 5% of boys with the disorder [7]. ADHD symptoms and related problems tend to become more prominent in girls when they reach puberty, in contrast to boys, whose symptoms are more evident in childhood [5]. The prevailing social norms influence the standards of what is considered appropriate behavior, as well as the way in which ADHD is portrayed and perceived by most members of society [5]. What individuals are known for – for example, a moral deficit or a neurodevelopmental disorder – and how they experience their symptoms and impairments are highly relevant [5].

Many women with ADHD make an effort to suppress disruptive, hyperactive, impulsive, and disorganized behavior because they understand that such symptoms violate norms of expected femininity [7]. These symptoms are often interpreted as signs of emotional difficulties, discipline issues, learning disabilities, or inattention, rather than as symptoms of ADHD [5]. Girls are encouraged to exhibit both traditionally feminine qualities, such as empathy, kindness, obedience, and mothering and relationship skills, and traditionally masculine qualities, such as assertiveness, competitiveness, academic prowess, and career-focused skills. When girls exhibit disruptive, hyperactive, impulsive, and disorganized behavior, they are at risk of social judgment because they violate the norms of female behavior. In an attempt to avoid social sanctions, many girls with ADHD spend excess energy trying to hide their problems [7]. To some women, inattention, procrastination, and difficulty resuming a task after interruptions become more evident after they have children. These women often take a long time to focus on anything, and their child constantly distracts them from the task at hand. Motherhood poses additional challenges related to increasing organizational and structural demands [5].

Stigma involves the deep discrediting of an individual due to their membership in a group which is devalued and has low social power [14]. Mental illness has been identified as one of the most stigmatized attributes a person can have in modern society. A growing body of research shows that ADHD carries a strong social stigma, as do other mental disorders. The negative effects of stigma add significantly to the impairment caused by the disorder itself [13]. Several variables contribute to the stigma surrounding ADHD, including uncertainty in the lay public about the very validity of the diagnosis and negative pressures on how it is diagnosed and its pharmacotherapy. The heterogeneous course of this disorder can also hinder its understanding and leaves room for interpretations of the impairment involved as trivial or caused by a lack of willpower. If a diagnosis is not regarded as a real disorder, it is less likely to be understood [14].

Potential mediating pathways for the link of childhood ADHD to adolescent tobacco and marijuana problems were evaluated in two large, prospectively assessed twin samples. Explicit consequences of childhood ADHD on tobacco and marijuana issues in late adolescence and repercussion by means of ADHD symptoms all along adolescence were important for females only. Results of childhood ADHD on substance problems were also moderated by peer impairment, despite it was surprisingly stronger for males than females. Still outcomes of childhood ADHD on tobacco and marijuana issues in late adolescence were broadly mediated through early substance problems for male and female. Regarding earlier drug use, depression and anxiety had consequences that were linked simultaneously – not prospectively – with tobacco and marijuana abuse. Former data on possible causal effects of inattention in females imply that these might increment their sensitivity to self-medicate attentional problems with nicotine, as straight events of ADHD on marijuana were owing to familial risk alone [15].

Data on the use of methylphenidate and amphetamines during pregnancy show that there is no increment in major congenital anomalies. There is very little information regarding the use of atomoxetine and guanfacine in pregnancy, and

although there is no evidence on the use of clonidine for ADHD, the data on its use as an antihypertensive drug have not revealed any perinatal serious adverse effect. Bupropion does not seem to increase the rate of congenital anomalies. There are no data-relevant studies that investigate the possible long-term neurodevelopmental effects of any of these drugs. Most of them are secreted in human milk, but the concentrations in infant's blood, except for clonidine and amphetamines, have been very low. Hence, breastfeeding with clonidine and amphetamines is usually contraindicated. There seems to be no safety concerns for the other drugs [16].

Observational studies cannot conclude causality in statistically significant associations, so it cannot be affirmed that psychostimulants are accountable for adverse gestational outcomes. However, the current medical evidence implies the plausibility that particularly amphetamines can raise the risk of preeclampsia; the absolute risk, however, is low, with NNH values ranging from about 60 to over 500. No adverse links have been recognized with atomoxetine maybe because of underpowered analyses. Women with ADHD should therefore balance the benefits of their medications against the potential risks associated with these drugs during pregnancy when they consider their options during pregnancy [17].

Final Considerations

In women, ADHD is associated with particular features, including a difference in presentation between boys and girls and a markedly different gender predilection in childhood as compared with adulthood, which reflects the difficulty of diagnosing this disorder in girls. If diagnosed late or not at all, ADHD is associated with increased risk of depression, anxiety, sleep disorders, substance abuse, and self-image issues. In addition, delayed diagnosis deprives patients of a key opportunity to initiate early treatment and achieve more positive outcomes. Furthermore, women face specific impacts on ADHD on social adjustment and childrearing skills. This complexity must be addressed and understood if more effective strategies for managing this disorder in women are to be developed.

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Suicide and Suicidality in Women

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Gender Suicide Behavior Differences

Suicide is a complex public health problem, is the 13th leading cause of death globally, and accounts for about 800,000 deaths in the world [8]. But those dramatical numbers are only the tip of the iceberg: about 10–20 million attempt suicides and 50–120 million persons are profoundly affected by the suicide or attempted suicide of a close relative or associate worldwide [22].

One of the suicide behavior complexities is the fact that it can be rather different between genders with differences involving both successful suicides and suicidal behaviors. For suicide attempt/suicide the rate is estimated to be 10–20 (all ages and both genders included) but women are about three times more likely to attempt suicide, though men are around three times more likely to die from suicide, a phenomenon, known as the gender paradox of suicidal behavior [21]. This paradox is strengthened by the fact that we know that more than 90% of all suicidal people had a mental disorder when they kill themselves and major depression underlie more than half of all suicides, nevertheless major depression is about twice more frequent in females when compared with men [2, 17].

Globally, the male/female ratio of suicide rates is 1.9 [21], but this is mainly due to China data, the only country in the world where female die by suicide more than male [15] (we will discuss the China data above). Excluding China the male/female rate would be about 3–4.

There are also differences in the risk of suicide between men and women based on a previous attempt [4]. Most of the women who are successful in suicide have made a previous attempt, but when it comes to men, 60% of those who die from suicide have not had a previous attempt. Otherwise said, men are more prone to die in their first intent than women [20]. This fact can be rather important when focusing on suicide strategies of prevention between men and women.

Those differences in attempts and suicides in women may superficially induce people to think

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that suicide attempts in women could be a method of getting attention. This is absolutely not true considering that a suicide attempt is the most important predictor of future suicide behavior both in women and men. Culturally, men and women differ in their roles, responsibilities, status, and power, and these socially constructed roles interacting with biological differences contribute to differences in their suicidal behavior [5].

Women Suicide in China

China is the only country in the world where the suicide rate in women is greater than men. In 2002, a suicide survey in China caught the attention of the world [15]. The rate in women was 25% higher than in men, mainly due to the large number of suicides in young rural women. Rural rates were three times higher than urban rates – a difference that remained true for both sexes, for all age groups and over time. China accounts for more than 30% of the world's suicides and exhibits a unique pattern of suicide rates.

Another study by Yip et al. [23] examined trends in suicide rates at the national, regional, gender, and age levels and the ratios of suicide rates in China between 1991 and 2000, a time when rapid economic and social changes occurred. These authors found that national, urban, and rural suicide rates for men and women decreased significantly in the period 1991–2000. Age-specific suicide rates, however, showed that there were different patterns of changes in suicide rates in rural and urban areas. Although elderly suicide rates showed the most significant reduction in urban areas, younger women had the largest reduction in rural areas. The proportion of men to women in suicide increased significantly in urban areas, but no significant change was found in rural areas. Longer historical studies are needed to reveal the relationship between macrosocial changes and the pattern of suicide [23].

Another recent study [24] showed that temporal trends in the suicide rate of elderly rural and urban men and women were decreasing, but only rural trends were significant ($p < 0.001$). The differences between rural-urban and male-female suicide rates in the elderly were declining over time (slope = −4.2 and −3.0, $p \leq 0.006$), but the differences between rural-urban and male-female in 2014 remained large (16.3/100,000 and 9.8/100,000, $p < 0.001$). There has been a significant decrease over the past three decades; the current rate of suicide among the elderly remains high in China. In addition, the age pattern of Chinese suicide is in transition to the predominance of the elderly. Particularly the rural should be a public health priority in China.

Suicide and Perinatal Period

Pregnancy is a state of sensitivity for women due to great biological and psychological changes. Despite the common thought that pregnancy is a period of health among women, studies have indicated that two-thirds of pregnant women manifest psychological symptoms such as anxiety, irritability, and lability in mood [12].

Specifically, concerning depression, it is not only common but even possibly more frequent during pregnancy compared with any other time in a woman's life. Furthermore, pregnancy might trigger the appearance and recurrence of depressive symptoms in vulnerable women. Previous authors have found that AD affects an estimated 15–20% of women, although rates vary by country and measurement type [3]. Postpartum depression prevalence is also important and affects approximately 10–15% of adult mothers yearly.

These data are important considering that more than 90% of all suicidal people had a mental disorder when they kill themselves and major depression underlies more than half of all suicides [22].

Suicide and suicidal attempts occur at a lower rate during pregnancy and the postpartum period than in general population, but perinatal suicidality, which comprises completed suicides, suicide attempts, and thoughts, is one of the leading causes of maternal mortality in the first 12 months postpartum [6].

Risk Factors for Suicide in Peripartum

Suicide risk factors in peripartum are rather similar to general population, like a previous history of suicidal attempt or a family suicide behavior history. Some other factors are specific. For example, women who have had a postpartum psychiatric admission have a 70 times greater risk of suicide in their first postpartum year [11].

Following the recent review of Orsolini et al. [12], the main risk factors are as follows:

1. *Individual risk factors*
   - Younger maternal age
   - Being unmarried
   - Personal and/or family history of psychiatric disorders
   - Personal and/or family history of suicidal attempt or suicidal ideation
2. *Socioeconomic risk factors*
   - Family conflict
   - Exposure to (domestic) physical/psychological violence
   - Loneliness and lack of social/family/partner support
   - Partner who rejected paternity
3. *Environmental risk factors*
   - Social and gender inequalities
   - Social and racial discrimination
   - Belonging to an ethnic or religious minority
   - Crowded or inadequate housing
   - Living in rural areas
   - Exposure to disaster, conflict, war
4. *Gestational risk factors*
   - Unwanted/unintended pregnancy
   - Nulliparity
5. *Clinical risk factors*
   - Previous history of psychiatric disorders
   - Psychiatric comorbidity
   - Shorter illness duration

Psychological symptoms (i.e., premenstrual irritability, perceived pregnancy complications, negative attitude toward the pregnancy, anxiety about birth, distancing pattern of coping, etc.)

Suicide and Gender Differences Between Doctors

The occupations most associated with suicide, if we consider the occupational categories, are physicians, police officers, artists, dentists, mechanics, and security agents who have been considered the highest risk for suicide [14]. A systematic review and meta-analysis have compared the mortality of physicians with the general population and have found that suicides are more frequent among physicians [16] in both men and women doctors.

In the United States, it has been reliably estimated that, on average, up to 400 physicians are lost to suicide each year, equivalent to at least one entire medical school class – approximately one physician per day. This means that more than one million American patients lose their doctor per suicide each year. Physicians have a lower risk of mortality from cancer and heart disease than the general population, which is presumably related to self-care and early diagnosis. Unfortunately, they have a significantly greater risk of dying of suicide, which represents the final stage of an eminently treatable disease [9].

Studies agree with the fact that women doctors have a higher suicide risk than other women. In the United States, the annual suicide rate for physicians is 41 per 100,000, compared with 12 per 100,000 among all white women over 25 years of age. Studies show that physicians who commit suicide have a mental disorder, more often depressive disorder, substance dependency, or both [18]. Doctors of both sexes commit suicide with significantly greater frequency often through overdose of substances, and less often by firearm than people of the general population. The ease of obtaining drugs and the knowledge about toxicity are important factors in these cases. In this category, it is considered that psychiatrists and anesthesiologists are at greater risk; however, all specialties are vulnerable.

In the Brazilian study [13] on causes of death among physicians in the State of São Paulo, Brazil, in the period from 200 to 2009, the proportion of suicide among female doctors is another notable finding. Women comprised

13.2% of the total sample and 24% of the suicide death group; thus, women are overrepresented in the suicide group (p = 0.02). It is important to emphasize that this result does not reflect the suicide rate of the Brazilian population, in which men are between 2.3 and 4.0 times more at risk compared with women [7]. To calculate the mortality rate, however, the total number of living individuals in the Brazilian study sample is used as the denominator (women represent 35% of living doctors). This discrepancy could be the result of an age difference between men and women in medicine: women have only recently achieved a numerical representation in the profession proportional to that of men. Therefore, if the total reported deaths are the basis of the calculation, women are overrepresented. However, when the living medical population is used as a basis, men are more likely than women to complete suicide, reflecting the behavior of the general population [1, 7].

The research, which was conducted in Australia by Roy Morgan [10] with more than 14,000 doctors and medical students, is considered the first anywhere in the world to provide a mental health picture of such a large proportion of the medical community of a country. This research pointed out some of the main findings, which include the following: (1) One in five medical students and one in ten doctors had suicidal thoughts in the past year. Four in 10 students and a quarter of physicians are highly likely to have a minor psychiatric disorder, such as mild depression or mild anxiety. (2) Oncologists are clearly the most psychologically stressed specialists, whereas physicians who do not deal with patients (researchers, administrators, etc.) think of suicide more often. (3) Male doctors work for longer hours (46 hours per week) and engage in riskier drinking, but female doctors are more psychologically distressed and think of suicide more often. (4) Young doctors work longer hours (50 hours per week on average), are much more psychologically distressed, think more about suicide, and become more exhausted than their older counterparts. (5) The perceived stigma is large, with nearly half of respondents feeling that doctors are less likely to appoint doctors with a history of depression or anxiety, and 4 in 10 agree that many doctors think less about the possibility of doctors who have experienced depression, anxiety, bullying, and racism as a cause of stress for them.

Morgan [10] found that about a quarter of physicians reported having thought about taking their own lives before the last 12 months and 10.4% reported having these thoughts in the past 12 months. Approximately 2% of doctors report having ever attempted suicide. Women had a significantly higher rate of suicide attempts compared with male physicians (3.3% and 1.6%, respectively). Doctors without children reported higher rates of suicide attempts compared with physicians with children (3.2%, 95% CI = 2.6–3.8 and 1.86%, 95% CI = 1.6–2.2, respectively). Doctors who were separated or divorced (6.4%, 95% CI = 4.3–8.5) had a higher rate of suicide attempt compared with both physicians (3.6%, 95% CI = 2.5–4.6) and those in compromised relationships (1.9%, 95% CI = 1.6–2.2). There were no significant differences in the proportion of physicians who attempted suicide in different work contexts. Rates of suicidal ideation and attempted suicide are substantially higher than those reported by the general population and other professionals.

High rates of medical suicide have been reported since 1858. However, more than 150 years later, the causes of these suicides remain unresolved. The doctor's suicide is a public health crisis. One million Americans lose their doctors to suicide every year. Many doctors have lost a colleague to suicide. Some lost up to eight during their careers – no chance to cry.

Doctors are masters of disguise, but may be suffering in silence. Ignoring the suicide of a doctor only leads to more medical suicides [19]. Suicide is preventable, but we must reduce stigma, stop the secret, and face what it is to be a doctor, and it can be so emotionally difficult. Medical institutions need to openly acknowledge the problem and make changes to support the mental health of doctors and medical students.

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Psychopharmacology and Women

Marcelo Allevato and Juliana Bancovsky

Women are meant to be loved, not to be understood. (Oscar Wilde)

Introduction

The so-called pharmacology of special populations, including psychopharmacology, usually refers to children and adolescents, the elderly, and pregnant or breastfeeding women. However, one fact that is historically neglected in psychiatric practice and psychopharmacological prescriptions is the existence of considerable differences between men and women: although there is consensus as to the relevance of obvious factors such as muscle mass and percentage of body fat, the importance of hormonal factors occupies an intermediate position, since it will hardly be considered irrelevant but almost certainly will not decisively influence prescriptive decisions [1–6]. A more sophisticated view, taking into account factors such as the regional distribution of pharmacological targets and the ability to metabolize is, at least, gender-dimorphic and clearly polymorphic between individuals, has begun to gain relevance more recently, and pharmacogenomic differences are likely to be a first step toward the introduction of understanding sexual dimorphism into psychopharmacology in the arsenal of knowledge required to practice precision medicine in psychiatry [3, 4, 6–9].

To organize our journey through this field, it is important to emphasize that the first scientific evidences available about these issues date back only to the 1990s of the last century [1, 10, 11], which means very recent in scientific terms. When we look at the scientific production specifically addressed to the theme during these almost only four decades of evolution, some findings are quite interesting and make us think once again how imprecise and empirical psychiatric

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clinical practice remains, even in this second decade of the twenty-first century, after of some "decades of the brain" of neuroscientific advances. Bringing the question of clinical practice to the fore, we first come to the question of the validity of current psychiatric diagnoses that are still based on categories erected from empirical observation of syndromes [12]. Some of them are exclusive to women, such as premenstrual dysphoric disorder and postpartum depressions and psychoses [6, 13–15], which adds complexity to the issues discussed here. This question of general knowledge, with which we are confronted in a daily basis, faces us with something crucial and often unnoticed: if the diagnoses are syndromic and poorly reasoned neurobiologically, what about the validity of the therapeutic interventions that will have to be evaluated based on scales that evaluate the magnitude of signs and symptoms in a longitudinal way in patients exposed to active treatment arms and placebo arms; in a randomized, double-blind manner; and with simultaneous exposure in parallel arms? This apparently sophisticated design may, in fact, reflect our lack of neurobiological knowledge about the so-called disorders that afflict our patients.

It is interesting, at this point, to observe that there is a consensus regarding the diversity of clinical presentations of psychiatric diseases among men and women, including about epidemiology, with different incidence and prevalence rates, as well as with respect to observed signs such as age of onset and symptoms reported as more relevant by the patients [13, 15–17]. From this distinct clinical presentation, it is possible to infer that the therapeutic intervention choice must be, ideally, equally dimorphic. However, the clinical studies in psychopharmacology itself generally do not take this demographic question into account when determining the criteria for inclusion of the subjects, and it is easy to see that interventions in clinical trials cannot be customized, since they are intended to establish effectiveness in globally analyzed populations [4, 18]. This fact puts us in the throes of a dilemma, which is to judge the efficacy data presented to us without considering differences between genders or to take the most challenging course of considering such data as indications that should guide the exploration of this still little known territory whose cartography is essential to the establishment of a clinical practice based on evidence but also carefully personalized.

In the following sections, we will discuss the influences of gender differences in pharmacodynamics and pharmacokinetics. Next, pharmacological interventions in pregnancy and lactation will be detailed, preceding questions on the psychopharmacological treatment of conditions such as premenstrual dysphoria, postpartum depression, and puerperal psychoses.

Pharmacodynamics and Women

As we know, psychopharmacology arose from the empirical observation of the effects of drugs on behavior and, later, from the elucidation of the synaptic mechanisms of action of these so-called psychotropic drugs. These were the theoretical foundations of various hyphothesis on the pathophysiology of mental disorders, based on inferences now considered simple, but aligned with the scientific knowledge of the time. Thus, it was natural to consider, for example, that psychoses were derived from excess of dopamine and mood disorders from changes in the serotonergic function, since dopamine receptor blockers and inhibitors of serotonin metabolism, respectively, were shown to be generally effective in affected populations of such diseases. It's important to keep in mind that we are talking about the late 1950s, and over the ensuing decades, scientific knowledge has advanced exponentially; thus more sophisticated theories have been formulated in an attempt to shed light on the pathophysiology of mental disorders and make the understanding of psychotropic drug efficacy more convincing. At that stage, thinking about personalized medicine was premature and almost chimerical. In fact, only in the 1990s of the twentieth century did the gender differences in psychopharmacology begun to be explored in a detailed way and in early years of the twenty-first century specific animal models for females considered and developed, yet in an incipient way [18–20]. Despite all the advances

achieved in the field, the development of psychoactive drugs was still based on the knowledge of the mechanism of synaptic action, which was considered very sophisticated and even sufficient at that time. As a matter of fact, we must recognize that we remain relatively attached to such a model at the threshold of the third decade of the twenty-first century, in our so-called "designer drugs" era. Anyway, efforts to understand the differences between the sexes in pharmacological terms arose from the perception of the behavioral and clinical peculiarities described in the introduction of this chapter, among which we can highlight the patterns of response to environmental stressors, markedly different between the sexes, and whose paradigmatic example is, probably, the stress response mediated by the HPA axis and noradrenergic system [2, 6, 21]. One finding to remember at this point is that diseases in which the relative weight of environmental stressors acting as triggers or maintainers in relation to genetic propensity is presumably stronger, such as depression and posttraumatic stress, are more prevalent in women [1, 3, 6, 9, 22]. Such perception made these disorders feasible models for the perception of neurophysiological and, consequently, cognitive, sexually dimorphic differences in the face of environmental stressors. Although these differences suggest a potential unique response to drugs with distinct mechanisms of action, there is a considerable paucity of data concerning the sexually dimorphic aspects of pharmacodynamics [2, 4, 11]. Therefore, the current clinical management in terms of choice of mechanisms of action is basically the same despite gender, although empirical evidence suggests that men and women might respond differently to antipsychotics and antidepressants [3, 20, 23]. Regarding pharmacokinetics, the picture is already different, as we will see in the following section.

Pharmacokinetics

In a review published in 2013, Marazziti et al. [3] concluded that, at the time, there were abundant evidence that the pharmacokinetic profiles of a particular medication differ between sexes in the classical parameters of absorption, distribution, metabolization, and elimination. These pharmacokinetic variables may influence the plasma levels of a drug and, perhaps, its ability to bind to the pharmacological targets already mentioned in the section on pharmacodynamics and, consequently, the clinical response [1–4]. These differences also make the sensitivity to adverse events distinct in men and women. An interesting fact about how neglected these differences were throughout the history of psychopharmacology is that, until 1993, women were not included in bioequivalence studies, since this would enhance interindividual variability and, consequently, would require larger study populations, with deleterious consequences on cost [3]. This fact itself illustrates how the subject of underestimation of sex differences was absolutely trivial until recently. At this point, we are ready to get in a brief account of the main evidence of differences between the sexes in the classic acronym ADME, i.e., absorption, distribution, metabolism, and elimination [3–5, 9, 11, 20, 24–29].

So, let's begin with absorption, the first pharmacokinetic phase, which normally encompasses the previous liberation phenomenon. In this regard, women have a reduced capacity for gastric emptying and accelerated bowel movements, which could mean lower plasma levels [3, 4, 9]. On the other hand, the lower gastric acidity of women may facilitate the absorption of certain benzodiazepines and tricyclic antidepressants, and the lower activity of some gastric enzymes may also favor the attainment of higher plasma levels [3, 20, 25]. These latest perceptions corroborate data from bioequivalence studies conducted over the past 20 years, which show higher drug plasma concentrations in women [4, 9].

Regarding the next phase, distribution, several factors are known to influence it, such as weight, percentage of body fat, blood flow, and binding to plasma proteins [9]. On average, women have lower body weight than men, which is a factor currently not considered when calculating the recommended doses of drugs for adult patients, in addition to a higher percentage of body fat and lower blood flow. Lower weight and lower blood volume suggest higher plasma levels in women, while the higher percentage of

body fat increases the volume of distribution and initially leads to lower plasma concentrations of lipophilic drugs [3, 9, 20]. An example of a class of drugs with high lipophilicity are the benzodiazepines, which are known for its propensity to accumulate with increasing in body fat associated with aging. As elderly women are among the most frequent users of benzodiazepines, they are also among the more vulnerable patients regarding this phenomenon of artificially increasing half-life, accumulation, and exposure to higher plasma levels [3, 10]. However, studies about this very relevant issue of the complex interactions between gender and aging are not available at this point. After being absorbed and once in the bloodstream, drugs bind to proteins at different rates, especially albumin and acid alpha-1-glycoprotein. It's very relevant to note that the total drug concentration consists of a fraction bound to plasma proteins and an unbound fraction, called free fraction. Generally, only the free fraction is active, and only the free drug fraction is able to cross the blood-brain barrier in order to reach the cerebral microcirculation and diffuse into the interstitial space toward its pharmacological targets [3, 9]. There are also no studies available on sexual dimorphism related to the effect of gender on the whole permeability of the blood-brain barrier, nor on the efficiency of the ABC transporters of this barrier regarding sex differences [4]. Still on this issue, although albumin is not influenced by gonadal steroids, acid glycoprotein can be reduced in women, since estradiol decreases its concentrations [30–32]. This effect may increase the proportion of free drug when medicines whose active principle preferentially binds to acid alpha-1-glycoprotein, although there is controversy about this [33, 34]. In general, plasma protein binding capacity appears to be lower in women than in men. This difference may be of relative importance for drugs with high plasma protein binding rates such as benzodiazepines and some antidepressants [3, 9]. An issue to be observed when simultaneously administering two drugs with a high plasma protein binding index is the displacement phenomenon: one of them may be displaced from its binding sites, what leads to increased free, and thus active, fraction. This displacement phenomenon can lead to unexpected adverse events. As a clinical example, for most antidepressants the binding occurs with acid alpha-1-glycoprotein, and the affinity is low, which allows the displacement of these molecules when, for example, warfarin is simultaneously administrated. Thus, the anticoagulant action of warfarin is not affected, and the high SSRI therapeutic index prevents them from becoming toxic in this situation [3, 35].

Turning our attention to the metabolism, the pharmacokinetic phase responsible for the inactivation of exogenous substances including drugs, the main role with regard to psychotropic drugs is played by hepatic metabolism, basically dependent on hepatic blood flow and liver enzymatic activity. Likewise, in the body as a whole, hepatic blood flow is reduced in women compared to men. In addition to this, there are also significant differences between genders regarding enzyme activity [7, 9, 24, 28]. As one example, some ABC, or P-glycoprotein-type transporters, which regulate the biliary excretion of certain drugs, an important component of the first-pass metabolism, are subject to hormonal influences and have 50% reduced activity in women [36, 37]. In the liver hepatocytes, the metabolism of most psychotropics occurs through two distinct enzyme systems: Phase I enzymes, responsible for oxidative metabolism, which modifies the activity of some drugs and inactivates others and generates metabolites not ready for renal excretion and Phase II enzymes responsible for conjugation, mainly with glucuronic acid, reactions which usually inactivate the original compounds or active metabolites previously generated by Phase I reactions, resulting in inactive and polar compounds ready for renal excretion. It's important to keep in mind that some reactions of both phases are slower in women, which may lead to higher plasma concentrations of drugs metabolized by these systems [4, 24], and when we evaluate the metabolism and elimination steps together, as we do in the clinical practice, we should consider that glomerular filtration rates are also

lower in women. As the final step in the elimination of metabolites of psychotropics, which are often not devoid of some pharmacological activity, is essentially renal, the net effect of the reduced efficiency of hepatic metabolism and the lower rate of renal clearance can lead to a slower elimination of most compounds [3, 38]. Going back to the cytochrome P450 enzymatic systems responsible for Phase I oxidative metabolism, and introducing the emerging field of gender-related pharmacogenomics, it is important to remember that these enzymes are encoded by genes located on autosomal chromosomes and consequently not so prone to gender-related differences in their metabolic phenotypes. However, it is possible that hormonal factors affect gene expression and, consequently, the activity of these enzymes [4, 8, 11]. Among these enzymes, the 2D6 subtype is extremely important for the metabolism of psychoactive drugs, and it has high affinity for its substrates, metabolizing them quickly and efficiently. However, this is a low capacity enzyme system, which is easily saturated by the simultaneous administration of more than one substrate, and this common situation in clinical practice leads to increased plasma levels of these substrates, with variable consequences. Despite these considerations, there is usually no difference in 2D6 activity between genders [39], but their activity is increased in pregnancy [40], which suggests that this system is influenced by female sex steroids [28, 41]. Still regarding P450, another important enzymatic system is 2C19, for which differences between sexes have been reported, with a greater activity in women [39, 42], one potentially relevant issue to consider while prescribing psychotropic drugs preferentially metabolized by this system. However, ethnic background and influences arising from the use of oral contraceptives may be confounding variants relative to these findings, and these controversies remain to be clarified [43–45]. The 2C9 system accounts for about 20% of hepatic CYP enzyme activity and has considerable genetic homology with 2C19, which sometimes means also relevant functional shared rules in metabolism. For 2C9, there is no evidence of sex-related activity changes strongly documented so far [46]. Another important enzyme, 1A2, appears to have reduced activity in women, which makes them potentially more susceptible to adverse effects of the same dose of substrates of this enzyme system, compared to men [47–49]. A frequently relevant fact for psychopharmacological practice is that this enzyme has its activity increased by the habit of smoking. This phenomenon of induction may also underlie the perception of variations of enzymatic activity. In summary, this enzyme appears to be more efficient in men, but it is highly prone to being induced by smoking [50].

The enzyme 3A4 can be considered the most important enzymatic subtype of the hepatic microsomal systems of the cytochrome P450 [51], and significant differences in its activity between genders have been noted [39]. The activity of these enzymes appears to be influenced by gender and age, and young women appear to be the most competent metabolizers, which may have some relevant clinical implications in the case of some benzodiazepines specifically metabolized by these enzymes, since this increased competence may lower plasma levels and greater withdrawal potential [52]. Regarding the activity of 3A4 enzymatic system, we must consider that there may be an increase in populations of younger women in relation to those of more advanced age, which may reduce the plasma levels of their preferred substrates, such as oral contraceptives or even preferential substrates of other systems, such as tamoxifen (preferential 2D6 substrate), which may lead to therapeutic ineffectiveness. With aging, there is a decline in the activity of this enzyme, which is more relevant in men than in women [3].

Regarding renal elimination, differences between sexes regarding glomerular filtration, passive diffusion, and active secretion, all of which were more efficient in males, have been reported, and the potential clinical significance of these findings is related to the accumulation of active metabolites of Phase I reactions or, less frequently, Phase II metabolites with some residual activity [38, 53].

Specific Groups of Drugs and Gender Differences

Benzodiazepines

Regarding the pharmacokinetics of benzodiazepines, the main observation to be considered in clinical practice is that the metabolism of lorazepam and oxazepam, which depends on Phase II conjugation reactions, is slower in women, and the potential concern is accumulation of these drugs under certain circumstances. Conversely, concerning this group of compounds, it seems unlikely to see significant gender differences in Phase I oxidative metabolism in clinical practice [10].

Antipsychotics

Regarding the main enzymes responsible for the metabolism of antipsychotics, subtle differences in cytochrome P450 1A2 enzyme activity have been reported between men and women. This enzymatic system is the main route of metabolization of clozapine and olanzapine, and discrete differences in plasma levels of clozapine, higher in women, were observed only at the beginning of treatment [54]. Another potentially relevant pharmacokinetic difference, mainly during the treatment with depot formulations, is the increased muscle mass in men and the higher percentage of body fat in women, which may lead to accumulation of lipophilic drugs, influencing plasma levels when depot formulations are administered at conventional intervals. Regarding the adverse effects related to antipsychotics, there is no consensus about differences in incidence and prevalence between sexes. The most consistently observed adverse effects observed more frequently in women are QT interval prolongation [55], hyperprolactinemia [56], and metabolic syndrome [57].

Antidepressants

Due to physiological characteristics related to lower acidity and slower intestinal transit, the absorption of antidepressants may be greater in women, a characteristic that persists after menopause and is potentiated by exogenous estrogen and progesterone [20, 58]. The higher percentage of fat in women may favor accumulation in adipose tissue and reduced plasma levels of very lipophilic antidepressants. Regarding plasma protein binding adverse reactions related to the concomitant administration of tricyclic antidepressants and drugs that may displace them from their protein binding is something to be considered [35]. As discussed earlier, most antidepressants are metabolized by the cytochrome P450 enzyme systems, and potential differences in gene expression can influence the metabolic efficiency of these systems and lead to unexpected modifications in plasma levels, generating insufficient ones, related to inefficacy, or elevated ones, related to adverse events. However, despite some studies reporting differences in plasma levels of antidepressants between genders, these variations appear to be related more to ethnic, genomic, or biographic factors than to gender differences [3].

Section Summary

In summary, the relative role of sex in pharmacokinetics and pharmacodynamics should be considered as one of the relevant factors along with genetics, age, lifestyle, disease, and concomitant administration of other medications. As previously mentioned, data are scarce and controversial, but the relevance of differences between sexes should not be underestimated, since they may impact the efficacy and tolerability of the drugs and, therefore, their effectiveness in clinical practice.

Psychopharmacological Treatment During Pregnancy and Lactation

The treatment of psychiatric illnesses during pregnancy is one of the most challenging situations in the practice of psychopharmacology. This challenge, ideally, begins when the patient decides to attempt to conceive or unexpectedly

arises in unplanned cases of pregnancy. Of course, it is best to plan for treatment before pregnancy. It is prudent for psychiatrists dealing with women of childbearing age to seriously consider the hypothesis of pregnancy and to actively discuss it with patients, ranging from the choice of contraceptive methods to psychoeducation over safe medications for use in pregnancy. It is important to note that decisions in these cases will almost inevitably be influenced by partners and family members and that stigmatization of patients and cultural prejudice regarding psychiatric medications are a significant challenge [59]. Ideally, planning should precede months of attempted pregnancies so that the prescription in use can be tailored to include only medications that are proven to be safe in this particular situation. As patients often become pregnant without planning, it is necessary to manage this situation when it is already in place, when the risk of discontinuation of treatment and, consequently, the increase in the psychiatric condition is significant [60].

Pregnancy prior planning should be individualized, and consider prior psychiatric history, severity of illness, prior response to medication, issues of tolerability and, of course, the wishes and fears of the patient and her family regarding treatment during the pregnancy. Initially, it is part of the clinician's task to encourage the patient to maintain psychiatric treatment during and postpregnancy [60, 61]. To create a sense of stability, ideally all changes and adjustments of medications should be made, if possible, before pregnancy. Also obvious is the fact that it is desirable that the symptomatic picture of the patient be compensated before pregnancy, which will facilitate the maintenance treatment without great prescriptive variations. Given the scarcity of data imposed by ethical issues that prevent specific studies, the choice of medications should be careful and based on the available evidence and the professional's clinical experience. In the case of pregnancy, the old maxim of using the lowest effective dose is especially valid, since exposure to drugs should be minimized, but without impairing efficacy, since exposure of the fetus to the mother's psychiatric illness should also be avoided or reduced to a minimum [59, 62].

Each case should be planned according to a detailed analysis of the factors associated with the risks and benefits of the various options. A key factor to take into consideration is the will of the patient and family members, since their impact on adherence is absolute. If one of the partners is radically against the use of medication during pregnancy, the most prudent is to clarify the risks of giving up treatment, including on the risk of relapse and its consequences for the fetus. A careful follow-up, with psychosocial measures if indicated, is better than the insistence on medication, due to the risk of potentiating nonadherence. However, we must remember that a significant number of pregnancies are unplanned, that is, most clinicians must have already faced psychiatric patients in regular use of psychoactive drugs who became unexpectedly pregnant. This is a situation to be managed with caution, and radical measures such as abrupt cessation of medication should be avoided, since they can aggravate the patient's stress, precipitate symptoms of discontinuation, and favor relapse. The best course is to review the prescription, keeping in mind that the fetus has already been exposed to the components of the prescription and that if any of the medications should be discontinued, it is best to do so gradually [59, 63].

Also, we must keep in mind the factors that should be considered in the prescriptive decision on pregnancy, and it is necessary to observe the alterations in the metabolism and renal clearance of drugs during pregnancy. Adaptive physiological changes in pregnancy lead to significant pharmacokinetic changes with an impact on absorption, distribution, metabolism, and elimination. Changes include increased plasma volume, body fat, renal blood flow, glomerular filtration rate, and drug clearance. On the other hand, several alterations of the enzymatic activity also occur, with reduction of 1A2 activity and increase of 2D6 and 3A4 activity [40, 64, 65]. These changes, which depend primarily on hormonal variations, may result in both increased and decreased metabolism and are significant for most psychotropic drugs. As the resources to guide the prescriptive decisions on the dosage aspect in this situation are scarce, some aphorisms such as the use of the aforementioned

effective minimal dose, in order to maximize benefit to the mother and reduce fetal exposure, often reassess the patient's mental state, and adjusting the dose whenever necessary may seem obvious, but remain useful [59].

When planning the prescription during pregnancy, ideally clinicians have to foresee the possibility of maintaining the treatment during breastfeeding. If the fetus is exposed to medication during pregnancy, it does not make much sense to interrupt it during breastfeeding, except in special situations, such as in cases of relapse due to ineffectiveness of the current therapeutic regimen, use of medications to which continuous exposure is not advisable, or if the infant is apparently experiencing adverse events potentially related to the medication. It is important the participation of childcare in this process, to assist in the timely detection of the cited adverse events [60, 63].

Concerning the effects of specific classes of psychoactive drugs when used in pregnancy and breastfeeding, antipsychotics appear to be relatively safe in pregnancy, and the benefits of their use appear to largely outweigh the risks of maintaining a pregnant patient with a serious untreated mental illness [60]. A precaution to be taken is attention to the worsening of metabolic changes characteristic of pregnancy and the risk of gestational diabetes, associated with excessive weight gain of mothers and excessive weight at birth [66]. The risk of hyperglycemia is a real concern, which makes careful monitoring of blood glucose in these patients advisable [67]. As for the consequences of exposure in intrauterine life, some reports include restlessness, dystonia, and tremors [67], and there is an FDA recommendation dated 2011 on withdrawal symptoms and muscle twitching [60]. As for developmental changes, there is no evidence that any delays persist beyond the 12 months of life [68, 69].

Regarding the use in lactation, although the levels of antipsychotics in breast milk appear to be low, there is a near total shortage of long-term follow-up data on developmental effects and extrapyramidal effects, which makes it advisable to carefully monitor infants and the familiar clarification for making prescriptive decisions. Concerning anxiolytics, there are controversies regarding the use of benzodiazepines in pregnancy by association with reports of perinatal toxicity, with temperature dysregulation, apnea, low APGAR levels, hypotonia, and feeding difficulties. There is evidence that exposure to the combination of benzodiazepines with SSRIs may be associated with an increased risk of congenital heart defects. Other anxiolytic compounds, such as buspirone, are not associated with teratogenesis in animal studies, but there is no evidence available in humans. Other potentially anxiolytic compounds are pregabalin and gabapentin, which have no formal indication. As for breastfeeding, short acting agents are preferable to reduce the risk of sedation. Both have a benign profile in animal studies, but there are few data in humans. In the absence of gabapentin, there is a recent study that has associated it with a higher number of preterm births with low birth weight and need for admission to a neonatal intensive care unit. Also for anxiolytics, the ratio between risk and benefit of pregnancy and lactation prescription should be carefully evaluated, since the consequences of pathological anxiety go beyond subjective distress and extend to the commitment of personal care, mood, sleep disturbances, and functional changes [60].

For the psychostimulants, the data in pregnancy and lactation are sparse and contaminated by the concomitant use of multiple drugs. Many women discontinue their use because of safety concerns, although there is no evidence of malformations. To date, there is only evidence linking them, albeit not definitively, to an increased risk of spontaneous abortion [60, 70].

Concerning the class of antidepressants, the psychoactive medications most prescribed during pregnancy, the good quality studies that have been performed more recently show the absence or the small incidence of adverse outcomes. In general, the use of antidepressants during pregnancy appears to be relatively safe. Four meta-analyses on the risk of exposure-related malformations in the first trimester of pregnancy did not evidence an increased risk [71–74].

The literature on the risk of cardiac malformations is an example of the importance of method-

ological refinement for the stratification of factors that can lead to confusion. Although some of the previous studies with SSRIs showed an increased risk of cardiac malformations, these studies compared the population to the general population, regardless of risk factors and behavior associated with depression. When comparing patients with depression using SSRIs in pregnancy with depressed patients who do not use them, there is no difference in the risk of cardiac malformations, suggesting that the risk is associated with intrinsic factors and behaviors associated with depression, rather than with the use of SSRIs [74, 75]. A similar result has been observed for persistent pulmonary hypertension, an inability of the pulmonary vasculature to reduce its resistance at birth, which can lead to respiratory difficulties, hypoxia, and intubation, and associated with 20% mortality. In 2006, the results of a single study led to the issuance of an alert by the FDA, including this warning in the package insert. Since this alert, five additional studies have generated controversial results, with an association observed in two and absence of association observed in other three [60], whereas a large more recent observational study analyzed three million and eight hundred thousand cases and found no relation between the use of SSRIs and pulmonary hypertension [76].

Other associations observed during the use of antidepressants were low birth weight, preterm birth, and autism. However, when one looks at the confounding factors, the results are generally negative. A recent meta-analysis looked at neonatal outcomes in women with depression who received treatment and those who did not. Untreated depression was associated with an increased risk of preterm birth and low birth weight. Similar findings have been observed regarding autism, with recent evidence that maternal psychiatric illness is a major confounding factor between SSRI use and causal relationship with autism [77].

Another outcome apparently unrelated to exposure to antidepressants in intrauterine life is deficient neonatal adaptation syndrome, reportedly related to an alleged withdrawal of antidepressants at exposure in the third trimester of gestation, being its first report from 1973 [78]. In 2004, the FDA included a label warning for SSRIs and SNRIs about this supposed association, which would be characterized by respiratory discomfort, cyanosis, apnea, convulsions, unstable temperature, difficulty feeding, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, weakness, irritability, and constant crying, and recommends the gradual reduction and withdrawal of medication before delivery. This recommendation was not based on evidence, and the issue of safety for mothers and the reduction of risks to the fetus from such withdrawal remain unclear. Most of these cases are mild and of spontaneous remission in the short term, without sequelae [79]. The risk of at least moderate symptoms appears to be associated with the association of benzodiazepines with antidepressants. The need for methodologically stricter studies on this syndrome, as well as the development of risk minimization strategies, is very clear [60]. Currently, there is no evidence that dose reduction and antidepressant withdrawal are recommended especially in cases of moderate to severe mental illness. In fact, many women will need increased doses in the third trimester, as increased volume of distribution can lead to reduced drug concentrations and increased symptoms [60].

In lactation, antidepressants are generally considered safe, with low or undetectable plasma levels. Monitoring is recommended for sedation, sleep disorders, and feeding difficulties, although these adverse effects are uncommon [80].

In the case of mood stabilizers, the evidence for carbamazepine and valproic acid is consistent: in the case of carbamazepine, the most firmly established risks are spina bifida and other neural tube malformations, facial and skeletal abnormalities, hypospadias, and diaphragmatic hernias. In the case of valproic acid, there is also risk of malformations of the whole neural, effects on brain volume, cognitive effects, craniofacial abnormalities, cardiac malformations, cleft palate, and also hypospadias [68]. Carbamazepine is also a competitive inhibitor of prothrombin precursors and may be associated with an increased risk of neonatal hemorrhage. Contrary to what these risks

might suggest, both agents are considered safe in breastfeeding [68]. Lamotrigine has been suspected of increased risk of cleft palate, but recent data do not support this hypothesis. There may be a need for dose adjustment during pregnancy, as their plasma levels may decrease. Lamotrigine is considered safe in breastfeeding [80, 81].

Regarding lithium, there is an association between its use in the first trimester and the congenital heart abnormality called Ebstein's anomaly. Although this risk was initially considered extremely high, a unified analysis showed the occurrence of this abnormality in less than 1% of pregnancies. Lithium was also associated with perinatal toxicity, with risk of hypotonia, cyanosis, neonatal goiter, and diabetes insipidus. In view of the above, the benefit risk between the high possibility of relapse in mothers with severe bipolar disorder and the relatively low risk of Ebstein's anomaly should be assessed [62, 82, 83].

On the other hand, for mothers with less severe and stable moods, it appears to be more prudent to withdraw lithium gradually to reintroduce it from the second trimester. Although follow-up data are limited in the evolution of exposed children in intrauterine life, no cognitive abnormalities have been reported. Lithium levels should be closely monitored during pregnancy, and their administration should be discontinued at the onset of labor. In breastfeeding the use of lithium can be problematic, also because of the risk of high levels in case of dehydration [59, 60].

Section Summary

In summary, data on the safety of psychiatric medications during pregnancy are still limited, mainly due to the existence of the various behavioral and risk factors inherent in psychiatric populations whose control is complicated from a methodological point of view and can influence the course and outcome of pregnancy. The best quality data are for antidepressants and point to satisfactory safety. Regarding areas such as the safety of antipsychotics in pregnancy and lactation and the long-term prognosis of children exposed to psychiatric medications more evidence based studies are still needed to clarify some issues. There is also a need for further investigations regarding the posology of psychiatric medications in pregnancy and efficacy in preventing relapses during and after pregnancy. A clear fact that arises from the evaluation of the current literature is that active psychiatric illnesses are associated with a negative prognosis for both mothers and children and should be actively investigated and treated in the clinical setting, even when data are apparently scarce.

Conclusion

Until the last decade of the twentieth century, there was little awareness about how relevant gender differences could be in terms of efficacy, tolerability, and safety of the psychopharmacological treatment. Since then, a growing body of evidences has been published, and gender differences in terms of pharmacokinetics and pharmacodynamics of psychotropic are now clearly seen as a relevant issue in psychopharmacology. One example of this change of mind in the field is the fact that zolpidem, a sleep inducer, is since 2013 the only medicine in psychopharmacology with different dosing recommendations by the FDA between men and women, with the initial recommended daily dose for women being half of the recommended for men [6]. Beside pharmacodynamic and pharmacokinetic questions, there is a plenty of issues regarding hormonal differences along the life cycle in women and also concerning the menstrual cycle. If it was not enough, pregnancy and breastfeeding issues can both add additional concerns to the psychopharmacological practice in women. In this chapter, we briefly summarized the current knowledge available about this ever-evolving field, emphasizing the clinical relevance of gender differences for the clinical practice; we have advanced, but there are still controversies and limited practical applications. To go further Oscar Wilde's quote and support understanding beyond love, we need to continue to invest research efforts in this area of precision medicine.

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Medical Conditions Affecting Women's Mental Health

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The diagnosis of disease is often easy, often difficult, and often impossible.
Perfect health, like perfect beauty, is a rare thing; and so, it seems, is perfect disease.
– Peter Mere Latham, MD, 1789–1875, British physician and medical educator, physician extraordinary to Queen Victoria [1].

There are no really safe biologically drugs. There are only "safe" physicians
– Harold A. Kaminetzky, Contemporary American Physician [2].

...If we wish to know about a person, we ask what is his story–his real, inmost story? For each of us is a biography, a story. Each of us is a single narrative, which is constructed, continually, unconsciously, by, through, and in us–through our perceptions, our feelings, our thoughts, our actions; and, not least, our discourse, our spoken narration. Biologically, physiologically, we are not so different from each other; historically, we are each of us unique.
– Oliver Sacks, Jewish neurologist and author of Awakenings [3].

Introduction

Historically, medicine is characterized by observation. A systematic approach through clinical history-taking, physical examination, and mental state assessment allows subjective and objective evaluations to clinical diagnosis [4]. Unfortunately, because of the belief that the body is not related to mental disorders, the physical examination is not common practice in psychiatry. However, it is a valuable tool, since (1) physical illnesses are frequent in psychiatric patients; (2) physical examination provides important diagnostic evidences; (3) and it can be therapeutically important [5]. Beyond that, physical examination can help to differentiate between organic

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and nonorganic disorders. Existing data demonstrate that patients with severe mental illness (SMI) have 13 to 30-years shortened life expectancy when compared to the general population, and 60% of this excess mortality is caused by physical illnesses [6]. Cardiovascular disease including obesity, hyperlipidemia, hypertension, and diabetes mellitus, in addition to cancer, kidney disorders, hepatitis, and human immunodeficiency virus (HIV) are heightened among people diagnosed with SMI [7]. Many risk factors are related to the higher rates of medical illness in the SMI population. At the individual level, behavioral (e.g., lack of physical activity, poor diet, high rates of smoking, psychotropic medication side effects) and social risk factors can be considered (e.g., poverty, unemployment, homelessness, disability) [7, 8]. Furthermore, factors related to the health system such as a poor quality of physical healthcare offer can also contribute to these rates [8].

Sex and gender are individual risk factors and both account for the expression of disorders. Sex is biological and determines reproductive function, sexual hormones, and gene expression. On the other hand, gender is associated with behavior and life experience [9]. Moreover, gender is considered an independent risk factor, even when controlling for age, comorbidities, lifestyle, and ethnicity [10]. Both, sex and gender, impact on physiological functions, which affect body systems, such as the cardiovascular, pulmonary, and autoimmune, as well as disorders of the gastroentointestinal, hepatobiliary, urinary, endocrine, hematologic, and neurological systems [10].

When considering women's health, some medical conditions (e.g., thyroid disorders) are more prevalent, and they can affect women's mental health. Medical conditions can relate to psychiatric disorders in four possible ways: (1) a medical condition can be the primary cause of the mental and behavioral manifestations (e.g., thyroid disturbance and depression-like symptoms); (2) a medical condition can aggravate the mental disorder (e.g., mobility limitation due to obesity in a patient previously diagnosed with major depression); (3) a mental disorder can exacerbate a medical condition (e.g., a patient diagnosed with schizophrenia and tobacco dependence); and (4) there is no direct relationship between a medical condition and a mental disorder (e.g., post-traumatic stress disorder and nephropathy). Then, the main medical conditions affecting women's mental health are discussed.

Cardiovascular Disorders

Cardiovascular disorders (CVD) are the leading cause of death among women and men, and they are associated with significant disability [11]. When considering gender differences, women are at higher risk for coronary artery disease (CAD) in the postmenopausal period, because of the decrease of endogenous estrogens, which are considered cardioprotective [12].

Coronary Artery Disease

Coronary artery disease (CAD) is caused by atherosclerotic plaques in one or more coronary arteries, which cause imbalance between oxygen supply and demand, leading to tissue hypoxia [12]. Risk factors for atherosclerosis include blood lipid abnormalities, smoking, hypertension, diabetes mellitus, history of first-degree relatives with early onset CVD events, male sex, physical inactivity, abdominal obesity, alcohol consumption, low intake of fruits and vegetables, and psychosocial factors [13, 14]. Hypertension, diabetes mellitus, physical inactivity, alcohol consumption [15], and depression [16] are strongly associated with myocardial infarction (MI) in women. Unfavorable lipid profile, smoking, abdominal obesity, and high-risk diet are similarly associated with MI in women and men [15].

The clinical manifestations of MI in women differ significantly from male patients. Women show more vagal activation, nausea, and arm/back/jaw ache. Besides that, sweating, general weakness, and craniofacial pain, in the absence of chest pain, are more common in females [17]. Sudden death is more usual in women, and mortality within a year after MI is around 26% in women, compared to 19% in men [18]. Additionally, women are at higher risk of rehospitalization in the first month and the first year after MI [19].

Psychiatric Disorders Related to Coronary Artery Disease

Some personality traits, psychological characteristics, and psychiatric disorders have been associated with CAD. When considering personality traits, type A behavior pattern can be a risk factor for coronary artery disease [20–22], while type D personality [23] was related to a worse prognosis and impaired quality of life [22, 24, 25]. Psychological characteristics such as hostility and anger [26], acute [27–29] and chronic mental stress [30], vital exhaustion [31, 32], depression [33], and anxiety [32] can contribute to the development of CAD. Moreover, there seems to be a dose-response relationship between negative emotions and the incidence of CAD [34, 35] as well as an association between psychological distress and a higher mortality [36]. Conversely, the presence of jollity and sense of humor was associated with lower cardiovascular risk [37]. Likewise, positive psychological characteristics, such as high emotional vitality, were associated with a lower risk of incident stroke [38].

CAD and Mood Disorders

Accumulating evidence has been demonstrating that mood disorders are strongly related to CAD. Depression is not only a risk factor for coronary artery disease and cerebrovascular accident but also a complication [39]. According to a meta-analysis by Rugulies, individuals with clinical depression or depressive mood show an overall risk of 1.64 for the development of CAD [33]. Additionally, Larson et al. showed that those diagnosed with dysthymia or depression have a relative risk of 3.3 for cerebrovascular accident [40].

The prevalence of depression in CAD patients is higher, when compared to the general population, 18% versus 7%, respectively [41, 42]. Depression increases not only the risk of development and progression of CAD, but also the adverse coronary disease-related outcomes, including MI, revascularization, procedures for unstable angina, and death [43–47]. A combination of depression and previous stroke is associated with a higher all-cause mortality than either condition alone, and the presence of depressive symptoms after stroke increases the mortality 35-fold [48]. Because of the evidence, we strongly recommend the screening, stratification, and treatment of depression in CAD patients with complications [43, 45, 49–51] and attending cardiac rehabilitation [52].

Bipolar affective disorder (BAD) is also related to CAD, and there is evidence demonstrating that BAD predispose youth to accelerated atherosclerosis and early CVD, and is associated with metabolic syndrome [53], type 2 diabetes mellitus [54], and a higher cardiovascular mortality than the general population [55]. Besides that, while the severity of manic symptom predicts cardiovascular mortality [56], depressive symptoms are associated with metabolic and cardiovascular risks [53].

CAD and Anxiety Disorders

In the last years, anxiety has emerged as one of the most important risk factors for CVD disease, since it determines other known risk factors for CVD such as depression, substance use, overweight, and a sedentary lifestyle [57]. Recent studies have been demonstrating that anxiety disorders (AD) are highly prevalent in patients with CVD [58] and are associated with the onset and progression of CVD, as well as adverse cardiovascular outcomes, including mortality [58, 59]. Patients with high levels of anxiety, independent from other risk factors, are at higher risk for incident stroke [60] and major cardiac events [57]. When considering specific anxiety disorders, the prevalence of panic disorder (PD) is four times higher in patients with CAD, when compared to the general population [59]. Generalized anxiety disorder (GAD) is related to an increased risk of adverse coronary disease-related outcomes, including MI, urgency revascularization, cardiac arrest, and death, regardless of other cardiovascular risk factors [61]. Furthermore, post-traumatic stress disorder (PTSD) affects the development and course of cardiovascular and cerebrovascular disease [62]. It occurs in one of every eight patients diagnosed with acute coronary syndrome and seems to be associated with an increased risk for subsequent CVD events and mortality [63–65]. Additionally, in women, social phobia may be related to an increased risk of CAD and sudden cardiac death [66].

Heart Failure

Heart failure (HF) is a heterogeneous and complex syndrome, characterized by structural or functional impairment of ventricular filling or ejection of blood, which results in inadequate metabolic supply of body tissues. In developed countries, the prevalence is 2%. However, both prevalence and incidence are increasing, since it is considered an age-related disorder. The prevalence rises from less than 1% in individuals below 60 years to nearly 10% in those over 80 years old [67, 68]. Because HF is a common condition in the elderly, it is associated with several clinical comorbidities, such as renal insufficiency, respiratory disorders, liver diseases, and neoplasia. Moreover, cognitive decline, also an age-related condition, can impact on the prognosis of HF patients, by a lack of adherence to medical recommendations, rehabilitation programs, and self-care [39].

Mood Disorders and Heart Failure

The prevalence of depression in HF patients is higher than the general population, ranging from 13% to 42% in outpatients, and from 13% to 77.8% in hospitalized patients. Severely ill individuals, with decreased social support, [69] and women seem to be the most affected [70]. According to a meta-analysis, depression increases the risk of all-cause mortality in short-, medium-, and long-term follow-up studies. The relationship between depression and HF is mediated by behavioral, psychosocial factors or the underlying pathophysiology, or even a combination of these elements [71]. Along with the depressive symptoms, the state and trait anxiety and a poor quality of life are related to older age, lower education, unemployment, poor economic status, multiple hospitalizations, and heart failure stages III and IV [72]. Moreover, reduced emotional support is related to physical and depressive symptoms, which are associated with lower health-related quality of life [73]. Social isolation, a symptom of depression, impairs the prognosis of HF, and both predict mortality, independently of demographic data and the clinical status of HF outpatients [74]. A study compared HF and depression patients to HF patients with no depression, and the first group showed higher levels of brain natriuretic peptide, a marker related to the impairment of ventricular wall. Further, higher scores of depression and increased levels of brain natriuretic peptide predicted adverse cardiac events in a six-month follow-up [75]. Another study evaluated the levels of C-reactive protein, an inflammatory marker, and found that they were higher in patients diagnosed with HF and depression, when compared to patients with HF and no depression, and no HF and no depression, suggesting that depression contribute to a much more intensive inflammatory state, which may, therefore, lead to a poorer prognosis of HF in the elderly [76].

Structural and functional brain studies also show correlations between HF, depressive, and cognitive symptoms. Decreased regional cerebral blood flow (rCBF) in areas such as the left anterior parahippocampal gyrus, hippocampus, and the right posterior hippocampus and parahippocampal gyrus in patients diagnosed with depression and HF could be demonstrated. Moreover, in the predominantly HF group, a negative correlation between the severity of depressive symptoms and rCBF in the right posterior hippocampal/parahippocampal region was found. These findings reveal that the medial temporal region can be affected by perfusion deficits related to HF, suggesting that functional deficits are related to depression associated with HF [77]. Additionally, HF patients showed decreased rCBF in the left and right precuneus and cuneus, the right lateral temporoparietal cortex, and the posterior cingulate gyrus, which were related to cognitive impairment [78]. In a structural study, higher levels of depressive symptoms in HF patients correlated with white matter hyperintensities in the periventricular frontal region [79], while depressive symptoms and cerebral hypoperfusion, measured by transcranial doppler, were related to a more reduced cognitive performance in older adults with HF [80]. Additionally, HF patients showed higher rates of cognitive impairment and dementia syndromes [81, 82]. These findings suggest that the onset, the progress, and the severity of the depressive symptoms associated HF

might have cardiovascular origins. However, more studies are necessary to confirm these data.

Heart Failure and Anxiety Disorders

Around 13% of HF patients have anxiety disorders, 28.79% showed clinically significant anxiety, and 55.5% reported symptoms of anxiety [83]. Women are more affected than men [83]. Anxiety disorders are often underdiagnosed in HF patients, being the cause of distress, disability, and higher mortality risk [84]. Moreover, anxiety has been linked with a worse prognosis, morbidity, and functional status in HF patients [25].

The type D personality, an important determinant of anxiety in HF patients [85], is independently associated with an increased risk of depression and anxiety [86]. Anxiety can inhibit the engagement of patients in cardiovascular rehabilitation since it is associated with excessive preoccupations about physical overload [87]. Moreover, physiopathological mechanisms related to anxiety such as autonomic dysfunction, inflammation, endothelial dysfunction, platelet aggregation, hypothalamic-pituitary-adrenal axis (HPA), inflammatory cascades, and health behaviors impose an overload to the cardiac-vascular system already affected by HF [88–90].

Functional Cardiac Symptoms

Functional cardiac symptoms account for 30% of all ambulatory and emergency consultations in cardiology and general medicine. The most commonly reported symptoms are palpitations and non-cardiological chest pain (NCCP). They are usually recurrent, impair the activities of daily living, and relate to psychiatric disorders such as somatic disorders, AD (mainly PD) and depression [39, 62].

In a three-year period study, at an emergency department, approximately 58.7% of all chest pain complaints were actually a noncardiac diagnose as "anxiety," "panic," or "chest pain of unknown cause" [91]. Although clinical and cardiology investigations are mandatory [92], some characteristics such as the absence of CAD, atypical chest pain, female sex, young age, and high levels of self-reported anxiety predict NCCP [93]. Moreover, type D personality, AD (mainly PD), and depression are usually associated with noncardiac chest pain [93]. About 27% of patients with suspected cardiac chest pain, referred to invasive coronary angiography, presented normal or near-normal coronary arteries on visual assessment. These patients were significantly more often female, younger, and nondiabetic. Around 40% of these patients, who showed normal or near-normal coronary arteries at coronary angiography, had troponin augmentation because of the exam, suggesting that premenopausal women with suspected cardiac chest pain should be initially referred to noninvasive coronary imaging [94]. Clinicians should be aware that most of NCCP patients suffer significant disability and differential diagnosis, psychiatric comorbidities, and therapeutic techniques for NCCP are essential and mandatory [95].

Respiratory Diseases

Pulmonary diseases can be divided into (1) obstructive lung diseases, (2) restrictive, and (3) abnormalities of the vasculature [96]. Obstructive lung diseases are the most frequent and include asthma and chronic obstructive pulmonary disease (COPD). These disorders kill approximately four million people/year and are associated with high levels of morbidity and mortality [97].

Asthma

Asthma is a chronic and inflammatory disease, which affects 7 to 10% of the population, mainly male children and adult women. It is characterized by hyperresponsiveness of the airways, chronic and/or sporadic airflow obstruction, which is reversible if treated, but in untreated cases, a remodeling of the airways can occur [98, 99]. The clinical manifestations include recurrent episodes of coughing, wheezing, dyspnea, chest tightness, particularly at night, and in the morning upon awakening [98, 99].

The association between asthma and anxiety disorder is well established. Asthma is strongly associated with anxiety (OR = 1.5), GAD (OR = 5.5), PD (OR = 2.6), and panic attacks (OR = 2.8) [100]. PD is the most prevalent anxiety disorder (7–10%) and a significant predictive factor for asthma patients' emergency visiting [100]. The worse the pulmonary function is, the more intensive the panic attack will be [101]. A common pathophysiological substrate seems to connect the two disorders. About 11% of the patients referred for pulmonary function tests were diagnosed with PD, while 40% of PD patients had a previous history of asthma in childhood. Beyond that, a familial association between asthma and PD was already reported [102, 103]. Post-traumatic stress disorder diagnosis was correlated with severe cases [100].

When depressive symptoms are taken into consideration, about 50% of asthma patients report them. Depression is related to asthma (OR = 1.7), especially in severe cases, possibly due to lack of adherence to treatment [100].

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease characterized by not fully reversible and usually progressive airflow limitation, which is based on abnormal intrapulmonary inflammatory responses to noxious particles or gases, most prominently tobacco smoke. Cardinal symptoms include dyspnea, chronic cough, and increased sputum production [104]. COPD is currently estimated to reach number three in 2020 among the diseases with the highest incidence worldwide. Female smokers are at higher risk to develop COPD than men. Female COPD patients appear to be younger, smoke less, have a more severe disease and increased risk of hospitalization compared to their male counterparts. Afro-American women display the highest risk of disease development upon smoking [105]. In patients with COPD, comorbid psychiatric symptoms are highly prevalent, such as anxiety and depression. A meta-analysis demonstrated prevalence rates for anxiety and depression of 36% and 40%, respectively [106]. These will ultimately lead to an enormous healthcare costs because psychiatric comorbidities are associated with a considerably worse course of the disease [104]. For example, in a study by Papaioannou [107], COPD patients with comorbid symptoms of depression showed more acute COPD exacerbations and exacerbation-related hospitalizations in a one-year period than patients without depressive symptoms. Moreover, patients with comorbid depressive symptoms required longer hospitalizations than those with no depression (11.6 vs. 5.6 days) [107], with the average annual all-cause cost per COPD patient being $28,961 for those with comorbid depression and anxiety, compared with $22,512 for those without these comorbidities [108]. More severe stages of COPD are related to higher levels of anxiety and depression; however, even in milder forms, these symptoms are highly prevalent. Nevertheless, anxiety and depression often remain undetected and untreated [105]. Among COPD patients with high depression levels, only 35% reported having ever received a diagnosis of treatment-relevant depression. In addition, only 22% reported the use of antidepressants [104]. Treatment interventions include psychopharmacology and exercise [109]. Benzodiazepines should be used with caution [110].

Nephrological and Urological Diseases

The main symptoms of kidney disorders are hypertension, edema, nausea, or hematuria. The severity of renal dysfunction can be estimated through the duration of the injury associated with physical examination and laboratory exams such as urinalysis and glomerular filtration rate [111].

According to the length of the injury, kidney disorders can be classified in acute and chronic. Acute kidney disorders are related to the worsening of kidney function over hours to days which result in azotemia, the retention of nitrogenous

wastes, and creatinine. On the other side, chronic kidney disorder is characterized by the loss of kidney function over months to years. Despite this classification, they are interconnected syndromes [112].

Acute Kidney Injury

Acute kidney injury (AKI) comprehends a heterogeneous group of disorders, which are characterized by clinical manifestations varying from elevation in serum creatinine to anuric renal failure [113]. Other common laboratory findings are accumulation of metabolic acids and the augmentation of potassium and phosphate concentrations [114]. According to the Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines, the following criteria define AKI: (1) an increase in serum creatinine levels by ≥0.3 mg/dl within 48 hours; (2) an increase in serum creatinine to ≥1.5 times baseline within the previous seven days; (3) and an increase in urine volume ≤0.5 ml/kg/h for six hours [115].

One in every five adults and one in every three children hospitalized with acute illness is diagnosed with AKI [116]. Elderly black male patients are the most affected [117]. Other risk factors associated with AKI are hypovolemia, hypotension, sepsis, pre-existing renal, hepatic or cardiac dysfunction, diabetes mellitus, and exposure to nephrotoxins, as for example aminoglycosides, amphotericin, immunosuppressive agents, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme (ACE) inhibitors, intravenous contrast media [118].

According to the etiology and pathophysiology, AKI is classified in (1) prerenal azotemia, (2) intrinsic renal parenchymal disease, and (3) postrenal obstruction. Prerenal azotemia is the most common type of AKI and is characterized by both inadequate renal plasma flow and low intraglomerular hydrostatic pressure, which results in augmentation in serum creatinine and blood urea nitrogen. This condition is reversible by the recovery of the intraglomerular hemodynamics. However, if azotemia persists for prolonged periods, an ischemic injury might occur, leading to acute tubular necrosis. In intrinsic AKI, the injury mechanisms involve inflammation, apoptosis, and impaired regional perfusion. Postrenal obstruction leads to the augmentation of retrograde hydrostatic pressure and impairs the glomerular filtration [115].

The main complications of AKI are related to volume control, blood pressure, plasma electrolyte composition, acid-base balance, and the excretions of nitrogenous and other catabolites. Therefore, the management of patients with AKI depends on the cause, and the optimization of hemodynamics, correction of fluid and electrolyte imbalances, discontinuation of nephrotoxic substances, and adjustment of administered medications are critically important [118].

Renal failure can cause encephalopathy, a clinical syndrome characterized by an acute decline in the level of awareness and cognition, especially attention, and the symptoms fluctuate overtime [119]. The symptoms vary from sensorial clouding to delirium and coma. Moreover, headache, altered visual perception, tremor, asterixis, myoclonus, chorea, and seizures can be present. The treatment consists in approaching the underlying cause, which can be uremia, thiamine deficiency, dialysis, transplant rejection, hypertension, fluid and electrolyte disturbances, or drug toxicity [120]. Because of its fewer anticholinergic side effects, haloperidol is the most used antipsychotic to treat delirium. It can be administered orally and intramuscularly. The intravenous use of haloperidol should be monitored since it is associated with an increased risk of QTc prolongation [120].

Chronic Kidney Injury and Depression

Chronic kidney injury is defined by the reduction of glomerular filtration rate, the increase of albumin excretion, or both [121]. Its prevalence ranges from 8% to 16% worldwide [122], and the main risk factors associated with chronic kidney injury are related to race (e.g., black and Asian people in the UK, black, Hispanic, and Native Americans in the USA) [123] and age

[122]. The leading causes of CKI are diabetes, hypertension, and obesity, even in developing countries [124]. Depression prevails in 20% of the patients diagnosed with chronic renal injury [125]. Both share common biological pathways such as inflammation, immune system disturbances, alterations in the hypothalamic-pituitary axis, and in the parasympathetic and sympathetic nervous systems [126].

Depression is often underdiagnosed in patients with CKI, and depressive symptoms such as apathy, lack of energy, and impaired cognition are related to poor compliance and nonadherence to treatment, decreasing the survival rates of CKI patients [126]. When considering the treatment of depression in CKI patients, some characteristics of antidepressants should be taken into consideration. Firstly, antidepressants are unlikely to be removed by dialysis since they are protein bound and are largely distributed and metabolized by the liver [127]. According to Shirazian et al., the pharmacokinetics of antidepressants can be modified by kidney function. Elevated urea levels and changes in gastrin, along with the use of phosphate binders or antacids, lead to gastric alkalization, which decreases the oral bioavailability of antidepressants. Moreover, because of the volume overload, the volume distribution of antidepressants can be altered. Finally, uremic solutes retention may change the binding between albumin and antidepressant, inflating their free fraction [128]. Table 1 shows antidepressant dosing in CKI.

Table 1 Antidepressants dose in CKD

Drug	Dose in CKD 1–4	Dose in CKD 5 and ESRD
Sertraline	No adjustment required 50–200 mg/d	Start at 25 mg/d. Decrease the maximum dose
Paroxetine	IR: 10–40 mg/d. CR: 12.5–50 mg/d	Similar to CKD 1–4
Citalopram	No adjustment required 10–40 mg/d	No recommendation available. Use with caution
Fluoxetine	No adjustment required 20–60 mg/d	Similar to CKD 1–4
Escitalopram	No adjustment required 10–20 mg/d	No recommendation available. Use with caution
Imipramine	No adjustment required 100–300 mg/d	No recommendation available. Use with caution
Nortriptyline	No adjustment required 75–150 mg/d	No recommendation available. Use with caution
Desipramine	No adjustment required 100–300 mg/d	Effects of metabolite accumulation. Use with caution.
Venlafaxine	75–225 mg/d. eGFR 10–70: reduce daily dose 25–50%	Reduce daily dose by 50%
Duloxetine	If eGFR >30: 40 mg–120 mg/d	Not recommended if eGFR <30
Mirtazapine	No dosage adjustment recommended: 15–45 mg/d	Dosage adjustment. Clearance reduced by 50%
Bupropione	Consider reduce dose and/or frequency 140–450 mg/d	Similar to CKD 1–4

Adapted after Hedayat et al. [127]
CKD chronic kidney disease, *CR* controlled release, *ESRD* end stage renal disease, *eGFR* glomerular filtration rate, *IR* immediate release

Chronic Kidney Injury and Restless Legs Syndrome

The prevalence of restless legs syndrome ranges from 15% to 68% in people diagnosed with CKI [129]. It is defined as a sensorimotor disorder, which has a circadian rhythmicity. Diagnose criteria include (1) an urge to move legs, (2) symptom induction or exacerbation if resting, (3) relief of symptoms on activity, and (4) symptom variation during the day and worsening at night [130]. The treatment includes iron supplementation and other agents such as dopaminergic agonists, opioids, and anticonvulsants.

Lithium and Kidney Injury

Some psychotropic drugs can cause acute and chronic kidney injury, as for example, lithium. Lithium is a monovalent cation, of the family of alkali metal, and is mostly excreted by the

kidneys. It is considered an effective mood stabilizer with antimanic effect and can be used not only in the prophylaxis of suicide but also in the prevention of recurrence of episodes in bipolar disorder [131]. The most common kidney alterations related to this drug are (1) nephrogenic diabetes insipidus, and (2) chronic kidney injury. Twenty to eighty-seven percent of the patients treated with lithium will present nephrogenic diabetes insipidus [132]. It is characterized by a decrease in urine osmolality and an increase in urine volume, which can result in polyuria despite normal or elevated concentrations of the antidiuretic hormone vasopressin. Lithium-induced nephrogenic diabetes insipidus can be treated with amiloride, which will restore the urine osmolality [133]. Hydrochlorothiazide can also be used, but lithium dosage should be reduced by one third [134].

About 20% of lithium-treated patients will develop progressive kidney insufficiency [135]. The progression to CKI is slow, within a period of ten to 20 years [136], and is characterized by a progressive rise in serum creatinine and a decrease in creatinine clearance over the years. The main risk factors related to lithium-induced nephropathy are age, preceding episodes of lithium toxicity, and the treatment duration [134]. Monitoring serum creatinine and eGFR regularly, preventing episodes of lithium toxicity, maintaining lithium levels within the low therapeutic range, and once-daily dosing might diminish the risk of renal damage [134].

Endocrine and Metabolic Diseases

Thyroid Disorders

Hypothyroidism and hyperthyroidism are common endocrinology disorders in which the thyroid gland does not produce adequate thyroid hormone, leading to low (hypo) or high (hyper) thyroxine levels. Causally, it can be primary (e.g., thyroid glandule defect), secondary (e.g., thyroid stimulating hormone deficiency), or tertiary (e.g., thyrotropin-releasing hormone deficiency in the hypothalamus). Thyroid diseases prevail in five percent of the general population, and women are predominantly affected [137]. Early life hypothyroidism results in cretinism, a disorder characterized by mental and growth retardation. In adulthood, clinical and subclinical hypothyroidism can cause mood disorders. Therefore, the American Association of Clinical Endocrinologists recommends that the diagnosis of hypothyroidism should be considered in every patient with depression [138]. Even though depression is traditionally more associated with hypothyroidism, it has also been described in 31–69% of patients with hyperthyroidism. Moreover, among patients with hyperthyroidism, 60% meet diagnostic criteria for AD [138]. When considering treatment, hormone imbalance should be initially addressed. Psychiatric symptoms may persist, and, therefore, mental health treatment will be concomitantly required [138]. Finally, lithium could cause hypo- (more likely to occur in women) or hyperthyroidism [139]. Hypothyroidism usually develops in weeks to months but can take years, while hyperthyroidism is more likely to emerge earlier in the treatment. Since lithium does not cause but aggravate thyroid autoimmunity and accelerate antibodies formation, antithyroid antibodies should be checked at baseline to undercover patients at risk for developing thyroid disorders secondary to lithium. TSH levels should be checked three months after the initiation of lithium therapy and afterward, yearly. Clinicians should decide if lithium should be continued in case of clinical hypothyroidism. However, it might not be reversible. If lithium usage remains, levothyroxine is indicated [140].

In case of hyperthyroidism secondary to lithium, patients should be referred to an endocrinologist for investigation. It can be associated to destructive thyroiditis or autoimmune disease [140].

Adrenal Disorders

The function of corticoids is to (1) promote energetic and hydroelectrolytic balance, (2) increase catecholamine activity during stress, and (3)

inhibit inflammatory reactions. Its production is under control of adrenocorticotropic hormone (ACTH), which is produced in the anterior pituitary, which, in turn, is regulated by corticotrophin releasing hormone (CRH) in the hypothalamus. Negative cortisol feedback occurs at pituitary, hypothalamic, and thalamic levels.

CRH secretion follows a circadian pattern, consequently producing circadian patterns of ACTH and cortisol levels, with peaks in early morning and a nadir in the evening. CRH release is also influenced by emotional and physical stress [141]. Female sex hormones attenuate the sympathoadrenal and HPA axis responsiveness, leading to sluggish cortisol feedback in the brain and less or delayed containment of the stress response. The tendency of women to develop depression can be related to this compromised cortisol feedback effects on HPA arousal [142]. At least, half of hypercortisolemia patients will experience depressive or manic symptoms, and these symptoms will be moderate to severe in half of them. Many will also experience psychotic symptoms. The symptoms are usually dose-related when caused by the administration of exogenous steroids. They remit gradually along with the correction of the hypercortisolemia. However, if depression or mania symptoms persist, treatment with antidepressants or mood stabilizers is needed [139]. Patients with adrenal insufficiency may be misdiagnosed with depression, personality disorder, dementia, or somatoform disorders. They will require a permanent replacement of corticoids. When treating resistant depression patients, one should always have in mind that Addison's disease is a differential diagnosis [139].

Diabetes Mellitus

Diabetes mellitus (DM) results from insufficient insulin secretion or resistance to insulin. Women are more sensitive to insulin than men. Higher bioavailable testosterone levels are associated with increased DM risk in women, whereas lower bioavailable testosterone levels are associated with increased DM risk in men [143]. Depression and DM are the two most common chronic diseases in the USA and frequently co-occur. Overall lifetime prevalence of depression among people with DM types 1 and 2 is about 29%, more than two times than the general population. The risk relationship between depression and DM is bidirectional. AD are also common among people with DM and prevail in 14% of these patients [138]. DM is also prevalent among patients with severe mental illness (SMI). For example, in schizophrenia patients, the prevalence of diabetes is twice as high as in the general population (10% versus 6%) [138]. Diabetic patients, who have psychiatric disorders associated, have lower disease morbidity if their psychiatric disorders are appropriately treated [139], since depressive and anxiety symptoms are mainly associated with poor glycemic control [138].

Obesity

Fundamentally, obesity is the result of an imbalance between energy intake and expenditure. However, the development of obesity is far more complex than this simplified view portrays [144]. Researchers have shown that food can become an addiction akin to other substance use disorders. More specifically, studies suggest that recurrent exposures to highly palatable foods result in diminished dopamine levels in response to eating. As a result, individuals must consume larger amounts of food to feel satisfied, resulting in a cycle of overeating [144]. The prevalence of both obesity (body mass index $\geq$30 kg/m^2) and abdominal obesity (waist circumference $\geq$88 cm in women and $\geq$102 cm in men) is higher in women than men in the USA. More than 80% of patients who undergo bariatric surgery are women. Pregnancy and menopause are risk factors [143]. Moreover, there are significant sex differences in body fat distribution, which ultimately seems to be modulated by endogenous androgen levels. Characteristically, women have a gluteal, femoral or gynoid pattern of fat distribution, whereas men have a central or android pattern. Sex steroids may also play a role in modulating food intake and energy expenditure [143].

Obesity has a negative impact on quality of life, mobility, mental health, and stress level. Patients should have a routine blood work for hyperlipidemia, hypertension, thyroid function, and hyperglycosemia. Sleep studies to identify obstructive sleep apnea and vitamin level panel to identify vitamin deficiencies are also indicated [144]. When considering treatment, adjunctive therapy such as cognitive behavioral weight management, diet/exercise/lifestyle changes, and choosing medications with lower weight gain profile can mitigate weight gain [144].

Rheumatic and Immunological Diseases

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease, of unknown cause, and autoimmune nature, characterized by the presence of several autoantibodies. It results in polymorphic clinical manifestations, with periods of exacerbations and remissions. Young women in their reproductive years are the most frequently affected, in a proportion of nine to ten women for one man. Hormonal factors, especially estrogen, may be involved in the pathogenesis since symptoms get worse before the menstrual period and during pregnancy [137]. When considering psychiatric disorders related to SLE, mood syndromes are the most common. However, mood changes are not always a consequence of the involvement of the central nervous system, but a consequence of the use of steroids in SLE treatment. Moreover, autoantibodies directed to neuronal membranes or CNS vasculitis may also produce psychosis, delirium, seizures, and cognitive dysfunction [139].

Infectious Diseases

Human Immunodeficiency Virus (HIV) Infection

Neuropsychiatric disturbances in patients with HIV infection are usually related to a primary psychiatric illness, the effects of HIV infection in the CNS itself, and opportunistic infections [145]. Women account for almost 50% of the 34 million people infected with HIV worldwide, and they seem to be more susceptible to HIV infection than men. Progesterone increases the susceptibility to HIV infection in nonhuman primate models, suggesting that hormonal contraceptives could increase the risk of HIV transmission. HIV women show a more rapid decrease in their CD4 cell counts than men [143]. The prevalence of psychiatric comorbidities ranges from 20% to 36% for depression; 16% and 10% for generalized anxiety disorder (GAD) and panic disorder (PD), respectively; and more than 25% for substance use disorders, as would be expected, given that IV drug use is the second most common HIV transmission way [146]. When considering treatment, selective serotonin reuptake inhibitors (SSRIs) are preferable in depressive and anxiety syndromes, and atypical antipsychotics should be administered in psychosis [147]. When the psychiatric symptomatology is caused by medications used to treat HIV-related illnesses, their discontinuation/switching can be necessary [147].

Syphilis

Syphilis is a chronic systemic infection caused by a spirochaete bacterium, *Treponema pallidum*. It is usually sexually transmitted and characterized by episodes of active disease interrupted by periods of latency. Globally, syphilis remains a significant health problem, and the number of new infections is estimated at 11 million per year [148]. Syphilis facilitates coinfection with HIV, while HIV accelerates the progression of syphilis. Thus, patients with HIV have a higher frequency of neurosyphilis (NS). NS affects 4 to 9% of non-treated cases [149]. While early NS and cerebrospinal fluid abnormalities are equally common among men and women, clinical NS is three to four times more likely to occur among men [152]. Prompt treatment of NS with antibiotics is necessary to stop the progression of the illness. However, patients' mental status may not improve completely, because of neuronal loss

[149]. After the antibiotic regimen, the remaining psychiatric symptoms should be addressed accordingly to their complexity and severity.

Encephalitis

Encephalitis is a complex condition caused by brain inflammation, and mostly, the cause is not identified. There is often no definitive treatment, and a high rate of mortality and morbidity can be expected. It is inferred by the presence of acute central nervous system (CNS) dysfunction, fever, and/or inflammation in the cerebrospinal fluid (CSF) and/or on neuroimaging [150]. It can occur after autoimmune diseases, vaccination, bacteria, and viral infections [147, 150]. The highest admission rates are observed in males and those aged less than nine or over 60 years of age [150]. The presentation is often acute, and symptoms such as fever, altered mental status, seizures, and focal neurologic signs, such as aphasia, and hemiparesis can be expected. Without treatment, patients may progress to coma. Initially, before the disease onset, a prodromal phase characterized by headache, fatigue, mild fever, and irritability may occur [149]. If a causal agent is identified, therapy should be instituted according to consultations with relevant specialists and national/international antimicrobial guidelines [150]. The most common cause of acute viral encephalitis, the herpes simplex virus-1, which causes orolabial lesions, must be treated with intravenous acyclovir [149, 150]. The treatment of neurobehavioral sequelae of encephalitis should include anticonvulsants, benzodiazepines, antipsychotics, stimulants, mood stabilizers, and cholinesterase inhibitors [149].

Neurocysticercosis

Neurocysticercosis (NCC) is one of the most common neuroparasitic infections. With the increase of travel and immigration, NCC can be encountered not only in developing countries but also in developed countries. In NCC, the larval form of *Taenia solium* (cysticerci) infects the CNS. A high percentage of NCC infection remains either asymptomatic or inactive and undiagnosed [151]. Symptomatology was related to the CSF leukocyte-counts, which were higher in women than men [152]. Up to 15% of people infected with NCC exhibit only psychiatric sequelae [149]. The type of psychiatric manifestations depends on the degree and part of the CNS involved. Psychosis, delirium, depression, and dementia are the most common clinical presentations. Typically, the patient does not have a history of psychiatric disorders and has an acute decompensation. Often, the differential diagnosis includes seizures [151]. Clinical evidence suggests that the treatment can exacerbate the inflammatory response caused by the infection, leading to a symptomatic worsening. Nevertheless, according to the American Academy of Neurology, albendazole associated with corticosteroids should be considered. Surgery is indicated for the placement of ventricular shunts to treat hydrocephalus secondary to arachnoiditis [149].

Dermatologic Diseases

Cultural and media feminine stereotypes exert psychological pressure on women, who often link their acceptability to their appearance. Therefore, women are far more prone to be concerned about their body image when compared to men, and conditions which cause changes in appearance, such as skin diseases, will have a more significant impact on women than men.

According to Koo [153], conditions involving interactions between mind and skin can be divided into five categories, which are not mutually exclusive:

1. Psychophysiologic disorders: skin problems related to stress, such as acne, eczema, psoriasis, atopic dermatitis, alopecia areata, urticaria, and angioedema.
2. Primary psychiatric disorders with self-induced cutaneous manifestations, such as body dysmorphic disorder, psychogenic excoriation, trichotillomania, delusions of parasit-

osis, delusions of a defect in appearance, delusions of a foul body odor, and factitious disorder.
3. Disfiguring skin disorders (e.g., acne, alopecia areata, hirsutism, and vitiligo) leading to secondary psychiatric disorders (e.g., depression and social phobia).
4. Cutaneous sensory disorders without proven skin-based etiology but with unpleasant sensations on the skin (e.g., itching, stinging, burning, or crawling) and in which a psychiatric diagnosis may or may not be evident (e.g., chronic idiopathic pruritus).
5. Use of psychotropic medications that may be more efficacious than traditional dermatological treatments: it is a separated category which can help dermatologists to select an optimal treatment approach (e.g., doxepin has more powerful antipruritic action than traditional antihistamines).

Earlier disease onset, chronic and recurrent skin problems, higher degrees of disfigurement, visible lesions on the face or hands, and symptoms of persistent itching, burning, or pain are associated with higher psychological impact, lower quality of life, and distress. Social stigma can impact on the individual functioning and impair not only social interactions but also inner security and relationship intimacy, causing sexual problems [154]. The relationship between skin diseases and psychopathology is usually bidirectional, and one condition aggravates the other (see Fig. 1). Therefore, for effective intervention, practitioners should detect psychological distress and be aware of the available treatment options [155].

Some antidepressants (e.g., doxepin, trimipramine, amitriptyline, paroxetine, sertraline, fluvoxamine, fluoxetine, and mirtazapine) and anticonvulsants (e.g., gabapentin and pregabalin) have antipruritic properties, being useful not only for the management of the dermatological condition but also for the treatment of the psychiatric comorbidity. Psychotropic medications such as lithium can precipitate or aggravate psoriasis, and there are similar case reports with the use of fluoxetine and bupropion. When considering dermatological side effects of psychotropic medications, they are usually benign and easily treatable. On the other hand, isotretinoin used to treat acne vulgaris may be associated with psychiatric complications such as depression, aggressive behavior, and suicidality. If the symptoms are temporally related to the introduction of isotretinoin, this medication should be stopped [154].

Gastroenterological Diseases

The term gut-brain axis refers to the intercommunication between the gut and the brain. Psychological symptoms, like stress or anxiety, for example, modulate gastrointestinal (GI) motility,

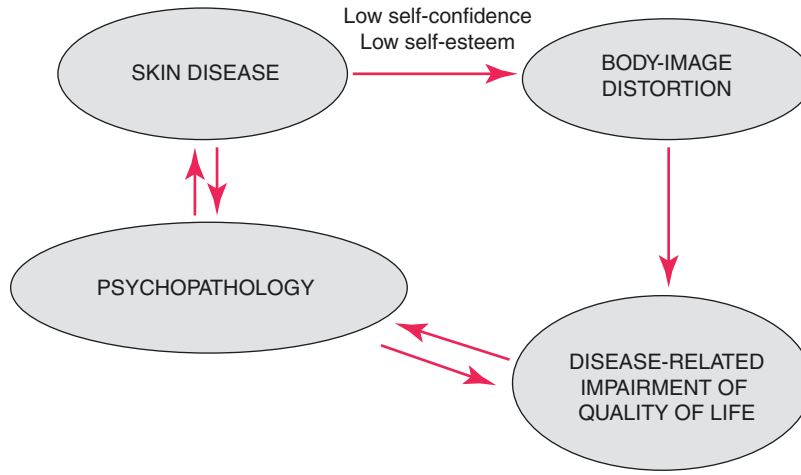

Fig. 1 Interactions between skin and mind

lower pain thresholds, increase gut inflammation, and result in symptoms such as diarrhea, bloating, nausea, and discomfort. On the other way, chronic GI symptoms can lead to anxiety behavior and higher pain experience. Independently of a psychiatric diagnosis, psychological distress caused by chronic GI conditions, has a negative effect on a patient's well-being, quality of life, and mental health [156]. Sex hormone receptors along the GI tract lead to gender-related physiological differences in GI symptomatology. In most studies, independently of the underlying disease, diarrhea is the most common GI symptom reported during the menstrual period [157].

Inflammatory Bowel Diseases

Inflammatory bowel disease (IBD) includes ulcerative colitis (UC) and Crohn's disease (CD). IBD is a chronic idiopathic inflammatory condition which affects equally men and women and prevails in 1 of 500 people in the USA [158]. Natural history of IBD varies between remission and inflammatory activity. Symptoms include changes in bowel habit, abdominal pain, and rectal bleeding. Medical interventions such as systemic corticosteroids or immunosuppressive drugs may result in secondary health problems [156]. Surgery will be necessary for up to 30% individuals with of UC and 80% with CD [159]. Psychiatric comorbidities are common in IBD patients, and about 20% of these patients suffer from anxiety, while depression can be diagnosed in 15% [160]. When the IBD is active, the prevalence of these disorders is even higher, 66% and 34%, respectively [161]. Tobacco smoking has a greater negative impact on disease course in women than in men [158], so appropriate treatment for nicotine addiction must be offered. Ideally, women with IBD need a multispecialty approach, which includes gastroenterologists, gynecologists, psychiatrists, and psychologists [157].

Functional Bowel Diseases

Functional GI disorders are a heterogeneous group characterized by chronic abdominal pain and discomfort in the absence of any organic or structural causes. Irritable bowel syndrome (IBS) is the most prevalent functional GI disorder in the general population. Worldwide prevalence ranges between 10% and 15%, affecting twice as many women as men [157]. Non-GI symptoms are often present, including impaired sexual function, dysmenorrhea, dyspareunia, increased urinary frequency and urgency, and body pain [156]. About half of patients present with psychiatric comorbidity, mainly depression, anxiety disorders, and hypochondriasis [156].

When providing care to women with IBS and IBD, physicians should be aware of gender-specific issues, including symptom fluctuations during the menstrual cycle, family planning, contraception, fertility, pregnancy and lactation, menopause, and hormone replacement therapy [157]. Chronic GI symptoms, like abdominal pain, diarrhea, bloating, flatulence, and fear of fecal incontinence, have the potential to affect both body image and sexuality [158]. The higher the number of physical symptoms, the greater the degree of psychological distress [156]. IBD may affect patients' physical appearance due to fistulae, surgical scarring, and/or ostomy placement. Women and postoperative patients may be at a higher risk for impaired body image [158]. Psychological health and stress influence on disease activity in patients with IBS and IBD [157], so addressing psychologic symptoms is a critical issue. Psychotherapy can help to reduce anxiety. Antidepressants are the most used pharmacotherapy class, acting to relief chronic pain, functional GI symptoms, and psychological symptoms. Antipsychotics and mood stabilizers are indicated for visceral pain associated with agitation. Anxiolytic agents are effective for reducing anxiety in the short term, but their continuous use should be avoided [156].

Neoplastic Diseases

The gender difference in cancer incidence rates is well documented, and most of the malignancies are more common in men [162]. The lifetime probability of having cancer is 44.8% for men,

and 38.08% for women and females are more affected by gallbladder, anus, and thyroid tumors when compared to males [163].

Cancer is the second cause of women's death. Nearly two of three patients diagnosed with cancer respond to the available treatment techniques, and among female cancer survivors, the leading types of cancer are breast cancer (41%), cancer of the uterus (excluding cervix cancer, 8%), and colorectal cancer (8%) [164]. A cancer diagnosis impacts profoundly on psychological aspects. It affects global functioning, self-image, elicits fear of death and abandonment, preoccupations about fertility and financial status, leading to changes in conjugal, familial, and work relationships. Body image is a female concern, and cancer affecting the breast and colorectal and gynecological systems can have important implications since they are strongly related to symbolic significance associated with femininity and sense of one's sexual self [165]. Consequences of surgical treatment or adjuvant chemotherapy are not only aesthetic but also physical and functional and include the presence of a lifelong scar or an ostomy, breast shape alteration, long-term bowel and GI dysfunction, sexual dysfunction, lack of sexual interest, vaginal dryness, dyspareunia, and alopecia.

Cancer-related distress can negatively impact cancer morbidity and mortality [166]. Psychiatric morbidity post-cancer diagnosis is directly related to the level of disability, advanced disease, poor prognosis, and pain. Most psychiatric symptoms are related to the cancer itself or treatment side effects. Approximately half of cancer patients have psychiatric disorders. More than two-thirds can be diagnosed with adjustment disorders, 10–15% with major depression, and about with 10% delirium. Cancer patients have higher suicidality than the general population, and uncontrolled pain is a major factor in cancer-related suicide. Such conditions, despite their high prevalence, remain underdiagnosed and undertreated [167]. The detection and management of psychiatric disorders are essential to treatment adherence and consequently patient's survival.

Neurological Diseases

Stroke

Stroke is the most common neurological disorder and results from the sudden loss of blood supply in a brain area. The ischemic type occurs more frequently than the hemorrhagic and accounts for 80–85% of all cases [168]. Psychological distress is independently associated with an increased risk of stroke, and women seem to be at higher risk than men [169]. People with mental illnesses have up to three times greater likelihood of having a stroke [170]. Delirium post-stroke impacts on 30–40% of patients in the acute phase, while dementia can be diagnosed in approximately 25% of patients in the 3-month period after stroke [146]. Beyond that, 40% of the patients will develop depression, 25% anxiety, and 25% emotionalism [146, 171]. Psychiatric manifestations post-stroke should be routinely accessed due to their high prevalence. SSRI have shown to be the most effective drugs to treat these conditions [168], along with physical activity. The best outcomes are related to depression treatment within 3 months post-stroke, which impacts on cognition and physical activity [168].

Traumatic Brain Injury

Traumatic brain injury (TBI) is a leading cause of death and disability in the USA; nearly 1.4 million head injuries occur every year. It is estimated that 80,000–90,000 will present permanent neuropsychiatric disabilities after a TBI [172]. Severe injuries and mortality seem to be more pronounced among female patients [173]. In addition to the agitation, aggression, and confusion often observed in the acute recovery stage, survivors of TBI are at higher risk for more severe, long-term psychiatric disturbances, including personality change, post-traumatic stress disorder, anxiety, mania, psychosis, and depression. Among adults, alcohol is a contributing factor in 40–56% of cases [172]. Psychiatric morbidity following TBI is reported to exert a deleterious effect on

the recovery process and psychosocial outcome, even following mild injury [174].

Generally, effective medications for primary psychiatric disorders in non-TBI patients are similarly useful in TBI patients. Because brain-injured patients are often more sensitive to certain medications and their side effects, guidelines should be consulted. A wise principle: "start low, and go slow" [172].

Epilepsy

An epileptic seizure has been defined as a clinical manifestation, which presumably results from an abnormal and excessive discharge of a set of neurons in the brain. A diagnosis of epilepsy applies in the recurrence of two or more unprovoked seizures [175]. Many published studies indicate that females have a marginally lower incidence of epilepsy and unprovoked seizures than males [176]. Progesterone and its metabolites have anticonvulsant effects, while estrogens are mainly proconvulsant. Epileptic activity, especially mediated via amygdala, alters the reproductive function [177]. Approximately half of all patients with epilepsy have psychiatric symptoms and syndromes, with higher prevalence among patients with poorly controlled seizures [175, 178]. Psychiatric comorbidities have a complex relationship with epilepsy, since they are associated with a negative course of the seizure disorder, lower antiepileptic drugs tolerance, development of iatrogenic psychiatric complications from pharmacologic and surgical treatments, and increased mortality [179]. This relationship is so important that a new definition of epilepsy recognizes the psychiatric comorbidities as part of the seizure disorder and states that they should be recognized and treated together with the epileptic seizures [179]. Complex partial seizures are the most common form of epilepsy seen in adults. Nevertheless, temporal lobe epilepsy is the most frequently associated with psychiatric symptoms, including affective, perceptual, behavioral, and cognitive symptoms [175, 180].

Depression is the most common psychiatric disorder associated with epilepsy and affects around 35% of epilepsy patients [181]. Interictally, around 20% of these patients have panic attacks. Moreover, 8–10% of epilepsy patients have postictal symptoms, ranging from mood disturbance to psychosis [138]. When considering treatment, seizures should be initially controlled, preferably with monotherapy. If the psychiatric symptoms persist, each syndrome should be treated accordingly to the best practice established therapy [175, 178].

Parkinson's Disease

Parkinson's disease (PD), a neurodegenerative disorder, is characterized by resting tremor, rigidity, and bradykinesia/akinesia. It affects up to 2.5% of the geriatric population, although its onset in young adults has also been reported [145]. The pathophysiology of PD involves loss of dopamine neurons in the midbrain substantia nigra, with subsequent downstream effects in striatal, frontal, and cingulate regions and disruption of the cortical-basal ganglia-thalamic circuitry [145]. The dopamine neurons loss leads to disturbances in the serotoninergic, cholinergic, and norepinephrine pathways with subsequent effects on other subcortical nuclei, the limbic system, and the cerebral cortex [145, 168, 182]. When compared to women, men are more prone to exhibit rigidity, rapid eye movement (REM) behavior disorder, and deficits in aspects of cognition that contribute to activities of daily living, such as verbal fluency and facial emotion recognition, whereas women show more dyskinesia, depression, and deficits in visuospatial cognition [183]. One possible source of male-female differences in the clinical and cognitive characteristics of PD is the neuroprotective effect of the estrogen on dopaminergic neurons [183].

Depression, psychotic symptoms, and dementia are the most prevalent psychiatric comorbidities in PD [168, 182]. To treat depression, antidepressants with strong anticholinergic effects (e.g., tricyclics) should be avoided, and antidepressant with a better profile of side effects such as

SSRI is preferable. Atypical neuroleptics, such as clozapine, have lower D2 receptor affinity and fewer extrapyramidal side effects and are therefore desirable. They can be efficient even in lower doses than those recommended for primary psychosis. Cholinesterase inhibitors may also be helpful in treating psychotic symptoms in patients with cognitive impairment [168].

Multiple Sclerosis

Multiple sclerosis (MS) is a common neurological disease, which affects 50 to 60 per 100,000 inhabitants. The prevalence of the relapsing-remitting type of MS is roughly twice as high in women than in men [145]. MS usually starts between 20 and 40 years old and is characterized by multiple demyelinating lesions with a predilection for the optic nerves, cerebellum, brainstem, and spinal cord [168]. The inflammatory white matter changes are thought to be immune-mediated. Subcortical cognitive impairment impacts on at least half of all patients with MS and is manifested by the decreased speed of processing, executive dysfunction, and memory deficits. Disease-modifying therapies for MS may slow down cognitive impairment, but the evidence is insufficient. The same applies to cholinesterase inhibitors. Cognitive rehabilitation has so far been disappointing [168]. More than half of patients with MS report depressive symptoms, which can be difficult to distinguish from fatigue and pain, often associated with the illness [138]. Depression, the strongest predictor of poor quality of life in MS, responds well to treatment with antidepressants and psychotherapy [145].

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Diet, Nutrition, and Women's Mental Health

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Psychiatric disorders represent an increasing problem in public health. According to the World Health Organization, more than 400 million people suffer from at least one of these disorders, depression being the most prevalent [1]. These disorders result from a complex interaction between genetic, environmental, psychological, and biochemical factors; hence different approaches are studied in order to improve the effectiveness of currently known treatments [2]. One of them is through the adequate consumption of food and/or supplementation, which can potentiate the action of some drugs [3]. Because nutrients are involved in the production and functioning of hormones and neurotransmitters directly related to the physiopathology and etiology of the aforementioned disorders, they can help modulate some cerebral functions [4].

However, adequate nourishment becomes more challenging every day. In many countries, the feeding pattern has been altered throughout the last decade, with increasingly shorter meals and out of the family context, if not neglected or replaced by fast food [5]. This trend is part of the known nutritional transition, where non-processed, natural food consumption decreases, and there is an increase in ultra-processed, nutrient-poor foods. In psychiatric patients, potentially limiting particularities of the disorder add up, which can lead to the development of even worse feeding habits, low motivation to go shopping and cooking, poor meal planning, and frequent intake of more convenient food, usually semi-ready stuff [6, 7].

Considering that the brain works under a high metabolic rate, its demands for macro- and micronutrients require a substantial portion of the nutrients consumed during the day [8]. In that sense, a diet rich in whole grain foods, vegetables, fruits, and the least possible amount of processed food favors resilience to psychiatric disorders, since they are a more rich source of fundamental nutrients for the brain [9]. A healthy diet can also modulate the function of the immune system, which relates to mood disorders [10]. At the same time, various nutrients are involved in the antioxidant defenses – the property of protecting the organism by inhibiting the reactions related to the formation of free radicals and loss of cell integrity and the ability to repair damage caused by free radicals [11]. It is those defenses which positively contribute to the plasticity and repair of the neural cells [12].

When talking about women, we cannot think only about food and nutrients. Women's bodies have always been an expression of femininity. Current sociocultural norms perpetuate the stereotype of association between thinness and

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positive attributes, especially among women [13]. Therefore, to some women, the desire to improve their physical appearance and stop being the target for discrimination seems to motivate changes to body size and shape, often inadequate [14]. This chapter discusses women who, because of special needs, require psychiatric treatment. They can eventually develop nutritional deficiencies, as well as alterations in their appetite and compulsive eating. They usually have altered weight, are unhappy with their bodies, and have low self-esteem. Women have special vitamin and mineral needs for many life cycles, such as pregnancy, lactation, menopause, and hormonal fluctuations associated with the menstrual cycle. In that sense, the nutritional care aims for nutritional excellence but also to correct these mistakes in their eating patterns and the relationship with food, in order to help patients to deal with their body without imposing consequences to their health, quality of life, and self-esteem.

Nutritional evaluation is the starting point for nutritional care. Besides providing the initial direction, it enables the follow-up and redirection of the intervention, when needed [15]. It involves the interpretation of several indicators for the definition of a nutritional diagnosis, in order to implement interventions and adequate monitoring [16]. To do so, normally four parameters have been used: dietary anamnesis, physical exam, biochemical exams, and anthropometry. It is important to highlight that each isolated parameter does not provide a thorough nutritional diagnosis, which should be analyzed as a whole [17, 18]. Concerning mental health, the nutritional assessment involves some challenges which deserve special attention from the professional performing it. One example refers to the fact that each disorder has its own peculiarities, which must be taken into consideration when performing the evaluation. Nevertheless, numerous drug interactions must be also taken into account.

The anamnesis is an interview that allows detailed collection of physiological, pathological, and socioeconomic-cultural antecedents of the patients and their families, aiming at facilitating the diagnosis. It investigates the dietary habits of the patient, as well as their dietary history. It has been pointed out as the most important part of the data collection process, because, when the patient is listened to, the professional can formulate hypotheses about reported complaints and establish necessary bonds to attend to his patient [19].

The clinical history aims to find information related to complaints, occurrence of past and present diseases, recent loss or gain of weight, medicine use, allergies, dental problems, intestinal function, pregnancy, breast-feeding, menarche, and menopause, that is, everything that can have an important role in the dietary behavior [20]. The use of psychoactive drugs deserves special attention, considering many of them can lead to dyslipidemia, weight gain, and binge eating [18].

The dietary assessment provides data regarding the ingestion of macro- and micronutrients, allowing the professional to identify food inadequacies and nutritional risk. At this point, the professional must understand and determine the pattern of food consumption, the quantity of energy and nutrients consumed, preferred and avoided foods; investigate inadequacies (e.g., binge, purging); and detect food beliefs and myths [18]. It is at that moment that bonding with the patient becomes necessary, to allow her to open up and share her issues about her self-image, her inability to follow dietary standards and her attempts to pursue the ideal body. All the factors that influence the food consumption or the ingestion control become important to mentor them, aiming at improving their quality of life and prevent relapses from psychiatric problems [13].

In the physical exam, it is possible to evaluate signals and symptoms associated with malnutrition. In these cases, it is important to remember that the signs reflect chronic malnutrition, which means they only appear in advanced stages of nutritional depletion; therefore negative physical exams are not always reliable. For acute malnutrition, biochemical exams are safer. For the psychiatric patients, the physical exam might also disclose self-mutilation, trichotillomania, skin picking, and Russell's sign (mark on the hands of

patients that frequently purge), among others [18]. However, in such patients the physical evaluation is not always possible. Compelled by embarrassment, often they do not allow it to be evaluated. In these cases, the anthropometric evaluation might be used as a resource to an experienced evaluator.

The measurement of the changes in biochemical markers of nutritional status provides objective measurements of the nutritional changes, even in early stages, and holds the advantage of enabling monitoring along the treatment. Each psychiatric disorder has its own peculiarities and demands specific attention. However, it is important to remember that nutritional deficiencies may favor the manifestation of irregularities in physical and mental health, generating symptoms such as anxiety, irritability, mood swings, or depression, among others, possibly worsening the psychiatric situation [18]. It is important to remember that some psychiatric drugs might compromise the patient's nutritional state. Some atypical kinds of antipsychotic (i.e., olanzapine and clozapine) may lead to significant metabolic alterations [21]. The clozapine may also compromise the immune status and lead to leukopenia. Lithium may lead to hepatotoxicity [22].

It is intrinsic to the nutritional treatment controlling of anthropometric measurements, more specifically body weighing. The protocol intends to compare the recommended weight by health professionals and provide the patients with feedback of their progress [23]. The issue is that weighing and gauging measurements involve comparisons to social rules that may facilitate the perception of abnormality and/or insatisfaction with the body and worsen the patient's self-esteem [18]. Considering that reaching a specific esthetic standard has not always been the main goal of the nutritional care of psychiatric patients, the anthropometric evaluation aims to monitor weight changes without becoming a burden to the patient. We must remember that the body issue can be very complicated in some pathologies such as mood and anxiety disorders and may be the main issue in others, such as eating disorders.

Considering this peculiarity, in many cases, the act of weighing may be a reason to miss doctor appointments. In these cases, it is necessary to do the basics in order to follow the aims, without causing damage to the patient's self-esteem. Thus, gauging weight and height, as well as the waist and calf circumference, are sufficient, always discussing results with the patients to minimize distress. One must also consider the possibility that the patient will refuse to undress to perform the anthropometric exam. In specific cases, skinfolds and bioimpedance analysis might be required.

When we talk about conduct with the psychiatric patient, we are referring to very fragile, unstable patients that require a different approach, which goes beyond the orientation of food and nutrients. In this context, apart from helping the patients regarding the structure of their food intake, the professional must make an effort to help them to grasp the connection between emotions and dietary behavior, which means relate food consumption and thoughts and feelings that might be interfering in this inadequate diet [13]. Considering that it is usual for patients to present guilty feelings regarding their eating habits, the professional must make it clear that his intention is to help, not judge. By being careful when approaching these matters, mood symptoms, loss of weight, and self-esteem improvements can be noticed [13].

Thereby, at the same time orientation toward *what* to eat is done, it is important to discuss *how* to eat. That means the treatment must be based on strategies of nutritional counseling, cognitive behavior therapy techniques, intuitive eating techniques, and mindful eating techniques, among others, that facilitate real change in eating behavior [24, 25].

In order to make patients feel motivated, it is important that realistic, short-, medium-, and long-term goals are outlined. In each consultation, small interventions should be performed concerning the patient's eating habits, so that they are permanently incorporated into their daily lives [25]. Small changes in eating habits are sustainable and sufficient to have a positive impact in health [26]. Elaboration of a food diary by patients has been used as a method by nutritionists from several clinical specialities. It is a self-

monitoring behavioral instrument, which allows the patients to perceive and improve their relationship with food, besides controlling their daily intake [26]. With that, intervention becomes more personal, since it can be performed based on the patient's eating habits. It also allows them to realize when they are eating because of hunger or for other motivations [13]. The nutritionist should also remember that food is carried with symbologies and meaning and, therefore, putting it in a scientific context only might be dangerous. Food involves pleasure and affective memories, and for that reason nutritional issues cannot be reduced to a matter of substituting it with pills and shakes. It is necessary to fit alimentation into a broader context and understand what drives the patient to eat beyond hunger [27].

It is known that women are subject to a higher risk than men to develop depression and that this risk is particularly associated with events regarding the reproductive cycle. Because several psychiatric disorders have their own characteristics, their relationship with food maintains specificities. We will consider in this chapter the more relevant nutritional aspects of some psychiatric disorders that permeate the female reproductive cycle. Every month the female body goes through hormonal changes due to the menstrual cycle. Because of those oscillations, there may be water retention, vitamin B6 deficiency, hyperprolactinemia, hormonal allergies, and prostaglandin abnormalities in the late luteal phase, also known as premenstrual phase [35]. Such symptoms result from a complex interplay between sexual steroids and brain neurotransmitters and are classified in a group as premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD), the last one being more intense, incapacitating women to perform their daily activities [27].

A variety of vitamins and dietary supplements, including vitamin B6, vitamin E, calcium, magnesium, and omega 3, have been studied as therapeutic agents for the PMS symptoms; however, evidence that some of those are more effective than placebo, is inconsistent [28]. Even with low quality of evidence, some authors suggest the supplementation of the aforementioned nutrients [29–31]. Vitamin B6 and magnesium deficiency could be responsible for stress and hormonal imbalance, and the administration of vitamin B6 seems to increase the serum progesterone level during the mid-luteal period, influencing the serotonin levels [30, 33]. Serotonin, a neurotransmitter synthesized from tryptophan, is also implicated in the modulation of mood and premenstrual symptoms, as well as being related to food control. It is suggested that this neurotransmitter would have a cyclic rhythm that would influence the fluctuation of appetite and total energy consumption observed in women during the premenstrual phase [13].

The literature also reports changes in types of ingested macronutrients, besides citing alterations in the selection of food products, as well as developing an increased desire for determined food [34]. Therefore, carbohydrate-rich foods are great sources of tryptophan, since their bioavailability is enhanced by insulin secretion, the natural transporter of the amino acid to the central nervous system. Moreover, increase in the desire for some kinds of food, usually rich in this nutrient, observed during the premenstrual phase of many women, could happen because of a homeostatic mechanism, looking to increase the availability of tryptophan and, consequently, the synthesis of serotonin [13]. The ingestion of a mix of simple and complex carbohydrates (e.g., dextrose and maltodextrin) has been effective in the improvement of some premenstrual symptoms, such as mood swings and increased appetite. It is important to clarify that women that do not suffer from clinical depression, during these periods, also make the above food choices, although on a smaller scale [35]. Changes in lifestyle should be encouraged, such as incentives to regularly practicing physical exercise, small fractional meals, tobacco suppression, moderated use of alcohol, sufficient sleep, and reduction of caffeine intake. The sodium reduction is also indicated for bloating complaints during this period [32].

Pregnancy causes physiological modifications in the maternal body, which generates an increased need for essential nutrients, including proteins, carbohydrates, and lipids in order to maintain the

maternal nutritional state and to guarantee the adequate fetal growth and development, since its only source of nutrients are the nutritional reserves and the maternal food intake [35]. In that sense, the pregnant woman's nutritional state is recognized as an important factor for a healthy and complication-free pregnancy. Depletion of nutrient reserves during pregnancy and the lack of postpartum recovery may increase the risk of depression in women [13]. On the other hand, a high food intake at this stage may lead to obesity, which increases the risk of complications, such as gestational diabetes, hypertensive disorders, and perinatal morbidity and mortality [36]. Important changes in the levels of estrogen and progesterone occur at this stage, as well as significant suppression of the hypothalamic-pituitary-gonadal axis, which has an enormous psychobiological and physiological effect on women's body and mind. Such endocrine changes have led to the hypothesis that, as a result of these modifications, pregnant women are more susceptible to depression [37]. Depression during pregnancy does not only affect the mother; there has been strong evidence that maternal depression also affects the psychological and intellectual development of the child [36]. Some nutrients are essential to the prevention of depression during pregnancy and postpartum – this is the case of omega-3 polyunsaturated fatty acids (PUFAs). Clinical finding and epidemiological evidence suggest that low dietary intake and/or low tissue levels of PUFAs contribute to its etiology. It is suggested that lowering the content of omega-3 PUFAs in the brain may cause a number of neurobiological effects that also occur in major depression [38]. Deep-water fish constitute the main dietary source of omega-3 (PUFAs), and genetic-based investigations regarding the metabolism of those fatty acids provide evidence that they may be involved in the prevention of depression [39]. Studies show that fish consumption is associated with lower frequency of symptoms of maternal depression and anxiety during pregnancy and less intrauterine growth retardation.

We should also remember that nausea and vomiting are common during the first trimester of pregnancy, and dietary guidelines to diminish discomfort and avoid malnutrition are important at this stage. The scenario may progress to hyperemesis gravidarum (HG), a syndrome marked by uncontrollable vomiting in the first trimester of pregnancy, resulting in metabolic disturbances, with weight loss and risk to pregnancy. A lot is discussed about if the HG is related to the aggravation or development of an eating disorder (ED) during pregnancy. The prevalence of ED throughout pregnancy is unknown, but it is suggested that it is less common than in the overall population. The signs of a hypothetical ED during pregnancy include the absence of weight gain in two consecutive visits within the second trimester of pregnancy, HG and a progressive history of ED [40]. Considering the severity of both the HG and the ED, a detailed anamnesis is necessary in order to identify the adequacy of the pregnant body weight, her eating behavior, and possible signs of ED.

Another important subject to highlight is alcohol consumption during pregnancy. Alcohol is a substance that crosses the placental barrier and also passes into breast milk, and since the fetus and the baby have difficulties in metabolizing and eliminating alcohol, even in small quantities, this consumption may lead to significative mental health issues and, in more serious cases, to the fetal alcohol syndrome (FAS). Since there have been no studies to determine safe doses of alcohol consumption, it is recommended not to drink at this stage of life [41]. It is important that the nutritionist is aware of any excessive alcohol consumption and always questions its intake during consultations.

Recent long-term prospective studies have shown that the transition to menopause is associated with a higher risk of development or recurrence of depression. A range of independent biological and environmental factors are predictors to depression in this population, including the presence of hot flushes, sleep disorders, history of severe premenstrual syndrome or postpartum depression, ethnicity, life history with stressing events, body mass index, socioeconomic status, hormone use, and antidepressants [42]. The prevalence of common mental disorders is higher in the sample of climacteric women, and it is associated with negative repercussions about their quality of life, and psychosocial factors

have a significant influence [43]. But it is not only the changes in the estrogen levels that lead to metabolic changes during menopause causing a variety of health conditions in a middle aged or elderly woman. Aging, increase in body weight, and accumulation of fat in the abdominal area also affect women's body image during the climacteric, contributing to low self-esteem and even decrease of sexual desire. Among the predisposing factors of weight gain is a sedentary lifestyle, which is natural in senescence, inadequate intake of nutrients, and lower basal metabolism, as well as an increase of the intake of calories. As mentioned in the introduction of this chapter, the nutritional transition which our society has been facing has a strict influence on the increase of the caloric values and decrease of the nutritional values consumed [6, 7]. These nutritional deficiencies may be risk factors for mental disorders, such as depression [13]. Therefore, the loss of weight during this period, for women with overweight and obesity, improves body image, raising the female self-esteem, and also contributes to an improvement in health parameters. That means that lifestyle and nutrition accumulated up to this age are also responsible for those changes in the female body. In particular, poor diets, physical inactivity, alcohol, and tobacco are related to the negative results in most described conditions. Besides that, specific types of nutrients such as omega-3, calcium, and vitamin D or specific food such as soy is linked to positive health outcomes [44].

Population studies relate the high intake of fish to the low incidence of mental disorders, which, in turn, has been proved to be a direct result of the omega-3 fatty acid ingestion [45], suggesting a relationship between increased incidence of depression and decrease of the intake of omega-3 fatty acid sources [45]. Correcting the deficiency in long-chained omega-3 fatty acid (LCO3-PUFAS) seems to improve depressive and psychotic symptoms, and its intake has not been associated with increased risk to any kind of cancer. However, more data on that matter is necessary to confirm the benefits of LCO3-PUFAs in alleviating menopausal symptoms and osteoporosis [46, 47].

With regard to the importance of calcium, it is known that in this stage of life there is a reduction of bone mass, which can be aggravated when associated with inadequate calcium intake. This way, during the climacteric period, there is an increase in prevalence of osteoporosis and osteopenia due to the progressive decrease of ovarian function and consequently the production of steroid hormones. For most women, osteoporosis can be prevented by a balanced diet, rich in calcium and vitamin D, regular physical activity, avoiding smoking and excessive consumption of alcohol, as well as routine bone mass monitoring (densitometry), and use of medications/supplements when necessary [13].

Concern about the risks regarding hormone replacement therapy (HRT) led to an increase in the use of alternative therapies. In this context, phytoestrogen supplements show as an option. Thereby, food rich in phytoestrogens such as isoflavones, lignans, and coumestans has been identified as functional foods to decrease menopause symptoms, even though its efficacy remains controversial [46]. Clinical and epidemiological data indicate that the addition of soy derivatives – rich in isoflavones – to the diet might contribute to postmenopausal women's health. Isoflavone supplements rich in genistein seem to alleviate "hot flashes," a common complaint among women in menopause [48]. Clinical and epidemiological evidence suggests that isoflavones, in particular, can offer a safe and well-tolerated option to deal with depression in this stage of life. Besides, the intervention doses used in the clinical trials fall well within the dietary range [49].

Nutrition is a recent science, which has not yet revealed all its possibilities. In that sense, some new (or maybe old?) approaches have arisen to complement the vitamin-mineral food supplementation. One of them is the study of phytotherapy, a science that uses medicinal plants to prevent and treat diseases. If we consider that functional foods are those natural foods which, when frequently consumed, can reduce the risks of some disease or improve the functioning of some organ, then in that sense, the use of medicinal plants obeys the same principle. There are many ways to use medicinal plants, and the most common ones are teas and infusions, liquid extracts (tincture), seasoning, oils, and dry extracts. It is important to emphasize that each

plant has a specific purpose and that, even though they have been known for quite some time, it is always a good idea to check for adverse effects. However, the active principles present very low overall toxicity when consumed in teas and infusions, the safest way to be prescribed by nutritionists, while also increasing the liquid consumption of their patients [50].

In the form of seasoning and spices, they enhance results of a good dietary plan, at the same time adding value to the diet. Good examples are chamomile tea to relieve cramps, blackberry tea to ease menopause symptoms, and lemon balm tea, which promotes a good night's sleep. Among the spices, cloves and cinnamon might help with depression and self-esteem improvement, as well as saffron (*Crocus sativus*) [50–52]. On the other hand, many herbal medicines used for mood disorders may have serious adverse effects when not related to a health professional, since they can enhance the effects of psychiatric drugs, specially when considering the St John's case (*Hypericum perforatum*) [51, 53, 54]. It must be taken into account that the majority of the patients do not understand herbal medicine as drugs; they use it without prescription, underreport their use, and, when prescribed, often neglect the rhythm of use or, on the contrary, increase the doses on their own thinking there is no adverse effect. For those reasons, its use and efficacy cannot be totally measured, reducing the support from the scientific community [55].

In the last 30 years, the interest regarding the intestinal microbial population has intensified. It was discovered that these microorganisms are far from being passive inhabitants of the gastrointestinal tract (GIT) but interact with their host in an intense way. They are capable of modulating the effects of potentially harmful bacteria, with impact on the gastrointestinal tract, digestion, metabolism, the immune system, and also the brain [56]. It is known today that GIT bacteria can activate neural pathways and signalling systems of the central nervous system (CNS). Current and future animal and clinical studies focused on understanding the functioning of the microbiota-gut-brain axis may offer new approaches for the prevention and treatment of mental disorders, including anxiety and depression [57]. These same bacteria also influence nREM sleep, stress, and sensitivity to pain [58, 59]. Some authors state that the intestinal flora is not only involved with the CNS but also with human behavior [59–61].

Considering that patients with anxiety and depression have more GI symptoms than healthy control groups [62] and that the inverse is also true [63], the use of probiotic food and/or probiotic supplements has been widely studied for prevention and treatment in mental health [59–61]. Probiotics are designated as "living microorganisms that, when administered in adequate quantities, provide benefits to the host's health" [64, 65]. These microorganisms may be managed as dietary supplements or added to food, since its final product maintains an adequate quantity of living probiotics till expiry [56, 65] . Since the diet has a significative impact in the composition and function of the human intestinal microbiome, dietary patterns must be considered when interventions are necessary [58].

Several probiotics belong to the genera represented in the functional group of bacteria known as lactic acid bacteria, which have been safely consumed for many years [56]. However, difficulty in backing up their benefits has always been limited thanks to the complexity of the intestinal ecosystem. In the last decades, with the use of molecular techniques, great advances have been achieved in characterizing specific probiotics for each case [56, 65]. Even so, the nature of interaction in the gut-brain microbiome still remains poorly understood, and real data are scarce, thus the widespread use of probiotics still is not supported by randomized controlled studies [62].

Women are complex beings, and their existence is defined by cycles: birth, growth, fertile age, and aging. Their body goes through hormonal swings every month that influence their mood and food intake. Considering that certain foods and nutrients influence mental health, specific and individualized nutritional care should be encouraged in order to improve women's quality of life. Despite clinical and scientific evidence of the relationship between various foods and nutrients to women's mental health, more studies are necessary to better understand the mechanisms involved.

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Assisted Reproduction: General Concepts and Psychological Aspects Involved

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General Concepts

Family constitution is considered a fundamental human right [1]. Although international efforts are made to prevent and treat infertility, it has been becoming more prevalent in developed countries. There is a reported 9% prevalence of infertility with 56% of couples seeking medical care [2].

The decay of general health's population, could, at least partly, assist to explain the increase of infertility, as prevalence of obesity associated with anovulation and polycystic ovary syndrome [3], and the increased incidence of sexually transmitted diseases which affects reproductive organs (e.g., chlamydia) [4]. Besides, to postpone motherhood is becoming a very common option among women of developed societies, which are deferring more and more the initiation of the family constitution process [5]. Thereafter, this delayed parenthood results in an ovarian aging, related to infertility. Also, the prevalence of uterine and pelvic diseases such as leiomyomas and deep endometriosis rises with women's age, impairing reproductive outcomes and increasing infertility rates as a delayed stage of these pelvic diseases [6, 7].

Together, these medical and social considerations indicate that the prevalence of infertility is growing, resulting in progressive rise of the requirement for assisted reproductive technologies (ART) [8]. According to the International Committee Monitoring Assisted Reproductive Technologies, infertility is defined as the failure to conceive after at least 1 year of unprotected sexual intercourse, while assisted reproduction (AR) consists of all treatments or procedures that include in vitro manipulation of oocytes, spermatozoa, or human embryos with the purpose of establishing pregnancy [9]. Clinical definition of infertility doesn't reckon "social infertility" found in a crescent number of people that, due their lifestyle or career, will seek the AR for a late pregnancy when their natural fertility reduces. Social transitions lived in the last decades, including the possibility of homoaffective couples' gestation by gamete donation or surrogate mother, are situations that changed the contemporary concept of family through AR [10]. Therefore assisted reproductive technologies consist of available medical tools not only for infertile indi-

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viduals but also for the entire society, allowing them the chance to conceive even when the natural situation would make it unlikely.

Infertile couples who submitted to AR often experience high levels of stress, anxiety, and depression, symptoms commonly manifested in variable scores among men and women and also could differ according to the infertility factor or yet with the conducted treatment [11, 12]. A recent meta-analysis points that a fifth of subfertile patients seeking for infertility treatments exhibits clinically significant levels of anxiety, depression, or stress [13]. Therefore it is recommended in several cases that the patients perform psychological counseling during the AR cycles, especially in those with treatment failure, where the emotional impact is usually increased [14–16].

Assisted Reproductive Technologies

There are some professionals that consider the control of ovulatory process to set the ideal moment for intercourse, procedure known as programmed intercourse or low complexity assisted fertilization technique. However, it is preferred not to include such therapeutic modality inside the assisted fertilization techniques, considering it a usual treatment for infertility. Assisted reproductive techniques (ART) could be low complexity, when fecundation occurs in the female reproductive system, or high complexity, when fecundation is performed at laboratory and the resulting embryos are transferred into the mother's womb.

Among the low complexity techniques, we highlight the intrauterine insemination. Furthermore, among the high complexity, we detach the in vitro fertilization (IVF), which can be performed by conventional insemination or intracytoplasmic sperm injection (ICSI).

Intrauterine Insemination (IUI)

It is defined as the intrauterine deposition of spermatozoa processed in laboratory. The procedure includes the follicular development by pharmacological stimulation, aiming the obtainment of two or three ovulatory follicles, the seminal processing, performed at the day of insemination, and the insemination itself, whereby the spermatozoa, in culture media, are directly introduced in the uterine cavity by a proper catheter.

Indications Indications for IUI include Cervical issues, anovulation (p. ex. polycystic ovary syndrome), unexplained/ idiopathic infertility, minimal endometriosis and mild male factors. Other indications are the incapacity to maintain sexual intercourse and the use of donated semen (including homosexual women). The main condition for IUI indication is the existence of at least one functional pelvic tube. Besides, the seminal concentration ideally must be higher than five million motile spermatozoa for the best procedure efficiency.

Techniques and Results Although IUI may be performed on natural cycle, ovarian stimulation increases its effectiveness. There are several different protocols for ovarian stimulation. The main drugs for ovulation induction are the clomiphene citrate and the gonadotropins (FSH, LH, hMG). They may be urinary compounds (purified hormone originating from urine of postmenopause women) or recombinant compounds. At IUI a minor ovarian stimulation is conducted, avoiding the excessive follicular growth. Stimulation is always monitored by ultrasound, which allows monitoring follicular development and determines the number of preovulatory follicles. When more than four follicles are detected, the cycle must be cancelled or converted to high complexity treatment, due to unacceptable risks of high-order multiple pregnancies. In the presence of preovulatory follicles, follicular rupture is unleashed by administration of human chorionic gonadotropin (hCG), and the insemination is performed about 36 hours later. Intrauterine insemination is a simple procedure, conducted with the patient awake, on gynecological position. After speculum positioning, vaginal and cervix washing with physiological saline solution, the insemination catheter is introduced through the cervix. After process and capacita-

tion in laboratory, 0.5 mL of culture media with the spermatozoa is injected. Pregnancy rates obtained with IUI are variable and depend on numerous factors. References varying from 8% to 35% can be found in literature. Usually, success rates are about 18% in one attempt [17]. In young women, under 35 years old, rates could reach 20%. We recommend the maximum of three IUI attempts; if these treatments fail, more effective techniques should be considered.

In Vitro Fertilization and Embryo Transfer (IVF)

The great revolution on infertility treatment occurred with the publication, in 1978, of the first birth after external fecundation and embryo transfer to the womb cavity of a patient with bilateral salpingectomy. Currently, the indications for IVF are much wider, including endometriosis, unexplained infertility, male factor, immunological factor, and IUI failure. The oocyte/embryo donation programs in patients with ovarian failure, surrogate womb, use of frozen oocyte or embryos for further transfers, and the cryopreservation of oocyte or embryos before an oncological therapy are also IVF-related techniques. The steps involved in IVF comprehend ovarian stimulation, follicular aspiration for oocyte pickup, laboratory fertilization, and embryo transfer.

Ovarian Stimulation Pharmacological ovarian stimulation is the first step of treatment and has fundamental role to increase pregnancy odds through the induction of multiple follicular development for assisted reproduction procedure. However, in some selected cases, the procedure may be performed in a natural cycle. The gonadotropins represent the major therapeutic modality in ovarian stimulation for assisted reproduction. From urinary preparation we highlight the hMG, an equal proportion preparation (75/75 IU/ampoule), from FSH/LH, the purified FSH with <1.0 IU of LH/75 IU of FSH, and the highly purified FSH, with <0.1 IU of LH/75 IU of FSH. Among the recombinant gonadotropins, we highlight the recombinant FSH, with exclusive activity of FSH, and the recombinant LH, with exclusive activity of LH, as well as their combined preparations. It is important to note that the multiple follicular development may result in an early elevation on levels of estradiol and spontaneous release of LH, leading to a premature luteinization. To avoid this undesired effect, GnRH analogue agonist or antagonist analogues are applied for hypophyseal suppression. Nowadays, the commonly ovarian stimulation protocol used for IVF is the suppression with GnRH antagonist analogue (GnRH-ant). The GnRH-ant causes a prompt cessation of the gonadotropin release, without the acute initial discharge, known as flare-up that occurs when GnRH agonists (GnRH-a) are used. Typically, stimulation with gonadotropins starts on the second or third day of the cycle, combining the antagonist on 6th day of stimulation or in the presence of follicles higher than 13–14 mm diameter. Another classic way to achieve hypophysis suppression is using the GnRH-a, managed during the luteal phase, by depot or daily subcutaneously administration, between the day 18 and 22 of menstrual cycle. Stimulation starts between 15 and 20 days after pituitary suppression, using 150–300 IU of recombinant FSH or highly purified urinary hMG. The first ultrasound scan for cycle monitoring occurs around the 7th day of gonadotropin stimulation. From then on, it is monitored in accordance with the follicular development, until the triggering of final follicular maturation, performed with an hCG administration, at doses of 5000 up to 10,000 IU of the urinary product or 250 μcg of recombinant product. The hCG is given in presence of at least three follicles with average diameter ≥17 mm. Luteal phase supplementation is a mandatory step in IVF cycles; although there are controversy if the estrogens should be used, the progesterone supplementation is fundamental. Currently, the usage of micronized natural progesterone is preferred, in capsules with 200 mg, or in an 8% progesterone gel, both with intravaginal administration.

In Vitro Fertilization After processing, progressive motile spermatozoa are incubated with the oocytes in a proper plate with culture media and then taken into a 37 °C and proper pH CO_2 incubators. In conventional IVF about 100.000, spermatozoa are put for each oocyte. After a period of 18–20 hours, the occurrence of fertilization is observed, which is assessed by the presence of two pronuclei. The fertilized embryos proceed with their development inside the incubator, for 2–3 days, and then transferred to the uterus. It may also proceed with an extended culture, whereby embryos are transferred on the 5th or 6th day after follicular aspiration, in blastocyst stage.

The Embryo Transfer Embryo transfer (ET) is performed transcervically, and it is the final step of in vitro fertilization. It is scheduled, usually, after 48–72 hours after the oocyte insemination, with the patient on gynecological position and guided by pelvic ultrasound on abdominal approach. In relation to the results, quantified by the several factors that interfere on success rates of the treatment, it is estimated that women age, and the oocyte quality takes part of over 40% of it. The laboratory quality, the physician's experience, the choice of culture media, and the appropriate control of the environmental toxicity conditions participate in another 40%. The remaining 20% are defined at the timing of ET.

Intracytoplasmic Sperm Injection (ICSI)

This method consists the injection of a spermatozoon directly inside the oocyte, using a micromanipulator. With this technique, the fertilization is "enforced" in the laboratory, so it becomes possible even in severe male factor cases, since one spermatozoon is enough to fertilize the oocyte. With the advent of ICSI, the indications for use of donor semen become very rare, once the fecundation is achieved even with severe male factor. Therefore, the main indications for ICSI are severe male factor and previous fertilization failures in IVF. One of the major advantages of ICSI is that the technique can be employed in obstructive azoospermia, as vasectomy. Besides, ICSI may be indicated in cases of congenital absence of vas deferens and of azoospermia after bilateral hernia surgery. In such cases, employed techniques allow the retrieval of spermatozoa through the epididymal or testicular aspiration.

Embryo Cryopreservation

The embryo cryopreservation is used when there is an embryo surplus in IVF cycles, in the cases of cancelation of embryo transfer by risk of ovarian hyperstimulation syndrome, before chemotherapy or radiotherapy treatments in young patients desiring fertility preservation. The cryopreservation is possible since zygote pronuclear stage until blastocyst stage. A controversial aspect is the use of those embryos for research, *particularly* in order to obtain embryonic stem cells. In Brazil, the law 11.015, which came into force on 24 March 2005, provides the use of cryopreserved embryos for this purpose, since they were regarded as unfeasible for in vitro fertilization, or has been kept frozen for 3 years or more. In agreement with the CFM resolution from 2015, the cryopreserved embryos kept frozen for 5 years or more may be discarded if in accordance with the patient's wish [18]. The use of embryos in stem cell research is not mandatory, as envisaged by the by safety law.

Fertility Preservation

Several oncological and non-oncological diseases may affect current or future fertility, caused by the cancer or the gonadotoxic treatment, and need an adequate Fertility Preservation Program. Women wishing to postpone maternity, women affected by severe endometriosis that will be submitted to pelvic surgery, and transgender individuals before starting hormone therapy or

undergoing surgery to remove/alter their reproductive organs should be counseled properly. Embryo and oocyte vitrification are first-line methods for fertility preservation (FP) in postpubertal women. Vitrification of metaphase II oocyte is the preferred option, since it guarantees female fertility, not necessarily related to the partner [5]. Women undergoing egg freezing for fertility preservation have special medical needs and concerns, which require particular forms of patient-centered care [19].

Social Fertility Preservation

There are a rising number of women postponing motherhood for a variety of reasons, including lack of partner, to achieve career plans and financial stability or to finish scholar education. Oocyte cryopreservation has become a valuable option to reassure this group of patients. Nevertheless, primary care physicians or even gynecologists are not always fully prepared to discuss oocyte cryopreservation with their patients, and some of them even question whether oocyte cryopreservation should be used for elective reasons (Pascale P) [20].

Besides ethical and personal opinion regarding this issue, egg banking via vitrification has proved an efficient technique in assisted reproduction [20, 21]. Currently, there are consolidated vitrification programs in assisted reproductive technology (ART) clinical practice, which has led to an increasing number of children born with the use of this technique. A retrospective multicenter study included 1,468 women who electively vitrified their oocytes for FP purposes due to their age or history of a medical condition that threatens fertility other than cancer, like endometriosis or low ovarian reserve. This study revealed a higher live birth rate per patient in women ≤35 years old than ≥36 years old (50% [95% CI 32.7–67.3] vs. 22.9% [95% CI 14.9–30.9]). Cumulative live birth rate was higher and increased faster in younger women [21]. In our context, Brazilian women seem to be in favor of oocyte cryopreservation. Most survey participants considered safeguarding their reproductive potential. Although most of the responders had a partner (86.9%) and had already planned the pregnancy of their first child (69.6%), 85.4% potentially considered social oocyte freezing to improve their chances of giving birth later in life [22].

In contrast, oocyte banking does not seem to impact future relational status and reproductive choices, indicating that freezing oocytes does not appear to influence women's life choices. Previous study enriches the importance of psychological aspect of reassurance associated with preventive oocyte banking, expressed by high satisfaction after banking in combination with a decreased intention of ever using the eggs [23].

Fertility Preservation Before Oncologic Treatment

The early diagnosis of malignant neoplasm, associated with increased efficiency of chirurgical treatments, chemotherapy, and radiotherapy, promotes the remission of cancer in a considerable number of patients, many of them in reproductive age. With improved cure rates of cancer in young patients, greater attention has been focused in fertility preservation procedures. Hematologic cancers and other malignancies that strike young people may be in the 90% to 95% range of 5-year survival rate [24]. Breast cancer is the most common malignancy in adult women, and in the USA, 5–7% of cases of invasive breast cancer (~11,000/year) occur in women who are under age 40 at diagnosis [25]. Given the advent of early breast cancer diagnosis and effective cancer treatments, survival rates following breast cancer are increasing, with a 5-year survival rate over 80% [26–28]. This fact justifies the concern about chemotherapy-related gonadal toxicity in women with reproductive wishes. Chemotherapy treatment may have deleterious effects on the ovarian reserve, by affecting the resting pool of primordial follicles or the growing follicle population [27, 29]. Thus, it is crucial that fertility-related aspects be discussed with all patients in reproductive age who will be submitted to onco-

Table 1 Outcomes in 109 breast cancer patients undergoing COS for fertility preservation

Variables	All patients	IFP	LFP	LP	*p*-value
	(*n* = 109)	(*n* = 41)	(*n* = 21)	(*n* = 47)	
Aspirated oocytes	11.62 ± 7.96	10.95 ± 7.23	10.38 ± 8.0	12.77 ± 8.54	NS
Vitrified oocytes	9.60 ± 6.87	8.927 ± 6.75	7.952 ± 5.38	10.94 ± 7.43	NS
Age (years)	31.27 ± 4.23	31.37 ± 3.48	29.76 ± 4.94	31.85 ± 4.41	NS
FSH/hMG dose (IU)	2610 ± 716.51	2577 ± 670.19	2387 ± 615.31	2738 ± 780.9	0,04457[a]
Days of stimulation	10 ± 1.39	9.854 ± 1.33	9.714 ± 1.31	10.26 ± 1.45	NS
Estradiol levels (pg/mL)	706.3 ± 450.48	761 ± 439.93	677.8 ± 503.39	671.2 ± 440.1	NS

Data are expressed as means ± standard deviation, *IFP* initial follicular phase, *LFP* late follicular phase, *LP* luteal phase, *NS* not statistically significant

[a]Significant statistical difference between groups LFP and LP

logical treatment and with their parents or legal guardians in case of children.

Fertility Preservation Techniques For male cases, the sperm cryopreservation is a well-established technique, so even teenagers over the age of 12 years old can show both physical and emotional maturity to understand the problem and provide semen sample. On the other hand, the cryopreservation of testicular tissue and spermatogonia is still considered an experimental technique, and the testicular suppression with GnRH analogues was not effective in the protection of gonadal function. The ethical and emotional aspects that interfere in semen collection must not be negligible, and the parent's participation is indispensable for the upcoming decisions. With regard to adult men, undoubtedly the option of semen collection must be discussed and offer to all patients that will be submitted to an oncological treatment.

Among women, the possibilities become more complex. The main alternatives consist of an embryo, oocyte, or ovarian tissue cryopreservation and, in cases of pelvic radiotherapy, the surgical ovarian transposition. It should also be considered the option of ovarian function suppression with GnRH analogues, simultaneous with chemotherapy, and the use of salvage surgery for some sorts of cancer that compromise the female reproductive system. In the Human Reproduction Center from the Women's Health Reference Center, we have studied 109 breast cancer patients who underwent ovarian stimulation for oocyte cryopreservation. The endpoints evaluated were number of oocytes retrieved and number of mature oocytes cryopreserved, total number of days of ovarian stimulation, total dose of gonadotropin administered, and estradiol levels on the day of the trigger. The outcomes were also analyzed according to the phase of the cycle in which COS had commenced. The mean age of patients was 31.27 ± 4.23 years. The average duration of COS was 10.0 ± 1.39 days. The mean number of collected oocytes was 11.62 ± 7.96, and the mean number of vitrified oocytes was 9.60 ± 6.87. The mean estradiol concentrations on the triggering day was 706.30 ± 450.48 pg/mL, and the mean dose of FSH administered was 2610.00 ± 716.51 IU. When comparing the outcomes according to the phase of the cycle in which COS was commenced, there were no significant differences in the number of oocytes collected and vitrified, ovarian stimulation length, and estradiol levels on the trigger day. It was observed a statistically increase of the total FSH/hMG dose administered in the group starting COS in the luteal phase when compared to the late follicular phase. The results of our investigation are shown in Table 1. Our data suggest that oocyte cryopreservation with a specific protocol for breast cancer patients is effective and safe and may be offered to young women undergoing oncologic treatment who have concerns related to their reproductive future.

Preimplantation Genetic Diagnosis (PGD)

The PGD consists of chromosomal analysis of the embryo cells before embryo transfer to the womb. The removal of the cells for biopsy can be made on the 3rd day of in vitro development, when the embryos have between six and eight cells (blastomere) or on the 5th/6th day in the blastocyst stage. Generally one or two blastomeres are removed, which do not harm the embryo. The blastomeres are extracted by an aspiration method after drilling the zona pellucida with a Tyrode's acid solution or by a laser shot. The evolution of the embryo culture techniques until day 5 or 6, when embryos reach the blastocyst stage, allows the biopsy to be performed at this stage with less harmful impact for the embryo and more reliable genetic results. In such cases, the biopsy is made in trophectoderm cells, which will give rise to the placenta.

The PGD is indicated for detection of aneuploidies and monogenic diseases, when there are risks for such situations. The PGD may be performed through techniques of CGH-array or next-generation sequencing (NGS). Both techniques are used for chromosomal disorders. Meanwhile the polymerase chain reaction (PCR) or newer techniques, including karyomapping and next-generation sequencing, emerge in recent decade in order to identify monogenic disorders. Nowadays the application of PGD to social sexual selection raises questions and ethical debate, with divergent opinions from various segments of society [30].

Special Situations in Assisted Reproduction

Oocyte Donation The oocyte donation is indicated in cases of premature ovarian failure, low-responding patients, high FSH levels, and advanced female age. All women with age equal or higher than 40 years old, who need ART, are candidates to be an oocyte receiver. To be an oocyte donor, the woman needs to fulfill some basic requirements. According to the American Society of Assisted Reproduction, the donor must be between 21 and 34 years old and possess a good psychophysical status, negative history for genetic transmission disease, negative tests for HIV, syphilis, hepatitis B and C, and cervix culture with negative results for *Neisseria gonorrhea* and *Chlamydia trachomatis* [31]. In the USA, the gamete donation may have a commercial nature, in such a way that the woman in need of ovodonation may choose the donor and remunerate her for the procedure. In Brazil, the Federal Council of Medicine, in a 2015 resolution [18], determines that oocyte donation cannot have profit nature, and the donor anonymity must be preserved, which makes more difficult the obtainment of donors.

Surrogate Mother The surrogate mother is indicated in cases where a young woman, with normal ovarian function, is hysterectomized or does not have a uterus capable to a fetal development. The Federal Council of Medicine recommends that the uterus donor should belong to the family of the genetic mother up to the fourth degree of relationship. The Regional Council of Medicine of the state of São Paulo, through the Report n° 43.765/01, does not require such relationship and has made the following recommendations: (1) It is forbidden the "profit with surrogate uterus" with any way of payment or financial compensation for the gestational mother; (2) It is required the acquisition of the informed consent for this purpose from the mother who will donate the uterus, remembering about biopsychosocial involved in the pregnant and puerperal cycle, and about the risks inherent to the motherhood; (3) In this consent must be mentioned the impossibility of the termination of pregnancy after the gestation has been started, even in face of a genetic anomaly, excepting few cases legally authorized; (4) Until the puerperium, the access to medical assistance and multidisciplinary staff will be

ensured to the surrogate mother; otherwise the register childbirth is guarantee for the genetic parents; and (5) These documents must be provided during the pregnancy, in conjunction with the "contract" between the parts clearly establishing the situation. It must be signed by all parts involved, namely, the couple and the surrogate mother, and then forwarded to local CRM.

Complications of ART

The most commonly related ART complications are the multiple pregnancy and ovarian hyperstimulation syndrome. The multiple pregnancies, by its frequency and potential perinatal morbidity, should be considered the main ART complication. Its prevention resides essentially in reducing the number of embryos transferred; in some countries, particularly Nordic, the single-embryo transfer is strongly encouraged and even provided by law. In Brazil, the Federal Council of Medicine, from 2015 [18], resolves the following determinations with respect to the number of embryos to be transferred, accordingly with the age of the patient: (a) women up to 35 years old, maximum of two embryos; (b) women between 36 and 39 years old, maximum of three embryos; (c) women above 40 years old, maximum of four embryos; and (d) in case of oocyte or embryo donation will be considered is the giver age in the time of oocyte pickup. However, in our society, there is a generalized tendency of transferring a maximum of two embryos, and the transfer of three embryos is currently an exception. In ovarian stimulation for programmed sexual intercourse, or low complexity ART, the treatment should be suspended when there are more than three follicles with maximum diameter of 16 mm; the alternative to cancelation is the conversion of those cycles to high complexity ART cycles, when it is possible to determine the number of transferred embryos. The ovarian hyperstimulation syndrome (OHSS) is a complication caused by the pharmacological stimulation of the ovaries. The symptoms appear typically a few days after the hCG administration for the final follicular maturation. The mild forms of OHSS are relatively common, meanwhile the severe form affects around 1% of patients undergoing follicular stimulation. The main factors for OHSS are (1) young women (<35 years old); (2) serum levels of estradiol above 3000 pg/mL; (3) a large number of follicles during the ovarian stimulation (more than 15 follicles per ovary); and (4) polycystic ovary syndrome. The physiopathology of the OHSS remains unclear, although the accentuated increase of capillary permeability, with loss of liquid for the third space it is fundamental component of the syndrome. The symptoms range from abdominal distension and distress, in mild forms, until ascites, hypovolemia, hydrothorax, hemoconcentration, coagulation disorders, and renal insufficiency, in severe forms. The OHSS prevention is based mainly on the suspension of risk cases, avoiding the hCG administration. They may also proceed with embryo cryopreservation and transfer them in another cycle, avoiding clinical deterioration resulting in pregnancy. The treatment of mild forms is ambulatory and requires, basically, rest and symptomatic treatment. In severe forms, the hospitalization is mandatory, with administration of human albumin, heparin, and proceed with paracentesis. Although infrequent, complications, such as anesthetic, infectious, and hemorrhagic, must be also considered as follicular aspiration consequence.

Assisted Reproduction: Psychological Aspects Involved

The integrated and interdisciplinary action, during many years, in an assisted reproduction center of a public hospital, and not only the clinical practice, allows a deep and concise delineation of contribution of psychology in infertile couple's treatment and of the psychological aspects involved. Virtually, all national and international literature, relevant to the conjugal infertility theme, refers to the same psychological aspects involving the infertile couple [32–38].

Feeling incapable, frustrated, and inferior than other women and guilty for not getting pregnant are common to infertile women, after some or many years of unsuccessful attempts of pregnancy.

We often hear during group or individual psychological intervention that they do not understand why other women do not want it. They say: "Those women who have just had a child and leave on the street" are succeed, and we are not" (this represents one of many statements found in most articles and books about infertility thematics [39, 40]). And as soon as this resentment is expressed, actually mobilized by one of the key questions of our script of semi-structured interview [41] – "how do you feel about not be able to achieve pregnancy?" – the relevant emotion, mixed feelings of sadness and anger, speak out with tears that have been shed many times before. And at this moment this cathartic manifestation initiates a process of mental construction that will lead the patient to release a long repressed suffering.

This symptomatic array leads to the development of a high level of anxiety that may interfere in the assisted fertilization treatment and raise the hypothesis of obstruction of pregnancy occurrence. This is a controversial point in the material found; some authors support that anxiety interferes in the assisted fertilization success, preventing the couple from getting pregnant [42], and others observe the opposite or claim to have inconclusive results [43, 44].

A Model of Psychological Action in AR

The Psychological Assistance to the Infertile Couples program was implanted at CRHM-HPB in 1996, which enabled us to monitor different stages of AR, in an estimated universe of 2000 couples.

In this service we consider to be fundamentally important the contact with the couples, since the first moment in the hospital for medical triage and further investigation of the infertility diagnosis.

Screening Group/Evaluative: 3 Couples

In this screening group, following the diagnosis and insertion of the couples in the service, we retake our orientations. They concern about life project and must include the personal and professional fulfillment of the woman, regardless of the condition of being a mother and having a child or not.

We talk about "take the focus away from the child," and with that we intend to help the couple to understand that their lives must continue with objectives and actions toward other projects (we find an article that corroborates our guidance) [45].

In the group or individual psychological attendance, we show to the couple their unconscious content (which we may perceive and understand during the interview) and explain that we believe that this may be contributing to their nonpregnancy. However, we clarify not be able to affirm that, if submitted to treatment, will certainty become pregnant, but, according to what we have observed, might increase success rate. We have already accompanied many cases of couples that, when treating the psychological conflicts, combined with economics, familiar and the relational conflicts, treating their psychological and existential universe, achieved significant changes in their lives, and, in some point, close or distant, they could get pregnant [41].

Although the so-called psychogenic infertility, first propose by psychoanalysis is being reviewed, the current psychoanalytic literature are searching for the comprehension of the meaning of infertility and not its causality [39, 42]. Our data support that pregnancy occurs first in the unconscious, and we have also found studies that corroborate with this premise [33, 40].

Our experience allow us to hypothesize that those who do not get pregnant may have an unconscious desire of not getting pregnant (because of fear, guilt, or feeling of unworthiness, among other reasons) that get into conflict with the conscientious desire of motherhood.

Such conflicts tend to be overcome, in some point, with our psychotherapy.

Pre-fertilization Group: 3 Couple

We start our psychological work with couples when they are requested for the checklist exams and beginning AR procedure, when first came into the service.

In this group we focus our attention on the level of anxiety and expectation about the upcoming fertilization attempt. We deepen our contact in an individual interview with the couple where we realize that there may be conflicts in some aspects of the couple's relationship or even individual issues of each of them. And, when necessary, we suggest psychotherapy and postponement of the procedure in cases that we notice that the woman (commonly has been the woman) presents deep and complex emotional questions to solve. We have had no difficulty accepting this postponement, for we have always made it very clear that our only intention is to help them to be well – with or without a child in their arms.

About the Controversial Questions of Oocyte Donors

The human reproduction center of CSRM considers that the psychological aspects have major importance, and couples may undergo the program only after psychological assessment. This evaluation is carried in a group of three couples, and group ant individual interventions are offered according to their emotional questions.

The standard script of semi-structured interview applied in all groups and individuals attendance, derived for this evaluation.

To the donor, we ask about her motivation for donating, and we hear from most of them the same justification:

- "I think that if I needed, I would like to have someone who donated, and if my remaining oocytes will be discarded, why can't I help another woman who will not have a child by another way?"

We contraindicate those donators who cannot stop thinking that they may have a child somewhere. This question, when doesn't come up naturally, is put on debate by the psychologist.

Controversial Questions Regarding Oocyte Receivers

Questions slightly more complex are placed for reflection between the receptors and psychologist. When investigating the feeling behind receiving oocytes from another woman, we have realized very clearly that those who accept well the adoption will accept also well the receiving. And they could still realize the dream of experiencing pregnancy, watch the belly filling out, and have the chance of generating a child.

We clarify, according to bioethics, that the child will have two biological mothers – one of the oocyte and another of the uterine – and will receive from the last one, through the pregnancy, important hormonal, neural, and humor information and from the first one half of genetic heritage [46].

And we deepen more the debate around a theme that has caused controversies among physicians and psychologists – in case of pregnancy, tell or not to tell the child how it was conceived? And in which moment we should do it?

We tell the couple that the decision always belongs to them, but we reflect with them what we consider relevant.

Applegarth [32] exposes exactly our vision of the subject:

> (…) keep familiar secrets tends to imply that there is something bad or wrong with the family. Is this how the couple feels about the conception through donation? Absolutely, the decision about privacy puts a lie right in the middle of the most basic relationship: that one between parents and children. As the child gets more integrated to the couple's life, this secret may become an increasing struggle for the couple.
> In the case of opting to maintain the confidentiality, we foresee the countless questions that will require the maintenance of untruths and the possi-

> bility of an unexpected situation requiring the breach of the confidentiality.
> The discovered lie may have a destructive potential for family relationships and child self-esteem.

Probasco (in Applegarth [32]) explains:

> The sharing of the information may be a process of construction by bricks that will extend through a certain number of stages of child development. And ads that emphasizing the decision of tell there is an unconditional love and acceptance of the child"

Professional Ethics

Our internal posture guided by Aristotle's ethics, which defines ethics as the expression of the measure and whose object is the relation of the soul to the environment [43], makes us take a new path when we consider the psychological aspects involved in assisted reproduction. Our professional posture distances us from the maintenance of the "status quo" of AR universe, in which the professionals tend to feel penalized and committed to assist the woman to get pregnant, because she seems to believe that if not, she will not be able to feel complete and fulfilled as a woman. We choose to encourage the pursuit of woman's mental health, stimulating her to have a fuller and happier life, helping her to discover her potentials for a significant action in the world, regardless of the exercise of motherhood tied with procreation.

Here we want to highlight some points for expanding the scope of this theme. We're convinced that this is not only about helping a couple to fulfill their desire to have children. We have a bigger role than this; however getting pregnant, in many cases, happens as a consequence of psychological or assisted reproduction treatment or yet naturally. The role of asking them their the desire to have a child, the role of clarifying what we capture in their subliminal (unconscious) messages and what constitutes the practice of psychotherapy, and, mainly, clarify the important role of being a father and mother. Children must not be conceived because "its part of life have children," "for ensuring the continuity of the family" or "because the pression of the society or couple's family" or "to prove masculinity and femininity."

In the psychological evaluation, in group intervention with several couples as much as individual or single couple, we put on debate the desire of parenthood, the real questions involved in being a father and mother, the meaning of a child into a person's life, adoption, and how to raise healthy children.

Seeking to reflect on parents and children, we have paraphrased Kahlil Gibran [47]:

> …your children are not yours, they come through you, but not from you… do not belong to you, they belong to the world.

It is fundamental to raise awareness that children do not fulfill "existential emptiness," do not save marriages, do not "hold younger husbands with older women," and must not be generated with intention of repair flaws that happened when they were reared – "I want to give what I didn't receive from my parents to my child, material and emotionally," statement made from many of them.

Adoption has been also questioned by us and makes us notice that, in most cases, an adoptive child is seen as "palliative" to impossibility of biological child. It's not rare we hear answers like: "Oh! We have discussed adoption, but we'll really think about it after trying to conceive and fail." For this reason it is easy to understand the mistaken adoptions, which results in problematic children in the future.

Expanding more this debate, we may reflect that the reproductive technologies are part of the range of existent technologies in our contemporaneous society, which offers different kinds of products that are replaced by others more sophisticated, in a speed that move away the possibility of an psychological elaboration of what is offered, and makes the people increasingly consumerist and shallow. What you will do after obtaining the desired product doesn't matter. In this case the product is a "human being," which will grow up and will have his own life and individuality that must be respected from early on in order for him/her to develop all his/her potential

talents and have a healthy and happy life (Raise children it's an art!).

When we assess a couple and realize their conflicts and anguishes, it is our duty to point to them the issues involved in those conflicts and indicate the possibility of, in psychotherapy, solving these questions. It is only then, after rescuing her psychic integrity, when we think about carrying out the attempt of pregnancy with AR.

More than receive and support to the issues regarding the difficult of get pregnant, the psychologist has an important role of guidance, clarify, based on the diagnosis made by psychological perspective.

According to this, a woman who desire having children comes from her socio-cultural designated role and when she is not able to achieve this goal (not only by reproductive impediments), it's the unleash of feelings commons to the most part of women in this situations, already quoted in this text. Those feelings are encountered in relevant literature and certified by clinical practice.

Applegarth [32] declares that regardless of advances of the feminist movement, social and cultural factors still affect the points of view of men and women as fathers and mothers. Moreover infertility is lived as the first crisis of life, because it strongly shakes the basis of early construction of the relationship for many couples, which is conceiving and raising children.

Final Considerations

The psychological elements of the entire problematic of the infertile couple, handled by the health professional, should be seen in a holistic way, more direct and broad. The conduct of the health professional, especially of public and mental health, necessarily implies into prevention. In our service, we carry out health promotion guidelines, such as physical exercise (yoga, pilates, walking) and food care. Our orientation is based on the autogenetic paradigm, proposed in the second half of the twentieth century by the American physician and sociologist Aaron Antonovsky. This paradigm is opposed to the pathogenetic paradigm, based on the search for diseases. While the pathogenesis asks how and why we get sick, Salutogenese asks how we can stay healthy [49].

When we started this work 20 years ago, to be able to fulfill the high demand of couple, we used the interview as Bleger [50] tell us it is:

> A fundamental instrument of clinical method, and a technique of scientific investigation in psychology. The interview reaches the application of scientific expertise and, simultaneously, achieves or allows taking the daily life of the human being to the level of knowledge and scientific elaboration.

Guided by a peculiar way of conducting the interview and a semi-structured script, that step-by-step leads the couple to unravel themselves, without embarrassment and very honestly.

Led by psychoanalytical theoretical grounds, by the empathy and by intuition, but, mainly by the principles of bioethics that must be observed by every psychologist, especially those who work with AR, the respect to autonomy and justice, and the real comprehension that more than do good (beneficence principle), we must do no harm (non-maleficence principle) [51].

The rectitude of principles and the direct form of approach, showing real interest in helping the couple, which doesn't mean necessarily prepare them with the only objective of having their desire fulfilled, of conceiving a biological child or even an adoptive child, makes us question what is believed to be the desire. And we made it, with the intention of taking them out from the plan of obsession [52] (from Latin*o* *obsessione*, which define itself as the concern with particular idea that controls sickly the spirit).

The obsession is worked through facts from reality. We know that the human being is the least fertile of all creatures of the world and that only 20% of the couple who try to become pregnant naturally will be successful [53].

Such knowledge indicate us one direction: not all people get pregnant and not all people will be able to exercise parenthood in a conventional way, attached to procreation and child-rearing, but they may be able to do it, exercising the core essence of parenthood which is the *unveil* (reveal).

We found several definitions to unveil [52], being the most interesting to us the veil – from Latin *vigilare* – be alert, guard, and unveil, be very zealous, be very carefulness, remove the veils, bring to light.

In our profession, we also exercise the unveil in both meanings: of zeal, take care and to remove the veils to bring to light, because the moment we reveal to the couple that he may not have children, we take his dream away. We feel responsible to show them a new path, unveiling it as a social being, culturally inserted that has the inherent potential (your talents) to be exercised in life. Doesn't matter the segment, because we all live in society and we need to have a dignified action and with individual meaning. To live is a scientific knowledge, empirically learning and observing the facts and judging with defined principles, everything that occurs around us. And through this we learn that science and technology are fundamentals for social life, but remembering that, mediating the "knowledge and products" which they provide exists the acting of the soul in the world, praised by ethics. This is the exercise of what we are in essence – human beings.

The origin and definition of the word human [52] – from Latin – *belongs or relative to man*: kind and humanitarian – having this a French origin – *humanitaire*– word that expand the definition and reaches our scope: *humanitarian is anyone seeks the well being of humanity, who loves your peers*.

And in many areas of social life, mainly in ours "Modern Times" exists the need of people, who exercise their essence of "human being" and contribute for a fairer, more dignified and more humane world.

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Violence and Women's Mental Health

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Abbreviations

BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BHS	Beck Hopelessness Inventory
BSI	Beck Scale for Suicide Ideation
CBT	Cognitive behavioural therapy
DV, FV	Domestic or family violence (anyone in family including children)
FGM	Female genital mutilation
GBV	Gender-based violence violence/abuse based on gender
HIC	High-income countries
IPV	Intimate partner violence
IPV	IPV-Scale Lourenço and Baptista Scale
IV	Interpersonal violence (between any individual)
LLMIC	Low- and lower-middle-income countries
SDG	Sustainable Development Goal
PE	Prolonged exposure
P-IPV	Perinatal intimate partner violence
PTSD	Post-traumatic stress disorder
PTSD	Scale CAPS-5
SA	Sexual assault or sexual violence (SV) or rape (not restricted to intimate partner)
SA	Spousal abuse (wife abuse, wife battering or abuse of partner of any gender)
SO	Sexual offense
IES-R	Impact of Event Scale-Revised
STIs	Sexually transmitted infections
VAW	Violence against women
VAWG	Violence against women and girls
VFR	Violence with femicide risk

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Introduction

Every Woman Has a Horrible History to Tell. But Who Listens?

When one cannot silence a woman, the strategy used goes beyond symbolic violence and deviates psychological, economic, sexual and physical, reaching the extreme, that is, the femicide, the final stage of this violent continuum [1]. Violence against women (VAW) or gender-based violence (GBV) is pandemic all over the world, includes many forms and takes place in public and private spaces, for turbulent and peaceful times. In order to

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understand how violence impacts women's mental health, the starting point is to recognize that gender equity is a goal itself. Equity is also essential for achieving other overall society objectives, such as peace, security and sustainable development [2].

Most of health professionals ignore the prevalence of VAW and ask about violence issues during routine appointments only if they perceive signs of IPV or when someone close to the patient referred to it. But if the women report VAW, they usually forward her to psychologist, to social worker or to another facility that "deals" with this condition. However, it is true that the majority of them would like more information and a protocol that guide them about VAW.

It is essential to stimulate medical update and awareness of the prevalence, risk factors, sequela and implications of IPV and GBV as opportunities for early prevention, psychosocial and pharmacological treatment and long-lasting interventions.

Why Did Violence Against Women Became an Important Subject in Science and Society?

Violence impact ranges from immediate to long-term multiple physical, sexual and psychic consequences on women and girls, including death. It negatively affects their general well-being and prevents them from fully participating in society. Violence not only is detrimental to women but also to their families, their community and their country. It has tremendous costs, with medical and legal expenses and productivity losses impacting nationals and global development [3]. Clinical and social concerns at VAW have generated worldwide initiatives to effectively prevent or stop its persistence and escalation.

Worldwide one in three women will experience physical and/or sexual violence in their lifetime, mostly by an intimate partner. When accounting for sexual harassment, this statistic is even higher. Worldwide 1 in 2 women killed were killed by partners or family, while 1 in 20 of all were men killed in such circumstances. This is a stark reminder of the scale of gender inequality and discrimination against women. While some women are more at risk than others, violence can happen to any woman, in any country – regardless of culture, religion or economic status.

The feminist international policy begins and ends with reality. If it is not based on daily lives facts and on statistics of women, and if it does not produce results, it loses its own relevance: 104 countries around the world have laws preventing women from carrying out certain jobs (e.g. in mining, manufacturing, the construction industry, energy, agriculture, water and transport); in 18 countries, men can legally prevent their wives from working; 9 countries have no laws forbidding sexual harassment in the workplace; 23 countries have no laws regarding sexual harassment in education; 37 countries have no laws to protect pregnant employees from being dismissed; 45 economies have no laws to protect women against violence at home; in many countries, women do not have the legal right to own land [4].

Globally, 300 million fewer women own a mobile phone compared to men, narrowing the opportunities for access to information, participation and services including credit, which are provided via mobile telephony in several countries. Only 17 women are Heads of State in all the world's nations [2].

A dominant view postulates that VAW and femicide research fosters that if one investigates closely perpetrators' and victims' characteristics and their relationships, one betrays the social and cultural nature of it. At other side, endeavours need to grasp complexity, to avoid moral panic or other forms of reductionism in scientific research. It requires an integrated perspective in which individual, relational and social dimensions are not artificially separated [5]. Some authors separate individual from social perspectives and settings; others try to understand the processes that trigger VAW and escalate to femicide embracing forensic and legal medicine, psychology and risk assessment researches. Findings on epidemiological aspects, the circumstances and risk factors surroundings GBV as the perpetrator's motive or other specific risk factors (e.g. legal possession of firearms, previous violence and

threats, time occurred after the ending of the relationship) are devoted to profiling some possible preventive strategies that could decrease rates of this crime.

Historical achievements for women's rights, as well as economic targets, did not take place globally. One of the factors responsible for the different nuances of VAW in the world is the cultural representation of the role of women and how women are seen in society. Culture promotes and maintains beliefs that determine dysfunctional behaviours in men and women and sustains the cycle of violence. These nuances range from 70.9% of women in Ethiopia with misguided beliefs that it is right for a man to beat up a woman when she disobeys him [6] till the female population of Sweden backed by an official feminist government policy [2, 7].

Why Does It Seem So Difficult to Care for Women Survivals of Violence at Health Facilities?

Health professionals deal at daily practice with the aftermath of GBV and are in constant need to review research and evidence that show up the magnitude of VAW, its risk factors and its consequences and identify effective treatment and prevention. Some of them find it hard to listen to survivals; they interrupt women's narratives, question their report and send them to other specialists less regarding their emotional suffering at moment. They use medications as a "miracle solution" for everything and consider that women complain unnecessarily even while they identify signs of violence. Some circumstances interfere with asking and care women at most of health services such as pressure to attend many patients, which does not allow them to speak about VAW; professionals, themselves, suffer or commit IPV or experience it with their loved ones and this closeness hampers action; living and working at the same area as the perpetrators or their relatives make professionals ashamed to address the matter or fearing to confront the perpetrator with subsequent retaliation.

Despite appreciating the connection between social factors and poor health, doctors justify their reluctance by overload, not knowing how to ask and what to do about if the report confirms VAW. They question themselves whether it is part of their role to approach violence and choose to avoid opening the "Pandora's box" which brings feelings of impotence and incompetence. It is not easy to feel confident as a devoted health professional when the social gradient has such a strong impact on the health of our patients while, at same time, decreasing income, education, socioeconomic status and social support correlate with increased morbidity and premature mortality [8].

Gynaecologists, psychiatrists, paediatricians and family doctors are the medical specialists closest to the conflicts and the intimate life of women. When doctors ask during a routine visit if there is GBV or IPV, most women perceive a real interest in their overall health. This screening is quite important as it is known that femicide is preceded by other forms of violence that are often reported at health institutions of health or justice and therefore is preventable.

The curriculum of medical schools often neglects GBV issues and focus on a list of symptoms, nosological diagnoses and neuromolecular repercussions. The medical student and resident training reveal opportunities for introducing the gender perspective helping to diagnose, treat and prevent the transgenerational transmission of VAW and allow the expansion of the mental universe of future caregivers.

Table 1 shows frequent questions asked during mentoring programme for residents in psychiatry and obstetrician according to their male (m) or female (f) gender role.

Working sensitively in the testimony of women's mental suffering leads us to discover that, in addition to the molecular aspects that influence the central nervous system, relational and social issues clearly affect female behaviour and mental health. Therefore, professionals devoted to women's mental health become activists, as well as experts on hormones, genetics, psychopharmacology and reproduction, due to the evident inequality at the base of the pyramid of female mental illness.

Table 1 Issues brought by young professionals to a women's mental health service

Frequent questions during the supervision of residents in psychiatry and obstetrician according to their male (m) or female (f) gender role
1. What is empowerment? Can empowerment be trained? Isn't it only a political issue? (m)
2. How can I question a patient about her sexual life and about violence, isn't it an invasion of her private life? (m)
3. If she says she has IPV problem, I do not know what to do or what to say (m,f)
4. Should I ask the partner to leave the consultation room? (m,f)
5. When I went to ask about VPI, I realized that I am myself experiencing the same (f)
6. It happened to me; a relative abused me, after I told my mother, and she complained; the whole family turned on us. I don't know if I will be able to attend these classes and service (f)

Guidelines and tools and setting norms and standards for an effective health response to VAW have been developed by the World Health Organization (WHO) in order to achieve the *Sustainable Development Goals* (SDG). They are free for download in many languages at its website, contributing to sensitize students and health professionals about VAW and to encourage initiatives that seek the expansion of networks to support victims. Inadequate contact with GBV survivors ends up turning into another type of preventable violence [3].

How Women Suffer from Violence

Historical Aspects of Gender Violence

Gender-based violence (GBV) does not exclusively limit man-made violence against women (VAW), since the term "gender" includes other interfaces. However, these concepts began to be used as synonyms by the feminist movement in the 1970s. At that time, the evidence of VAW gained repercussion and were debated in such bunt way that GBV came to be understood as a particular phenomenon of the feminine gender, becoming target of studies and political debate. It is known that there is an overlap in terms of the severity and prevalence of man-made violence against women. In the United States and France, 1 in 4 women (27.4%) and 1 in 9 men (11.0%) have experienced sexual violence, physical violence and/or stalking by an intimate partner in their lifetime [5, 9]. It is such an old and terribly common phenomenon that its trivialization stopped the cry for help of women raped for millennia.

There is the assumption that VAW was seized during the primary processes of socialization and displaced to the sphere of society in secondary processes. Among the possible reasons for inequity between men and women, some will insist on the biological nature. Would men be more subject to impulsivity/aggressive reactions due to the greater contribution of androgenic hormones such as testosterone? Was the woman in an imperative position of inferiority due to the small physical size? Or is she alienated from other capacities than motherhood, since it is her fundamental and non-transferable socially stigmatized role? [10]. It is already quite clear that the origin of GBV is of a social nature, protected by judicial and political structures. To understand the sectarian character of the domination-submission relationship between genders, it is necessary to first understand what the concept of gender is about. The concept of gender has worked for our ancestors as the structurer of the social division of labour and did not necessarily imply the devaluation of the activities attributed to women [11]. The patriarchate, which would have emerged after the agricultural revolution, had begun 12,000 years ago, changing these values. Some evolutionary psychologists' postulate that our hunter-gatherer ancestors lived in troops not composed of nuclear families centred on monogamous couples. Instead, the women in one troop could have sex with several men or women, and parental care was exercised by everyone in the group since no one knew how to definitely recognize their biological children. When one began to sow and harvest grain and to breed cut or traction animals, reproduction was of great economic value, since the man realized that the more children he had, the greater his economic power [12]. Therefore, sexual domination is present in the

beginnings of patriarchalism. It is not by chance that such a relationship establishes the necessary conditions for the manifestation of violence in its most varied forms, especially sexual violence (SV). While men judge themselves superior to women, oppressing and subjugating them, they consider themselves the masters of these women and their bodies. This behaviour is reinforced through the families' roles, with boys valued for strength and aggressiveness, wagging with trolleys and arms, while girls are valued for sweetness and care of the house, the family and the domestic routine, playing with dolls and pans [13].

Types of Violence

VAW encompasses many forms and shapes including stalking, patrimonial, psychological, sexual and physical violence. It can be acted out through behaviour or can be psychological almost invisible and difficult to measure. It can last long periods or be brief but always intense. Violence is considered as an action that involves the use of real or symbolic force, on the part of someone, with the purpose of subjecting the body and mind to the will and freedom of others. It is not exclusive to men, but women could also be perpetrators. Data from many researchers as from the World Health Organization (WHO) are clear in evidences that women are more likely than men to be the target of violence, sexual abuse, psychological abuse, domestic violence and intimate partner violence (IPV). VAW is one of the highest concerns global wise, and much attention, resources and sensitivity are required to put in motion coordinated strategies to intervene to stop its escalation and worsening. In the last decade, there has been a rapid increase in the body of research and evidence on the prevalence of IPV and its effects on health. There are also other forms of violence that are common and go unnoticed in everyday life and are therefore no less harmful. There are other forms of violence that are common and go unnoticed in everyday life and are therefore no less harmful, such as institutional violence, lack of housing, sexual orientation or race and precarious insertion in the labour market [14]. VAW can occur isolated or simultaneously, struck harder in the body, while other forms deeply wound the soul. VAW can occur in cycles and recur daily, for a long time, with a dangerous escalation that can lead to death [15].

A. Intimate Partner Violence (IPV) It is a global public health and human rights problem that includes physical aggression, sexual coercion, psychological abuse and/or controlling behaviours perpetrated by a current or previous intimate partner in a heterosexual or same-sex relationship. IPV affects both men and women, but there are evidences that women are largely more affected during their lifetime. Physical and sexual harms from IPV include injury, increased risk for sexually transmitted diseases, unwanted pregnancy, perinatal complications and sometimes death. Psychological suffering manifests by depression, anxiety, post-traumatic stress disorder, substance abuse, impulsivity and suicidality and non-specific physical complaints thought to be related to the traumatic nature and chronic stress of IPV. Children who witness IPV are also negatively impacted in short and long term. IPV is largely prevalent with significant negative impingement and must be target for prevention and intervention all over the world. The World Health Organization (WHO) in a multi-country survey found that 15–71% of women reported lifetime physical or sexual violence by a partner, with the highest rates found in rural than urban areas of all countries although quite worse at Ethiopia and Peru [16]. The WHO also found in a Global Status Report on Violence Prevention, that one in three women have been victim of physical and/or sexual violence by an intimate partner during her lifetime. The most prevalent age is between 18 and 30 years. Methodological differences could influence prevalence evaluation as threats of violence and psychological violence are considered in some population sample and in others not [15].

IPV presents itself with constant threats and/or physical, sexual and psychological violence, controlling and abusive behaviour and economic

restrictions. Even after the end of the violence, there are important long-term sequels. It can cause death, frequent visits to health services with low resolution of complaints and psychosocial, physical and sexual problems.

Unfortunately, little has been done in tracking this type of violence and active actions to change the current panorama avoiding sequels and giving women conditions to leave the IPV circuit. Screening increases the identification of survivals of IPV in health services. Pregnant women are more likely to talk about IPV during prenatal care; however, there is no evidence for universal screening in health services. The information about main types of IPV can be found at: http://www.who.int/bulletin/volumes/96/9/18-211607/en/; www.womenshealth.gov

Domestic Violence or Abuse

Intimate partner violence (IPV) or domestic violence (DV) can include forced sex and physical and emotional abuse (such as cruel words or threats). It can occur between married people, a couple living together or separated or a couple of the same sex. Psychoeducation for VAW at facilities waiting rooms, handing out flyers can stimulate conversation wheel coordinated by a health professional focusing gender issues as:

It is domestic violence if partner:

- Controls what you're doing
- Checks your phone, email or social networks without your permission
- Forces you to have sex when you don't want to
- Controls your birth control or insists that you get pregnant
- Decides what you wear or eat or how you spend money
- Prevents or discourages you from going to work or school or seeing your family or friends
- Humiliates you on purpose in front of others
- Unfairly accuses you of being unfaithful
- Destroys your objects
- Threatens to hurt you, your children, other loved ones or your pets
- Hurts you physically (e.g. hitting, beating, punching, pushing, kicking), including with objects or a weapon
- Blames you for his or her violent outbursts
- Threatens to hurt herself or himself because of being upset with you
- Threatens to report you to the authorities for imagined crimes
- Says things like, "If I can't have you, then no one can"

In a same-sex relationship, the signs of an abusive relationship are the same as other people so the partner may hit you, try to control you or force you to have sex, but you may also experience additional signs of abuse, including:

- Threatening to "out you" to your family, friends, employer or community
- Telling that you have to be legally married to be considered a victim of domestic violence and to get help
- Saying women aren't or can't be violent
- Telling you the authorities won't help a lesbian, bisexual, transgender or other nonconforming persons
- Forcing you to "prove" your sexuality by performing sex acts that you do not consent to

DV or IPV happens in all types of relationships, including couples dating, married, same-sex, former or ex and couples who live together but are not married; IPV happens more often among younger couples. Almost half of American Indian and Alaskan Native women, more than 4 in 10 African-American women and more than 1 in 3 white and Hispanic women have experienced sexual or physical violence or stalking by their intimate partner.

- Nearly 23 million women in the United States have been raped or experienced attempted rape in their lifetimes.
- More than 33 million women – including 1 in 3 African-American and white women and 1 in 4 Hispanic women – have experienced unwanted sexual contact, other than rape, by an intimate partner.
- Gender and sexual minority women, such as lesbian or bisexual women, may be more likely than heterosexual women to experience

DV. Two in five lesbian women and three in five bisexual women experience IPV at some point in their lifetimes. But there is not yet enough research on all types of gender and sexual minority women to know for sure (www.womenshealth.gov).

Most of the time, women are not prone to disclosure of IPV at first visit or early interviews. They may be more willing when they trust the psychiatrist, feel safe and are reassured about confidentiality. Stages of trust till IPV was disclosed include precontemplation, contemplation, determination, action, maintenance and termination.

It's important to have a respectful attitude towards the survival. Depression/Anxiety assessment, diagnosis and treatment should include discussion of IPV and its association with symptoms and family status, including the way children act during violent events [17].

Children and IPV Important to mention is the fragility of children who witness IPV. Not only their physical and mental health suffers but their role as future men and women who could stop gender violence. Children who grow up in families where violence is present may suffer a range of behavioural and emotional disturbances. These can also be associated with perpetrating or experiencing violence later in life. IPV has also been associated with higher rates of infant and child mortality and morbidity (e.g. through diarrheal disease or malnutrition). Children exposed to IPV are at increased risk of attention-deficit/hyperactive disorder (ADHD), anxiety and post-traumatic stress symptoms, mostly among girls. It is quite important to assess them for all types of maltreatment. The health professional needs to approach by interviewing family members individually about their experiences at home as excessive alcohol use is a risk indicator for different types of IPV which are sometimes not recognized as violence by the victims.

Asking children about their daily experiences in family could identify problems associated with IPV such as neglect. Non-offending parents underestimate the likelihood that their children have been exposed to IPV and need help to understand care giving that each child needs to receive in the family. The healthcare provider must know the importance of addressing safety of each family member, as assisting the mother and children priorities include not compromising her safety but helping her to see the relationships between the children's problems and exposure to IPV [17].

B. Sexual Violence (SV) and Sexual Offense (SO)

SV is a serious violation of human rights – admittedly a problem of legal, social and a public health concern. Studies and research over decades have demonstrated a strong correlation between SV, mortality and morbidity of women, with a high association with mental illness prevalence.

SV is included in the broader spectrum defined as gender violence, which, according to the Declaration on the Elimination of Violence Against Women [18], encompasses any act of gender-based violence (GBV) that results in injury or physical, sexual or psychological suffering, including threats, coercion or deprivation of liberty, in a public or private space, as said before. VAW is not only a manifestation of gender inequality but also an instrument for maintaining the imbalance of rights between men and women. It is therefore important to note that the conditions favouring a manifestation of gender inequity favour the occurrence of any other GBV.

SV is any sexual act, directed against a person's sexuality using coercion, by any person regardless of their relationship to the victim, in any setting, including but not limited to home or work. SV ranges from verbal harassment to forced penetration, and an array of types of coercion, by social pressure and intimidation to physical force. It includes but is not limited to: rape within marriage or dating relationships; rape by strangers or acquaintances; unwanted sexual advances or sexual harassment (at school, work, etc.); systematic rape; sexual slavery and other forms of exploitation/violence, which are particularly common in armed conflicts includ-

ing forced impregnation; sexual abuse of a person who is unable to understand the act nature or condition, to decline participation or to communicate unwillingness to engage in the sexual act due to illness, disability or under influence of alcohol or drugs or because of intimidation or pressure; incest, rape and sexual abuse of children; "customary" forms of SV, such as forced marriage or cohabitation; whether or not the act is completed.

Coercive penetration and the attempted penetration of orifice or forcing to do something sexual that woman perceive as degrading/humiliating are other types of SV. It could be under circumstances of threats (physical harm, not obtaining a job/grade, etc.), drug use, during or post-conflict/war and during humanitarian crises [3].

Perpetrator of SV could be a strange or an acquaintance and, unusually, may be women or children.

Transactional sexual relationships need special attention if women are in position of victims and are obliged to "sex for basic needs", deserving interventions to protect them from exploitation. In parallel "sex as material expressions of love" draws attention to the idealized connections between love and money and the central role of men as providers in relationships. These two paradigm positions of transactional sex contrast with "sex for improved social status" when women stay as sexual agents [19].

In 2010, 7.2% of women worldwide reported had ever experienced non-partner sexual violence. The highest estimates of prevalence were in sub-Saharan Africa, central 21% and southern 17.4%, with lowest prevalence for Asia, south. Limited data were available from other regions. Although large variations between settings need to be interpreted with caution because of differences in data availability and levels of disclosure, findings indicate a pressing health and human rights concern [20]. A Latin American study estimated that around 5% of adult victims of sexual violence reported the incident to the police and 10–15% report to health professionals. The best quality prevalence data on SV come from population-based surveys as other sources of data on SV include police reports, studies from clinical settings and nongovernmental organizations. However, because only a small proportion of cases are reported in these settings, they underestimate prevalence [21].

Risk factors: The most important risk factor associated with SO is being a woman and being a child. In societies with greater gender inequity, there are higher prevalence of GBV, less cases reported, less aggressors' punishment and less possibility of breaking with the violent context. Cultural aspects such as well-defined and statics gender roles, conservatives religious and family values based on abusive hierarchy and racism are associated with SO. The victims' financial dependence, personal factors and history are also risking for the repetition of violence. The literature consistently demonstrates evidence that child sexual abuse survivors are at greater risk of victimization later in life than the general population (47.9%) although the whole process involved has not yet been characterized [22].

The transgenerational transmission of violence is linked to child's interaction with traumatic events at domestic environment, where greater tolerance for abusive behaviour predisposes the child and future adult to maintain a cycle of deleterious experiences. Mental illness or other vulnerability conditions are also SO risk factors.

We can conclude that factors at individual, family, community and society levels are associated with intimate partner and sexual violence. We notice a growing concern on determining factors specifically associated with perpetrating SV as we can see below on Tables 2, 3 and 4 that lists IPV, SV and perpetrating SV risks [3].

Sexual Violence and Women's Health SV is considered one of the worst traumas experienced by a woman. When does not result in death, it predisposes the victim to acute and chronic mental illness, as well as other comorbidities and repercussions on physical health [25]. The most frequent mental health disorders associated with SV are mood disorders (depression, dysthymia and bipolar affective disorder), post-traumatic

Table 2 Risk factors for intimate partner and sexual violence

Lower levels of education (both perpetration and experience of SV
Exposure to child maltreatment (perpetration and experience)
Witnessing family violence (perpetration and experience)
Antisocial personality disorder (perpetration)
Harmful use of alcohol (perpetration and experience)
Multiple partners or suspected by their partners of infidelity (perpetration);
Attitudes that condone violence (perpetration)
Norms that privilege higher status to men and lower status to women
Low levels of women's access to paid employment

Note: Adapted from WHO_RHR_12.37_eng.pdf

Table 3 Indirect signs of child and adolescents victims of sexual offense

Age-inappropriate sexual attitudes
Demonstration by speech, gestures or attitudes knowledge about sexual activity superior to its development phase
Frequent or compulsive masturbation independent of the environment
Frequent interruption of play to enable intimacy contact, genital manipulation, repetition of offender's attitudes
Recurrent urinary tract infections
Nutritional disorders
Offended children do not look like victims. Young children perceive sexual offense as love and affection. Adolescents begin to realize that there is something wrong but are afraid to report

Note: Adapted from Nahas [23]

Table 4 Factors specifically associated with SV perpetrator

Beliefs in family honour and sexual purity
Ideologies of male sexual entitlement
Weak legal sanctions for sexual violence
Previous violent criminal behaviour
Mental illness

Note: Adapted from WHO_RHR_12.37_eng.pdf, Henrik [24]

stress disorder, anxiety disorders (generalized anxiety, acute stress disorder, panic, agoraphobia, social phobia, obsessive-compulsive disorder), sleep difficulties, somatic complaints and suicidal behaviour [26]. In addition, there is a high prevalence of alcohol and drug abuse and other self-destructive behaviours, leading to a higher prevalence of cluster B personality disorder especially the stigmatizing borderline disorder, which would be more adequately defined as complex trauma disorder (CTD). Studies are inconclusive about the correlation between schizophrenia or atypical psychoses and SO in childhood [27, 28].

Reproductive health is impaired by gynaecological trauma, unintended pregnancy, unsafe abortion, sexual dysfunction, sexually transmitted infections including HIV, traumatic fistulae and pelvic chronic pain. These survivals have greater susceptibility to symptoms associated with hormonal oscillation throughout the reproductive cycle, predisposing them to premenstrual dysphoria, postpartum and climacteric mental disorders. As survivals of SV can have a high-risk and self-harm behaviour, they live with greater chance of suffering subsequent sexual violence. Fatal outcomes are not that rare, and deaths could be due to suicide, pregnancy complications, unsafe abortion, AIDS, murder during rape or for "honour" and infanticide of a child born of rape [3].

Some health problems frequently associated with SV are obesity, asthma, chronic headache and higher prevalence of cardiovascular diseases at medium and long term. There is also the possibility of intense reactions to diagnoses and treatment of STI notably if associated with unwanted pregnancy or during the decision-making process of legal interruption or maintenance of pregnancy after rape.

Chronic sexual offense (regardless of age) with consequent prolonged suffering restricts women's possibility of taking care of herself and others with poor adherence to preventive tests and treatment in general.

C. Emotional and Verbal Abuse (EVA)

As there are different forms of violence, some hit the body harder, the others deeply the soul. EVA can have short-term and long-lasting effects that are just as serious as the effects of physical abuse. EVA includes insults and attempts to scare, isolate or control. It is also often a sign that physical abuse may follow. EVA begins suddenly and con-

tinues if physical abuse starts. Some perpetrators may start out behaving normally and then begin abuse after a relationship is established. They may purposefully give a lot of love and attention, including compliments and requests to see the victim often, tries to make her feel strongly bonded to them, as though it is the two of them "against the world". Over time, abusers begin to insult or threaten their victims and begin controlling different parts of their lives. This change can leave victims feeling shocked, confused and embarrassed or foolish for getting into the relationship. Some men use gaslighting, a form of emotional abuse, to maintain power and control. Abuser stimulates the victim to question her memories and psychological sanity becoming more likely to feel dependent and stay in the relationship. It happens over time and may not be noticed at first. Staying in an emotionally or verbally abusive relationship can have long-lasting effects on physical and mental health, including chronic pain, depression, or anxiety.

D. Digital Abuse (DA)

It uses technology, especially texting or social media. DA is more common among younger adults, but it can happen to anyone who uses smartphones or computers. It can include repeated unwanted calls or texts; harassment on social media; pressure to send nude or private pictures (sexting); texts or social media to check up, insult or control whom she can see or be friend with; demanding her passwords to social media sites and email; and demanding her reply right away to texts, emails and calls.

E. Financial Abuse

This form of GBV happens when an abuser has control over finances in a relationship and withholds money from the victim or damages her loved objects. Often, a woman does not leave a financial abusive relationship because she fears not being able to provide for herself or her children. Often, financial abuse is subtle and gradual, so it may be hard to recognize. The partner may act as though taking over the finances is a way to make life easier for women, as if he is doing her a favour and might explain that giving her a set amount of money will help keep the family on track financially. But slowly, she is asking for money and being refused.

It can include:

- Control, retain or take money from her
- Cause deliberate damage to object she likes
- Destroy or retain instruments of work, personal documents, goods and rights
- Urging to or demanding her to quit job or preventing from working
- Stalking or harassing her at work
- Giving her a set amount of money to spend and no more
- Constantly questioning purchases and demanding to see receipts
- Making financial decisions without consulting her and selling her properties
- Filing documents with her name attached to his
- Not paying child support so she can't afford rent, food and other needed items
- Forcing her to open lines of credit

F. Human Trafficking

It is a form of slavery**.** It happens when a person is forced or tricked into working in dangerous and illegal conditions or having sexual contact with others against their will. A person who is trafficked may be drugged, locked up, beaten, starved or made to work for many hours a day. Girls and women are the most common victims of sex trafficking.

Traffickers control victims by:

- Threatening to hurt them or their families
- Threatening to have them deported
- Taking away their passports, birth certificates and ID cards
- Making them work to pay back money they claim is owed
- Giving them drugs in order to create an addiction or control them
- Making them perform sexually to get money or more drugs
- Preventing their contact with friends, family or the outside world

A trafficked person may be forced to prostitution, farm work, cleaning, child care, sweatshop work, etc. Sometimes a woman or girl may "end up" trafficked after being forced to marry someone against her will; her husband and his family have control over her. Not all people who are trafficked are taken across state lines or national borders. A global study by the United Nations identified trafficked persons originated from 106 countries. Of over 17,000 victims, 28% were children, with girls outnumbering boys by a factor of 2.5. According to United States, federal law sex trafficking involves "recruitment, harbouring, transportation, provision, obtaining, soliciting or patronizing of a person for the purpose of a commercial sex act (any sex act on account of which anything of value is given to or received by any person) using force, fraud, or coercion, or involving a child less than 18 years of age" [29].

The physical and mental health effects of sexual trafficking are quite serious. Studies show higher levels of fear, more isolation. Victims have greater trauma and more mental health needs than other victims of crime. Women and girls trafficked may also misuse alcohol or drugs to cope with their situation.

It is not easy to recognize signs of women trafficking, and health services need to know how to do that [29]:

- Appears fearful, anxious, depressed, submissive, tense or overly paranoid
- Seems very scared if law enforcement is talked about
- Does not make eye contact
- Very underweight
- Shows signs of physical abuse (bruising, cuts, restraint marks on the wrists)
- Has very few or no personal possessions
- Has someone else in control and insisting on being present or translating
- Cannot say her address
- Does not know where she is (the country, state, town or city)
- Has no sense of time of day or time of year

Their health needs' span is associated with STIs, pregnancy, injuries from physical and sexual assault, post-traumatic stress disorder (PTSD), depression with suicidality and other behavioural problems. Adolescent girls in one study had a 47% prevalence of STIs at the time of evaluation and a 32% rate of prior pregnancies. Forty-seven percent of youth in another study reported suicide attempts within the past year, and 78% met DSM criteria for PTSD. As they can experience both sexual and labour exploitation, health complications are related to either form of trafficking [29].

G. Stalking

It is repeated contact that makes a victim feel afraid or harassed, by following or calling often. Stalkers may also use technology sending unwanted emails or social media messages. A woman can be stalked by a stranger, but most stalkers are people she knows, even an intimate partner or a past one. Threats to disseminate intimate photographs or details of their sexual relationships without the woman's permission are also forms of IPV. Stalking may get worse or become violent over time and may threaten the victim's safety by clearly saying the wish to harm her. It can occur in heterosexual and homosexual relationships.

Stalking may include following around or spying on her; sending her unwanted emails or letters; calling her often; showing up uninvited at her house, school or work; leaving her unwanted gifts; damaging her home, car or other properties; and threatening her, her family or pets with violence.

"Adolescent victims report more symptoms of post-traumatic stress, mood disorder, and hopelessness, as well as more instances of alcohol use, binge drinking, and physical dating violence victimization. They also reported engaging in sexting behaviours and oral sex with significantly more partners than their non-victim peers. As such, this population merits further attention by prevention researchers and practitioners" [30].

H. Violence Against Immigrant and Refugee Women

Female immigrants or refugees face many of the same challenges as other abused women.

However, they may also face some unique challenges, such as a fear of being deported or of losing custody of their children. Physical, sexual, emotional or other types of abuse are never OK, even if it happens within a marriage. The prevalence of depression among refugees is comparable to that in the general population. They face significant trauma and loss so are at risk for mental health consequences, including post-traumatic stress disorder. Most (estimated at 80%) individuals who experience traumatic events heal spontaneously after reaching safety. Empathy, reassurance and advocacy are key clinical elements for recovery process, it is remarkable that pushing for disclosure of traumatic events by well-functioning individuals may result in more harm than good. Primary care practitioners play a key role in the recognition and management of PTSD in immigrants and refugees as they underutilize formal mental health services. Integrated treatment approach is often needed for extreme traumas, such as torture and rape, which have severe and long-lasting consequences for both physical and mental health. Torture and rape tend to affect the whole family, particularly children, who may not display dramatic or easily recognizable symptoms. Certain symptom should alert clinicians including unexplained physical complaints, sleep disorders, depression, panic disorder and somatoform disorder. Other presentations, such as severe dissociation mimicking brief reactive psychosis, dissociative disorders (amnesia and conversion) and psychotic depression, although less frequent, may also be related to post-traumatic stress disorder. Key elements for assessment include level of psychological distress, the impairment associated with the symptoms for the patient and her family, substance abuse and suicidality [31].

I. Perinatal Intimate Partner Violence (P-IPV)

Conception, pregnancy, childbirth and transition to parenthood present challenges to parents individually and their relationship, over physical, emotional, social and financial changes accompanying pregnancy. These challenges could cause stresses affecting each parent and both leading to the initiation, continuation or increased frequency or severity of psychological, sexual and physical aggression, even if the couple are together or not. IPV is frequent at this period and could be worsened by use of alcohol and drugs and if the pregnancy was not desired and accepted.

Maternal mental health problems associated with P-IPV include depression, anxiety, post-traumatic stress disorder (PTSD), psychosis, inability to trust others, self-harm, risky behaviours and multiple psychosomatic conditions including chronic pain, all of which may be referred to psychiatrists. There is evidence of varying quality of P-IPV being associated with miscarriage, placental abruption, preterm birth, low birthweight, foetal death and other sequelae [32].

A systematic literature review [33] shows effects of IPV during pregnancy on perinatal mental disorders in low- and lower-middle-income countries (LLMIC). The prevalence of physical IPV ranged 2–35%; sexual IPV ranged 9–40%; psychological IPV ranged 22–65% and depression ranged 15–65% during pregnancy and 5–35% during the postpartum period. Suicidal ideation ranged 5–11% during pregnancy and 2–22% during the postpartum period. Results of untreated mental disorder include adverse pregnancy outcomes, preterm delivery, low birthweight, and perinatal and infant death. Further, depression and anxiety disorders during pregnancy can increase the risk of postpartum depression, impairing mother-child attachment, caregiving and child growth and development. In LLMIC, 16% of pregnant and 20% of postpartum women experience some type of mental disorder, double rates found in high-income countries. Poverty, social networks, infant sex and health, relationship quality and exposure to traumatic events including IPV are social risk factors related to mental illness during pregnancy and postpartum period. IPV prevalence was calculated at 19.8% in LLMIC ranging from 12% in Bangladesh to 57% in Uganda. Association between IPV with onset, duration and recurrence of mental disorders at this specific period was found in high-income countries (HIC) data.

As the proportion of pregnant women who experience a mental disorder may vary by trimester with greater risk in the second and third trimesters, health system and professional need to be aware of the high prevalence of P-IPV and its consequences in order to proper screening and treat besides organizing methods to prevent dissemination of this public health threaten.

The screening for different forms of abuse and controlling behaviors (as chiding her for having a girl, taking away her mobile phone) are very important, as much as helping women to deal with overburden at postpartum, the increased vulnerability and disappointment with her baby for various reasons. It is valuable to take actions to prevent P-IPV, self-harm and suicide being supportive and making with the woman at risk a safety plan immediately. Orientation on cultural issues related to patriarchy, sex of the child, nature of marriage and role of in-laws could go along with the benefit of nurse home visits addressing depression, child care and IPV. Women need to be encouraged to use protective web and to fight for a longer paternity leave enabling husband to get more involved with the baby care reinforcing love and family bonding. It should be necessary, if diagnosed, to prescribe adequate medicine for moderate or severe depressive symptoms, considering breastfeeding possibility and safety for woman and the neonate.

Perinatal Violence at Healthcare Settings/ Obstetric Violence (OV) Abusive, disrespectful and neglectful treatment of women during childbirth in healthcare systems is another emerging concern as a form of violence named "obstetric violence". In some Latin American countries, it is also included in legislation. The challenge is clearly identifying which acts constitute abuse and disrespect and which are related to poor quality of care within weak health systems. Enlightening the structural dimension of this violence, increase its visibility and generate actions from health systems to ensure that all sexual and reproductive health services are provided in a manner that fully respects women's choice, autonomy and rights. The same principle should apply to women who search for post rape gestational interruption, permitted by law in many countries but barred in practice revictimizing women [14].

J. Violence Against Women with Disabilities
Research suggests that women with disabilities are more likely to experience DV, emotional abuse and sexual assault than those without disabilities. They may be more isolated and could feel unable to report the abuse or even may be dependent on the perpetrator for their care. Women with disabilities are usually abused by a known one such as a partner, family member, caregivers or personal assistants. Women who need help with daily activities like bathing, dressing or eating may be more at risk of abuse due to their physically or mentally vulnerability during life span.

Mental illness plays a mediating role in the relationship of child abuse and IPV. It could also be the effect of IPV experience and modulate the risk for further revictimization. There is need to generate more evidence through pathways between previous child abuse, mental illness and IPV victimization. The identification of potential arena for violence prevention and response interventions is quite necessary [34].

The violence against women with disabilities could include suddenly being unable to meet essential day-to-day living needs that affect health, safety, or well-being; lack of contact with friends or family; visible handprints or bruising on the face, neck, arms or wrists; burns, cuts or puncture wounds; unexplained sprains, fractures or dislocations; signs of injuries to internal organs, such as vomiting; wearing torn, stained, soiled or bloody clothing; and appearing hungry, malnourished, disoriented or confused.

K. Violence Against Girls and Adolescents
Estimates of child maltreatment indicate that nearly a quarter of adults (22.6%) worldwide suffered physical abuse as a child, 36.3% experienced emotional abuse and 16.3% experienced physical neglect, with no significant differences between boys and girls (30–32). However, the

lifetime prevalence rate of childhood sexual abuse indicates more marked differences by sex – 18% for girls and 7.6% for boys. Girls are also more likely to be exposed to certain harmful practices, such as child marriage and female genital mutilation/cutting (FGM/C) both of which are direct manifestations of gender inequality [35].

Sexual violence is one of the most disturbing violations of children's rights. As such, it is subject of international legal instruments dedicated to protect children from its multiple forms. Acts of sexual violence, which often occur together and with other forms of violence, can range from direct physical contact to unwanted exposure to sexual languages and images [19]. More evidence is needed on other old and new forms of violence that adolescent and girls are exposed to. Although children of all ages are susceptible, adolescence is a time of marked vulnerability, as a transition into womanhood when sexuality and gender roles assume greater importance in how adolescent girls are viewed socially. Puberty is also a time in which girls are more likely to engage in risky behaviours such as drug and alcohol abuse and unprotected, unsafe sex that increase their susceptibility to violence. They may also face increased social criticism if they do not adhere to, and comply with, expected gender roles, and this can lead to circumstances in which girls are sometimes blamed for their own victimization [35]. Alarming prevalence data collected between 2005 and 2016, around 15 million adolescent girls between ages of 15 and 19 suffered forced sex during their lifetime; 9 million of these girls had been victimized in the last year. Nevertheless, this issue is not approached with adequate proportion in medical consultations and other healthcare, which contributes to the perpetuation of the problem. Research shows that only 1% of adolescent girls who have had forced sex sought professional help.

Sexual violence against children and adolescents is often silenced. Among the reasons is the fact that it is perpetrated mostly by adults of the family nucleus itself. By far the most common perpetrators of violence against young women in all countries are intimate partners, defined as current or former husband or boyfriend. Silence is due to subordination, fear and guilt. Data from 28 countries indicate that 9 out of 10 adolescent girls who have suffered forced sex reported having been victimized by someone close to them. Friends, classmates and caregivers are other common perpetrators [35].

Factors such as schooling and unfavourable social class are seriously related. In 17 low-average countries, about 17 million adult women were victims of childhood sexual abuse [36]. In 28 countries in Europe, about 2.5 million young women report contact and contactless sexual violence before the age of 15. It is not only prevalence, but violence is less strong among girls who have access to education, social security and the principles of gender equity. Gender inequity contributes not only to the spread of violence against girls but also to its acceptance. In some society's sexual violence, child marriage and FGM/C are not considered forms of violence, not even problems to be solved, and many girls do not identify these violations as abuse (Table 5).

There is no other way to combat the problem but collaborate with the diffusion of information and empowerment of girls and adolescents. In this context, it is of paramount importance for the health professional to understand his role as responsible for the care and guidance of his patients in a potential risk of violence. Investigate whenever possible and in the absence of screening tools, deepen communication, undress prejudices and judgment to listen and welcome patient testimonials. Seeking training and problem awareness are the initial and essencial steps for taking the necessary measures and conducting the indentification of a situation of violence, remembering that an unprepared approach can cause even more damage.

L. Female Genital Mutilation (FGM)

WHO defines FGM as any procedure that alters or causes intentional injury to the female genitalia for non-medical reason. It therefore comprises all procedures involving the partial or total removal of the external female genitalia or other injuries of the female genitalia.

It is estimated that today, more than 200 million girls and women have been victims of FGM in 30 countries in Africa, the Middle East and

Table 5 Incestuous families

Parents' attitude and/or guardians in incestuous families
Geographic and social isolated families: preservation of secrecy
Perversion of family roles with imbalance of parental power by the protection of secrecy
Three levels of dysfunction: power, confidence and inappropriate use of sexuality
Intergenerational breakages do not internalize the law, impairing the psyche structuring
Independent of social level
Family members are substances misusers (alcohol, licit and illicit drugs)
Intrafamilial offender behaviour
Extremely protective or possessive with child/teenager, denying her usual social contacts
Can be seductive, insinuating especially with children and adolescents
Believes that sexual contact is a form of family love
May accuse the victim of promiscuity, seduction and sexual activity outside the home
Can tell stories of offenses referring to others in order to protect himself or other relative
Threatens physical, psychological and economic integrity of the victim and the family
Deny the offense, fear the consequences
Offender often has history physical, sexual or emotional abuse in childhood
Mother's characteristics
Childhood history of SO, abandoning behaviour, grew up in conflicting families, suffered from maternal deprivation
Depressed, passive, isolated, "sleep of death"
She eases incest unconsciously through doubt, denial
Confusion and ambiguity: love and hate, believe and deny, perceive and do not know
Guilty: not perceive, not protect, ruin of family unit
Fear of being without basic resources, of being overwhelmed with responsibilities and frustrated as a woman due to the incest

Note: Adapted from Nahas [23]

Asia where it is concentrated. Although there are some divergences regarding age, the agent responsible for the practice and method of mutilation practiced in each country, it is known that the main victims are children from newborn to age 15. In most countries, girls are cut before age 5. More than half live in Indonesia, Egypt and Ethiopia. However, the practice is also found in pockets in Europe, Australia and North America which in the last decades have been migrants' destinations. There are still less quantifiable traces of practice in various regions around the world [35].

Among the FGM, there are three main methods: clitoridectomy consisting of ablation, cutting and extirpation of the clitoris, often accompanied by ablation of the vulva's inner lips and infibulation, which consists of suturing the labia majora's lips, leaving a small orifice to drain menstruation and other fluids. Mutilation does not happen at a single moment in a woman's life. Each time the infibulated woman has a child, for example, or if she cuts the suture she has made before, or the larger vulva lips are torn by the baby's passage, later she is again infibulated. Not infrequently the three mutilations are imposed on the same woman, still in infancy, with the purpose of limiting the pleasure of the sexual relation and making it a torture. There are people who require girls to dance, still bleeding and howling in pain immediately after the procedure.

FGM is recognized internationally as a violation of the human rights of girls and women. It reflects deep inequity between the sexes and constitutes an extreme form of discrimination against women. It violates a person's rights to health, safety and physical integrity; the right to be free from torture and cruel, inhuman or degrading treatment; as well as the right to life when the procedure results in death.

The motivation, especially of cultural and ritualistic nature, therefore, violates governmental, social and healthcare apparatus. Although in almost all countries, FGM is usually performed by traditional practitioners, more than half of the girls in Indonesia go through the procedure by a medical professional (*Female Genital Mutilation/Cutting: A Global Concern*, UNICEF, New York, 2017). Even in other countries, in many contexts, health professionals perform FGM believing that the procedure will be safer. It is well-known that the procedure does not bring any benefit to the health of girls (major victims) and women. Instead, they can cause severe bleeding, urine problems and later cysts, infections and death. The consequences are perpetuated throughout the woman's life and through generations, with increased complica-

tions in childbirth and increased risk of newborn death. Why then are genital mutilations still so prevalent? Available data reveal that FGM often persists in spite of individual preferences to stop it. In most countries where FGM/C is concentrated, the majority of girls think it should end and say they do not see any benefits or advantages to undergo the practice unless gaining social acceptance. Marriageability was posited as a motivating factor in FGM/C at one time, but the available data show that relatively few girls report concern over marriage as a justification for FGM/C [35].

The rule seems, however, to be that individuals can undergo a final review on their parents and society. But, some practices are not modified by educational and political policies, remaining based on dysfunctional beliefs and impositions towards the feminine gender in patriarchal culture, often in the context of undemocractic local politics. It is known that, in many cases, FGM crosses borders through migrations and is done in countries where are prohibited, including in health services. We conclude, therefore, that we find FGM disproportionately and even neglect by the community of communities able to recognize and combat the problem. The role of the medical community, rather than the threats of war, is of great importance in informing and raising awareness among the civil community and politicians to combat FGM as all forms of FGM may have negative health outcomes.

Women who endured extensive forms of FGM present with higher risk for mental disorders. They report more severe symptoms of PTSD and trauma-related problems, including shutdown dissociation, depression and anxiety. These findings are corroborated by heightened levels of hair cortisol in this group. Furthermore, women who endured FGM during their first year of life showed higher concentration of cortisol, despite the lack of more obvious mental health implications. Evidence-based trauma interventions have been developed and must be scaled up along with integral approaches to mitigate the negative consequences of FGM [37].

M. Gender-Based Violence (GBV) Among Health Professionals

Women are more likely to suffer from IPV if they have low schooling, witness their mothers' exposure to IPV, underwent SV during childhood and cope with attitudes that accept GBV as male privileges and a subordinate status of women. The losses of a woman who has gone through all this can hinder her education and career advancement. This suggests that women with a high level of schooling and purchasing power are protected from gender-based violence, since they probably do not carry such vulnerabilities.

It is known, however, that these women, besides not escaping violence in their most varied forms, face methods of violence that translate into great challenges.

In the professional market, for example, gender discrepancies are discouraging. The ratio of women's and men's median annual earnings was 80.5% for full-time/year-round workers in 2017, unchanged since 2016.This means a gender wage gap for full-time/year-round workers of 19.5%. Women's median full-time, year-round earnings in 2017 were $41,977 compared with $52,146 for men. If the pace of change in the annual earnings ratio continues at the same rate as it has since 1960, it will take another 41 years, until 2059, for men and women to reach parity.

Yes, Western populations have already moved a great deal towards gender equity, but a lot is yet to come. The possibility of change depends largely on the actions of the women themselves. The speed at which such a change will take place depends on commitment and persistence, awareness of the intrinsic factors and the need to combat individually and collectively any GBV and of transmitting the example and information to others. When a woman of great social influence goes to the authorities and denounces her husband, boss or co-worker perpetrators of violence, a major transformation happens. Women who are empowered, unite can change their history. We know that one of the great reasons for the woman to remain silent when violated is shame, which mixes with a sense of guilt. Often the woman prefers to cover

her offender for fear of exposure, including to other women of her own community. When women see that the problem also happens to other women, especially those admired by her, she feels liberated and motivated to break the silence and seek for justice.

For this reason, seeking to welcome and alert all women around, enlighten and inform the entire community including men, children and the elderly to break with all practices of violence, especially gender violence is a good start. For instance, if you do not do it, who will?

N. Elder Women and GBV

Elder abuse happens when a trusted caregiver or adult knowingly harms an older person (someone 60 and older). Domestic violence in later life can be perpetrated against someone healthy, ailing or disabled, by a partner, spouse or companion. Often the perpetrator is the primary caregiver, thus making the victim even more dependent and isolated from others. It includes many types of violence, such as physical, sexual, emotional, verbal and financial. Elder abuse can also mean knowingly neglecting an older person to the point that they are harmed, such as by withholding food or medical care. 2/3 of elder domestic abuse and neglect victims are women.

Abused older women are less likely to be recognized as such because the media usually portrays domestic violence as a younger woman's problem, and friends, neighbours and even healthcare providers often assume that older women's injuries and behaviour are due simply to "old age", when symptoms are caused by abuse and neglect (http://www.domesticviolenceroundtable.org). The signs and symptoms mentioned above for women with disabilities should be observed for the detection of violence in elderly women, taking care to notify protective institutions especially in the countries where this is mandatory.

O. Racism and GBV

Racism is a form of structural oppression such as sexism, classism and xenophobia which not only profoundly influence people's identities but also intersect to create unique social locations that carry varying degrees of privilege. When GBV rates are examined by race and ethnicity, patterns reveal that certain women groups (African, Indian, multiracial) are at even higher risk of victimization. In addition, DV survivors from racial and ethnic minority groups face unique, intersecting challenges that affect their experience of abuse, help-seeking, interactions with systems and health outcomes. The concept of intersectionality has been used to analyse and understand how multiple forms of identity and oppression interact to shape life experiences of marginalized groups, including GBV experiences [38]. Adolescent dating violent shows that 40.1% reported experiencing both racial and gender discrimination and nearly all (93%) experienced dating violence adjusted for age and sex. "The interlocking identities at the micro level reflect multiple interlocking forms of structural inequality at the macrolevels of society". Implications include promoting community-based dissemination, conducting quantitative studies with larger sample sizes of DV survivors and encouraging culturally specific services that address DV survivor intersectional needs because being black and female (social identities) may not only pose greater risk of teen dating violence but also garner different responses from the larger society (social inequalities), especially if the abuser or protector is black and male. Improved specification of exposures experienced by marginalized populations who experience intersecting forms of violence can help explain intra- and intergroup differences in health outcomes and may also lead to improved intervention models, with the purpose of understanding why there are such large health differences among women who share a racial/ethnic, economic or gender status in an environment with universal healthcare policies and to understand how racism alters the context at each intersection. There is a need for health professionals and researchers for being attentive to and address various contexts of life, as well as forms of identity and inequality that deserve to be developed and implemented within worldwide healthcare settings [39].

P. Femicide: The Most Terrible Face of Violence Against Women

A UN's report shows that each hour 6 women are murdered due to being women. 58% of these deaths were perpetrated by a known one (partners, ex partners or family member), showing a reality of home being the most dangerous place for women. Africa and the Americas are the continents at greatest risk of women paying with their lives for gender stereotypes and inequalities. Murder of women by their partners is often the peak of long-term violence and can be prevented. El Salvador, Colombia and Guatemala (three Latin American countries) and the Russian Federation posted higher rates followed by Brazil. An estimated of 91,000 women die annually in India from burn-related injuries, according to the Indian National Burns Programme. These deaths are entirely preventable. While many, if not most, are result of DV, these cases are often categorized as accident, suicide and sometimes homicide, without being linked to GBV. In the domestic sphere, the understandings of consent, safety and sexual pleasure are not only more negotiated but also ambiguous, not least because marital rape is not recognized as a crime in Indian law. In Brazil, more than 600 cases of DV are registered per day. Every week, at least 20 Brazilians are killed, victims of femicide.

Violence with femicide risk (VFR) increases symptoms of depression (three- to eightfold) as well as alcohol and tobacco consumption, even while pregnant. Women living with VFR are in high risk of chronic pain, memory loss, dizziness, anxiety and vaginal discharge. Their children had significantly more recent episodes of bloody stool, diarrhoea, fever and coughing, heterogeneous effects based on violence characteristics and on victims' socioeconomic status. Their children also show higher scores of internalizing (anxiety, depression, withdrawal and somatic complaints) and externalizing behavioural problems (aggressive and rule-breaking actions) than children whose mothers were not abused. Children bereaved of their mother by their father's hand run an elevated risk of future mental disorder, self-harm, criminal behaviour and suicide.

Figure 1 describes the cycle of IPV, whose repetition leads to risk of culminating in the women's death.

Finally, focusing on the effects of VFR in women and their children is crucial for survivals to recover the social functioning. At the same time, it cannot take the place of the more important discussion of how to reduce and prevent IPV, and therefore much more work needs to be done regarding the latter.

Previous violent criminal behaviour and mental illness, but not substance use disorders, are risk factors for men to kill a female partner (Table 6) [24, 40].

Mental Illness, Psychiatric Disorders and Gender Violence

Etiopathogenic Mechanisms: Evidence and Clinical Aspects

The role of sex and gender is a fundamental issue in medicine to understand the prevalence,

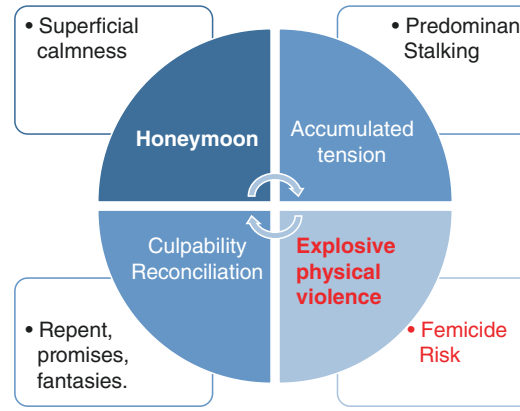

Fig. 1 The cycle of IPV

Table 6 Factors specifically associated with SV perpetrator

Beliefs in family honour and sexual purity
Ideologies of male sexual entitlement
Weak legal sanctions for sexual violence
Previous violent criminal behaviour
Mental illness

Note: Adapted from WHO_RHR_12.37_eng.pdf, Henrik [24]

age of onset and clinical symptoms of many neuropsychiatric diseases which substantially differ between males and females. How biological, social risk and protective factors influence these illnesses gradient remains a question.

"Unfortunately, in preclinical research, in most cases, researchers avoid experimenting with female animals considering no sex differences in brain function outside of reproductive behaviour, with single-sex studies of male animals outnumbering those of females by 5.5–1. Evidence on the influence of different intrauterine brain development between men and women suggests a vulnerability to organ and mental pathologies sex related, secondarily to genetic and hormonal factors. Placental cell mechanisms influence immunological and behavioural resilience throughout life span, bringing to light the doubts about the magnitude of biological processes in major risk of depression for women than men. However, it is not clear that such differences translate into clinical practice could provide opportunity to target abnormalities early in the natural history in a sex-dependent way" [41].

It is tempting to consider how reproductive events, gonadal hormone effects on CNS and their relation to acute stress response, variations in cortisol secretion patterns and epigenetic influences on glucocorticoid receptors may explain why women become depressed more frequently or attempt suicide more than men. A focus only on biological differences would deprive us of taking the weight of gender disparities, equally important into account [13].

Newer emerging issues that need more research include mental health consequences of women in conflict zones and among same-sex relationships. There are also few studies on the violence experienced by both older and adolescent women as the need to better delineate the psychopathology of complex manifestations of PTSD.

Besides the biological differences, social pressure, chronic stress and low satisfaction associated with performing traditional female roles and gender differences in dealing with problems and seek for solutions have been associated with increasing risk for depression [42].

There are several explanations for gender differences in higher prevalence rates of anxiety disorders. According to Barlow [43], women are more susceptible to stressful events during childhood and adolescence associated with the perception that their behaviours cause little impact on environment with a pessimistic maladaptive patterns of reality evaluation. These, associated with a genetically determined biologic vulnerability reactive to the environmental changes, would explain the higher occurrence of anxiety disorders in women [44–46].

How to Treat Women Survival of Violence

Well-Established Principles While Caring for Violence Survival

(a) Care focused on the women and her needs. Provide empathetic support and listening with privacy and without judging or interrupting her report.

It is of utmost importance not to cause more suffering, and, to this end, fundamental rights must be preserved: good quality health rights, privacy and confidentiality of medical information (including the family), self-determination respecting the freedom of decision about any and all procedures, provide legal information and stay available in an individualized way, independent of professional's own personal beliefs.

(b) Ask for IPV while accessing conditions that could be caused or worsened by it in order to accelerate a diagnose and subsequent treatment according to the woman's clinical conditions. Offer a basic care with emergency contraception and STI's prophylaxis, collect and take note of the complete history and exam the patient avoiding revictimization and explaining every part to her. Collect biological material which can be foster used for aggressor identification if she wishes to. Take detailed note of every observation and

integrate the first care with others as social, psychological and legal support.

(c) Make her aware of policies and provision she could need integrating healthcare with other equipments. Offer to report her assault to police but she is the one who decides on when and what to do.

(d) Prescribe preventive treatments and vaccines according to her status.

(e) Give her a detailed medical report keeping one copy at health service.

(f) Mental healthcare at first hours after the trauma could successfully prevent severe consequences by support and redetermination of trauma as alleviating shame and guilty often experienced by survivors. Researches without sufficient evidence recommend PTSD pharmacological preventive treatment.

(g) Attention and treatment should also be considered for families, who may be disorganized, presenting feelings and compensatory reactions of guilt or anger, as well as shame and fear, especially if the offender belongs to the group.

(h) Great part of the symptoms may disappear over time, without intervention, but if the offense occurred less than 2–3 months and the victim remains with subjective symptoms of stress for more than 2 weeks, not improving with support and psychological intervention and leading to frequent medical care demand, the use of medication should be considered. The duration of treatment varies with chosen treatment and the response of symptoms that impair the survival's functionality. The WHO discourages the acute use of psychoactive drugs. Pharmacological treatment for acute trauma and for post-traumatic stress disorder will be the theme of another chapter.

Violence Against Women and Cognitive Behavioural Therapy (CBT)

The clinical presentation of mental disorders symptoms emerges from the context of violence in which the woman is inserted. Symptoms can occur gradually and progressively in the environment of DV or by intense acute crisis just after serious traumatic events. The mental disorders more frequent in women with a history of violence are generalized anxiety disorder (GAD), major depression (MD), post-traumatic stress disorder (PTSD), substance abuse (SA), panic disorder (PD) and obsessive-compulsive disorder (OCD), with high risk of suicide attempts [3]. Other disorders also arise from a violent context: eating disorders and obesity, self-harm and sexual dysfunctions.

Childhood sexual abuse (CSA) in women is associated with bipolar disorder, borderline personality disorder, increased incidence of preterm birth, impaired reproductive cycle and increased risk behaviours [47].

Physical symptoms as headache, muscle pain, pelvic pain and gastrointestinal complaints are also frequent in women survivals of violence and patients with PTSD use health services more frequently [48, 49]. It is relevant to prevent harm to women's health approaching violence in routine medical consultations, considering that 80% of violence occur in the domestic environment.

The challenges for cognitive behavioural therapist, in such diverse and complex environment, are cognitive restructuring, modification of dysfunctional beliefs, management of excessive emotional reactions and development of assertive behaviours not only in women affected by violence but also in her aggressors, searching for a deep cultural transformation. In order to reduce the rates of violence and mental illness in women, it is essential that their partners and family members are also included in the intervention planning, considering the safety, physical, mental and social well-being of the woman and her family.

What Cognitive Behavioural Therapy Can Do: The first strategy of cognitive behavioural intervention is to deconstruct the belief of professionals involved in the care of victim that violence is so serious that we cannot do anything. A conscious and unified multidisciplinary team is desirable, particularly in complex cultural contexts where VAW is openly sustained by the community with social pressure to hidden it.

The purpose of cognitive behavioural therapy intervention:

- Modify cognitive distortions
- Reduce exacerbated emotional reactions
- Modifying dysfunctional behaviours
- Restructure cognition

The CBT approach follows strategic patterns of intervention according to the mental disorder defined by diagnostic criteria predicting greater efficiency for psychotherapy. The treatment of different disorders follows similar objectives, but use specific action plans and techniques. CBT shows positive results in reducing PTSD, depression and anxiety symptoms in the long term [50, 51]. If interventions in dysfunctional beliefs of violence and cultural transformation are not performed directly, the risk for the maintenance of the disorder is high, and the dysfunctional cycle of violence remains. Symptoms of PTSD may persist if the traumatic event is not targeted [52].

The approach to VAW cases differs from acute situations (such as in acute SV, the primary event of DV, including IPV) till stress management of chronic violence and its secondary conditions (depression, anxiety, substance abuse and PTSD). IPV and SV committed by well-known or strangers are pragmatically highlighted here due to high incidence and grasp of interventions.

The diagnostic evaluation of the most common mental disorders should be considered just before performing CBT and the trauma approach prioritized to prevent the development of PTSD. The prevalence of PTSD in women in violent settings is high and has 80% chance of comorbidities diagnostic criteria is achieved [53]. In veterans' studies at the National Centre for PTSD in the United States, it was observed that rape victims had the same PTSD profile as soldiers returning from war fighting, and due to that they were called survivors of SV and not of victims [54].

Scales should be used to assess comorbidities. It is important not only for the diagnostic and disorder's severity evaluations but for monitoring the survival's improvement and the violence recurrence. The high prevalence of women's' mental disorders in violence settings justifies the scales' detailed application in a standardized and systematic way.

Data Collection, Diagnostics and Parameters

Scales

The scales are here devoted to the diagnosis, severity assessment and monitoring the main disorders presented. Other scales may be applied according to symptomatology, women's previous personal and family history.

The Beck scales are self-administered, objective and include physical symptoms of anxiety, which makes it easier to evaluate symptoms that are often neglected in the clinical approach [55, 56].

The Clinical-Administered PTSD Scale for DSM-5 (CAPS-5) follows the DSM-5 criteria and allows objective evaluation of trauma relapse symptoms, avoidance, cognitive changes, mood, reactivity to the stressor event, the severity of the disorder and its evolution. It is also possible to evaluate the functional and social impacts of the current and life-long traumatic event. This scale requires a mental health professional to apply it [57].

The Post-Traumatic Checklist for DSM-5 (PTSD Checklist PCL-5) is also used; it is simple and self-applied and accesses the 20 screening symptoms of DSM-5 for PTSD.

The event impact is used to screen the symptoms of PTSD [55] closer to the cultural context.

IPV Scale assesses violent behaviours by IP and their frequency. It helps to give a structured direction for the interview with specific questions and not only the question of whether to suffer violence [58]. It allows culturally accepted violent behaviours to be enlightened [59].

- BDI (Beck Depression Inventory)
- BAI (Beck Anxiety Inventory)
- BHS (Beck Hopelessness Inventory)
- BSI (Beck Scale for Suicide Ideation)
- PTSD Scale CAPS-5
- IES-R Impact of Event Scale-Revised
- IPV Scale – Lourenço and Baptista

Prevalence The experience of violence is quite damaging impacting the prevalence of mental disorders in a negative way for women and their children. Children are directly affected by the

domestic violence environment. Children who grow in violent environments have more chance to suffer with learning difficulties, behavioural, emotional and sleep disorders. They present increased risk behaviours and contribute to the perpetuation of violence in and out their family [60]. SV in childhood is associated with smoking, substance abuse and at-risk sexual behaviour [61].

Women who have experienced IPV are more likely to neglect healthcare; if pregnant, they are more likely to miscarry and to have premature and low birthweight babies. The rate of depression is twice as high in IPV comparing to women with negative history of violence [3]. Gestational depression symptoms extend to postpartum enhancing rates of anxiety and suicide attempts.

Three to 30 days after the traumatic event, 13–33% of adults will develop acute stress disorder (ASD) [55]. SV and IPV are related to higher prevalence of PTSD than other traumatic events [51]. The prevalence of PTSD is 10.4% in women and 5.0% in men in the United States [62], in Brazil were observed 10.2% of adults at São Paulo and 8.7% at Rio de Janeiro [63]. In SV survivors 30% to 50% will develop PTSD [64], and within IPV 45%–60% develop PTSD [65].

As shortly after the trauma, 94% of the patients met PTSD criteria and 47% at 3 months after the event, and 17.5 years later, 16.5% still had symptoms of PTSD [51]; early interventions are welcome.

Cognitive Behavioural Therapy (CBT) and Domestic Violence (DV)

Women survivors of DV and PTSD frequent are:

- More dependent
- More suggestible
- Have greater difficulty in making decisions
- Have difficulty making plans related to family, children and career [66]

Women survivors of IPV have:

- High depression rates
- Ideation and suicide attempts
- Substance abuse
- Sleep and eating disorders
- PTSD symptoms

PTSD risk factors Most women who have suffered violence must have their risk factors for developing PTSD [55] evaluated in order to attack them early as crisis intervention can prevent PTSD when the approach is in the primary event of DV or just after episode of SV.

Pre-trauma risks:

- Gender (woman)
- Low socioeconomic level
- Low schooling (less than 12 years of education)
- History of mental disorder
- Early childhood trauma (up to age 6)
- History of mental disorder in the family

Peri-trauma risks:

- Severity of trauma
- Dissociation

Post-trauma risks:

- Late intervention
- Subsequent trauma
- Losses due to trauma
- Fragile social/family support

Suicide risks:

- Multi-trauma history (including childhood sexual abuse)
- Psychiatric comorbidities
- Personality disorder

PTSD and comorbidities PTSD have high prevalence of comorbidities such as anxiety and mood disorders (92%), depression (69%), substance abuse (31%), panic disorder (23%) and obsessive-compulsive disorder (23%) requiring careful diagnostic evaluation and early intervention taking PTSD as priority [53].

The ASD and PTSD will be highlighted here to stress the importance of direct approach and early intervention.

Acute Stress Disorder (ASD) The ASD can be diagnosed by the presence of 9 or more symptoms, any of the 5 categories of intrusion, negative mood, dissociation, avoidance and excitement, starting or worsening after exposure to a traumatic event, according to DSM-5. It lasts from 3 days to a month. Catastrophic or negative thinking about their role in the traumatic event, their response to the traumatic experience or the likelihood of future harm can be observed [64].

Post-Traumatic Stress Disorder (PTSD) It is diagnosed in children over 6 years of age, adolescents and adults. The symptoms should last for more than 30 days. CAPS-5 or PCL-5 scales can be used to diagnose PTSD. Attention should be drawn to anecdotal and dysphoric symptoms, expression of anger and aggressiveness and dissociative symptoms that may appear with or without symptoms of anxiety and fear.

It is important to emphasize that avoidance, present in patients with PTSD, should be approached in a careful, direct and cosy way, ensuring survivals' protection and safety. Of importance also is the close listening of distorted cognitions presented by women victims of violence, which manifest the specific cognitive disorder model characterized by dysfunctional beliefs, and with exacerbated emotional reactions. Passive and aggressive behaviours alternate according to stress reaction.

Cognitions, Beliefs and Culture

Depressed women have cognitive distortions with negative bias, impaired self-esteem, sadness as predominant emotion and paralyzing and isolation behaviours. Somatic manifestation of anxiety intensifies cognitive distortions prevailing in anxiety disorders, and the risk assessment is compromised by patients' difficulties in shaping the risk of danger and assessing the resources to cope with them.

In PTSD cases, there is a complete change in mental functioning, with a predominance of the reptilian brain stress reaction. The alert mode activation determines fight-flight behaviours, as well as the possibility of paralysis or freezing.

Within mental illness, there is a change in the perception of oneself, of the world and of the future. Cognitive distortions and dysfunctional beliefs are found in women in a DV situation, IPV and SV (Table 7).

Cognitive Behavioural Therapy Intervention

The intervention with women survivors of violence is divided into crisis interventions, performed individually and early after the event as just after episodes of SV, DV, IPV or GBV.

The intervention correlates with the ASD delimited from 3 to 30 days after the traumatic event.

CBT for women within 30 days after the event: crisis interventions are weekly up to 30 days to manage the acute reaction to the traumatic event and PTSD development prevention. They are evaluated by scales and monitored periodically till 3 months due to high manifestation of PTSD symptoms at this period and at 6 months for late manifestation or in a shorter time in case of clinical symptoms worsening.

Table 7 Dysfunctional beliefs

Self-beliefs	World beliefs	Future beliefs
"This just happens to me" "It seems like I attract the bad" "It's my fault, my mom warned me" "If I had not worn that clothe it would not have happened" "I deserve to pay" "I can't survive alone without him"	"Man are not good" "I can't trust anyone" "The world is very dangerous" "There is no safe place" "The world belongs to men" "Woman was born to suffer, life is like this"	"From now, my life is over" "There is nothing else I can do" "If I report it, he will kill me" "I won't survive" "How am I going to carry part of a marginal within me" "I will never love this baby"

When the search for care take place after 30 days of the event, the intervention is focused on diagnosis, prevention and treatment of PTSD, settled after 30 days, with a peak at the third month that may stay underpin for many years after the traumatic event.

Cognitive Behavioural Therapy for Sexual Violence

PTSD in SV survivors have high prevalence, severity and duration. Its severity levels were compared to those of veterans in studies developed by the National Centre for PTSD in the United States [54].

Cognitive distortions are developed throughout life as a result of experiences, models or stressful events, which may be present trough individual development [67]. Afflictive experiences of SO at childhood and adulthood may be the target of CBT interventions for cognitive restructuring. Understanding the SO, as well as exploring the cognitive conceptualization developed by survivors about the event, has a positive impact in reducing the symptoms of the all disorders resulting from violence. The trauma approach reduces stress symptoms and enhances anger, anxiety and fear management [68].

The host of SV survivors should ensure safety and reliability by providing support and the rights guaranteed by law in each country. In cases of pregnancy due to SV existential, religious and legal conflicts may overlap, exacerbating the survival's level of stress. Sustained and collaborative therapeutic alliance allows the support so that the woman can understand her questioning and assertively execute the resolution of her problems.

Cognitive Behavioural Therapy Focused on Trauma

Trauma-focused cognitive-behavioural therapy accesses traumatic memories; conditioned responses to aversive stimuli; negative perception of oneself, of the world and of the future; and the distorted cognitions coming from the traumatic event. Interventions aim to develop the capacity to express emotions, to learn new coping strategies, to challenge and filter negative automatic thoughts, to dissolve feelings of guilt, to improve problem-solving skills and to promote the development of social skills [69]. The initial goal is to emotionally stabilize patients in order to reduce the high level of anxiety and modulate the fear processing response. Techniques of breathing and relaxation facilitate anxiety decrease and facilitate the establishment of the therapeutic alliance. Avoid touching the patient not to stimulate the reaction of fear and panic (Table 8).

Cognitive Behavioural Therapy for PTSD

CBT for coping with PTSD can be divided into exposure procedures, procedures for anxiety management and cognitive restructure.

Exposure therapy contemplates a set of defined techniques for the reduction of dysfunctional and pathological anxiety and dysfunctional cognitions,

Table 8 Crisis interventions

Earliest possible intervention
Avoidance enhances anxiety and strengthens stimulus avoidance
Avoidance leads to chronic PTSD
The session
Crisis intervention is short term, usually 1–4 sessions
Duration 90 m
Focus on emotionally stabilizing the patient and developing adaptive coping strategies
Talk about the event at the beginning to have time to finish well and avoid generalization
Goals
Establish sustained therapeutic alliance
Addressing trauma early in the session
Restructure cognitions with punctual interventions in dysfunctional thoughts and beliefs
Obtain and provide information about the symptoms
Psychoeducation
Apply and teach coping strategies
Goals
Prevention of PTSD, anxiety and depression
Dissolution of feelings of guilt, shame and fear
Reduced symptoms of ASD (PTSD)
Recover self-esteem
Fighting against dysfunctional beliefs

through a safe and repetitive confrontation with objects, situations, memories and traumatic images. Violence survivors need a safe environment, non-judgmental care and they should be informed that avoidance boosts anxiety and strengthens aversive stimuli. Avoidance is a symptom of PTSD and contributes to prolong her discomfort and suffering. Avoidance leads to chronic PTSD.

1. *Exposure Therapy*
   - Early verbal narrative for an attentive and supportive listener.
   - Describing the event to the therapist and expressing cognitions and emotions related may represent the first complete exposure of the images of the violence suffered.
   - Offering more signals, during in vitro exposure, can improve and organize memory and intensify confrontation with trauma.
   - Event description repeatedly.
   - Flashback, nightmares and intrusive memories do not have the same effect because they do not have conditioned stimuli [70].
2. *Anxiety Management*
   - Respiratory training
   - Progressive muscle relaxation
   - Meditation and mindfulness [71]
3. *Cognitive*
   - Socratic questioning.
   - Automatic Thoughts challenge.
   - Cognitive errors: catastrophizing and role play.
   - Distorted beliefs ("bad things should never happen to me").
   - Do not allow the patient to take the blame for the abuse and accommodate the belief that they will never feel safe again.
   - Modify dysfunctional cognitions underlying PTSD [55].

Trauma Processing Techniques

CBT presents effective results for PTSD, and prolonged exposure (PE) therapy presents empirical evidence on a broad spectrum of trauma and a greater number of efficacy studies [72]. Some psychotherapies present evidence-based therapies for trauma processing, the most well-established being cognitive processing therapy (CPT), with repeated writing of traumatic experience and focused cognitive restructuring processed in 12 sessions per week (Beck, Ellis); stress inoculation therapy, TIE also in 12 sessions; and eye movement desensitization and reprocessing (EMDR) that accesses images and traumatic memories with alternative positive cognitions while affecting lateral eye movements [73]. Cognitive hypnosis is indicated when resistance is high with intense dysfunctional beliefs and avoidance already established [74].

Prolonged Exposure Therapy

- 10–12 weekly sessions of 90 m.
- Evaluation of the anxiety hierarchy 0–10.
- Detailed description of the event progressively up to a maximum of 60 minutes.
- Imaginary exhibition: memories, images and sounds.
- In vivo exposure: Exposure to real-world stimuli that are similar or related to the traumatic event.
- Clarify about common reactions; advise that 20–25% of patients feel worse before they improve.
- Instil hope and confidence.
- Overcoming the natural tendency to avoid aversive stimuli. Instruct "The memory does not have the power to hurt you".

Homework assignments:
- Use applications to record traumatic event description reports such as the PTSD National Centre for PTSD.
- Recording event on mobile phone.
- Write in a diary.

Treatment Second Stage

The second stage of the PTSD approach in women survivors of violence involves the development of assertive behaviours and social skills necessary for greater coping capacity. Cognitive restructur-

ing enables adequate emotional processing and a realistic perception of risks and resources.

Goals:

- Develop realistic risk and vulnerability assessment.
- Develop social skills.
- Develop problem-solving skills.
- Develop resilience.

Goals:

- Remember the trauma.
- Accept/resignify.
- Process emotions related to trauma.
- Reduce anxiety.
- Extinguishing avoidance behaviour.

Resilience: From Latin *Resiliens*, ability to return to normal. The ability to adapt your strength. Concept derived from engineering, from material resistance, is the ability of a material to return to its normal state after being subjected to stress. More than just resistance to stress, resilience is a proactive and adaptive process that emphasizes the conversion of challenges into opportunities. It is part of a positive and healthy growth. The balance must be physical, psychological, spiritual and social to withstand the rigors of extreme stress [54]. The development of resilience is a protective factor for coping with conflict and stress situations.

What promotes resilience:

- Higher level of education
- Age (older)
- Social support
- Specific training
- Absence of early trauma and good stress management
- Optimism
- Genetics

Family, social support and resilience:

- Identify redemption alternatives and promote linkage.
- Welcoming and approaching the family.
- Support for decision to denounce; people help us recover.

Spirituality and resilience Stimulate the quest for spirituality to broaden the hope of overcoming the obstacles to self-development; spiritual strength gives us hope [54].

Cognitive Behavioural Therapy for DV: Focus on Cognitive Interventions

- Changing beliefs, cognitions and behaviours
- Culture change, requires 3–4 years and requires multidisciplinary team trained to approach violence

Identify in survivors whether there are any attempts to:

- Deny violence.
- Minimize violent actions.
- To assume a sense of guilt in relation to the situation.

Central objectives:

- Assess the safety and physical integrity of women and children.
- Teach the woman to protect herself.
- Build instruction cards for emergency coping.
- Help the woman identify the reasons that keep her in an abusive relationship or environment of violence – codependency.
- Interventions associated with the role of gender.

Domestic Violence and the Belief System

- Cultural beliefs that men can beat in women.
- The wife cannot offend the honour of her husband.

- Man has the right to assault women as a form of discipline.
- Women are guilty. "It's my fault, I have to catch up if I do something wrong".
- "There is nothing I can do to change the situation even when I understand it is not fair".

How to Approach?

- Identify episodes of violence and learned behaviours – cognitive restructuring.
- Recognize and develop the management of repressed emotions such as anger and fear that precipitate impulsive reactions.
- Conscientization and education about autonomy, control and power in close relationships.
- Communication: learning to dialogue.
- Apply IPV Scale.
- Fighting belief system creatively.

And the Partner?

The partners' approach is indispensable for there to build a cognitive restructuring and a sustainable behavioral change. Nelson Mandela fought for overcoming differences. He taught that "if you speak to a man in a language he understands, it gets in his head. If you speak to him in his language, you reach his heart" [75].

Perpetrators were more likely to have witnessed violence among their parents as a victim of child abuse, alcohol and drug use [76]. The aggressive partner approach could be developed in group therapy. The small number of studies about aggressive partners' psychotherapeutic interventions reveal that the results are stimulating for the institution of programs to prevent violence and interventions to reduce violent behavior.

Coping Strategies for DV

Questionnaires for the evaluation of coping strategies can be applied to assist in the development of social skills and assertive behaviours as The Coping Strategies Inventory – Ways of Coping Inventory [77].

For the woman

- Balanced handling of emotions of sadness.
- Reduce the risk of psychological stress and illness.
- Promote women's resilience and well-being.
- Emergency copying cards.

For the man

- Develop ability to cope with stress, anxiety, anger and fear.
- Learning to take responsibility for their actions [78].
- Identify and express emotions appropriately.
- Controlling the abusive use of alcohol and drugs.

Preventive Attitudes

1. *Prevention of violence at personal level can start with*:
   - Improve communication.
   - Conflict management and the triggers of violence.
   - Do not hit the child; educate without violence.
   - Psychoeducation and stimulus to collective actions.
   - If alcohol consumption increases rates of violence, stop it.
2. *Prevention of violence at family/community level*
   - Reducing childhood exposures to violence
   - Teaching safe and healthy relationship skills
   - Strengthening economic support for families
   - Challenging social norms that promote male authority over women
   - Offering bystander empowerment and education
   - Eliminating gender inequalities in employment and education
   - Creating protective environments

In addition, patient-centred medical care, therapeutic interventions, housing programmes and legal services can reduce the negative consequences experienced by survivors.

3. *Prevention of violence at social level*

Start prevention by consulting what do the statistics say about the differences between women and men, girls and boys?

An international agenda that covers the work with the feminist foreign policy [7] which is structured according to three Rs which are the basis for the analysis of the conditions where one works:

- *Rights* – Do they have the same rights to education, work, marriage, divorce and inheritance?
- *Representation* – Are women represented where decisions that affect them are made, in parliaments, on boards and in legal systems?
- *Resources* – Is gender equality taken into consideration when resources are allocated, in central government budgets or development projects?

There are initiatives that start and maintain a network of women mediators who are active all around the world:

- They have championed issues relating to women, peace and security within the UN Security Council.
- They have campaigned for women's and girls' sexual and reproductive health and rights and for greater access to midwives, as well as for increased female representation in peace processes, in legal systems and in the world's biggest digital reference work, Wikipedia.
- These initiatives also show that gender equality contributes to peace, and that peace negotiations in which women have taken part have a better chance of being effective and lasting.

WHO recommended some actions to promote gender-transformative approaches in the sustainable development goals to improve global health [79].

Final Considerations

CBT is an effective collaboration for harm reduction and prevention for survivors of violence and for their families and perpetrators, in order to promote comprehensive care, improve quality of life and cultural transformation and contribute to the development of economic equity and social. The Cognitive restructuring and proper processing of emotions and feelings with the expansion of the assertive behavioral repertoire allow for uplifting cultural transformations to a new social configuration. Specialized multidisciplinary teams trained to serve women in situations of violence are needed to achieve the World Health Organization's goals.

The prognoses for women survivors of violence who do not receive interventions are impoverished social and family relations, unemployment, lower academic and professional success and lower income. Eliminating all forms of violence against women and girls in the public and private spheres is one of the goals of the Sustainable Development Goal (SDG) 5 – Gender Equality. Achieve gender equality and empower all women and girls, from United Nation -Women – and it should also be the goal of all. https://www.unwomen.org/en/about-us/about-un-women.

Gender equity is a challenge for all, and it will not be possible to achieve it if violence against women perpetuates itself in the new generations. The insane cycle of violence against women cannot be fed by the fruit of her womb.

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Neuroimaging Research in Women's Mental Health: Current Research and Emerging Trends in Women and Transgender Women's Psychiatry and Mental Health

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Introduction

Neuroimaging techniques have evolved over the past decades. Magnetic resonance imaging (MRI) represents one of the greatest advances for the field of neuroscience. It is a versatile tool, which can perform structural and functional brain imaging. Structural neuroimaging studies are used to investigate gray matter (also known as anatomical studies); microstructural analyses are mainly employed to investigate white matter integrity. Complimentarily, functional resonance magnetic imaging (fMRI) is capable of measuring the brain activity and connectivity. It provides an indirect measure of neuronal activity by means of the neuronal oxygen extraction ratio, which is called blood-oxygen level dependent (BOLD). In other words, it measures the hemodynamic response in the surrounding region of interest. The principle of the technique relies on the different magnetic properties between hemoglobin and deoxygenated hemoglobin, which are diamagnetic and paramagnetic, respectively. Thus, they exhibit distinct response to the magnetic field. The hemodynamic response is a culmination of a series of events that allow for visualization of the BOLD signal. The increase in regional blood flow that follows a brief period of neuronal activity results in a greater amount of local hemoglobin that is required to replenish the depleted oxygen, thereby changing the ratio of deoxygenated to oxygenated hemoglobin. Therefore, magnetic field distortions are reduced and the local MR signal increases slightly allowing for visualization of the BOLD signal [1]. Functional connectivity refers to two or more cortical regions that are simultaneously engaged during task or resting state [2]. Together with anatomical parcellation, functional connectivity contributed to the development of brain functional maps, allowing a better understanding of potential therapeutic targets for neurological and psychiatric disorders [3, 4].

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Peripartum Depression

As seen in Chapter "Maternal Mental Health and Peripartum Depression", the peripartum period

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comprehends pregnancy and postpartum period. There are methodological challenges involved in research during peripartum period; some techniques might be contraindicated during pregnancy or breastfeeding (for example, imaging techniques involving radioligands) or if the risks during pregnancy are unknown. Another limitation is related to the pathophysiology of peripartum depression: Does it represent a different pathology in the brain or share the same mechanism of depression? Despite these limitations, there are a number of neuroimaging studies in women suffering from depression with peripartum onset. In this chapter, we will focus on neuroimaging studies, especially functional magnetic imaging (fMRI for its capacity to explore functional changes in different brain regions.

Some studies focused on examining the emotional processes during healthy postpartum period, especially related to the mother and the reaction to their own infants. Barret et al. (2011) assessed 22 healthy postpartum mothers using fMRI with a visual affective response task. The task comprehended positive and negative images of their own or unfamiliar infant faces. They found that postpartum mothers presented greater activation in the amygdala, thalamus, temporal gyrus, and cerebellum in response to own positive infant face compared to unfamiliar positive infant face. Viewing their own negative infant face elicited greater activation in the postcentral gyrus, anterior cingulate cortex (ACC), putamen, and superior temporal gyrus compared to unfamiliar negative infant face [5]. Gingnell et al. (2017) examined 26 healthy postpartum women immediately after delivery and after 4–6 weeks using fMRI while they performed an emotional anticipatory test. In that study, they found an increased activation in the anterior cingulate cortex (ACC) in the early postpartum assessment compared to the late scan in response to anticipation of negative emotions. They also found a negative functional connectivity between ACC and right insula in response to emotional negative anticipation in the assessment immediately after delivery [6]. Those studies in healthy postpartum population revealed what would be considered as a "healthy postpartum emotional response" in the brain: a pattern of increased activation of limbic structures such as amygdala, insula cortex, and ACC.

Another significant aspect of the postpartum period is the presence of depressive symptoms in the absence of postpartum depression. Silverman et al. (2007) examined eight postpartum women with no history of postpartum depression. Subjects underwent fMRI using an emotional word probe (positive, negative, and neutral words). Participants were divided into two groups: "depressed" group (based on EPDS scores > 12, number of subjects = 4) and euthymic group (N = 4). The "depressed group" showed decreased right amygdala activation in response to negative words and increased bilateral insula activation in response to negative versus neutral words compared to the euthymic group. Moreover, they found that in the group with higher depressive symptoms, there was a decreased striatal activation in response to positive words compared to the euthymic group. This study presented three important limitations: (1) small sample size, (2) the results were not corrected for multiple comparisons, and (3) the "depressed group" was not diagnosed with major depressive disorder (MDD) but defined by higher EPDS scores, which could be driven by anxiety symptoms [7]. The same author later assessed 20 postpartum women, and depressive and anxiety symptoms were measured by HAM-D and EPDS, respectively. The participants were not diagnosed with a major depressive episode during the study. The subjects underwent fMRI using a task with emotionally valence words. They found an increased BOLD response in the right amygdala in response to threat stimuli. Moreover, depression symptoms, as measured by EPDS, were negatively correlated with BOLD response in the right amygdala [8]. Although those two studies assigned postpartum women to the "depression group" according to their EPDS instead of clinical depression assessment, they focused on brain changes in response to depressive symptoms in this group. In summary, in nondepressed postpartum women, the presence of depressive symptoms seemed to be correlated with lesser activation of limbic brain structures.

However, what changes in brain function when women experience postpartum depression? Several studies try to explore the pathophysiology of PPD using the fMRI technique. Chase et al. (2014) examined 16 unmedicated depressed postpartum mothers and 28 healthy postpartum controls using resting-state fMRI. The depressed group comprehended cases of peripartum onset and onset before pregnancy. They found that depressed mothers presented decreased amygdala activity and decreased functional connectivity between amygdala and posterior cingulate cortex (PCC) compared to controls [9]. Wonch et al. (2016) examined 31 PDD women and 23 healthy postpartum mothers using fMRI in response to the same affect rating task as described by Barret et al. (2011). They replicated the finding of increased bilateral amygdala activation in healthy postpartum mother in response to their own infant face, whereas PDD mothers only elicited increased activation in the right amygdala. Also, PDD mothers showed decreased functional connectivity between bilateral amygdala and right insula compared to healthy postpartum mothers [10]. Deligiannidis et al. (2013) followed 32 pregnant women, who were divided into two groups: high-risk group for developing postpartum depression based on a previous history of major depressive disorder (MDD) or PPD, and the low-risk group. All participants did not present depressive episode when they were enrolled in the study. During postpartum period, 9 healthy controls and 8 high-risk women who develop PPD were scanned using resting-state fMRI. They found that the PPD group presented weaker functional connectivity between the following brain regions: (1) between bilateral ACC and the left dorsolateral prefrontal cortex (DLPFC) and bilateral amygdala; (2) between bilateral amygdala and bilateral ACC and DLPFC; and (3) between the left DLPFC and right amygdala, right hippocampus, and right DLPFC [11]. Moses-Kolko et al. (2010) examined 14 depressed postpartum women and 16 healthy postpartum controls, who underwent fMRI using a negative emotional face task. Depressed mothers presented lower activation in the left DLPFC than controls in response to negative emotional faces. Also using the same paradigm, the connectivity between left DLPFC and amygdala was only present in healthy controls. Depressed mother did not show abnormal amygdala activity in this study [12]. The same author later assessed 12 depressed postpartum subjects and 12 healthy postpartum controls using fMRI in response to a monetary reward paradigm. They found that depressed postpartum mothers did not differ from controls during the initial BOLD response to monetary reward in the left ventral striatal; however, depressed postpartum subjects presented rapid attenuation of the monetary reward in the striatal compared to healthy postpartum mothers [13]. Xiao-juan et al. (2011) examined 10 PPD women compared to 11 postpartum healthy controls using resting-state fMRI. Despite the low sample size, they found increased local spontaneous neuronal activity in the PPD group in the left posterior cingulate, and in the right frontal and parietal lobes compared to controls. Also PPD women showed decreased local spontaneous neuronal activity in the right temporal and left frontal lobes compared to control [14]. Laurent and Ablow (2012) studied 11 depressed postpartum mothers and 11 healthy postpartum controls. It is worth noting that the depressed postpartum participants were already depressed before pregnancy; therefore, the sample should not represent PPD (onset during perinatal period). Participants underwent fMRI when they were presented with infant cry sounds of own infant or others. Healthy postpartum women showed activation of anterior insula, OFC, dorsal mPFC, angular gyrus, posterior cingulate cortex, striatum, thalamus, midbrain, and cerebellum in response to their own infant cry. Depressed postpartum mothers did not present significant brain activation to the sound of neither their own infant cry nor other infant cry [15].

In summary, studies focusing on PPD showed mainly a pattern of decreased activation of limbic structures, such as amygdala, and decreased functional connectivity between frontolimbic structures compared to healthy postpartum mothers. Those findings might indicate a specific brain pattern related to postpartum depres-

sion that differentiates from a "non-postpartum" depression. In contrast, for example, several studies showed an increase in limbic activity in MDD compared to healthy controls (for a review, see Helm et al., 2018). However, even with the larger number of studies in MDD, it is not possible to define a reproducible model of depression possibly due to heterogeneity of the disease [16]. Future studies with larger sample size and longitudinal design are needed to clarify the possible pathophysiology of postpartum depression.

The Menstrual Cycle

As described in previous chapters, the menstrual cycle is a hormonally mediated process by which the female reproductive tract produces and releases a follicle/oocyte that has the potential of being fertilized and implanted into the uterus to achieve pregnancy. It is regulated by the hypothalamus. As a consequence of this process, the onset of menstrual flow is established [17].

The 17-β-estradiol (E2) is a primary sex hormone that affects numerous systems throughout the body, including cardiovascular, reproductive, skeletal, and central nervous system (CNS). Its effects on CNS suggest a role in the regulation of emotional and cognitive processes and the pathophysiology of mood disorders [18]. Estrogen receptor-α and estrogen receptor-β messenger RNA expression were found to be greatly expressed in the hippocampal formation, claustrum, cerebral cortex, amygdala, hypothalamus, subthalamic nucleus, and the thalamus [19–22]. Estradiol is known to (i) enhance 5HT synthesis through the increase of tryptophan hydrolase; (ii) regulate 5HT transporters in the synaptic cleft; (iii) increase 5HT receptors in brain regions dense in E2 receptors; (iv) increase 5HT2a receptor subtypes while decreasing 5HT1a subtypes; and (v) act as a monoamine oxidase inhibitor (MAO) by decreasing the activity of MAO-A and MAO-B. Furthermore, E2 exerts effects on other neurotransmitter systems by (i) enhancing norepinephrine synthesis by increasing tyrosine hydroxylase; (ii) enhancing dopaminergic (DA) synthesis, release, and turnover by modifying the firing rates of DA neurons via E2 membrane receptors; (iii) enhancing gene expression of dopamine B-hydroxylase; and (iv) upregulating CREB (cAMP response element binding) [23].

Progesterone is another important female sex hormone with reproductive and nonreproductive central nervous system functions, including mitochondrial function, neurogenesis, cognition, and emotional regulation [24]. Although there is no literature that investigates messenger RNA expression in the human brain, a postmortem study reported high concentrations of progesterone in the amygdala, hypothalamus, and cerebellum [25]. In the brain, progesterone is metabolized into its neuroactive metabolite allopregnanolone [26, 27].

Allopregnanolone (3α-hydroxy-5α-pregnane-20-one) is a γ-aminobutyric (GABA)-a receptor agonist and allosteric modulator. Its concentrations vary across the menstrual cycle, and mirror that of progesterone. As a GABA-a agonist, allopregnanolone exerts effects on the brain's major inhibitory system creating a foundation for its role in mood disorders and etiology for premenstrual syndrome [28]. As expected, due to its neurophysiologic properties, in high concentrations, it can be sedative and anxiolytic for most of the people, although in a certain subset of individuals, it may induce negative mood changes and provoke anxiogenic effects. The prevalence of adverse emotional reactions to allopregnanolone is postulated to occur in 20% of individuals, with 2–3% experiencing more severe emotional reactions [29]. These prevalence rates are in line with those seen for premenstrual syndrome and premenstrual dysphoric disorder (PMDD), respectively [30]. This is supported by evidence indicating that women with PMDD display altered sensitivity to other GABA-a receptor modulators such as barbiturates and alcohol in their late luteal phase [31]. Dehydroepiandrosterone sulfate (DHEAS) is a neuroactive metabolite of DHEA and another GABA-a receptor modulator. DHEAS also modulates GABA-a receptors and influences serotonin neuron firing and availability [32].

Premenstrual Dysphoric Disorder

Premenstrual dysphoric disorder (PMDD) is a mood disorder characterized by symptoms in affective, cognitive, behavioral, and somatic domains that occur in the late luteal phase of the menstrual cycle and ameliorate in the follicular phase. In order to meet criteria for a diagnosis of PMDD and distinguish from PMS, according to the DSM-5, an individual must present with one or more of the following symptoms: (i) marked affective liability; (ii) marked irritability or anger; (iii) marked depressed mood, feelings of hopelessness, or self-deprecating thoughts; and (iv) marked anxiety and tension. In addition to these, anhedonia, concentration, sleep/appetite, and/or physical features must to be present (see criteria C; DSM-5). While it is suggested that 20–50% of women experience moderate to severe premenstrual symptoms [33], approximately 3–9% of women of reproductive age experience PMDD [34]. Estimates from twin studies suggest that it carries a heritability of 44–56% [35, 36].

A large community-based study suggested that women with PMDD were more likely to develop psychiatric comorbidities, including anxiety disorders (47.4%), mood disorders (22.9%), and somatoform disorders (28.4%). From this sample, only 26.5% of women with PMDD had no psychiatric comorbidity [33]. PMDD causes significant impairment in functioning and diminished quality of life; thus, it is estimated to be responsible for 14.5 million disability-adjusted life years (DALYs) [37, 38]. Furthermore, PMDD is associated with a greater history of stressful life events [31, 32], sexual abuse [33, 34], and high levels of daily life stress [18, 35]. Among the theories to explain PMDD development, some authors consider a reduced GABA-a receptor sensitivity to allopregnanolone. Women without the disorder report decreased anxiety and depressive symptoms upon allopregnanolone administration [29, 39].

Serotonin has also been postulated to play a role in the pathophysiology of PMDD due to the complex relationship between sex hormones and neurotransmitters [23, 28, 40]. Support for this hypothesis comes from the use of selective serotonin reuptake inhibitors (SSRIs) as treatment to alleviate menstrual symptoms in women with PMDD [41] and literature highlighting lower whole blood serotonin levels in women with PMDD compared to controls in the late luteal phase [42].

Structurally, women with PMDD display greater volume in the posterior cerebellum and increased gray matter density of the left hippocampus compared to controls [43, 44]. Interestingly, increased activation in the right cerebellar vermis has also been found in women with PMDD compared to controls using positron emission topography (PET) with fluorodeoxyglucose [45]. This further supports the role of the cerebellum in the pathophysiology of PMDD. Recent literature has highlighted that the cerebellum may play a complex role in emotional regulation and mood disorders through the influence of cerebrocerebellar neural pathways and feedback loops [46]. Also, a decreased gray matter density has been reported in the parahippocampal gyrus [44].

A recent fMRI study found that women with PMDD had hypoactivation in the right dorsolateral prefrontal cortex in the late luteal phase during an emotional regulation task. This study also found that women with PMDD had hypoactivation in the motor cortex (precentral gyrus) in the late luteal phase versus follicular phase, and in the somatosensory cortex (postcentral gyrus) compared to healthy controls [47]. Other task-based fMRI studies support the notion of enhanced processing of stimuli with a negative emotional valance. Compared to controls, women with PMDD display greater medial and dorsolateral PFC activity during anticipation of negative images, greater amygdala activation induced by exposure to negative words [6], and lower nucleus accumben activity following positive word exposure in the luteal versus follicular phases [48].

Bipolar Disorder in Women

Although men and women are equally represented in BD type I, literature suggests that the presentation of BD in women is different than that within men. Clinically, women tend to report more depressive and mixed episodes than men

and are more prone to develop the type II and rapid-cycling subtypes of BD [49–52]. Bipolar females also experience higher rates of comorbidities, such as posttraumatic stress disorder, eating disorders, and personality disorders [53], and alcoholism, alcoholism in BP women being associated with comorbid polysubstance use [54]. Furthermore, independent studies have shown higher rates of premenstrual worsening of mood in women with BD as described below [55–57]. Moreover, periods of hormonal fluctuation associated with the reproductive lifespan may predispose some women with BD to the onset of a mood episode [58].

Bipolar Disorder and Menstrual Cycle Hormonal Fluctuations

Studies have shown that estradiol and progesterone regulate the availability and function of monoamines, neurogenesis, and inflammatory processes and play a role in cognitive and affective regulation [23, 24, 40]. Hormones may act to influence BD through (i) the influence of hormones on modulation of neurotransmitter systems [59]; (ii) through sex hormone binding to brain regions associated with affective and cognitive processes that are also implicated in the pathophysiology of BD [60, 61]. In this capacity, women with affective disorders such as BD may be more vulnerable to the actions of hormones on the CNS than women without a history of psychiatric disorders.

In a study by Reynolds-May et al., women with BD (n = 103) were followed for three consecutive menstrual cycles, during which serum hormone levels, ovulation, and biochemical markers were tracked through measurement of sex hormones (e.g., testosterone, estradiol, dehydroepiandrosterone sulphate [DHEAS], prolactin, follicle-stimulating hormone, luteinizing hormone, and 17-hydroxyprogesterone). In this sample, levels of DHEAS and 17-hydroxyprogesterone were lower in BD than in the control group, although levels of estradiol did not differ between groups [62]. Another study on DHEAS and pregnanolone in BD found that DHEAS levels correlated with performance on the Brief Assessment of Cognition in Affective Disorders (BACA) when controlling for age and years of education [63] Furthermore, DHEAS was also correlated with symptoms of mania in this population.

Dias and colleagues conducted a large prospective study and found that women with a diagnosis of BD and history of premenstrual exacerbation of mood have a worse course of their bipolar illness. This was characterized by shorter time to relapse, and greater symptom severity to a greater extent for depressive symptoms [57]. Further studies with a primary objective of examining the prevalence of PMDD in community-based samples have also highlighted its association with BD. Wittchen and colleagues reported that women with PMDD found that they are eight times more likely to have a diagnosis of BD. In a recent study of a large sample of women with BD (N = 1099), our group found that women with comorbid PMDD had an earlier onset of bipolar illness, higher rates of rapid cycling, increased number of mood episodes, and higher rates of psychiatric comorbidities. Notably, women with comorbid BD and PMDD had a shorter gap between BD onset and menarche, which points toward a potential link between puberty/sex hormones in the onset of BD in this population [64]. It is important to note that smaller studies have failed to find an association with BD and PMS [65–68].

Regarding neuroimaging studies to assess the association between BD and PMDD, Syan et al. (2018) used a multimodal approach to investigate functional and structural correlates of BD and comorbid PMDD. They well defined the samples of women at two points of their menstrual cycles (midfollicular and late luteal) and found an increased resting-state functional connectivity (rs-FC) between the L-hippocampus and the R-frontal cortex, with a decreased rs-FC between the R-hippocampus and the R-premotor cortex in BDPMDD versus BD (FDR-corrected, $p < 0.05$). Supplementary cortical thickness analysis revealed the decreased cortical thickness of the left pericalcarine, superior parietal and superior frontal, and of the right middle temporal and rostral middle frontal, with the increased cortical thickness of the left superior temporal gyri in

BDPMDD compared to BD [69]. Furthermore, increased left-caudate volume was found in BDPMDD versus BD (pCORR < 0.05). Interestingly, clinical variables examined between BD and BDPMDD groups also highlighted a worse course of bipolar illness in those individuals with both disorders as women in the BDPMDD group displayed greater disruption in biological rhythms and more subthreshold depressive and anxious symptoms through the menstrual cycle compared to the BD group [70].

Neuroimaging Research on Male-to-Female Transgender

Gender dysphoria (DSM-5), or gender incongruence, according to the upcoming International Code of Diseases (ICD-11), refers to a condition in which an individual does not perceive its gender in accordance to its sex designated at birth [71, 72]. People can refer belonging to the opposite gender in relation to their sex at birth, or only do not to identify as belonging to a binary system of gender classification. Individuals who were designated as males at birth and during life perceive themselves as women are referred as transgender women, trans women, or women with gender dysphoria. Likewise, a person who was born and designated a female and along life perceives its gender as male is named transgender man, trans man, or man with gender dysphoria [73]. Usually, trans people who identify with a binary system seek hormone therapy and/or gender-affirming surgeries in order to reduce the dysphoric feelings about the body.

There are no recognized therapies such as the so-called conversive therapies for individuals with gender dysphoria. As a matter of fact, these modalities of therapy are merely associated with an increase in self-harm ratio, as well as an increase in psychiatric morbidity. The evidence-based modality therapy is the gender affirming [74], which has been proved, along the past few decades, to improve the quality of life and ameliorate psychiatric morbidities in individuals living with gender dysphoria [75–77]. Indeed, several studies have been conducted in order to prove the benefits of this modality of therapy. By far, the outcomes of the affirming therapy support the prescription of the gender-affirming process, and thus should encourage clinicians and other professionals involved to offer the gender-affirming process [65, 66, 78].

In terms of mental health concerns, it is known that there is a link between gender and susceptibility to the development of specific mental disorders. In this regard, neuroimaging studies that were conducted to investigate brain sexual dimorphism as a potential etiological marker for gender dysphoria also raised the question whether transgender women would be more prone to female or male psychiatric disorders [67]. It has been extensively discussed whether the transgender brain would better fit, due to its anatomic and functional aspects, to the at-birth designated sex or to the gender identity [68, 69, 79, 80]. Different studies were conducted in order to respond this question, ranging from studies that enrolled cross-sex hormone therapy (CSHT) naive individuals [81–83] to studies including individuals under CSHT [84].

Although much investigation has been done in terms of brain sexual dimorphism [85], yet a few is known about the relationship between the triad: gender identity – brain sexual dimorphism – mental health. Longitudinal studies demonstrated that CSHT exposure is associated with brain changes toward dimorphic patterns [86]. This was observed not only in the direction of the sex at-birth, but also in the direction of the gender identity. For instance, Mueller et al. (2016) showed that testosterone therapy in transgender men approached the functional connectivity values of the inferior frontal gyrus to the values presented by cis gender females, whereas it approached the connectivity values of the post-central gyrus to those presented by cis gender men [87]. Furthermore, it was shown by Spizzirri et al. (2018) that the insular cortex of transgender people behaves in a very dimorphic fashion to sex hormones therapy. While estradiol therapy was associated with a reduction of insular volume [88], androgenic therapy with testosterone was associated with an increase in the insular gray matter volume [89]. Additionally, Seiger

et al. (2016) showed a decrease in the volume of the right hippocampus following 4 months of estradiol therapy in transgender women [90], which might be considered in line with large populational studies showing less gray matter volume for all subcortical structures in women [91].

Overall, neuroimaging studies in transgender people support the notion that, regardless of the stage of the affirming process (i.e., pre- or post-CSHT), there are brain structures of transgender people that resemble a more masculine or more feminine phenotype [68, 80–82, 89, 90, 92]. As sex hormones therapy induces changes in the brain phenotype, neuroplastic adaptations are seen as a consequence of hormonal affirming treatment. Yet, since neuroplasticity is associated with the development of psychiatric disorders and the capability of predicting future events of mood and psychotic episodes [93], the effects of CSHT in the brain received more and more attention from clinicians. The issue is: would masculinizing or feminizing some brain structures lead individuals, respectively, to a higher susceptibility to men's or women's mental health diseases, regardless of their sex at birth?

Answering this question is not an easy task, when in fact there are two major questionings concerning transgender women mental health. It is not clear whether ***trans women are more susceptible to sex-related disorders owning to being born as male, or whether trans women are more likely to have gender-related psychiatric morbidities. Theoretically, the last owning to cycling effects of estrogen therapy or simply due to the existence of brain structures are more similar to female individuals. The first hypothesis is underpinned by genetic bases, according to studies demonstrating the impact of sex chromosomes on the brain anatomy [94, 95]. The second concern can be, at least partially, answered based on studies showing the transcriptional neurotransmission mechanisms related to sex hormones [96–98]. For instance, would major depressive disorder, which exhibits a higher prevalence in women, also be higher in transgender women, compared to transgender men? Although this question remains unsolved, it is widely known that transgender women, as well as transgender men, are almost as twice susceptible to the development of depressive and anxiety symptoms along their lives [66].

There is no such distinction between the incidence of mental illness between transgender men and women as it has been established for non-transgender individuals. Researchers have worked diligently to establish the relationship between the improvement in quality of life and mental health during the gender-affirming process for both trans men and women. Overall, there is a consensus that attenuating the body incongruence has a positive impact on the mental health of transgender persons. For instance, improvements in self-esteem and mood have been demonstrated following the beginning of CSHT [76]. Nevertheless, the benefits of the affirming processes seem to go beyond the adjustment of the body to the gender: they might be linked to direct effects of CSHT in the brain, e.g., in brain functional and anatomical networks [99, 100]. Moreover, the impact that estradiol exerts in brain biomarkers, such as BDNF and interleukins, has also been under investigation [101–103]. Researchers aimed to find out whether biomarkers could measure the improvements associated with the affirming process (by means of attenuating dysphoric feelings), and even point out neuroprotective mechanisms associated with hormone therapy.

There is a continuous need for more research to keep providing the best approach to trans people to what concerns mental health. As the institutions are more engaged to guarantee assistance to trans people, additional research must to be conducted to improve, more and more, the current clinical approach regarding the impact of hormonal manipulation on the brain. This concern should not only be restricted to CSHT itself but should also be extended to investigations about the impact of the surgical procedures associated with the transitioning process. For instance, clinicians should be aware of the impacts of the transient hypogonadism that follows the gonadectomy related to gender-affirming surgery. Although all the affirming procedures are undoubtedly linked a better quality of life in short- and medium-term outcomes, endocrinologists, psychiatrists, psychologists, and other professionals involved in promoting

health in the transgender community must join efforts to conduct larger studies. Altogether, transgender health is a promising field and will emerge as a distinct niche that urges specialized attention concerning mental health and gender, as it might unify genetic and hormonal factors associated with the likeliness of developing psychiatric symptoms.

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Telehealth and Women's Perinatal Mental Health

Dawn Kingston and Renan Rocha

In the document entitled *Statement on guiding principles for the use of telehealth for the provision of health care* [1], the World Medical Association presents the following considerations:

(a) Telehealth is the use of information and communications technology to deliver health and healthcare services and information over large and small distances.
(b) Telemedicine is the practice of medicine over a distance, in which interventions, diagnostics and treatment decisions and recommendations are based on data, including voice and images, documents and other information transmitted through telecommunication system. This could include telephone and Internet.
(c) The physician must be satisfied that the standard of care delivered via telehealth is "reasonable" and at least equivalent to any other type of care that can be delivered to the patient/client, considering the specific context, location and timing, and relative availability of traditional care. If the "reasonable" standard cannot be satisfied via telehealth, the physician should inform the patient and suggest an alternative type of healthcare delivery/service.

Research and medical literature on telehealth have evolved significantly. The annual number of publications of the area registered in the Science Citation Index database increased from 10 in 1993 to 1996 in 2012 [2]. In 2018, the authors of this chapter searched the MEDLINE database – PubMed – using the keyword telehealth and 29,235 results were obtained. The outcomes and findings of original articles, systematic reviews and meta-analyses predominantly suggest the efficacy of telehealth due to similar, equivalent or even superior results compared to traditional local diagnostic and therapeutic procedures in various medical conditions such as stroke, chronic heart failure, acute myocardial infarction, diabetes mellitus and also in critically ill patients in intensive care services [3–14].

In psychiatry, this practice is called telepsychiatry, defined as the use of electronic communication technologies for performing the psychiatric clinic at a distance [15]. A similar concept is shared by the World Health Organization, for which telepsychiatry is the field of telemedicine that involves the use of information and communication technologies, such as audiovisual, for the practice of psychiatry. According to the World Health Organization,

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telepsychiatry is one of the most developed and established areas of telemedicine; worldwide, only teleradiology is more practiced than telepsychiatry. The first use of interactive audiovisual communication through videoconference to conduct psychiatric consultation occurred in 1956, allowing contact between the Nebraska Psychiatric Institute and the State Psychiatric Hospital, 320 km away. In 1973, the word "telepsychiatry" was first used by psychiatrist Thomas Dwyer in the article "Telepsychiatry: psychiatric consultation by interactive television", published in the *American Journal of Psychiatry* [16]. The author describes an "interactive television system" established between the Massachusetts General Hospital and a medical post in Boston. The system proved to be viable and well accepted by individuals and institutions in the community, allowing for faster and greater access to psychiatry. In 1976, in another pioneer initiative, telepsychiatry was used to integrate the Mount Sinai School of Medicine with a paediatric clinic in New York [17].

Therefore, audiovisual technology has been applied to telepsychiatry for about six decades. During this period, an extensive body of research was produced regarding its various aspects [15]. In fact, telepsychiatry was the first area of telemedicine to develop a comprehensive and critical analysis of its own. Thus, there is empirical data supporting the use of telehealth interventions in patients with mental disorders [17]. The medical literature presents consistent evidence and a significant number of studies regarding the diagnostic accuracy and reliability of telepsychiatry comparing it to face-to-face assessments [18–22]. Substantial evidence suggests absence of a significant difference between the outcomes of telepsychiatry and local (face-to-face) psychiatry [23–31]. These studies were carried out in several disorders, patients of various ages, ethnic groups and medical services [3, 32–39]. Meta-analysis concluded that there is no difference in the diagnostic accuracy between telepsychiatry and local psychiatry [40]. Among the psychometric instruments whose reliability in telepsychiatry is equivalent to that of local application, there are the Structured Clinical Interview for DSM-IV, Brief Psychiatric Rating Scale, Scale for Evaluation of Negative and Positive Symptoms, Global Performance Rating Scale and Scale of Hamilton Depression Assessment [41].

From the point of view of public health, telepsychiatry is of strategic importance due to the high prevalence of psychiatric disorders, the deficiencies of governmental assistance to patients and the need for qualification and expansion of public services. A World Psychiatric Association survey concluded that the availability of mental health services will depend on the convergence of three factors: increased participation of non-specialists, increased of specialist mental healthcare to provide effective clinical supervision and support and decentralization of skilled mental health work. Telepsychiatry works as a means to achieve these three topics [42]. Thus, there is a critical confluence in psychiatry considering the changes in the organization of health services and their financing, the intense transition to a society immersed in information technology, the development of research and clinical practice in telepsychiatry and its continuous advancement. Many physicians are unfamiliar with the subject and some approach it exclusively through personal bias [30]. Nonetheless, psychiatry is considered to be a particularly suitable specialty for telemedicine, especially through the use of relevant audiovisual resources based on the available scientific evidence [38]. Regarding mental health during pregnancy and postpartum, screening and interventions for mental disorders in this period should be considered a priority, since early identification, treatment and prevention could produce substantial benefits for maternal, child and family health. It should be considered that psychiatric episodes are associated with a greater risk of important obstetric, maternal, neonatal and puerperal intercurrences, with negative implications on child development and family relationships [43].

Perinatal mental health problems are the most common complications of the perinatal period, with up to 25% of women experiencing significant anxiety and depression symptoms during the prenatal and postnatal periods [44, 45]. Furthermore, 40% of women with prenatal

depression continue to have symptoms 4–5 years postpartum if left untreated [46]. In the absence of formal mental health screening, US-based studies indicate that maternity care providers fail to recognize 75% of women with DSM diagnoses [47, 48]. International guidelines, including the National Institute of Clinical Effectiveness Antenatal and Postnatal Mental Health Clinical Guideline [49], the recently updated Australian National Perinatal Mental Health Guideline [50] and the US Preventive Task Force Guidelines on Depression Screening [51], recommend depression and anxiety screening during the perinatal period. Other professional organizations (e.g. American Medical Association, Society of Obstetricians and Gynaecologists of Canada, Royal Australian and New Zealand College of Obstetricians and Gynaecologists, UK Royal College of General Practitioners) and non-profit organizations (e.g. UK Maternal Mental Health Alliance) have also advocated for implementation of mental health screening and treatment as part of prenatal and postnatal care. While perinatal mental health has traditionally been conceptualized as postpartum depression, evidence about the nature of perinatal mental distress [46, 52, 53] (Kingston, under review) has extended this conceptualization and practice across the whole perinatal period (conception to 12 months postpartum) and spectrum of disorders (e.g. anxiety, depression, bipolar disorder).

However, implementing mental health screening, referral processes and treatment remains a significant challenge, with substantial barriers cited by clinicians, women and policymakers [54, 55]. A recent report by the UK Royal College of General Practitioners [56] identified that "The biggest barrier to providing better support to women experiencing poor mental health in the perinatal period is the low level of identification of need" (p. 6), with specific barriers to identification including insufficient training and confidence among GPs to manage perinatal mental health problems, poor awareness of perinatal mental health problems among women and their families, time constraints during prenatal and postnatal visits, women feeling that their concerns are dismissed and women's experience of stigma. These barriers, also widely cited in the literature [57, 58], are layered onto existing, intractable health system issues, including low access to and availability of psychotherapy (which limits the range of treatment choices), as well as the lack of integration across screening, referral and treatment, leading to high attrition through the system and a resource-expensive need-to-service mismatch [56, 59]. These hindrances must be addressed for sustainable perinatal mental healthcare to be feasibly embedded in healthcare systems.

The reality is that most healthcare systems cannot meet existing (or future) demands for face-to-face psychological therapy [60], or the quality of psychological care in terms of timeliness or accessibility that has been recommended for pregnant and postpartum women [61, 62]. The use of e-technology as a platform for mental healthcare has been highlighted by several bodies as a potential solution for tackling the considerable challenges of providing acceptable, accessible, sustainable and timely mental healthcare delivery [63–65]. Organizing mental healthcare delivery on an e-technology platform offers the advantage of extended distribution of mental healthcare into underserviced areas, support in various languages, personalization, increased access to timely psychotherapy, routinized mental health screening with feedback to clinicians and patients (and with that, normalization of mental healthcare and reduction of stigma) and an increased standard of mental healthcare that is consistent with international guidelines [63, 66]. Indeed, international guidelines have taken the first step by recommending online cognitive behaviour therapy for treatment as part of a stepped care approach for women with mild to moderate symptoms of anxiety or depression in the perinatal period. E-mental healthcare has additional potential for enhancing the monitoring of patients' safety, progress and outcomes if the system is designed to automatically inform clinicians of changes in patient status [66]. While adherence to e-therapies can be impacted by severity of symptoms, particularly in depressed participants, attrition rates are comparable or better than face-to-face therapy [67] and signifi-

cantly better in guided versus unguided online therapy [68]. Furthermore, emerging evidence indicates that e-mental healthcare can be feasibly integrated into routine clinical care in general practices and hospital settings, with high patient acceptability (>90%) and favourable responses from clinicians [69, 70].

Research on e-screening is sparser than that of e-therapy, perhaps because screening is viewed as less of a resource drain than psychological therapy. Several trials in primary care have demonstrated that mental healthcare that encompasses screening and utilizes processes to link an individual by their identified need to the most appropriate service and member of the multidisciplinary team is more effective and cost-effective than usual GP care alone [71, 72]. However, implementation of screening poses significant barriers for many perinatal healthcare providers who may lack the time, knowledge and confidence about how to identify mental disorders, interpret and discuss screening tool results and support women going forward. For clinicians, e-screening can enhance the utility of mental health screening by automatically scoring the screening tool (thus reducing scoring errors and saving time), generating understandable and personalized interpretations for women and clinicians and linking screening results to care pathways. As such, e-screening can overcome some of the most common barriers that clinicians face in implementing mental healthcare (e.g. time, lack of knowledge of/connection with appropriate referral agencies). Importantly, e-screening can also create a better need-to-service match if screening tools that identify varying levels of severity are used (e.g. mild, moderate, high, severe versus a cut-off designating low and high). Because e-screening is resource-sparing, it can also be offered regularly across trimesters, early postpartum visits and well-child visits, providing continuity of care. Finally, early evidence suggests that e-screening can enhance the integration of screening–referral–treatment when screening results are linked by computerized algorithms to the best evidence-based options of care for the woman [69]. As such, e-screening represents the first link in a system of integrated mental healthcare.

Part of the challenge of measuring the effectiveness of mental health screening in general is to identify what are reasonable outcomes. There is some evidence that mental health screening on its own does not improve clinical symptoms [73]. However, as Kurt Kroenke aptly notes, the fact that depression screening is "not enough" does not mean "not at all" [74]. While some have tried to tease out the clinical and economic value of screening apart from management, this represents an academic exercise at best. Within the clinical realm, the role of screening is to inform and thus be delivered alongside management strategies. As such, the performance of mental health screening within the context of integrated care (screening–referral–treatment) should be measured against its primary purposes of accurately detecting symptoms of mental disorders (of varying severity), promoting disclosure (and thus contributing to accurate detection) and informing the most appropriate care to create the closest need-to-service match possible. In this regard, improvement in symptoms is the result of the combination of good management informed by accurate, informative screening. Little research has been conducted on the effectiveness of mental health e-screening in the perinatal population, although some emerging research demonstrates that e-screening is a promising approach within an integrated model of care.

Gerhard Andersson, a psychologist and early expert in the field of e-mental health, described the need to demonstrate that e-screening detects mental health disorders as accurately as traditional paper-based screens [66]. In a Canadian RCT of 636 pregnant women, Kingston et al. found that mean scores on the Edinburgh Postnatal Depression Scale were similar when completed by an intervention group randomized to complete screening on a computer tablet, desktop or smartphone (M = 5.62, SD 4.91) and by a control group randomized to paper-based screening (M = 6.21, SD 4.40) (p = 0.116) (under review). This study also found no significant difference between proportions of women identified as scoring 13 or above on the EPDS in the

e-screening (n = 31, 10.2%) and paper-based groups (n = 28, 9.0%) were also similar. The Kingston et al. RCT also examined whether women's ability to disclose differed between e-screening and paper-based modes [75]. While women's responses on disclosure scales indicated that they could disclose equally whether they responded using e-screening or paper models, women's actual responses on various items differed. In particular, when answering questions on the Antenatal Psychosocial Health Assessment (the ALPHA) [76–78], women in the e-screening group were significantly more likely to endorse sensitive questions (e.g. partner abuse, concerns about becoming a mother, partner conflict) than those in the paper-based group. We know of no study other than our RCT that is evaluating the effectiveness of e-screening within an integrated model of care on symptom reduction/remission.

The Integrated Maternal Psychosocial Assessment to Care Trial (IMPACT) was designed to evaluate the clinical and cost-effectiveness of an integrated model of prenatal e-screening, e-referral and e-therapy [79]. Women randomized to the intervention group completed e-screening in their maternity provider's waiting room (family physician, obstetrician or midwife) and were offered e-therapy as well as other community supports as indicated (e.g. substance use counselling). The control group received usual prenatal care, which in most cases did not include mental healthcare. In this model, a computerized algorithm uses the combined results of a depression screener (EPDS), an anxiety screener (DASS-21) and a psychosocial risk assessment (antenatal risk questionnaire) to generate the best care options for the woman. The trial stopped recruitment in December 2017 (N = 1905). Our interim results (n = 750) indicate that this model of integrated care significantly reduces anxiety and depression. On the basis of these promising interim results, we are scaling up this model in the form of an App that offers e-screening, e-referral and e-therapy and is going to be trialled in select communities across the province of Alberta, Canada, as a model of universal prenatal mental healthcare (launch: July 2018).

Findings from trials of paper-based and face-to-face screening in the perinatal period provide an evidence base for the effectiveness of screening on symptom reduction. In terms of screening outcomes, a recent systematic review demonstrated that routine postpartum mental health screening situated within a "screening programme" involving various degrees of clinician training, feedback of results and management strategies (which may include referral pathways) significantly reduced the risk of postpartum depression in 4 of 5 trials by 28% (RR 0.72, 95% CI 0.59–0.87) to 59% (RR 0.41, 95% CI 0.26–0.64) by 5 months postpartum [51]. This review also reported that three large trials from Norway, the UK and the USA showed significant increases in remission of postpartum depression symptoms (relative risk ranging RR 1.21, 95% CI 1.02–1.44, to RR 1.33, 95% CI 1.03–1.71). The only trial of prenatal screening showed significantly higher depression remission rates at a 3-month follow-up, with 52.4% (n = 22) of pregnant women no longer being above the EPDS cut-off score of 12 in the screening group versus 18.6% (n = 8) in the control group (RR 2.82, 95% CI 1.41–5.60) [51]. However, none of these trials used an e-screening model.

We know of no study other than our IMPACT RCT that is evaluating the effectiveness of e-screening in linking women with appropriate follow-up assessment and care within an integrated model [55, 79]. A key objective of the IMPACT trial and scale-up is to evaluate the accuracy of the need-to-service match created by the e-screening and computer algorithm process – a process that will be facilitated by the App's geolocating feature. However, evidence from other trials demonstrates the value of paper-based and face-to-face mental health screening in linking postpartum women to referral resources. For example, in the TRIPPD trial, a US-based cluster RCT of 28 general practitioner practices (N = 1897) [80], Yawn et al. found that postpartum women in the intervention practices were more likely to receive a diagnosis and therapy for postpartum depression and had significantly lower levels of depression at 12 months postpartum.

Emerging evidence suggests that e-screening is acceptable to pregnant women. In a cross-sectional survey of 460 Canadian women, Kingston et al. found that over 82% of pregnant women (without access to mental health screening) reported that they would be comfortable with mental health e-screening in their physician's waiting room or at home [81]. In a follow-up randomized controlled trial (RCT) comparing prenatal mental health web-based screening and risk assessment to paper-based screening/assessment ($N = 636$), Kingston et al. found that more women in the web-based group strongly or somewhat agreed that they would prefer using a tablet or smartphone for answering questions on emotional health (versus paper), compared with women in the paper-based group [82, 83]. Pregnant women in the e-screening group also consistently reported the features of e-screening more favourably (more private, more confidential, less impersonal, less time-consuming) than women in the paper-based group, suggesting that once women had opportunity to use e-screening, it was their preferred mode [82]. In qualitative interviews, women expressed the value of anonymity in disclosing sensitive information during e-screening. For example, one woman noted that "tablets don't raise eyebrows" (manuscript in preparation).

Other studies in the general population also support the feasibility and acceptability of mental health e-screening. In a study of web-based mental health assessment implemented in three general hospitals in London, UK, Rayner et al. (2014) found that less than 10% of patients declined screening [70]. Another study in New Zealand ($N = 196$) evaluated the feasibility and acceptability of eCHAT, a web-based mental health and lifestyle risk assessment (e.g. alcohol use, abuse) completed by patients on an iPAD in their family physician's waiting room [69]. This study reported that most patients found the iPAD easy to use (97%) and the questions appropriate, with 93% agreeing that mental health and risk screening was appropriate care for a family physician. A minority of patients objected to some of the questions asked (4%) or expressed concerns with privacy (9%). Patients reported that they "could be honest about things they might not want to say to the doctor", found that it "opens the door to discussions with the doctor", expressed that it "shows they [physician] actually care" and that it was "good to have a look at self." Physicians reported benefits related to the seamless, efficient way of collecting information, appreciated the way e-screening "cut to the chase" to get the problem on the table at the start of the consultation and valued the way it helped patients disclose problems they might not have otherwise [69].

A substantial body of trial evidence generated over the past decade (including several systematic reviews and meta-analyses [67, 84–87]) provides consistent support for the effectiveness of web-based e-therapies for a variety of mental health disorders in the general population, including generalized anxiety, phobias, social anxiety, post-traumatic stress disorder, major and minor depression and bipolar disorder. In many cases, meta-analyses reported moderate to large effect sizes between e-therapy intervention and wait list or treatment-as-usual control groups [84]. During the perinatal period, 10 studies (6 RCTs, 4 quasi-experimental) evaluating six different programmes of web-based therapy form a promising basis for the role of e-therapy in clinical care. Of the six web-based programmes, three targeted pregnant women, with two of the three studies demonstrating significant reduction in depression [88, 89]. In a quasi-experimental study ($N = 10$) of a web-based CBT programme of 8 sessions (not specifically tailored to pregnant women), Kim et al. (2014) found that 80% of participants with a diagnosis of major depressive disorder showed a reduction in depression symptoms pretest to post-test, with 60% showing remission at 3-month follow-up. Cornsweet Barber et al. (2013) reported a significant reduction in depression (but not stress) pretest to post-test in response to a quasi-experimental evaluation ($N = 9$) of a web-based stress management programme of relaxation and mindfulness targeting non-symptomatic pregnant women. Neither study showed an impact on anxiety. Both studies included weekly support through face-to-

face [88] or telephone contact [89]. While these results are promising, they are based on quasi-experimental studies with very small sample sizes, warranting further evaluation.

Of the six web-based programmes, three targeted postpartum women. Two of the three programmes ($n = 4$ studies) demonstrated significant reductions in postpartum depression in randomized controlled trials [90–93], with the third quasi-experimental study reporting non-significant results [94]. Notably, each of the significant trials evaluated the effectiveness of 6–12 cognitive behaviour therapy modules (CBT) in symptomatic women against treatment as usual. In their MumMoodBooster web-based CBT, Milgrom et al. demonstrated that 79% of women with SCID-IV (Structured Clinical Interview for DSM-IV) diagnoses of depression no longer met diagnostic criteria at 12 weeks post-randomization versus 18% in the control group. Of interest, the control group still received a diagnostic assessment with feedback to the woman's clinician recommending follow-up management, demonstrating the superiority of web-based therapy over this common management strategy. Cognitive behaviour therapy (CBT) remains the most prevalent form of e-therapy [67]. This core group of well-conducted e-CBT studies [90–94] provides a significant evidence base on which to grow our knowledge of e-therapy in the perinatal period. There is a need to conduct similar evaluations in the prenatal period [55]. Studies outside of the perinatal period can inform the development of effective perinatal e-therapies with respect to the application of e-therapy to diverse types of disorders, its role in prevention, its effectiveness across the symptom continuum, the potential for harm and the nature of concomitant support.

While many e-therapies have targeted specific disorders (e.g. social anxiety, major depression), evidence suggests that trans-diagnostic therapies that address "distress" in general are as effective as those for specific disorders [95, 96]. This is particularly important since many patients experience comorbid depression and anxiety in the perinatal period. Although the perinatal e-therapy trials to date have not shown a significant impact on anxiety, a recent Cochrane systematic review of 30 studies demonstrated that guided web-based CBT improves anxiety (RR 4.18, 95% CI 2.42–7.22) compared to wait list, attention, information or online discussion controls [97]. Other reviews have reported similar effects [67].

The role of e-therapy in prevention of anxiety and depression is increasing as a topic of interest; however, the evidence for a strong preventive effect is inconsistent at this time [98]. E-therapy may have some benefit for those with subclinical depression in terms of preventing worsening of symptoms and enhancing recovery [99–101]. While the NICE Antenatal and Postnatal Mental Health Guideline and the Australian National Perinatal Mental Health Guideline limit their recommendations of web-based CBT to pregnant and postpartum women with mild to moderate symptoms of depression, some studies demonstrate that e-therapies can also be effective (and in some cases, more effective) for patients with more severe symptoms (although it may be more acceptable in patients with mild/moderate symptoms than those with severe [102, 103].

The issue of harm is an important one, given that patients work through e-therapy independently with periodic clinician contact. However, a recent meta-analysis indicated that the risk of individuals in an e-therapy intervention group experiencing deterioration in symptom status was 53% less compared with the control group (RR 0.47, 95% CI 0.29–0.75) [87]. Some have also suggested that vigilance may be greater for patients completing e-therapy when systems are in place to automatically notify clinicians of deterioration [102].

Compared to face-to-face treatment, most systematic reviews and RCTs demonstrate that guided e-therapies show equivalent results for anxiety and depression, with enduring effects up to 3 years post-treatment [104]. A key point in these trials is that the e-therapy was guided (i.e. it was paired with a support component). Systematic reviews of unguided e-therapy generally show a lack of effect or a much smaller effect size compared with guided therapy [105]. However, the nature of support that is most effective in e-therapies remains an important area of inquiry.

Effective support is characterized by regular contact (most trials have assessed weekly support), with email, texting and telephone-based models all contributing to improved outcomes in terms of anxiety and depression symptom reduction [106]. Some studies suggest that "technical" support that offers encouragement to complete the e-therapy and help in navigating the process is as effective as therapeutic support, which raises important questions about the nature of support in e-therapy [66]. However, few studies have teased apart the type of support or how it is best delivered to understand the most effective approach. Of interest, a large virtual psychotherapy clinic found that only 75 of 2660 (2%) patients opted for therapist-guided psychotherapy over the self-guided option [107]. In a recent RCT comparing the level of support offered alongside the web-based CBT programme, MoodGYM, clinically depressed participants in the telephone-supported MoodGYM group (n = 187; received weekly telephone calls from a "telephone support worker" to aid participant in goal-setting and programme completion) were twice as likely to experience a significant reduction in depression symptoms at 4 months compared with those in the minimally supported MoodGYM group (n = 182) (OR 2.05, 95% CI 1.23–3.42) [106].

A large body of literature demonstrates the high acceptability of web-based e-therapies across diverse patient groups [84, 103, 108]. Within the perinatal population, women who screen positive for depression express a strong preference for self-management [109]. In a survey of 258 men and women, Hantsoo et al. (2017) asked participants (n = 111 pregnant women; n = 147 non-pregnant women; n = 54 men) to define their preferences for computer-based therapies versus traditional therapies (psychotherapy and medication). Participants provided responses to video telehealth therapy (VTT, therapist via a web camera instead of in-person), computer-assisted therapy (CAT, computer modules supplemented with brief in-person therapy) and self-guided online therapy (SGO, online therapy without any interaction with therapist – at home, own pace) [110]. Among pregnant women, 77.5% indicated they would consider some form of computer-based mental health treatment during pregnancy, with the order of preference as therapist via web camera (VTT), computer modules supplemented with brief in-person therapy (CAT) and finally self-guided online therapy (SGO). One-third of pregnant women chose some form of e-therapy as their top treatment preference. In a qualitative study (68) conducted alongside a RCT of therapist-support web-based CBT (unpublished), women with postpartum depression described the importance of the privacy and anonymity (feeling "less judged") afforded by the web-based approach, as well as the flexibility, convenience and accessibility, especially in the early acute phase when a face-to-face encounter was perceived as being too difficult. Women also valued the sense of control over their symptoms that they experienced, the feeling that they were taking a step in the right direction, the self-awareness they gained and the validation that the modules provided as they recognized their own symptoms and experiences in the content [111].

The evidence for e-screening and e-therapy and their potential to support an integrated model of mental healthcare is promising. Despite the substantial evidence for the clinical benefit of e-technology in mental healthcare, several areas of inquiry warrant further research if e-technology is to be widely implemented. Few trials have evaluated e-screening or e-therapy in the prenatal period. However, with epidemiological evidence suggesting that most cases of postpartum anxiety and depression begin during or before pregnancy, there is a need to evaluate e-mental healthcare in the prenatal period. There is also a significant lack of understanding (within the perinatal and general population) about who benefits most from e-mental healthcare. Attrition remains a significant issue, although reviews suggest that levels of dropout from e-therapy are similar to face-to-face psychotherapy. Given the lack of evidence for unguided e-therapy and the benefits that guided therapy have for clinical outcomes and programme retention, e-therapy should consistently be offered with some form of support. While recent evidence suggests that non-technical

telephone-based, text or email support may be sufficient (versus therapeutic support), trials comparing different forms of support (type, frequency, mode of delivery) alongside e-therapy are needed. The need for trials evaluating integrated models of e-screening, e-referral and e-therapy is great, particularly those that offer early screening and care across the perinatal period from pregnancy to postpartum. There is also a need for studies with longer follow-up to determine whether low-intensity e-therapies hold their effectiveness over time or whether booster-type approaches are needed. Understanding the patient experience more fully as e-mental health becomes embedded in mental healthcare will also be valuable in guiding future directions. Finally, economic evaluations of integrated models of e-screening, e-referral and e-therapy are needed in the perinatal population.

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Maternal Mental Health and Peripartum Depression

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Abbreviations

5-HTTPLR	Serotonin transporter
AAD	Antenatal anxiety and depression
ALLO	Allopregnanolone
BC	Before Christ
BDNF	Brain-derived neurotrophic factor
COMP	Cartilage *oligomeric* matrix protein
COMT	Catechol-O-methyl transferase
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
EBV	Epstein–Barr virus
ECT	Electroconvulsive therapy
ELBW	Extremely low birth weight
EPDS	Edinburgh Postnatal Depression Scale
ESR1	Oestrogen receptor alpha gene
fMRI	Functional magnetic resonance imaging
GABAARS	Gamma aminobutyric acid A receptors
HIC	High-income countries
HPA AXIS	Hypothalamic-pituitary-adrenal axis
IL-1RA	Interleukin-1 receptor antagonist
IL-6	Interleukin-6
IP	Intimate partner
IPT	Interpersonal therapy
IPV	Intimate partner violence
IUL	Intrauterine life
KM	Kangaroo method
LBW	Low birth weigh
LGBT	Lesbian, gay, bisexual, and transgender
MAO	Monoamine oxidase
MAO-A	Monoamine oxidase A
MLIC	Medium- and low-income countries
MRS	Magnetic resonance spectroscopy
NB	Newborn
NICU	Neonatal intensive care unit

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PET	Positron emission tomography
PMDD	Premenstrual dysphoric disorder
PMI	Peripartum mental illness
PNAS	Postnatal adaptation syndrome
PND	Prenatal depression
PPD	Peripartum depression
PPND	Paternal perinatal depression
PPTD	Postpartum depression
PPTDS	Postpartum depressive symptoms
PTNB	Preterm newborns
SSRIS	Selective serotonin reuptake inhibitors
TH1 OR TH2	T helper cells type 1 or 2
TMS	Transcranial magnetic stimulation
TPH2	Tryptophan hydroxylase-2
WHO	World Health Organization

Introduction

Pregnancy and postpartum are critical periods in a woman's life, during which she experiences physical, biological, hormonal, mental and social significant changes. The upheaval of pregnancy was first systematically described by Grete Bibring close to 60 years ago [6]. Medical knowledge on the physiology and pathophysiology of pregnancy and the peripartum is constantly growing. The birth of an infant, in all settings, represents a major biological and psychological challenge. Responsibility for a helpless newborn is at least stressful and more often than wished for potentially traumatic. For a significant number of women, it becomes a moment of both suffering and shame, due to the depressive and affective symptoms at a time when in most cultural groups birth is assimilated to joy. It is expected of women that they rejoice, share a sense of fulfilment and take appropriate care of their infant. The feeling of not being able to be a good enough parent is devastating and can add to the already heavy burden of depression and anxiety.

According to the World Health Organization (WHO) worldwide, it is estimated that the rate of mental disorders, primarily depression, is approximately 10% for women during pregnancy and 13% during the postpartum. In low- and middle-income countries (LMIC), prevalence is even higher, ranging between 19% and 25%, sometimes associated to anxiety. Early development and children's health and mental health are at heightened risk of negative outcome in part due to lack of timely responses to infant needs and lack of adequate bonding. In the most severe cases, women can commit suicide and/or infanticide [19, 82].

Peripartum depression (PPD) is now considered a major public health issue, the most common medical problem of the perinatal period and subsequently of parent and children long-term health and mental health [45].

PPD includes specific and core depressive symptoms. Therefore, treatment needs to be adapted, according to severity of women's symptoms per se, and in addition to parental specifics in order to prevent and/or address negative outcomes to pregnancy, neonate and infant health and parent–infant interaction. The benefit–risk balance of treatment and care during pregnancy and postpartum is a major challenge for the perinatal psychiatrist as well as for other specialists that care for women and babies. Absence of treatment and medication is far from being devoid of risk. No treatment is a major risk if treatment is necessary.

Perinatal mental illness (PMI) has been acknowledged and known to be recorded since the fifth century BCE by Hippocrates. In the nineteenth century, Louis-Victor Marcé, a young French psychiatrist, wrote the first treatise entirely devoted to puerperal mental illness. Published in 1858, it describes 79 cases of mental illness during pregnancy and/or after birth and during lactation. Across the twentieth century, the knowledge on prevalence, aetiology, risk factors, impact on women, mothers, pregnancy and foetal development, neonate, infant, child and the surrounding family including fathers has expanded dramatically. Guidelines for the prevention, detection and management of mental disorders during the peripartum are now issued in many countries and scientific societies have issued statements and recommendations on the topic (see Marcé and IAWMH websites) [30, 70]. Increased clinical

attention, research and financial resources are slowly being directed towards PMI even if disparities are still high worldwide.

It is hypothesized that peripartum vulnerability to mental illness is due to biological (hormonal), psychological and environmental (social) aspects. Teasing out each mechanism, knowing that they most certainly interact to buffer or potentiate each other is complex. Recently, studies on the lifelong impact of prenatal stress during pregnancy have led to more research [17, 21, 32]. We are currently unable to understand the exact processes involved and can only try to describe evidence-based heightened/lowered risk/protection factors and current state-of-the-art care. However, empirically, we now have data that is in favour of better short- and medium-term outcome for women when adapted tailored care is implemented during the peripartum [47, 52]. How to ensure better health and mental health for offspring remains based on better care for women who will then be provided with enhanced health care, lower risk of substance abuse and self-harm and benefit from environmental support. Integrated care including community and health care, parent–infant interaction and biological and social interventions need to be implemented in order to provide evidence-based knowledge for early identification and efficacious management of PPD.

The present chapter will first describe maternal PPD around the world and its psychiatric specificities. We will then go on to explain how to screen for PPD and assess protective and risk factors involved. Finally, we will offer an overview on treatments and tailored care for PPD. We hope to stimulate creativity in different settings in favour of integrative, tailored, gender-sensitive, cost-effective programmes in order to promote biopsychosocial care for women and mothers, children and their families.

Definition and Symptoms

Peripartum depression (PPD) encompasses depressive symptoms that occur during pregnancy as well as those that continue during or begin in the first year postpartum.

PPD can be defined, according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), as a depressive episode that occurs during pregnancy or in the first 4 weeks after childbirth [2]. Moreover, the DSM-5 introduces a new "peripartum" specifier for PPD. It points out that onset must occur within the first 4 weeks postpartum. Despite complaints from the scientific community since the publication of the fourth edition of the American Manual, the diagnosis of depression during the postpartum period has not changed in DSM-5, requiring five of nine symptoms for at least a 2-week period during the immediate postpartum.

According to ICD 10, the international diagnostic classification, used around the world for every type of disorder not just psychiatric illness, PPD is part of "mental disorders associated to the puerperium not classified elsewhere". Symptoms must appear within 6 weeks after delivery. However, observational data is also in favour of a peak 2–3 months after delivery for new onset postpartum depressive episodes [74]. Numerous international experts commonly extend and consider that PPD can occur during the first postpartum year, irrespective of the time of onset [51]. Therefore, the WHO or the Centers for Disease Control and Prevention in common agreement with specialized scientific societies such as the International Marcé Society or Perinatal Medicine extend PPD to the first 12 months after birth [70, 9].

Symptoms of PPD: Clinical Specificity and Heterogeneity

Depression is the most common, in the western world, complication of pregnancy and the postpartum. Depression may go unnoticed during gestation, since symptoms such as fatigue, sleep impairment and change in appetite are common within this period. It is the accumulation of numerous functional somatic symptoms that are strongly associated to antenatal depression risk [3].

The Blues

During the immediate postpartum, symptoms may be mild at first and only progressively worsen. They may initially be mistaken for those of postpartum "Blues". After childbirth, 26–84% of all mothers are affected by **postpartum blues**, featured by transient symptoms beginning a few days after parturition and lasting up to 2 weeks. The main differential criteria are that there is no functional impairment. It is important to emphasize that PPD differs from "Baby Blues" which causes dysphoric mood, emotional lability, crying, anxiety, insomnia, self-blaming, incapacity of caring for the newborn, loss of appetite and irritability. Four among seven symptoms of mild-to-moderate severity (3 on 6-point Blues Handley Scale) are required to make the diagnosis [26].

The "Blues" are generally short lived, lasting through the first week postpartum. Rapid fluctuations for positive emotions and excitement alternate during the "Blues".

Evidence shows that "Blues" mood symptoms worsen in the first week postpartum, with a peak of negative mood between days 3 and 5, and then gradually improve, mostly on days 10–12 postpartum. Symptoms are interpreted as reflecting hormonal and emotional readjustments after childbirth. However, in some cases, mood does not improve and the "Blues" then transform in full-blown postpartum depression (PPTD).

Postpartum Depression (PPD)

PPD shows a variety of symptoms often centred by the relationship with the child and feelings linked to the challenges parenthood entails.

The most common symptoms found are as follows:

- Intense fatigue
- Feeling physically incapable
- Moderate sadness or total numbness and absence of feeling
- Emotional fluctuation, crying suddenly without reason
- Anhedonia, that is, absence of feeling of joy originally expected from parenthood
- Alexithymia specifically around care for the infant and parenting tasks
- Intense and constant anxiety
- Phobias and ruminations concerning risk of harming the infant, heightening feelings of guilt and helplessness
- Heightened irritability and lack of patience towards other family members, spouse and children
- Infant care is not enjoyed, requiring immense efforts, heightening feelings of unreliability towards infant and triggering feelings of abandonment by spouse or others

More specific signs can also exist:

- Sleeping issues essentially linked to lack of sleep even when sleep is possible
- Loss of appetite and more weight loss than expected
- Numerous functional symptoms such as headaches or pain
- Memory loss and difficulty to concentrate
- Tendency to stay home and avoid socialization
- Lack of libido lasting many months after birth
- Loss of usual interests that is sometimes quite hard to asses given the change of habit that a new infant implements

In 2014, the Postpartum Depression: Action Towards Causes and Treatment (PACT) Consortium published its first study. Using data sets from 7 countries with 17,912 unique subject records, results showed that at least three distinct phenotypes exist, thus illustrating the heterogeneity of PPTD [65].

The different subtypes were based on degree of severity, time of onset, co-morbidity of anxiety and existence of suicidal ideation.

The first subtype showed mild-to-moderate depression with an overwhelming postpartum time of onset and absence of co-morbid anxiety or suicidal ideation.

The second subtype presented higher level of depressive symptoms with one-third of cases having prenatal onset and half of cases with co-morbid anxiety even though there still remained a majority of absence of suicidal ideation.

And the third subtype had severe depressive mood with a majority of women having pregnancy onset and history of mood disorders and anxiety.

The merit of the PACT Consortium is to push for more exploration of different forms of PPD and to advocate for more research in order to acknowledge the necessity to ameliorate capacity to diagnose and therefore to treat these episodes greatly impeaching women's and children's lives. PPD should not be underestimated and underdiagnosed.

We have summarized PPD DSM-5 criteria in Table 1.

Table 1 Clinical diagnosis of major depressive episode with peripartum onset

Onset of mood symptoms gradually occurs during pregnancy or within 4 weeks following delivery (within first year after giving birth, for experts' community)
Five or more symptoms present for 2 or more weeks, for most of nearly every day. One of the symptoms must include either **depressed mood** or **anhedonia** (markedly diminished interest or pleasure in activities).
Other symptoms can include the following: Excessive worry or anxiety Irritability or short temper Feeling overwhelmed, disturbance on ability to concentrate or make decisions **Sad mood, feelings of worthlessness, excessive or inappropriate guilt, phobias** **Hopelessness** Sleep disturbance (insomnia or hypersomnia), fatigue, decreased energy Physical symptoms or complaints without apparent physical cause Psychomotor disturbance (agitation or psychomotor slowing) **Discomfort around the baby, lack of feeling towards the baby** **Loss of interest or pleasure, decreased libido** Appetite disturbance, significant weight alterations (loss or gain) **Recurrent thoughts of death or suicidal ideation**
Depression may go unnoticed during gestation, since symptoms such as fatigue, sleep impairment and change in appetite are common during the gestational period.
The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of function are not due to direct physiological effects of a substance or another medical condition and are not better explained by schizoaffective disorder or other psychotic disorders. It must have never been accompanied by a manic or hypomanic episode.

Adapted from: **DSM-5 Manual Diagnostic and Statistical Manual of Mental Disorders, 2015**

PPTD should not be confused with postpartum psychosis (PPP). Psychotic episodes during the peripartum are a major emergency situation. Even though a relatively rare event occurring between 1 and 2 per 1000 women within the first 4 weeks after childbirth, it requires intensive immediate psychiatric care. It may include paranoia, mood shifts, hallucinations and/or delusions and suicidal and/or homicidal thoughts towards the woman herself and the infant. PPP is not in the present realm and will be discussed in another chapter of this book.

Epidemiology of PPD

Depression is a common complication of pregnancy and the postpartum period.

Up to 70% of women report some symptoms of depression and/or anxiety during pregnancy, and 10–16% fulfil criteria for major depressive disorder. This is close to the prevalence rate of depression in the general population.

Prevalence rates vary according to three parameters:

1. The issue of diagnostic criteria, specifically time of onset
2. When diagnosis is recognized
3. How PPD is screened and assessed

Some authors have argued that in fact the peripartum is not a period of heightened risk for depressive disorder. They do not find any difference between rates of depression during the first-year postpartum or other periods of women's lives [84]. Conversely, other studies have found that PPD rates are much higher in postpartum women than in the general female population [12]. In general, there is a consensus to consider that 10–15% of women experience some form of PPD and that there are wide differences in prevalence rates according to socio-demographic characteristics and to history of mental health disorders [72]. For example, maternal personal conditions of previous depression, co-morbid chronic illness, young age, substance use, marital discord, family violence, isolation, poverty, difficult infant temperament and family history of

depression greatly increase the risk of PPD. Multiple births, preterm birth and congenital or acquired developmental deficits in the infant are child-related risk factor as major stressful situations such as migration, absence of financial and social support or being part of a minority may also be considered high risk for PPD.

In fact, approximately 40% of women experiencing a major depressive episode will have their first episode during the postpartum period and approximately 33% during pregnancy. Suicide seems to account for at least 20% of postpartum deaths [37].

Despite being one of the most common complications of pregnancy, PPD remains underassessed, therefore underdiagnosed and subsequently under- or inadequately treated, partly due to stigma, sometimes linked to untrained professionals, often justified by limited access to specialized resources in several countries [84].

In high-income countries (HIC), prevalence is commonly 10–15% of women and will not only affect women but also put their children at physical, cognitive and emotional continuous developmental risk. Both antenatal and postnatal depressive symptoms have been associated with poor early child health and development [49]. In LMIC, estimates of prevalence are much higher contrary to what is most commonly believed. It is estimated between 15% and 50%. Both prenatal depression PND (20.5%) and PPTD (23.8%) show high prevalence rates. In these underprivileged surroundings, PPTD is correlated to intrauterine growth retardation, low birth weight and premature birth for antepartum depression and failure to thrive, childhood stunting and increase of childhood physical illness for postpartum illness [57].

Prevalence of PPD during the postpartum was found to be very high in rural South Africa (47%), with 67% of the depressed women reporting episode duration greater than 2 months. It is notable to say that they had a prior history of depression. Since women use psychological language to describe symptoms, standardized diagnostic tools need to be culturally sensitive; therefore, it is possible that recording of symptoms does not have exactly the same meaning in different settings. Pregnancy somatic symptoms are frequently reported and do not overestimate depression in LMIC [19]. Both HIV-positive and HIV-negative women were also at risk of being depressed [61].

Migrant women are also more likely to experience postpartum depressive symptoms (PPDS) 12.7% (95% CI: 9.31–16.09) compared to native-born Western Europeans 4.8% (2.26–7.34). Shakeel et al. [68] have reported a double risk of PPD among ethnic minority women with about 20% prevalence. As stated earlier, adverse life events, lack of social support and depressive symptoms during the index pregnancy were other significant risk factors. However, there is a lack of population-based studies, and little is known about prevalence among newly arrived migrants with limited local language skills, as they are often excluded from research. Moreover, the impact of migration and the harmful effects of perceived prejudice are observed across a range of mental health outcomes including PPD [78].

In a predominately Latina sample living in the USA, 1 in 5 mothers (20.4%) screened positive for depressive symptoms and over one-third (36.7%) reported one or more psychosocial issues such as harmful drinking 20.9%, drug abuse 4.3%, substance use 23% and current or recent intimate partner violence (IPV) 3.5% reported during the perinatal period. Multiple risk factor screening can help better management of issues related to PPD and is highly recommended [10].

Both prevalence and novel onset of PPD was higher among ethnic minorities than among native-born women indicating that clinicians should be aware of the increased risk in this population. A low level of integration was independently associated with PPD and depressive symptoms in general. This should clearly justify more systematic screening and allocation of heightened awareness and care for this high-risk group [56, 68].

Adolescent pregnancies are still numerous worldwide (*WHO Report*). As they are more often than their adult-age counterparts likely to suffer from low socioeconomic status (LSES),

family and/or partner conflict, social isolation, inadequate social support, low self-esteem, low confidence in parenting abilities and stress, they are at high risk of PPD. In general, their dire circumstances may result in high-risk sexual behaviour, substance use, low academic attainment, physical and psychological health problems and even suicide. This will subsequently add to pregnancy and postpartum risk of negative outcome and inadequate interaction with their children contributing to physical and behavioural health problems in infants and toddlers. Rates of PPD in adolescents can be as high as 28–56%, especially in low SES, ethnic minority mothers. Again, this high-risk group requires specific attention and response to their needs [36]. Results vary as to how PPD evolves. Without treatment, depressive symptoms could still be pervasive at near postpartum according to original studies [33]. Recurrence of PPD during subsequent pregnancy is very high, up to 50% in accordance with most studies [83]. This in itself should be enough to justify systematic assessment and screening.

Paternal PPD

The peripartum is now considered a risk period for mood disorders in general and not only women per se, therefore paternal peripartum disorder PPD needs to be mentioned.

Paternal PPD is defined as a major depressive disorder that occurs in men between the first trimester of pregnancy and the end of the first year of the infant. Although recent estimates indicate that 9–10% of fathers experience PPD, with rates increasing significantly in 3–6 months following birth, there has been very little research on this condition. Suggested risk factors include presence of maternal depression and own previous history of depression [20].

Observing similar PPD phenomenon with partners of pregnant women, whether or not they are the biological father, the hypothesis is that paternal mood disorder could be related to stress of developing parenthood rather than biological predisposition [58]. Evidence suggests that fathers experiencing depression and anxiety are more likely to be isolated, to have few effective interpersonal supports and to adopt coping strategies which could be harmful to themselves and their families. This could be due to even less likelihood for men to obtain care for mental health issues during this period than women. Studies, even if still scarce, have shown that children of fathers with PPD have an increased risk for behavioural problems and psychopathology at 3–5 years and for psychiatric diagnosis at age 7, even when controlling for maternal depression and fathers' depression beyond 1 year postpartum. Child mental health issues specifically concern hyperactivity in boys and emotional and social development in girls with cognitive and educational consequences for both genders.

In fact, fathers' mood and anxiety disorders could exacerbate maternal PPD, escalating the risk of a child developing emotional and behavioural problems, while fathers with better mental health may provide a buffer to the negative impact of maternal mental illness [53]. Identifying fathers at risk for depressive symptoms, specifically in case of maternal PPD, could help to better target interventions for families as a whole [76].

PPD in Lesbian–Gay–Bi–Transsexual (LGBT) Parents

Despite a paucity of research, recent studies aiming to evaluate PPD in LGBT population suggest that prevalence could be even higher among lesbian and bisexual women when compared to their heterosexual counterparts. These findings could be associated with the fact that in addition to sharing the same risk factors as heterosexual women, parenting for LGBT parents is associated with specific stressors such as homophobic discrimination and stigma [22]. Conversely, several women have identified LGBT groups as sources of support during the transition to parenthood. Three major issues related have emerged for this population. The first, women were particularly disappointed by the lack of support provided by their original family members. Second, negotiating parenting roles inside the couple was

a major challenge, and finally, legal barriers such as non-existent second parent adoption options were identified as a significant source of stress during the transition to parenthood. Only the last concern may represent a unique risk factor for this population as the first and second issues are also observed as risk factors for heterosexual mothers. Therefore, additional study of perinatal mental health among LGBT women is warranted [38].

PPD: Aetiological Hypotheses

As with depression, it is highly likely that the aetiology of PPD is multifactorial, with environmental, genetic, hormonal, and inflammatory factors being involved, among others. Several studies describe how the dynamic influence of biological, environmental, social and psychological factors affect the expression of lifelong illnesses ever since intrauterine life (IUL). IUL investigation shows that "foetal programming" (FP) is influenced by high levels of stress during pregnancy [32, 52]. Therefore, family history of anxiety and depression during the mother's peripartum may have an essential impact.

Several biomarkers have been proposed to identify risk for PPD. However, none of the results showing a lonely specific biomarker have been replicated across studies. This may be due to the heterogeneity of PPD as mentioned above or to confounders related to differences in experimental methods and populations. Some authors posit that useful information can still be gleaned from these biomarker studies despite the lack of confirmation that integration of these findings may point to potential common pathways [54]. The main common pathways hypothesized as involved in PPD include the following.

Neuro-inflammatory Mechanism

Several studies have shown a positive correlation between increased levels of interleukin-6 (IL-6) and interleukin-1 receptor antagonist (IL-1RA) with depressive and anxious symptoms, and increased levels of IL-1β were also shown to be associated with PPD symptoms. High levels of IL-6 and tumour necrosis factor alpha (TNF-α) at delivery were associated with depressed mood at postpartum. A positive interaction between the levels of these cytokines and previous adverse life events links neuro-inflammation as an established risk factor for PPD. Other authors show increases in IL-6 and IL-8 in PPD, but only in mothers who delivered preterm. During gestation a downregulation of T helper cell type 1 (Th1) occurs in the course of postpartum recovery. In women affected by PPD, it seems that the downregulation did not take place, whereas depressed mothers had a decreased Th1/Th2 ratio, suggesting suppression of cellular immunity. High levels of Epstein–Barr virus (EBV) viral capsid antigen antibodies, indicating leakage of herpes virus latent from the cellular immune control, and higher levels of neopterin were also found in women with PPD [18, 77]. Higher serum levels of prolyl endopeptidase (PEP) were positively correlated to increased anxiety and PPD symptomatology [43]. Positive associations of depressed mood in the perinatal period and Clara cell 16 protein (an inflammatory protein that suppresses IL-6, IL-1 and IFN-g) were also found in addition to the previously mentioned alterations. Further studies are warranted as results remain contradictory and not sufficiently replicated to establish the specific role of neuro-inflammation in the neurobiology of PPD [60].

Hormonal Mechanisms

Hypothalamic–Pituitary–Adrenal Axis (HPA)

Modification through functional suppression of the HPA axis is one of the suggested aetiological pathways for PPD that has been the most thoroughly explored. During pregnancy, the HPA axis is hyperactive with high levels of plasma cortisol. High production of corticotrophin-releasing hormone (CRH) by the placenta during pregnancy has also been hypothesized as a marker predicting onset of PPD. However, results have been disappointing, and no positive correla-

tion between higher levels of placental CRH during mid-pregnancy and heightened risk of PPD could be found. The HPA hyperactivity is supposed to readjust during the postpartum, since after birth, rapid hormonal decline is accompanied by decrease of CRH. This downregulation of the hypothalamic production of CRH, thus, induces a decrease in ACTH response and cortisol release.

However, in case of PPD, there could be an over-adjustment of feedback sensitivity, leading to hypocortisolism [44]. Studies have shown that serum hypercortisolism of pregnancy continues in postpartum for several weeks. The HPA stress response seems to be attenuated during late pregnancy in most women, and the presence of lower levels of free salivary cortisol found in depressed mothers suggests a disruption in the usual postpartum physiology [23].

Melancholia-type PPD is associated with hypercortisolaemia, while PPD may be more atypical and triggered by abrupt withdrawal of CRH and cortisol that occurs after childbirth as it is conversely characterized by hypocortisolaemia. The occurrence of PPD in women may be influenced by genetic factors that act at different times. Little is known about the relationship between the mutual influence of endocrine and immunological changes. Elevated stress hormones act via specific immune cell receptors to activate macrophages, inhibit the activity of Th1 cells and activate the Th2/1 axis [44].

Focus on adverse life events has been longstanding. We know that they alter the HPA axis increasing vulnerability to mood disorders. Thus, evidence pointing to HPA axis dysfunction in postpartum depression could be an epiphenomenon related to the increased risk in patients with previous adverse life events. Experimental animal models demonstrate that early stress induces HPA axis reprogramming and increases maternal depression-like behaviours during the postpartum period with deficits in maternal care [60].

Reproductive and Lactation Hormones

Oestrogen and progesterone are candidate hormones most probably involved in the etiopathogenesis of PPD. Their levels increase during gestation and abruptly decline after birth.

Oestrogen

It has been shown that oestrogen and progesterone act in monoamine brain regions and that oestrogen action interferes on the serotonergic system. Changes in oestradiol levels have not been reported in patients with PPD, although it has been suggested that they may exhibit increased sensitivity oestrogen signalling based on changes in oestrogen-sensitive transcript expression, possibly involving epigenetic variations. Oestrogen signalling is known to impact HPA axis function, another potential biochemical mediator of PPD as mentioned above. The presence of identified oestrogen-sensitive transcripts predicted PPD with 88% accuracy. Experiments show that withdrawal of reproductive hormones induces depression-like behaviours and oestrogen treatment simulates antidepressant effects in animal models of PPD [43].

Progesterone

Studies point out that women with puerperal blues suffer a more intense drop in postpartum progesterone levels than controls. However, research has shown controversial results in understanding the changes of progesterone levels. Some demonstrate that progesterone treatment shows an increase in risk and worsens depression scores of PPD, while others have indicated that progesterone treatment decreases the recurrence of PPD in women with previous postnatal depressive episodes. Lower progesterone levels have been correlated with increased depression scores. As mentioned in Payne's recent review, "interestingly, progesterone administration only induced depression-like behaviours in mice following 3 days of withdrawal, implicating decreased levels of progesterone-derived neurosteroids, such as allopregnanolone, in mediating the depression-like effects of progesterone withdrawal" [60].

Allopregnanolone (ALLO)

The neuroactive metabolite of progesterone, ALLO, has been shown to produce anxiolytic

and antidepressant effects thought to be mediated by activating allosterically gamma aminobutyric acid A receptors (GABAARs). ALLO diminished levels have been implicated in increased scores of PPD during late pregnancy and have been associated with reduced levels of GABA. A polymorphism in allo-keto reductase family 1, C2 (AKR1C2), a gene involved in ALLO synthesis, which results in lower allo levels, has been shown to be associated with an increase in PPD [27]. Interestingly, antidepressant treatments increase ALLO levels, and a PPD treatment with a formulation of ALLO, brexanolone, has demonstrated significant improvement of scores. Researchers found that disruption in ALLO signalling via δ-subunit-containing GABAARs mediates PPD by inability to suppress the stress-induced activation of the HPA axis during the peripartum period [39].

Oxytocin

Lower levels of oxytocin have been shown to be predictors of PPD occurrence and severity as well as early breastfeeding cessation. Oxytocin exerts a role in regulating emotion, social interaction, stress and the mother–infant relationships, including delivery, lactation and attachment. Another study demonstrated that oxytocin levels only predicted PPD symptoms in patients with a previous episode of major depressive disorder. However, intranasal oxytocin treatment fails to improve maternal scores [40], and in a separate study, exposure to peripartum oxytocin actually increased the risk of PPD. Thus, it appears that oxytocin is not associated with improvements but might worsen mood in women with PPD. Despite the clear mechanistic relationship between oxytocin and maternal behaviours, evidence for oxytocin as a critical mediator of the underlying neurobiology of PPD remains largely unsubstantiated [60].

Prolactin

Women with PPD are less likely to breastfeed and have lower serum prolactin levels, even if breastfeeding. Moreover, decreased prolactin levels were found in women with higher PPD scores and in those at increased risk for developing PPD. Animal studies point towards a role for prolactin in mediating normal maternal behaviours rather than being implicated specifically in PPD [60].

Brain Function

Functional magnetic resonance imaging (fMRI) has demonstrated dysfunctional connectivity in women with PPD compared to healthy controls. This includes attenuated activity within the anterior cingulate cortex, amygdala, hippocampus and dorsolateral prefrontal cortex as well as decreased corticocortical and corticolimbic connectivity (social cognition areas) when examined at rest. In response to negative facial expressions, as well as to their own infant's crying, women with PPD presented attenuated activation of the striatum, orbitofrontal, dorsal anterior cingulate, medial superior frontal gyrus, occipital fusiform areas and medial thalamic activation. Less responsivity to negative and positive stimuli in women with PPD showed attenuated activity in the dorsomedial prefrontal cortex and the amygdala. Many studies using imagery have demonstrated altered activity in the amygdala, prefrontal cortex, cingulate cortex and insula in PPD, implicating deficits in limbic regions. This region is known to be associated with processing emotionally relevant stimuli; therefore it could be suspected of impeaching emission and child care in women with PPD. Data is confirmed by molecular imaging using positron emission tomography (PET) and magnetic resonance spectroscopy (MRS) [67].

Genetics/Epigenetics

Studies on genetic etiopathogenesis of PPD show participation of genetic risk factors to be significant, based on twin and family studies. Genome-wide association studies have also identified individual candidate genes as well as potential pathways involved in PPD. Candidate gene studies have focused on genes previously implicated in major depressive disorder, such as the sero-

tonin transporter (5-HTTPLR), tryptophan hydroxylase-2 (TPH2), catechol-O-methyl transferase (COMT), cartilage *oligomeric* matrix protein (COMP), monoamine oxidase (MAO) and brain-derived neurotrophic factor (BDNF). Associations of genetic polymorphisms also seem to depend on PPD time of onset. The role of the MAOA and COMT was reported in the sixth week postpartum and during the sixth to eighth week for the COMP genes. Studies examining single nucleotide polymorphisms (SNPs) tend to show positive associations during the second or third gestational trimester [11].

Serotonin transporter polymorphisms (5-HTTPLR) studies have shown positive results in PPD. Research was more consistent when considering genetic–environmental interactions. Polymorphisms in the (5-HTTPLR) are predictive of depression in the early postpartum period. Moreover, a recent study has demonstrated that polymorphisms in 5-HTT predict symptoms of PPD only in patients with associated adverse life events, demonstrating an interaction between genes and environment as well as between two risk factors for postpartum depression, as stressful life events during pregnancy and serotonin transporter polymorphism [60, 75].

Oestrogen receptor alpha gene (ESR1) mediates hormonal changes during the peripartum period, making it an interesting candidate for genetic association studies in PPD, since symptoms have been associated with polymorphisms in ESR1. However, not all polymorphisms remain significant after correction for multiple testing. Furthermore, an unbiased screen of transcripts associated with PPD demonstrated an enrichment of transcription binding sites on ESR1 [43]. Therefore, risk of PPD could be mediated by an increased sensitivity to oestrogen-mediated epigenetic reprogramming. Further research on ESR1 polymorphisms is thus warranted.

Monoamine oxidase A (MAOA) is an enzyme involved in the oxidative deamination of dopamine, norepinephrine and serotonin. Its polymorphisms have also been identified in association with PPD and its variants have been correlated with severity of PPD. Genetic and epigenetic modifications in MAOA in adult women with adverse life experiences were related to higher risk of developing depression and increased cortisol levels, again adding to knowledge on impact of interaction between genes and environmental risk factors for PPD [60].

Catechol-O-methyltransferase (COMT) is an enzyme that degrades catecholamines, including dopamine, epinephrine and norepinephrine. Its polymorphisms are also considered as a risk factor for PPD and positively correlate with depression scores in postpartum women. Further investigation into the association between COMT mutations and PPD should include the role of environmental risk factors.

Tryptophan hydroxylase-2 (TPH2) catalyses the first step in the synthesis of serotonin. Its variants are associated with PPD at specific time points: Polymorphisms in the promoter region are associated with depressive symptoms during pregnancy and up to 6–8 months postpartum. However, polymorphisms in the intron 8 region were only associated with mood symptoms during pregnancy. There is an evidence that TPH2 gene expression is negatively regulated by glucocorticoid receptors. Interactions between stress, HPA axis, adverse life events and THP2 expression have still not been fully explored and need for further research is also warranted here [60].

OXT/OXTR single nucleotide polymorphisms (SNPs) in the gene encoding for oxytocin (OXT) or the oxytocin receptor (OXTR) have also raised interest in the field of PPD. Interestingly, a SNP in OXT was predictive of both variation in breastfeeding duration and postpartum depression scores. An interaction between an SNP in OXTR and adverse life events did not correlate with maternal depressive behaviours postpartum, but was predictive of depression scores prepartum [46].

Data on genetic alterations related to perinatal depression are scarce and studies are full of limitations [42].

Risk Factors and Protective Factors

PPD affects at least one in seven women in HIC and twice as many in LMIC. Marcé Society and other scientific or professional groups have advo-

cated that PPD should be systematically screened. PPD has durable negative impact with high risk of maternal mortality and long-term morbidity. PPD increases self- and to-other harm with heightened suicide and infanticide risks. It hinders lactation and reduces maternal sensitivity. This then has a major deleterious impact on infant attachment. It is also associated with lack of marital satisfaction and family and social support. PPD has medium- and long-term negative impact infant motor development at 1, 2, 6, 12, 18 and 24 months [1]. It has also been correlated to growth retardation at age 2. Poor behavioural and cognitive outcomes up until adolescence have been associated to higher incidence of anxiety and depressive disorders in mothers.

Almost two-thirds of PPD begins before or during pregnancy and 50% of PPD goes unrecognized. Although twice as common as gestational diabetes, no systematic awareness is implemented in most settings. Women with a history of PPD should be monitored, as they are at high risk for both unipolar and bipolar depression.

In most countries, routine screening tools for peripartum depression (PPD) are not applied. Therefore, obstetric, paediatric or basic health clinicians should be aware of risk factors, frequency and level of depressive symptoms during pregnancy and postpartum periods.

Peripartum depression risk could be described as personal (biological, obstetrical, psychological), socio-demographic and cultural factors. Protective factors exist, and a balance between both types of risks could help clinicians focus on higher risk groups given limited resources in many countries.

We have listed well-known and less-acknowledged risk factors for antenatal and postnatal depression, respectively, and some of these factors even overlap. Rather than attribute "weight" to each factor, we wish to underline that is the cumulative number of factors that is essential. Risk is not linear and therefore accumulation of factors will tip the scales at different levels for each woman. However, given a "heavy" enough burden of risk factors, PPD becomes highly likely. It is important for the clinician to have this in mind. It could help to avoid dismissing some risk factors, as if since they are so common or generic (migration, low SES, somatic high-risk pregnancy), it could seem that they do not count.

Risks Factor for Antenatal Depression (AND)

Socio-demographic non-independent risks are significantly associated with AND that include:

- Low educational level
- Low income
- Age: adolescence and late reproductive year pregnancy
- Acute and chronic stressful events
- Marital strain and discord
- Low social support outside of work
- Country of birth different from country of residence
- Working status, that is, being part of a work force

Medical history is a major issue:

- Chronic maternal health problems: including diabetes, hypertension, HIV, etc.
- Use of toxic substances: smoking, drug abuse, alcohol
- Maternal history of mental health issues

By performing a multivariate logistic regression analyses, after adjustment for all socio-demographic and vulnerability factors, Dayan et al. [14] and Dmitrovic et al. [15] identified the following independent risks for AND compared to women who are not afflicted by AND.

Independent risk factors:

- Stress related to the health and viability of the foetus: Previous foetal/pregnancy loss increases risk of AND by threefold [87].
- Previous delivery of a child with a major or minor birth defect (=0.038): Even if risk is lower for current pregnancy defect, health of pregnancy is a major issue for women and one of the simplest risk factors to assess and avoid dismissing [14].

- Stress related to severe marital conflicts: Exposure to domestic violence before or during pregnancy, particularly intimate partner violence (IPV), history of abuse or sexual assault, are all strong risk factors for antenatal anxiety and depression (AAD).
- Lack of partner support: PND depression in fathers predicted worsening PPD severity in mothers [14, 59].
- Educational level is a general very potent risk factor, but a possible bias must be considered as a study in Malawi found that mothers with "more years of schooling" were more likely to self-report major depressive episode. Within this population, PPD is associated with lower perceived social support and experience of IPV. This study demonstrates that AND is common in Malawi and is associated with factors that may be amenable to psychosocial interventions, questioning about which sociocultural aspect interferes on PDD prevalence [86].
- Younger age, specifically adolescent mothers even if some studies have also found that older age was also positively associated with AND.
- Past psychiatric history: Depression and anxiety are highly co-morbid and high anxiety increases risk for AND threefold [5].
- Childhood trauma: Women with a history of abuse often experience more than one traumatic event during their lives and have higher lifetime levels of depressive and post-traumatic symptoms than women who have only suffered a single trauma. This corroborates the theory that accumulation of adversity is more damaging than single events. Childhood sexual abuse has been identified as a particularly strong predictor for risk of developing antenatal anxiety and depression (AAD) [62].
- Sexual abuse after age 16: Sexual trauma screening is essential and meaningful. It should involve a twofold action plan focusing on both mental health referral and an obstetric care plan that addresses the anticipated stress triggers that a survivor is likely to face during delivery [80].
- Childhood adversity: Parental rejection or family secrets with long-term stressful relationships.
- Serious difficulties at work: AAD has been found to be more prevalent in unemployed and housewives than in employed ones. However, poor working conditions, discrimination and lack of key entitlements such as maternity leave during pregnancy are associated with higher levels of depression. Moreover, women whose partners were unemployed seem to be more likely to experience AND [5].
- Higher neuroticism including low self-esteem, perceived stress and social isolation was found to be positively correlated to AND by univariate analyses.

Physiological risk factors include:

- Cortisol, alpha amylase and pro-inflammatory cytokines showed that depressive symptoms were inversely correlated with three anti-inflammatory cytokines: Interleukin (IL)-1β, tumour necrosis factor (TNF) and IL-7. Cortisol was inversely related to the same pro-inflammatory cytokines (IL-1β and TNF) as well as anti-inflammatory cytokines (IL-4, IL-5, IL-10 and IL-13), suggesting that both excessive and inadequate inflammations are related to AND [48].
- Dopamine data suggests that its signalling can influence both depressive behaviours and maternal care capacity [60].
- Use of tobacco whether former or current smoking at rates of 3.0 pack/year. Second-hand exposure at home was independently associated with a higher prevalence of AND.
- Use of vitamins was negatively correlated with AND. However, confounding factors linked to population characteristics of taking vitamin need to be explored.

Some specific factors heightening risk of AND:

- Unplanned pregnancy and lack of preparation during index pregnancy could increase PPD risk.
- Sleep loss, stress and were associated with poor pregnancy outcome and hypnotics use [55].

- Prolonged nausea has increased risk for PPD regardless history of depression and is therefore highly exposed to antiemetics [31].
- Abuse of opioid analgesics during pregnancy had significantly higher rates of depression, anxiety, HIV, insomnia and chronic medical conditions such as hypertension, diabetes and renal disease [81].

Lifetime depression and risk factors assessment is therefore an essential component of the medical history of all reproductive-aged women. History of PPD significantly increases risk for a subsequent episode in 25%. Focus on women with a history of PPD should become standard care [45].

Risk Factor for Postnatal Depression (PND)

Most PND factors overlap those of AND. Both conditions share similar risk factors as seen in Tables 2 and 3. Concerning chronic illness, the literature is inconsistent about diabetes and PND. However, more vulnerable SES population still need to be targeted [13]. All major risk factors of index pregnancy and especially history of previous depressive episode and childhood sexual abuse are essential. Women with HIV infection are in need of specific attention [61].

Literature on demographic risk factors of PND is currently limited by focus on single variables. This only contributes partially to understanding the variance of PPD. Assessment of risk should include depression scales and demographic and physiological variables that have been documented as significant predictors. Profile analysis could be conducted to determine to whom specific focused interventions and early care need to be addressed [17].

Minority, immigrant and refugee populations are especially at risk. They face the added stress of adjusting and learning to function in a new environment, often without family support. Added financial concerns and cultural barriers such as language or not asking for help due to of cultural norms increase heightened risk for this group [16].

Anxiety is also well established as the strongest risk factor in the development of antenatal anxiety and depression. Conversely, absence of anxiety co-morbidity increases chance of recovery after the childbirth [5].

Based on known risk factors, targeted intervention programmes could be implemented. Addressing prevention and treatment of PPD of index pregnancy positive outcome for mothers as well as for subsequent pregnancies. Therefore, this should be a high-priority public health issue.

Table 2 *Risk factors* for antenatal depression

Obstetrical factors	Health-related factors	Environmental factors
Stress related to the health and viability of the foetus	History of depression	Lack of partner support
Previously delivering a child with a birth defect	Diabetes	Childhood abuse
Past high-risk pregnancy	Hypertension	Adverse life events
High-risk index pregnancy	HIV	Lack of social support
Unintended pregnancy	Drug abuse	Lower education
	Mental health problems	Low socioeconomic position

Protective Factors

When assessing need for screening, both risk and protective factors need to be evaluated.

Social Support One of the few well-known protective factors for PPD is social support. It could moderate the degree to which stress affects mothers both pre- and postnatally. The effective use of associated social and health resources during pregnancy and the peripartum could be highly effective. Context-tailored support enhancement should be based on the availability and sensitivity of family and social networks.

Table 3 Postnatal (PND) risk factors

Psychological factors	Obstetric factors	Biological factors	Social factors	Hormonal factors	Breastfeeding/ weaning
Past depressive bipolar Perinatal Other mental health disorders	High-risk pregnancy	Aged ≤18 years	Domestic violence, inadequate partner support	Oestrogen (transcription)	Breastfeeding problems
Stressful life events Sexual abuse	Labour and neonate complications (major malformation, death, stillbirth, necrotizing enterocolitis)	Diabetes	Inadequate social support	Cortisol	Weaning problems
Family history of psychiatric disorder	Low birth weight	Thyroid dysfunction	Low socioeconomic status	Progesterone	Sleep problems
Mood symptoms at oral contraceptive use	Preterm birth			Prolactin	
	Multiple births			Oxytocin	

Partner Support Seems to be an independent factor. It does not reduce the harmful effects of life stress but seems to buffer current stressful risk. This corroborates importance of paternal mental health, i.e. absence of paternal depression as a protective factor.

The components of social support that had the most protective impact against PPD were "support from partner", followed by "living conditions in the last year" and "support from parents". Other items like "support from neighbourhood", "participation in group activities" and "the number of close friends accessible of getting support" ranked much lower [35].

Enhancing relationships and facilitating partner support is therefore an ideal target for prevention efforts. Meta-analyses have consistently associated it with reduced risk of PPD and lower levels of anxiety following childbirth. The transition to parenthood is an opportune time for couples-based interventions as marital satisfaction often declines following the birth of a child. Focus of attention shifts from the self and the partner to the needs of the infant. Increased of household work, less opportunities for shared leisure activities and intimacy with breastfeeding and sleep disturbance place additional pressure on couples. Interventions that seek to reduce the impact of these changes could be helpful.

Resilience may serve as a protective factor for PPD. It is an everyday phenomenon that develops dynamically over the lifespan, is affected by the environment and varies over situations and time. Resilience can be defined as the ability to desist from coping strategies that are no longer adaptive, and in this sense, people who are incapable of adapting and restructuring will face more psychological difficulties. Consistently, low resilience predicts depression and anxiety. However, it has not been investigated in the context of peripartum disorders [25].

Cultural factors also need to be considered. For example, Asian women were more likely to describe religious beliefs and social support, whereas European women talked about recognizing their own needs and personal adjustment such as keeping busy and getting out the house every day. These findings suggest that culture can affect the way women interpret their own experiences and symptomatology, including beliefs in causes of PPD. This should be included in the search for culturally sensitive coping strategies. Culture can play an important role in women's experience of pregnancy and after childbirth. It concerns shared ideas, values, perspectives, beliefs and "perceived standards" for emotional and behavioural responses. Adoption of mainstream values was inconsistently associated with PPD. Conversely,

the more "traditional" female role of virtue, passivity and priority of others over oneself was inconsistently correlated with risk for depression in pregnancy, but significantly associated with PPD [34]. Further research on protective and risk factors of specific cultural orientations and or acculturation is needed.

Peripartum Depression Screening

Despite multiple contacts with medical professionals during pregnancy and postpartum period, PPD often goes unrecognized. Less than 20% of depressed women had spontaneously reported their symptoms to a health-care provider. Although symptoms of depression may remit spontaneously, women could be still depressed 1 year after childbirth. Psychosocial screening recommended for women seen in maternal child health settings provides unique opportunities to identify and intervene with the co-occurrence of PPD, perinatal anxiety, IPV and substance use problems [10].

Direct and indirect evidence suggested that screening pregnant and postpartum women for PPD may reduce depressive symptoms in women, regarding screening instrument accuracy, the benefits of screening and the benefits of treatment. Therefore, it is important for clinicians to ask the pregnant or postpartum patient about her mood.

Newborn care appointments also may be an opportunity to ask a mother about her mood. Obstetric providers should collaborate with their paediatric colleagues to facilitate treatment for women with mood disorders identified during newborn care [4].

Several screening instruments have been validated for use during pregnancy and the postpartum period and they are useful for starting conversation about PPD.

Edinburgh Postnatal Depression Scale (EPDS) is the most employed screening, self-rated with 10 questions, translated and validated in almost all languages. Score 10 or more indicates moderate-to-severe depression. If the last question about suicide thoughts was scored 1 or higher, it is recommended to immediately refer the woman to specialist follow-up. Table 4 shows a comparison of three of most commonly used screening tools.

Screening must be coupled with appropriate follow-up and treatment when indicated; clinical staff in obstetrics and gynaecology practices should be prepared to initiate medical therapy, refer patients to appropriate behavioural health resources when indicated, or both. Recent evidence suggests that collaborative care models implemented in obstetrics and gynaecology offices improve long-term patient outcomes.

Recommendations of American College of Obstetricians and Gynaecologists:

- Although definitive evidence of benefit is limited, the American College of Obstetricians and Gynaecologists (the College) recommends that clinicians screen patients at least once during the perinatal period for depression and anxiety symptoms using a standardized, validated tool.
- Women with current depression or anxiety, a history of perinatal mood disorders or risk factors for perinatal mood disorders warrant particularly close monitoring, evaluation and assessment (www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Screening-for-Perinatal-Depression) [85].

Table 4 Screening instruments frequently used

Screening tool	Number of questions	Time to answer (min)	Sensitivity and specificity
Edinburgh Postnatal Depression Scale (EPDS)	10	≤5 min	Sensitivity 59–100% Specificity 49–100%
Postpartum Depression Screening Scale (PDSS)	35	5–10	Sensitivity 91–94% Specificity 72–98%
Patient Health Questionnaire 9 (PHQ-9)	9	≤ 5	Sensitivity 75% Specificity 90%

Recommendations of American Academy of Paediatrics [29]:

- Routine screening for PPD should be integrated into well-child visits at 1, 2, 4 and 6 months of age. This screening schedule is recommended in *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents, Fourth Edition*.
- PPD screening has also been recognized as evidence based according to the USPSTF (Grade B recommendation).
- Training and continuing medical education programmes should be available for all paediatric providers on the subject of PPD screening and referral (http://pediatrics.aappublications.org/content/early/2018/12/13/peds.2018-3259).

Impact of Perinatal Depression

Impact on Women

Impact on women includes sleep disturbances and continuing depression into the postpartum period. Untreated depression during pregnancy has been associated with miscarriage, perinatal complications, increased risk of preeclampsia, low neonatal Apgar scores and increased admissions to neonatal intensive care units. The most serious maternal ramification of untreated depression during pregnancy is an increased risk of postpartum depression, which can have tragic consequences.

Abrupt discontinuation of antidepressants, common at early pregnancy stage, has been associated with withdrawal symptoms, including nausea and vomiting, diarrhoea, sweating, anxiety and panic attacks, mood swings and suicidal thoughts with resurface of primary psychiatric condition.

The adverse effects on mothers and babies of untreated depression during pregnancy combined with the known, serious risks associated with abrupt discontinuation of psychotropic medications appear to outweigh the risk of transient poor neonatal adaptation to antidepressants during the third trimester.

"A serious injury is expected when IPV is added to PPD as depressed women who experienced perinatal IPV are more likely to have high blood pressure, edema, vaginal bleeding in the second or third trimester, severe nausea, vomiting with dehydration, kidney infection or urinary tract infection, premature rupture of membranes, and premature birth. These women are 5 times more likely to experience placental abruption, associated with fetal growth restriction, preterm birth, and intrauterine fetal demise. Perinatal IPV is also associated with miscarriages.

Research results supports that psychological IPV had a greater impact than physical IPV on low birth weight and, further, women who experience perinatal IPV are also less likely to breastfeed and more likely to discontinue breastfeeding after 4 weeks of delivery. The worst outcome is death of the fetus, baby, and mother as women exposed to IPV during pregnancy were 3 times more likely to be the victim of attempted or completed femicide compared with those who did not. Perinatal IPV is associated with increased health care costs, emergency room attendances and intensive care unit stay during pregnancy. Unfortunately, these women are less likely to receive adequate prenatal care as they can face several barriers to attend prenatal visits including ongoing abuse, interpersonal and financial control from perpetrator, economic deprivation and emotional obstacle, such as shame" [24].

Besides impacts related above, concerns about pharmacological treatment are on balance, with all decisions carrying risks, as Table 5 shows.

Impact on Child

Peripartum depression (PPD) leads to increased costs of medical care, inappropriate medical treatment of the infant, discontinuity of breastfeeding, family dysfunction and an increased risk of abuse and neglect. PPD, as one of the most common adverse childhood events, has potential long-term health consequences for the mother, her partner, the infant, the mother–infant dyad and the family [84].

Research on early brain development, focusing on toxic stress, epigenetics and adverse childhood experiences has revealed the physiological effect of infant's environment on health development and learning in the short and long term.

Table 5 Untreated versus treated perinatal depression and obstetrical outcome

Untreated	Treated
Increased risk of caesarean section	Less risk of caesarean section
Emergency/emergency caesarean section	Less risk of emergency/ emergency caesarean
Risk of bleeding	Lower risk of bleeding
No difference on risk of hypertension in pregnancy	No difference in the risk of hypertension
Higher risk of preterm birth	Lower risk of preterm birth
No difference on risk of small for gestational age babies	No difference in small for gestational age babies
Higher risk of neonatal intensive care use	Greater risk for neonatal intensive care use
Higher risk of hospital stays after 7 days of life	No difference for hospital stays at 7 days of life
	Higher risk for Apgar less than 7 in the fifth minute Higher risk for respiratory problems

Toxic stress is an unhealthy prolonged activation of the stress response unbuffered by a caregiver. Physiologic responses to stress in the infant's environment affect the infant's social-emotional development. The infant, therefore, is at risk for impaired social interaction and delays in language, cognitive and social-emotional development [28].

The epigenetic reductions in hypothalamic glucocorticoid receptor gene expression can impair the negative feedback of the HPA axis, generating a heightened stress response, and also direct neuronal tracking and synaptic pruning, orienting the development of brain areas responsible for emotional regulation. Exposure to prenatal adversity is thought to alter the development of hypothalamus, increase synaptic density in the amygdala and decrease connectivity between limbic and prefrontal cortex areas. These changes may not only amplify the impact of environmental stressors but could also mute the protective effects of resilient factors, with implications for lifelong health, increasing disease susceptibility. Childhood adversity appears to have a cumulative effect on risk of adult mental illness, and repeated exposure to stress can result in the accumulation of allostatic load, increasing susceptibility to disease and predict adult psychopathology [69].

Because maternal depression compromises bonding, the infant withdraws from daily activities and may avoid interaction, and if the mother continues to experience depression, the child's developmental deviations are likely to persist and be less responsive to intervention over time. Long-term effects extend to preschoolers and older children. Maternal depression in infancy also is predictive of altered cortisol levels in preschoolers, and these changes are linked with anxiety, social wariness and withdrawal. Other consequences of untreated maternal PPD include failure to implement the injury-prevention components from anticipatory guidance and preventive health practices for the child (sleep time, teeth brushing) and difficulty managing chronic health conditions (such as asthma or disabilities) in the young child. Also untreated PPD can lead to discontinuation of breastfeeding, child abuse and neglect and family dysfunction. In extreme situations, it can result in suicide or infanticide [28].

Treatment

Concern on PPD by health professionals demonstrates the society's recognition of this pathology with a disabling and distressing problem that occurs with the mother after the birth of her baby. Providing information about where the woman can search for information and treatment improves the efficiency, as diagnosis is the first step to care for PPD.

Pregnant and postpartum women's treatment should be based on principles: Adequacy to diagnose, consider non-treated illness risk, consider non-pharmacological treatment, imbalance side effects and benefits of psychopharmacy, guide choice by previous answer, prefer monotherapy and use minimal effective dose (Table 6).

The facilities care available in the communities varies greatly from one country to

Table 6 Summary of treatment recommendations

Summary of recommendations
Treatment of depression in perinatal period
Depression in pregnant woman may affect the care and gestation development. Thus, the decision to treat the PND with medication should always consider the risk versus benefits and should prioritize the well-being of the mother and the baby
The psychosocial/psychological treatments alone often are first-line treatments for mild-to-moderate PD. IPT is ideally suited to address concerns about changing roles associated with motherhood, while CGT aims to reduce depressive symptoms by addressing unrealistic expectations
Antidepressant is recommended when symptoms are refractory to psychological treatment, if they are severe or require rapid treatment or when preferred by patient
Consider restarting the previously successful antidepressant taken by the patient
It is very common for women to stop using antidepressants when they find out pregnancy, which greatly increases chances of relapse. Even mothers with moderate-to-severe depression are often resistant to use antidepressants, to avoid foetal intrauterine exposure. Thus, the decision to use them or not should be widely discussed between psychiatrist, patient, relatives (preferably the partner), obstetrician and paediatricians in order to choose the best treatment strategy
Certain antidepressants are considered safer than others for breastfeeding women, but long-term outcomes for exposed babies are not well known. The SSRIs are considered less toxic than tricyclic antidepressants, and toxic side effects may be greater in very young, premature or systemically unwell babies
For new-onset PD consider SSRIs as first-line therapy including sertraline, fluoxetine and citalopram. Serotonin norepinephrine reuptake inhibitors (SNRIs) or mirtazapine can be useful if SSRIs were ineffective or the mother previously responded to SNRIs
The mother should be close to her child whenever possible. Separating them can reinforce their feelings of inadequacy and failure as a mother. Consider kangaroo mother care interventions for preterm and term babies
When mother–baby contact becomes harmful, it should be minimized by the presence of the partner, other relatives or health professional in order to minimize the newborn demands and to mediate and assist mother's difficulties with the baby's care. It is recommended to observe possible suffering signs of the baby, which are more discreet and silent than the maternal illness
Breastfeeding should be stimulated and maintained as long as possible, because it favours the affective bonding and all other benefices for the mother's and the baby's health. In very severe cases, such as in psychotic depression or within aggressiveness thoughts towards the baby, breastfeeding can be substituted by paediatrician guidance

another, but in most cases, there are no specialized mother mental health-care services. Maternal mental health facilities with hospitalization, day stay or outpatient services in general provide the best care they can, which is seen in public maternity hospitals in MLIC. There are still no randomized controlled studies that positively or negatively evaluate efficacy of high specialized service against basic general health services. Countries with health system with integrated complexity levels of care do not ever have knowledge or trained professionals to appropriately take care of women with PPD. So, advocacy devoted to PD by conjoint efforts of psychiatrist, obstetrician, paediatrician and family doctors has been spreading out the importance of screening and PPD treatment. Few countries have supported mothers'–babies' psychiatric units which house the mother with her new baby while she receives treatment for severe depression, bipolar disorder or psychosis. Both can remain together until the mother is able to cope with her illness and is discharged from hospital. There was a great development in research with radical and innovative studies on PPD. The knowledge about its effect on mother, baby, family and society supports the importance of PPD treatment.

Men whose partners are depressed describe the experience as overwhelming, frustrating and stigmatizing because they have difficulty coping with her depressive symptoms and feel unable to comprehend the insidious process of maternal depression that imposes an intrusion into their lives and into the lives of their family members. PPD interfere with children's readiness independent of being infant, toddlers, preschoolers, school age and adolescents. Increased incidence of childhood psychiatric disturbance, behavioural problems, impaired language and cognitive development and poor social interaction was observed in children of untreated depressive mother [64].

Management of mother's PPD must be in accordance with its intensity, so that women with mild depression receive psychosocial interventions, such as behavioural activation, and women

with moderate-to-severe depression can receive more intensive psychotherapy, such as cognitive behavioural therapy and antidepressant medication.

Since unwanted pregnancy, especially those after rape, is associated with an increased risk of PPD [7] and depression has severe consequences for mother and child, the abortion should be considered, according to the current legislation of each country. Reproductive rights and gender equity are goals related to society develop, as economic improvement occurs where violence against women was reduced. This issue could be better analysed in another chapter.

Psychosocial Care and Mothers as Protagonist

It is quite important in high- or low-income countries to stimulate pregnant and postpartum women to reflect and discuss about their own experiences. It's not possible, anymore, to avoid discussing stigmatization due to gender or mental health problems. Women in high-income countries, as the USA, that do not have conditions to breastfeed are urged to return to paid work, while others do not have permission to breastfeed in public spaces, prenatal services or safety homes to live and take care of their children. Women's equity is a pattern of society development. Some sociological views support motherhood concept, nowadays spread, as a patriarchal social institution, idealized by a disseminated vision that its aspects are all natural, which do not represent all mothers. The "good maternity" tends to regulate female and motherhood behaviour in patterns with unrestricted responsibility for the safety and well-being of children and broadcasting rules. Mothers not fulfilling the requirements for "good mothers" are ashamed of themselves and seek help late. Professionals who provide women's care during perinatal period would better have a team of consultants, obstetricians, psychiatrists, paediatricians, nurses, doulas and basic health agents in order to provide adequate care.

Pharmacological *Treatment* (Summarized as It Is Subject of Another Chapter)

Some patients may require pharmacological treatment to control depressive symptoms in the perinatal period. Antidepressant medication is recommended when the symptoms are severe or refractory to psychological intervention alone and require rapid treatment, and when preferred by the patient.

Although there is a great deal of evidence for the efficacy of antidepressant medication for PD, particularities about this period may influence the treatment efficacy.

Due to attempt to limit foetal exposure to psychotropic drugs, antidepressants may often be prescribed below therapeutic dosage, when in fact, most women require higher doses of antidepressant medication during pregnancy. Following the same concerns, women treated with antidepressants during lactation often receive subtherapeutic doses prescribed by non-specialist doctors.

Due to ethical issues involving clinical trials in pregnant women, although most of the antidepressants are considered safe, efficacy during pregnancy is limited to observational data, but discontinuation of antidepressant during pregnancy may clearly increase risk of relapse of major depression. Antidepressant use during pregnancy is associated with increased risk of spontaneous abortion and may be associated with adverse perinatal/neonatal events, such as preterm delivery, neonatal respiratory distress and neonatal intensive care unit admission. If patient is psychiatrically stable and wants to continue medication, it is important to discuss risks and benefits of continuing antidepressants and document discussion and patient's choice in medical records.

According to ACOG recommendations for psychiatric medications use during lactation, the benefits of breastfeeding should be weighed against risks to the neonate exposure to medication through breast milk. Most medications are transferred within breast milk, usually at low levels, not clinically relevant to neonate. It is impor-

tant to stop breastfeeding immediately but not permanently if the nursing infant develops abnormal symptoms likely associated with medication exposure as lack of responsiveness and signs of sedation, irritability, changes to sleep, feeding and growth.

In the literature, certain antidepressants are considered safer than others for use in breastfeeding women, but long-term outcomes for exposed babies are unknown. The selective serotonin reuptake inhibitors (SSRIs) are considered less toxic than tricyclic antidepressants, but toxic side effects may be greater in very young, premature or systemically unwell babies. If patient has previously responded positively to a specific antidepressant, the clinician should consider restarting that medication.

For new onset PPD, the recommendation is to consider selective serotonin reuptake inhibitors (SSRIs) as first-line therapy, including sertraline, fluoxetine and citalopram. Consider serotonin norepinephrine reuptake inhibitors (SNRIs) or mirtazapine if SSRIs are ineffective and if the woman had previously responded to these agents [73]. For any prescribed antidepressant, the pregnant and the postpartum women may be more sensitive to side effects, such as increase in anxiety, gastrointestinal intolerance and sleep disturbances. The initial dose should be one-half the recommended and then slowly increased, and once effective dose was reached, the recommendation is continuing treatment for 6–12 months to prevent relapse, although women with recurrent episodes may need longer use [73].

Psychotherapy

Psychosocial and psychological treatments alone often are first-line treatments for women with mild-to-moderate depression. They may receive it alone or with antidepressant medication. It is important to discuss and inform the patient that it may take several weeks for benefits be observed, as excessive expectation from both patient and health-care professional is detrimental. Despite delay in presenting observable effects, there is reliable evidence on psychological interventions' efficacy for PPD treatment [71].

The psychosocial and psychological interventions include antenatal and postnatal periods, group or individual psychoeducation, postpartum debriefing before hospital discharge, nondirective counselling, interpersonal psychotherapy, cognitive behavioural therapy and psychodynamic interventions. Interpersonal therapy or cognitive behavioural therapy may be preferred to women concerned about pharmacotherapy using while pregnant or breastfeeding, as they are technical directive and problem-focused with patent results in few sessions.

Interpersonal therapy (IPT) is ideally suited to postpartum mothers in order to address concerns about changing roles related to motherhood, while cognitive behavioural therapy aims to reduce depressive symptoms by addressing unrealistic expectations. A multicomponent intervention was associated with short-term improvement of depressive symptoms in low-income PPD women compared to a control group [66]. A systematic review shows evidence suggesting that non-pharmacological treatments for PPD may improve child cognitive development and mother–infant relationship with PPD [63].

Other Treatments: Exercises, TMS, ECT, Light Therapy, Mindfulness, Ketamine

A clinical trial suggests that an exercise intervention that involved encouragement to exercise and to seek out social support to exercise may be an effective treatment for women with PPD, including those with self-harm thoughts, and a systematic review evaluation found moderated evidence that light-to-moderate intensity aerobic exercise improves mild-to-moderate depressive symptoms in PPD [41].

Data shows that repetitive transcranial magnetic stimulation (rTMS) significantly improves depressive symptoms in drug-naïve women with PPD compared to placebo group for 20 sessions over 4 weeks [50].

The electroconvulsive therapy (ECT) is also a treatment option for severe depression. It is performed by a team consisting of a psychiatrist, medical consultant and anaesthesiologist and may be an option for resistant depression after first- and second-line treatment options proved to be ineffective. It is also recommended for severe depression, high suicide risk, catatonia, medication-resistant illness, psychotic agitation, severe physical decline and other life-threatening conditions, or when psychopharmacy cannot be used (as sometimes during pregnancy and lactation). There is no literature that consolidates all the evidence on maternal and foetal risks associated with untreated depression, medications and ECT, then translating it into one cohesive protocol that could serve as a management guide and a source of reassurance to health-care providers involved in such practice. The safety of ECT in pregnancy has been documented over the last 50 years, and the adverse effects are similar to those in any individual. The most common risk to the mother is premature contractions and preterm labour, which occur infrequently and are not clearly caused by ECT. The miscarriages rate was not significantly different from the general population. There have been no associations of ECT with congenital anomalies, either morphologic or behavioural, and no neurocognitive disturbances in the child. There are some treatment modifications in pregnancy-based physiological changes that occur during that period [79].

There is some evidence suggesting that light therapy could be useful in treatment of perinatal depression. In a 2008 double-blind RCT, 27 depressed pregnant women were randomly assigned to light treatment with 7000 lux fluorescent bright white or 70 lux dim red (placebo) light administered at home in the morning upon awakening for 1 hour a day in 5 weeks. Results of the trial showed that the bright white light treatment for 5 weeks improved depression during pregnancy significantly more than placebo dim red light. This could be a simple and cost-effective antidepressant modality with minimal side effects for the mother and no known risk for the unborn child. Acupuncture and yoga have been suggested by some authors as complementary therapy to the usual treatment of peripartum depression, but with few studies and little level of evidence so far [8]. No evidence was found to support mindfulness as an effective treatment for PD.

Use of ketamine is not recomended. Animal model prenatal exposure to ketamine during the brain development period has been shown to cause foetal brain damage and subsequent neurobehavioral abnormality. This may be associated with the imbalanced expression of NMDA receptor subunits during fetal development of pups [88].

How to Guide the Partner, Sibling, Family and Friends

The socio-familial environment in which the patient with PD is involved can stimulate the recovery capacity even when symptoms worsen. Thus, people close to the depressed patient, such as family and friends, can greatly influence the course of the illness (Table 7).

It is important that the partner knows that the earlier they engage in the recovery process of PD, more benefit there will be for both. In other words, the more the partner and relatives understand what she is experiencing, the better supported she will fell, and that can contribute for her recovery.

Table 7 Summary: what to say and what not to say

Summary: what to say and what not to say
The socio-familial environment can stimulate the recovery capacity
Family and friends can influence the course of the illness
Partners may feel guilty and frustrated at not being able to solve the problem. Recognize the feelings and empathically assist and stimulate partner to achieve his or her own support
Not to say phrases that minimize the patient's suffering
Instead, use phrases of encouragement and support
Reinforce children that they have not caused the mother's disease and can help her recovery as she is doing treatment and will improve soon. It is very important to tell the truth to children, even to small ones. Use descriptive words such as such as "sad", "grumpy", "worried" or "tired".

Sometimes partners may feel guilty as if they have caused PD and may feel frustrated at not being able to solve the problem. It is important for the health professional to recognize these feelings and empathically assist and stimulate the partner to achieve his or her own support from friends, relatives or professionals. Being present and letting her know that she has the partner support is often what patients with PD also need.

It is possible to guide the partner and close relatives to say, in a sincere way, phrases of encouragement and support, such as "we will get over it"; "I am here"; "if you have something I can do, please tell me"; "you are doing a great job" (about something specific); "this will go away, you will get well"; and "our baby loves you very much".

On the other hand, phrases that minimize the patient's suffering, such as "you should feel happy", "just relax and rest", "stop complaining", "just think positively", "you just need a break from your baby" and "I don't get it why you find it so difficult", can make a woman with PD feel alone and unsupported.

After childbirth, many changes occur in family functioning even when everyone is mentally healthy. Although older siblings may expect some of these changes, when the mother is depressed, even very young children will likely notice changes in her behaviour. They may realize that the mother was crying, irritable, emotionally explosive, discouraged, isolated and little affectionate. The mother then becomes different from what they were accustomed to.

Children need, therefore, honest and clear explanations of what is happening. Whenever possible, the mother should talk to her children and be reinforced by the partner. Instead of using descriptive words such as "depression" and "anxiety", perhaps it is best to use simple, straightforward words such as "sad", "grumpy", "worried" or "tired" to describe the mother's symptoms. It is important to reinforce to the children that they have not caused the mother's disease, that it is not contagious and that they can help in her recovery. They can be reassured when they hear that she is doing treatment and will improve soon. It is very important to tell the truth to children, even to small ones. They realize that the mother is not well, and it is not advisable to say that she is when it is not true. Sadness is a feeling, and hiding it saying that the mother cries for joy passes the message that it is not allowed to be sad.

Preventive Actions

Counselling Interventions

Studies on counselling interventions to prevent perinatal depression mainly included cognitive behavioural therapy and interpersonal therapy. This could include patient education, goal-setting, identifying and modifying maladaptive thought patterns and behavioural activation. Interpersonal therapy focuses on treating interpersonal issues that are thought to contribute to the development or maintenance of psychological disorders. Common therapeutic techniques include the use of counselling sessions that ranged from four to 20 meetings (median, 8 meeting) lasting for 4–70 weeks, which could be initiated during pregnancy, in group or individual sessions, with the majority involving in-person visits which staff included psychologists, midwives, nurses and any other mental health professional.

Some countries with prevention programmes recommend screening for depression in adults, including pregnant and postpartum women and adolescents ages 12–18 years. There is a need to trial several potentially valuable interventions, such as physical activity, infant sleep education, in-hospital perinatal education and peer counselling. More and larger-scale studies are needed on cognitive behavioural and interpersonal therapy interventions including lower-risk women. Several interventions related to developing clinical pathways, training health-care providers and facilitating access to behavioural health specialists show promise. Data are lacking on the benefits and harms of antidepressant medications for the prevention of perinatal depression. Likewise, dietary supplements, such as selenium and vitamin D, have shown promise, but more research is needed.

There are no current guidelines on how to prevent perinatal depression.

More information for patients can be obtained at:

- Read: https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/perinatal-depression-preventive-interventions
- Lifeline4Moms helps obstetricians support women with perinatal depression. UMMS perinatal expert explains why all mothers should be screened for depression during and after pregnancy.
- Perinatal depression expert urges calm on study linking antidepressant use to autism.
- Byatt tells Reuters Health new study will help pregnant women decide about antidepressants.
- Expert's corner: Consider all options for treating depression during pregnancy.
- WCVB-TV: New mothers getting help for postpartum depression through new state programme led by UMMS.

Conclusions

The transition to motherhood and parenthood is not restrained to stereotyped models since it has influences of biological, hormonal, individual, economic, social and political factors interfering with perinatal depressive or anxious symptoms. So, the vicissitudes of perinatal depression care involve the mother, the child and the family with a diversity of health professionals necessary for providing an adequate care. Considering perinatal depression as a quite prevalence disorder and the impact it promotes on women, children and family is quite important to continue observing, studying and researching on it to guarantee better mental health for future generation.

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Psychopharmacology in Pregnancy and Lactation

Jennifer L. Payne

Background

Psychiatric Disorders in the Perinatal Period and the Need for Medications

Pregnancy was, at one time, thought to be protective against psychiatric illness, particularly against depression [1, 2]. However, research in women with preexisting psychiatric conditions indicates that pregnancy and the postpartum time periods are vulnerable to relapse of psychiatric illness. Approximately 15% of all pregnant women have a psychiatric illness, and as many as 10% of pregnancies are exposed to at least one psychiatric medication [3, 4]. While the absolute risk of depression during pregnancy appears to be equivalent to the risk at any other time in a woman's life, the risk in the immediate postpartum time period is dramatically increased [5], particularly in women with a history of mood disorder [6–8]. Many women with psychiatric disorders experience relapse during pregnancy, even if taking psychiatric medications, but the relapse rate is far higher in women who stop medications for pregnancy. Cohen and colleagues demonstrated a 68% relapse rate in women with major depressive disorder (MDD) who discontinued their medications during the first trimester compared to 26% of those that maintained their medications during pregnancy [9]. In pregnant women with bipolar disorder (BD), Viguera reported that there was a recurrence risk of 81–85.5% in those who discontinued mood stabilizers compared to 29–37% in those who continued their medication [10, 11]. In schizophrenia, at least 50% of patients relapse if they discontinue medications and most women with schizophrenia are encouraged to continue their medications during pregnancy [12, 13]. These high rates of psychiatric relapse in the setting of medication discontinuation suggest that – for many patients – treatment during pregnancy is necessary in order to prevent recurrence, though continuing medications during pregnancy is not an absolute guarantee against relapse [12–14].

The treatment of psychiatric disorders during pregnancy and lactation is complicated by a dearth of studies – on what medications work, how changes in body weight and metabolism affect dosing, how to best manage medications both during and after pregnancy, and also on what the long-term effects of exposure may be on the fetus and infant. This chapter will synthesize what is currently known about the safety and best management of psychiatric medication use during pregnancy and lactation.

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Understanding the Literature

In order to be able to judge the potential risks and benefits of psychiatric medication use during pregnancy and lactation, one must first understand the limitations of the existing literature. There are many conflicting findings on infant outcomes after in utero exposure to psychiatric medications, and not all studies are conducted or controlled appropriately. It is important to understand that the population of women with psychiatric illness who take psychiatric medication during pregnancy often have different risk factors or behaviors than the general population of pregnant women and these risk factors may influence the outcomes of studies that are attempting to examine what risks there are for a child exposed in utero to a particular psychiatric medication. For example, diabetes, obesity, smoking, and substance use are more common in the psychiatric population than in the general population as a whole. Studies which have not controlled for the underlying psychiatric illness and its attendant risks and behaviors may find associations between psychiatric medications and outcomes that are not due to exposure to the medication itself, but rather due to other risk factors that are highly prevalent in the population of patients who take psychiatric medications during pregnancy. This not only complicates interpretation of the literature but also complicates recommendations for women who have psychiatric illness but no other inherent risk factors or behaviors. Overall, when reading the literature regarding the safety of psychiatric medications in pregnancy and lactation, one needs to keep in mind the quality of the studies and the general pattern of results: One study finding an association between a medication exposure and a particular infant outcome should not be considered alone without understanding the overall pattern of findings in the literature.

The Risks of Maternal Mental Illness

In utero exposure to maternal psychiatric illness is not benign. There is a strong literature demonstrating that, in addition to presenting risks to the mother, untreated maternal psychiatric illness during pregnancy is associated with poorer outcomes for the exposed child. For example, depression during pregnancy has been associated with low maternal weight gain; increased rates of preterm birth [15]; low birth weight; increased rates of cigarette, alcohol, and other substance use [16]; increased ambivalence about the pregnancy; and overall worse health status [17], including higher rates of preeclampsia and gestational diabetes [18, 19]. Prenatal exposure to maternal stress has also been shown to affect infant temperament [20]. Children exposed to perinatal depression have also been shown to have higher cortisol levels than infants of mothers who were not depressed [21–24] and this finding continues through at least adolescence [24]. Importantly, treatment of depression during pregnancy appears to help normalize infant cortisol levels [25].

The literature regarding maternal psychiatric illness during the postpartum period has repeatedly been associated with adverse infant outcomes. For example, maternal postpartum depression (PPD) has been associated with lower IQ, slower language development, increased risk of attention deficit hyperactivity disorder, increased risk of behavioral issues, and psychiatric illness in the exposed children [26]. Postpartum psychosis, mania, and other severe psychiatric presentations frequently result in psychiatric hospitalization interfering with maternal–infant bonding and breastfeeding. It is important to keep these risks in mind when determining whether or not to use psychiatric medications in the perinatal time period. Psychiatric illness during the perinatal time period should be considered an exposure for the child in the same way that medication use during pregnancy is an exposure for the child.

FDA Pregnancy Categories and Labeling

In 2014, the Federal Drug Administration (FDA) published the “Pregnancy and Lactation Labeling

Rule," mandating changes to the content and format of prescription drug labeling regarding medication use during pregnancy and lactation. The labeling changes went into effect in 2015 for all new FDA-approved medications and will be phased in over time for older medications. The new labeling will attempt to summarize all currently available information to help the clinician weigh the risks and benefits of prescribing a drug during pregnancy [27].

The former FDA pregnancy categories will be briefly discussed here since they will continue to be used as they are phased out over time. Categories include A, B, C, D, and X, and classification is based upon the amount of evidence for safety in animal and/or human studies. One might assume that there is an increasing level of risk from category A to X; however, this is inaccurate. For example, medications that are category B simply may not have been adequately studied in humans to warrant placing them in category A as safe (or in C, D, or X depending on the level of risk in humans), and most medications new to the market will therefore be placed in category B based on animal safety alone. Thus, a category B medication is not necessarily safer than a category C or D medication since there may not be human data available. In contrast, with category C or D, there is human data available, and while there may be risks, those risks may be appropriate to take with certain patients. It is hoped that by providing more information through the new labeling system, clinicians will make more informed choices for prescribing during pregnancy as well as lactation.

General Clinical Considerations

Prepregnancy Planning

The ideal situation is to begin planning for pregnancy *prior* to pregnancy, preferably at the time of initial prescribing of psychiatric medication. As many as 50% of pregnancies continue to be unplanned [28, 29], thus discussing ahead of time of what would be ideal, birth control options and contingency plans for an unplanned pregnancy will minimize the chance that psychiatric medications will be abruptly discontinued and result in a high likelihood of relapse.

Many women will initiate a discussion regarding their psychiatric medication regimen prior to attempting pregnancy, and in this case, prepregnancy planning should take into account (1) the patient's past psychiatric history, (2) severity of illness, (3) the patient's past history of medication response/nonresponse, and (4) the patient's, as well as the partner's (if possible), wishes for treatment during pregnancy. Every case should be considered individually and ultimately there are no hard and fast rules, just the weighing of risks and benefits of the various options for each individual patient.

Individual differences in history of response to medications and severity of illness will frequently dictate clinical care during pregnancy. Severity of illness is important to consider: A case in which the symptoms of depression were mild, responded well to medication, and did not recur could be considered for discontinuation of the medication prior to pregnancy. In contrast, a case in which depression was severe and dangerous and required hospitalization several times would not be a good candidate for medication discontinuation.

In general, if there is adequate time, an attempt can be made to simplify the medication regimen and to change newer medications with less data to older medications with more evidence for safety during pregnancy. However, the primary goal of treatment in pregnancy is to minimize the number of exposures, meaning not only minimizing the number of medications but also limiting exposure to psychiatric illness. If a woman is planning her pregnancy well in advance and she is on a newer, less-studied psychiatric medication, she and her provider can attempt to switch to a medication about which we have more safety data prior to pregnancy – but only if she does not have a history of nonresponse to that medication.

The patient and her partner's wishes regarding medication use during pregnancy should be taken into account when designing a treatment plan. If one or the other is strongly against medication

use during pregnancy, it is best for the treatment provider to make sure they both understand the risks of no treatment to both the mother and the baby, the high likelihood of relapse, and to provide close follow-up during and after pregnancy. Ultimately the patient herself must make the final decision regarding medication use during her pregnancy and the treatment provider should provide support and close follow-up during this vulnerable time.

Unplanned Pregnancy

Most practitioners will have the experience at some point in their career of having a patient on psychiatric medications get pregnant unexpectedly. The principles outlined above for prepregnancy planning also generally apply in the case of an unplanned pregnancy. However, there are some additional caveats. The most important principle to remember is to not stop all psychiatric medications immediately. Sudden discontinuation of psychiatric medications can (a) cause great stress and anxiety for the patient, (b) precipitate withdrawal, and (c) precipitate a relapse of mental illness [30]. The best approach is to review the medication list based on the principles outlined above for prepregnancy planning and, if it is decided to discontinue a medication, to taper the medication. Keep in mind that the fetus is exposed already, and while stopping some medications may make sense to minimize the impact on the fetus, doing so in a controlled and logical fashion is ideal.

One exception to the principles outlined above for prepregnancy planning is that it may not make sense to switch from a newer medication to an older one with more data. While this might have made sense prior to pregnancy, this plan would actually increase the exposures for the fetus significantly. The fetus has already been exposed to the newer medication and switching to a second medication would be another exposure. In addition, the likelihood that the patient would relapse while switching is high, thus exposure to the psychiatric illness would be a third exposure for the child.

It is also important to make a plan for treatment if the patient is psychiatrically ill. This seems obvious, but many patients and treatment providers overlook the fact that the patient may need *more* treatment, not less, in the excitement of an unplanned pregnancy. And always remember that untreated or undertreated psychiatric illness in the mother is an exposure for the fetus.

General Recommendations for Breastfeeding

The benefits of breastfeeding for the baby are well documented and currently the American Academy of Pediatrics advocates breastfeeding through the first 6 months of life. All psychotropic medications pass readily into breast milk, but most do so minimally. For most medications, if a fetus was exposed in utero, they can continue to be exposed to it in breastfeeding. Exceptions to this include: (1) the mother's psychiatric illness has relapsed and the current medication regimen is not working; (2) the mother is on a medication that has a risk of severe side effects with continued exposure for the infant; (3) the infant appears to be having side effects or medical complications related to the medication exposure during breastfeeding. As a general rule of thumb, most psychiatric medications can be safely taken during lactation, even those that are not recommended for use during pregnancy. Outside of infant side effects, the primary psychiatric medications that should not be used during breastfeeding include clozapine due to the risk of neutropenia and possibly lithium due to the risk of toxic levels, though there are exceptions to this rule (see lithium section below).

Involving the pediatrician in the decision-making process and treatment plan is helpful in terms of monitoring the baby for potential side effects, planning for blood draws when appropriate and often to reassure the mother. Many babies are fussy, colicky, or have feeding difficulties without exposure to medications during breastfeeding, so at times it can be difficult to distin-

guish what is due to medication side effects and what is simply a fussy baby. When in doubt, the wisest choice is to do what makes the parents the most comfortable.

Changes in Metabolism and Drug Clearance During Pregnancy

During pregnancy, major physiologic changes occur in a woman's gastrointestinal, cardiovascular, renal, and hepatic systems that can have a significant impact on the pharmacokinetic processes of drug absorption, distribution, metabolism, and excretion. Physiological changes throughout pregnancy result in approximately a 50% increase in plasma volume, increased body fat, and increased medication distribution volume. Renal blood flow, glomerular filtration rate, and medication elimination also increase [31] and changes in liver enzyme activation occur. For example, CYP1A2 activity decreases, while CYP2D6 and CYP3A activities increase [32]. These liver enzyme changes, many of which are hormone dependent, can result in either increased or decreased medication clearance and are relevant to many psychiatric medications [33, 34]. Because of the impact of pregnancy on these basic physiologic and pharmacokinetic processes, adjustments in medication dosing are often required in pregnancy.

When available, therapeutic monitoring of serum levels can help guide decisions regarding medication dosing. Currently, when therapeutic monitoring is unavailable, as is the case for most psychiatric medications, the general practice is to monitor a women's mental state more frequently during pregnancy and adjust the dosage based on symptomatology [32, 34]. This practice still results in a relatively high rate of relapse (of approximately 30%) in pregnant women taking psychiatric medications but is far lower than that seen in women who stop their medications for pregnancy. Monthly medication checks, particularly in the third trimester, can be helpful in reducing the length and severity of relapse.

Summary of Clinical Approaches to Management of Psychiatric Medications in Pregnancy

While each case should be considered individually and there are no hard and fast rules that can be used when designing a treatment strategy for psychiatric medication management, the following principles can be helpful (modified from Ref. [35]):

1. All medication changes should be done prior to pregnancy if possible. This minimizes the number of exposures to the baby and promotes mood stability for the mother.
2. Ideally the patient should be stable psychiatrically for several months before attempting pregnancy. This is not always practical but should provide some evidence and reassurance that the patient's illness is stable prior to entering pregnancy.
3. Use medications that we know something about: Older is usually better. If a medication has been available for a long period of time, there will be more evidence in the literature to support its safety or teratogenicity.
4. Minimize the number of exposures for the baby. Try to minimize the number of medications used but also limit exposure to psychiatric illness.
5. Monitor blood levels of medications when possible. Medications for which laboratory monitoring is not available must be managed based on clinical response. Many women need adjustment of doses during the late second and third trimesters and should be evaluated more often during this time period.
6. With a few exceptions, if a medication was used during pregnancy, it can continue to be used during breastfeeding. Exceptions include clozapine, sometimes lithium (see section on lithium), and medications that are associated with side effects (like sedation) in the nursing infant.
7. Use a team approach. This rule of thumb applies to two groups: (1) family and (2) other doctors involved in the patient's care.

Educating the family regarding the risks of benefits of treatment and no treatment, as well as signs and symptoms to be aware of for relapse, is essential to providing good care for both mother and child. Similarly, communicating directly with the other treatment providers of the patient will minimize miscommunication and differences of opinion and maximize treatment outcomes for the patient.

8. If a woman has stopped her medications for pregnancy, encourage restarting them postpartum. Several studies have shown that restarting psychiatric medications postpartum reduces the risk for psychiatric relapse [36–40].
9. Monitor women during the postpartum time period closely. Since the postpartum time period has an elevated risk for relapse, women should be seen frequently during this time period in order to promote early intervention.
10. Promote healthy sleep habits during the postpartum time period. Studies indicate that decreased sleep is associated with relapse during the postpartum time period [41, 42]. Emphasizing the need for regular sleep with the patient and the family may therefor help minimize this trigger for relapse.
11. If a woman required an increased dose of a medication during pregnancy, consider decreasing it postpartum. For example, many women require increased doses of lamotrigine during pregnancy [43]. Postpartum, lamotrigine concentrations have been shown to increase rapidly, possibly resulting in toxicity [43]. There are no studies that have demonstrated whether psychiatric medications that do not have blood level available should be decreased postpartum. For example, it remains unclear if an antidepressant was increased during the third trimester if it should be decreased postpartum. In general, given the high risk of relapse postpartum, most treatment providers continue a woman on the higher dosage of the antidepressant that was required during pregnancy. Patients should be followed closely, however, for the emergence of side effects, which would indicate a need for decreasing the dosage to the previously effective dose.

Psychiatric Medications in Pregnancy and Lactation

Antidepressants

The baseline rate of major birth defects or malformations is approximately 3% in the general population and less than 1% of these are thought to be secondary to an exposure to a medication [44]. Antidepressants are the most commonly prescribed psychotropic medication during pregnancy [45] and in utero antidepressant exposure has been studied extensively. However, the literature examining infant outcomes and antidepressant use in pregnancy is complicated by small samples, surveillance bias, and lack of controls for the underlying psychiatric illness, and associated risk factors [46] and results overall have been conflicting and inconsistent. A number of infant outcomes have been studied and we detail what is known about each below. Notably, more work has been conducted on the selective serotonin reuptake inhibitors (SSRIs) than on other classes of antidepressants.

Major Organ Malformations

A small increase in the absolute risk of rare defects with SSRI exposure has been reported [47], but four meta-analyses examining the risk of major malformation with first trimester SSRI exposure found no statistically significant increased risk of major malformations [48–51]. Compared with the SSRIs, there are limited data on major organ malformations for other types of antidepressants. Most studies examining the risk of congenital malformations with tricyclic antidepressant (TCA) exposure have found no increased risk of malformations [52–56] though one large epidemiological study found a significant increase in severe malformations (OR 1.36, 1.07–1.72) [57]. With the possible exception of heart defects (see below), bupropion has not been associated with major malformations in several

studies [58–60]. The data available for other types of antidepressants are small but reassuring (reviewed in [61, 62]).

Cardiovascular Defects

Early studies demonstrated a possible association between in utero antidepressant (particularly SSRI) exposure and heart defects (reviewed in [63]). However, most of these studies were "confounded by indication" and compared psychiatric population outcomes to general population outcomes instead of comparing women with psychiatric disorders who took antidepressants to women with psychiatric disorders who did not take antidepressants in pregnancy. More recent studies have done a better job of comparing "apples to apples" and have NOT found an association between antidepressant exposure and heart defects. For example, a recent study [64], with a sample size of over 900,000 women, did not find an association between first trimester antidepressant exposure and cardiac malformations when the statistical analyses were controlled for MDD by comparing the outcomes of women with MDD who took antidepressants to outcomes of women with MDD who did not take antidepressants in the first trimester. Another study [65] performed a meta-analysis of prospective cohort studies and found no association between SSRI use in the first trimester and heart defects when comparing women with MDD who took SSRIs in the first trimester with women with MDD who did not take antidepressants in pregnancy. Thus, the previously identified association between in utero antidepressant exposure and heart defects appears most likely to be associated with other risk factors and behaviors that are prevalent in the population of women taking antidepressants in pregnancy.

Persistent Pulmonary Hypertension (PPHN)

A similar story has evolved for the possible association between in utero antidepressant exposure and persistent pulmonary hypertension (PPHN) in the newborn. An association between SSRI exposure and PPHN was first noted in 2006 [66] and led to an FDA alert regarding the possible association of SSRIs and PPHN. Since this first study, six additional studies have been conducted: three found no association between SSRI exposure and PPHN [67–69] and two found an association [70, 71], although with lower odds ratios than the first study. The sixth and most recent [72] analyzed close to 3.8 million pregnancies and found an odds ratio of 1.51 (CI: 1.35–1.69) for an association between SSRI exposure and PPHN in the unadjusted analysis. However, when the analyses were adjusted for potential confounders associated with MDD, the odds ratio became insignificant (OR 1.10, CI: 0.94–1.29), although a statistical association remained when the analyses were limited to primary PPHN cases in full-term infants (OR 1.28, CI: 1.01–1.64).

Notably, several known risk factors of PPHN are more common in the psychiatric population including maternal obesity, diabetes, and smoking. Further, one study [71] found that a history of a psychiatric admission increased the risk of PPHN (odds ratio 1.3, CI 1.1–1.7), even when women did not take antidepressants during pregnancy. Thus, the psychiatric history in and of itself may be associated with a higher risk of PPHN due to concomitant risk factors and behaviors. Further, PPHN is an extremely rare condition, occurring in 1–2 infants out of 1000 in the general population [73, 74] and thus the absolute risk with exposure to SSRRIs remains small. If one assumes that SSRI use increases the odds of developing PPHN six times the rate in the general population, only 6–12 out of 1000 (0.6–1.2%) infants exposed to SSRIs will develop PPHN. Thus, if there is a true association between in utero SSRI exposure and PPHN, 99% of women who take SSRIs during pregnancy will give birth to a healthy infant who does not develop PPHN.

Autism

A number of researchers had examined whether in utero antidepressant exposure is associated with an elevated risk of autism in exposed children. However, once again, studies that control for underlying confounds associated with psychiatric illness, in general, are negative. Croen et al. [75] conducted a case–control study using data

extracted from medical records. A total of 298 children with ASD were matched for gender, birth year, and hospital to 1507 controls. Antidepressant use in the year before delivery was found to be associated with doubling the risk of ASD in the offspring (OR = 2.0 [1.2–3.6]) with the strongest effect found with first-trimester exposure (OR = 3.5 [1.5, 7.9]). There was no increased risk for the children of mothers with a history of mental health treatment who did not use antidepressants during pregnancy. Another [76] was a large, population-based, nested case–control study that examined both maternal and paternal depression as well as antidepressant use during early pregnancy and the risk of ASD in a Swedish cohort of over 500,000 children. Maternal depression was associated with an increased risk of ASD (OR = 1.49 [1.08–2.08]), while paternal depression was not (OR = 1.21 [0.75–1.96]). Maternal depression and antidepressant use did not increase the risk of ASD with intellectual disability but did increase the risk of ASD without intellectual disability (OR = 4.95 [1.85–13.23]), although not in the absence of maternal depression (OR = 2.1 [0.97–4.57]). This study was limited by not controlling for the underlying psychiatric illness. Another study [77] was a cohort study of 626,875 Danish live births between 1996 and 2005 in which they were able to link information on maternal use of SSRIs before and during pregnancy with ASD diagnoses in the offspring. When compared to women who had never used SSRIs, use of SSRIs during pregnancy was not associated with an increased risk of ASD (OR = 1.20 [0.90–1.61]). In contrast the OR for women who received SSRIs prior to but not during pregnancy was 1.46 [1.17, 1.81], indicating that the risk is likely due to the underlying illness and depression and not the use of antidepressants. Two of the most recent studies [78, 79] remain reassuring and found no association between maternal antidepressant exposure and autism spectrum disorder in exposed offspring after correcting for confounding variables. Experts in this area have generally concluded the previously observed association between in utero antidepressant exposure and autism is a product of maternal mental illness itself (and associated illness, behaviors, and genetics) and not directly due to the antidepressant exposure [80, 81].

Preterm Birth and Low Birth Weight

To summarize a large literature, the rate of preterm birth is higher among mothers who take antidepressants during pregnancy. However, most studies have not controlled for the severity of psychiatric illness and other confounding variables found more commonly in the psychiatric population [61, 62]. A systematic review and meta-analysis of 41 studies found that the pooled adjusted OR was 1.53 for use of antidepressants at any time and 1.96 for third trimester use [82]. Controlling for the diagnosis of depression did not eliminate the effect, but residual confounding could not be ruled out. Controlling for health habits, depressive disorders, *and* psychiatric illness, one study found greater risk of preterm birth in SSRI users, suggesting some biological role [83]. However, the duration of pregnancy was shortened only by 3–5 days and the overall risk was considered modest [83]. The literature examining the role of antidepressant use and low birth weight is similarly complicated by confounding by the underlying illness and the results have been inconsistent [61, 62, 84]. Notably, a recent meta-analysis examined neonatal outcomes in women with MDD receiving no treatment and compared them to outcomes in women without depression [85]. This study found that untreated depression was associated with significantly increased risks of preterm birth and low birth weight, indicating that exposure to the illness MDD affected infant outcomes. Overall, the evidence suggests that the association between in utero antidepressant exposure and preterm birth and low birth weight is complicated by the illness, MDD, and, in addition, the effect is modest.

Poor Neonatal Adaptation Syndrome (PNAS)

The first report of "withdrawal" symptoms in babies exposed to antidepressants occurred in 1973 [86]. It is unclear if "neonatal withdrawal syndrome" is actually a result of withdrawal from the antidepressant or is due to side effects/toxic-

ity due to exposure to medication. Thus, the alternative name poor neonatal adaptation syndrome or "PNAS" may be a better description. There are a number of limitations in the available literature, including inconsistent definitions, no measurement tool, a lack of blinded ratings, and a lack of studies investigating treatment or prevention of the syndrome. Regardless, the FDA instituted a class labeling change in 2004 for both SSRI and SNRI (serotonin-norepinephrine reuptake inhibitors) antidepressants warning that third-trimester exposure may be associated with PNAS. According to the label change, "reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying." Most cases of the PNAS appear to be mild and self-limited and are not associated with lasting repercussions [87]. Available data suggests that approximately one-third of exposed infants will have at least mild symptoms consistent with the syndrome and this risk increases when multiple agents, particularly benzodiazepines, are used [88]. Notably, a recent study found lower motor scores and more CNS stress signs across the first postnatal month after in utero antidepressant exposure indicating that PNAS may have more long-lasting consequences [89], but it remains unclear if this is secondary to antidepressant exposure or exposure to maternal mental illness. Nevertheless, approximately 50% of pregnant women taking antidepressants will discontinue their medication prior to the third trimester due to concerns about fetal exposure [90].

Clearly, larger, more rigorous studies of the syndrome, long-term infant outcomes, as well as strategies to minimize the severity and the rate of the syndrome are needed. At this time there is simply not enough evidence from a safety perspective to recommend tapering of antidepressants in the third trimester, particularly in cases of moderate-to-severe maternal mental illness.

Antidepressants and Breastfeeding

Overall, the preponderance of the data indicates that breastfeeding while taking antidepressants is safe. Studies indicate that antidepressant plasma levels in the infant are low though there are no long-term studies. There are rare case reports of individual infant side effects including sedation, hyperactivity, and feeding difficulty, but most studies have found few if any adverse outcomes [91].

Antianxiety Agents

Benzodiazepines

Studies of benzodiazepine use during pregnancy have also been contradictory and controversial. In utero benzodiazepine exposure has been associated with case reports of perinatal toxicity, including temperature dysregulation, apnea, depressed Apgar scores, hypotonia, and poor feeding. In addition, early studies revealed an elevated risk of oral cleft palate defects compared to the baseline risk in the general population. However, more recent and larger studies have shown that the overall risk of cleft lip and palate with benzodiazepine use in pregnancy is likely quite low and equivalent to the risk in the general population [92, 93]. Infants exposed to a SSRI in combination with a benzodiazepine may have a higher incidents of congenital heart defects even when controlling for maternal illness characteristics [94]. In considering the risks and benefits of benzodiazepines, clinicians should also consider the risks of untreated insomnia and anxiety in pregnancy, which may lead to physiologic effects as well as diminished self-care, worsening mood, and impaired functioning in the mother. Given the consequences of untreated psychiatric symptoms and the limited and controversial risks associated with benzodiazepine use, some women with overwhelming anxiety symptoms or sleep disturbance may find that the benefits outweigh any theoretical risks.

Buspirone

Buspirone is category B meaning that animal reproduction studies did not demonstrate evidence of teratogenesis, but there is no available evidence one way or the other in humans.

Gabapentin

Because gabapentin is an anticonvulsant, it has been studied in the population of pregnant women with seizure disorders in addition to psychiatric literature, thus increasing the amount of data available. Though it is not FDA approved for the treatment of anxiety, it is sometimes used as an alternative to benzodiazepines in patients with psychiatric disorders. Several studies have indicated that there is no increased risk of major congenital malformations with in utero gabapentin exposure [95, 96]. Another study confirmed no increased risk of major organ malformations but also found a higher rate of preterm birth, low birth weight, and need for neonatal intensive care admission [97]. In general gabapentin is considered a safe alternative for the management of anxiety symptoms during pregnancy.

Pregabalin

Like gabapentin, pregabalin is not approved for the treatment of anxiety but clinically has some utility in decreasing anxiety symptoms. It is less well studied than gabapentin, but to date there has been no association with an increased risk of malformations.

Antihistamines

Antihistamines are often used in early pregnancy as a treatment for nausea and vomiting and in late pregnancy for insomnia. They are also, at times, used for anxiety. These medications include diphenhydramine, doxylamine, hydroxyzine, and the pheniramines (latter not available in the USA). All are US FDA risk category A except diphenhydramine (category B) and hydroxyzine (category C). A recent systematic review of antihistamines and birth defects [98] identified two cohort (N = 31) and eight case–control (N = 23) studies that found an association between prenatal antihistamine exposure and congenital malformations; however, methodological concerns were raised regarding study population selection and measurement of antihistamine exposure and presence of malformations [98]. In addition, potentially confounding factors such as presence of hyperemesis gravidarum, a clinical condition for which antihistamines are often used and are itself associated with an increased risk of adverse fetal outcomes, were not addressed in the analysis [99]. The most recent meta-analysis on first trimester H1 antihistamine exposure remains reassuring with no increased risk of major organ malformations or other adverse fetal outcomes [100].

A recent systematic review of sleep-promoting medication use in pregnancy [101] identified only two studies on prenatal antihistamine exposure. One did not find any association between exposure and congenital malformations [102]. The other study is the only RCT of antihistamines in pregnancy, which compared antidepressant, antihistamine, and placebo for insomnia in third trimester [103]. Although this trial did not measure any delivery or neonatal outcomes, it did find diphenhydramine to be associated with significantly longer sleep duration and efficiency (and lower EPDS scores and fewer depressive symptoms) compared to placebo. Thus, taken as a whole, the current evidence suggests that antihistamine use in pregnancy is not associated with an increased risk of adverse pregnancy outcomes.

Mood Stabilizers

Lamotrigine

According to the Lamotrigine Pregnancy Registry (sponsored by the manufacturer) and other published studies [104], there appears to be no increased risk of congenital defects above the baseline risk with lamotrigine monotherapy. Although the North American Antiepileptic Drug Pregnancy Registry initially found that infants exposed to lamotrigine monotherapy during pregnancy have a higher risk of oral cleft defects [105], this association was later not confirmed in larger studies and is now thought to be inaccurate. Dolk and colleagues [106] assessed the association between exposure to lamotrigine and oral clefts using a population-based case–control design utilizing data from the EUROCAT congenital malformation registries. The study population included 3.9 million births from 19 registries from 1995 to 2005. The authors

identified 5511 cases of non-syndromic oral cleft. The control group consisted of 80,052 cases of nonchromosomal, non-oral cleft malformations. In this study, there was no evidence of an increased risk of isolated oral clefts relative to other malformations. Due to the metabolic effects of rising estrogen levels during pregnancy, lamotrigine levels have been shown to decrease over the course of pregnancy and thus should be followed and adjusted if needed [43]. Lamotrigine is also considered safe during lactation and no cases of infant Stevens–Johnson syndrome have been reported [91].

Valproic Acid

Valproic acid is associated with a high rate of approximately 10% of malformations with first trimester exposure. Associated outcomes include neural tube defects, effects on cognition and brain volume, craniofacial anomalies, cardiac defects, cleft palate, and hypospadias [84]. Valproic acid exposure has also been recently liked with autism [107, 108]. Providers should encourage pregnant women who elect to continue any anticonvulsant to take high-dose folate (4 mg per day) for the theoretical benefit of reducing the risk of neural tube defects and to undergo a second trimester ultrasound to screen for major congenital anomalies. Blood levels of valproic acid should also be followed and the dosing adjusted as necessarily. Unlike in pregnancy, valproic acid is considered safe during breastfeeding [91]. Notably, in 2017 the French National Agency for the Safety of Medicines and Health Products imposed a partial ban in prescribing valproic acid in women and girls with bipolar disorder who are of reproductive age though it can continue to be prescribed for women with seizure disorders [109]. Providers should discuss the teratogenicity of valproic acid when prescribing it to any reproductive age woman and, in addition, discuss contraception.

Carbamazepine

Carbamazepine also carries an increased risk of malformations, primarily of spina bifida, other neural tube defects, facial abnormalities, skeletal abnormalities, hypospadias, and diaphragmatic hernia [84]. Carbamazepine is also a competitive inhibitor of prothrombin precursors and may increase the risk of neonatal hemorrhage. As with valproic acid, high-dose folate should be taken and screening for malformations as well as therapeutic blood monitoring should be done. Carbamazepine, like valproic acid, is also considered safe for breastfeeding, despite its risk for adverse pregnancy outcomes [91]. Prescribing carbamazepine in women who are of reproductive age should also prompt a discussion of the risk of birth defects and options for contraception.

Lithium

Lithium use during the first trimester has been associated with an increased risk of a serious congenital heart defect known as Ebstein's anomaly, which occurs in approximately 1 out of 1000 live births. The risk for Ebstein's anomaly with first trimester exposure was originally thought to be much higher (400 times higher than baseline), but a pooled analysis of lithium-exposed pregnancies found that this defect only occurs in 1/1000 to 1/2000 exposed children [110] or less than 1% of those exposed to lithium in utero. Lithium has also been associated with perinatal toxicity, including case reports of hypotonia, cyanosis, neonatal goiter, and diabetes insipidus. For women with severe BD, the risk of recurrence during pregnancy may overshadow the relatively small risk of Ebstein's anomaly, and maintenance lithium therapy during pregnancy may be an appropriate treatment plan for women with severe illness. On the other hand, for women with significant periods of euthymia and few past mood episodes, slowly tapering off lithium and reintroducing lithium after the first trimester may help reduce infant exposure during the critical first trimester and also reduce the risk of maternal relapse during the rest of the pregnancy and the postpartum. There is limited data on the long-term outcomes of children exposed in utero, but a follow-up of children up to age 5 demonstrated no evidence of cognitive or behavioral issues in a small sample of children [111]. Lithium levels should be followed closely during pregnancy and doses adjusted as needed to maintain a therapeutic

level. Notably, serum levels tend to decrease across the course of pregnancy particularly in the third trimester. Lithium should generally be held with the initiation of labor and liberal hydration during delivery should be given to reduce the risk of lithium toxicity. After delivery, the lithium dosage should be reduced to prepregnancy levels (if it was increased during pregnancy) and serum levels monitored [84].

Breastfeeding while taking lithium remains controversial. Generally, lithium levels in exposed infants are non-detectable or very low [112]. However, in the setting of dehydration, an exposed infant could develop toxic blood levels. Mothers taking lithium while breastfeeding should remain vigilant for the possibility and signs of dehydration in their infants and be instructed to go to the ER if dehydration appears to be a concern. Psychiatrically disorganized mothers or those without easy access to the ER should not be candidates for breastfeeding while taking lithium. Blood levels should also be monitored in the infants though no specific regimen has been recommended.

Antipsychotics

A 2004 Cochrane report [113] on the use of antipsychotics for primary psychosis in pregnancy found no trials meeting their inclusion criteria and concluded that "continued use of antipsychotic drugs in these women in pregnancy and lactation without sound evidence raises serious clinical and ethical concerns." However, since that publication, more and more evidence has accumulated that antipsychotics are relatively safe to use in pregnancy and that *not* using these medications when indicated for serious mental illness poses a much greater risk to both mother and child, including suicide and infanticide [12]. Like the in utero antidepressant literature, studies which control for the underlying psychiatric illness and its attendant risk factors and behaviors have generally been reassuring. For example, one study examined birth outcomes in a matched cohort of women with psychiatric illness who used antipsychotics in pregnancy (n = 1021) and who did not (n = 1021) and an unmatched cohort of women who used antipsychotics in pregnancy (n = 1200) and women from the general population (n = 40,000). This study found an increased risk of adverse outcomes *in the unmatched cohort only* [114]. In the matched cohort (comparing women with psychiatric illness who did and did not take antipsychotics in pregnancy), there was no increased risk of preterm birth, gestational diabetes, hypertension, or large for gestational age infants. Overall, antipsychotic use in pregnancy has not been definitively associated with an increased risk of congenital anomalies or any other adverse outcomes [115, 116]. However, very few rigorously designed prospective studies have examined their safety in pregnancy which control for the underlying psychiatric illness.

When prescribing antipsychotics in pregnancy, pharmacokinetics must also be considered. Because, with advancing pregnancy, CYP1A2 enzymes are downregulated, doses of olanzapine and clozapine may need to be decreased, while doses of other antipsychotics that are metabolized by upregulated enzymes may need to be increased [117]. Because of wide individual variations in metabolism, there are no specific protocols for changing doses of antipsychotic medications during pregnancy; thus pregnant women taking antipsychotics should be evaluated frequently during and after pregnancy. It is worth noting that quetiapine, risperidone, haloperidol, and olanzapine have been shown to exhibit the lowest placental transfer from mother to fetus [118].

Normal metabolic changes associated with pregnancy may increase the risk for gestational diabetes in conjunction with the use of antipsychotics. In fact, many antipsychotics, particularly second-generation antipsychotics (SGAs), are associated with excessive maternal weight gain, increased infant birth weight, and increased risk of gestational diabetes infants being born large for gestational age [117, 119]. Several cases of gestational diabetes associated with the use antipsychotics, including clozapine and olanzapine, have been reported [13, 120, 121] suggesting the benefit of routine ultrasound monitoring of fetal size in late pregnancy for women who taking

these medications in pregnancy or for women who gain substantial weight [119, 122].

Behaviors observed in infants exposed to antipsychotics in utero include motor restlessness, dystonia, hypertonia, and tremor [121, 123]. The few studies examining the relationship between in utero exposure to the older, first-generation antipsychotics (FGAs), and neurodevelopment have shown no difference in IQ or behavioral functioning at 5 years [13, 124, 125]. Studies of SGAs have shown associated mild neurodevelopmental delays at 6 months of age [126, 127]. However, these delays were no longer evident at 12 months [126]. More recently, in utero exposure to FGAs has been associated with an increased risk of premature delivery [128] and exposure specifically in third trimester with transient extrapyramidal symptoms and withdrawal symptoms. The latter concerns prompted the FDA, in 2011, to issue a drug safety communication for all antipsychotics regarding the potential risks of abnormal muscle movements and withdrawal symptoms [129]. However, given that these extrapyramidal/withdrawal reactions are usually self-limited, the American Academy of Pediatrics Committee on Drugs guidelines recommend the preferential use of high-potency FGAs in order to minimize maternal anticholinergic, hypotensive, and antihistaminergic effects of the low-potency antipsychotics [130]. These 2000 guidelines also recommended against the use of any depot preparations of antipsychotics due to lack of flexibility in dosing and in order to limit exposure to the neonate of prolonged potential toxic effects.

SGAs have no evidence of being safer or riskier to use in pregnancy than FGAs. The best studied is olanzapine, which has global safety pregnancy surveillance data suggesting no difference in outcomes with fetal exposure to olanzapine compared to the general population [131]. However, there remains a concern that fetal exposure to these newer medications may increase infant birth weight and the risk of being born large for gestational age [119].

Recommendations for antipsychotic use in breastfeeding include monitoring the exposed infant for excessive weight gain and abnormal movements consistent with extrapyramidal side effects or tardive dyskinesia [91].

Clozapine

In addition to what has been described above, it is worth noting that clozapine has been associated with a floppy baby syndrome, and, in addition, it has been recommended that infants with in utero exposure to clozapine be monitored for agranulocytosis weekly for the first 6 months of life [121].

Stimulants

A systematic review in 2014 identified three articles of 41 methylphenidate pregnancy exposures, all of which involved polypharmacy with known teratogenic medications and/or drugs of abuse, and so the findings of various congenital malformations and adverse birth outcomes were not considered generalizable [132]. Although decreased fetal survival in rats has been reported [133], the data on the safety of prenatal exposure to atomoxetine in humans are also limited [134]. Not included in the 2014 systematic review are results from three population-based Danish cohort studies (N = 186 methylphenidate or atomoxetine; N = 480 methylphenidate, modafinil, and atomoxetine; N = 222 methylphenidate alone). The first study found that prenatal exposure was associated with an increased risk of spontaneous abortion and lower Apgar scores in infants [135]. The second found that prenatal exposure was associated with increased risk of elective pregnancy terminations and miscarriage [136]. However, the women using stimulants were more likely to be young, single, less educated, receiving social security, and taking other psychotropics. The third study found that first-trimester exposure was associated with no increased risk of major congenital malformations [137]. Thus, there is minimal data available to guide treatment recommendations. Stimulants are usually prescribed for attention deficit disorder and may be candidates for discontinuation during pregnancy in all but the most severe cases. Stimulants are also used as adjunctive therapy for

MDD and, in cases in which the mood benefit was significant, may be considered for continuation given the relatively reassuring data available to date. There have been no studies of stimulant use in breastfeeding; however monitoring the infant for overstimulation and difficulty sleeping is appropriate.

Conclusions

Interpretation of the literature regarding the association between psychotropic medication use during pregnancy and outcomes for the exposed baby is complicated by the fact that the population of women who require psychiatric medications during pregnancy have other associated risk factors and behaviors that may also influence outcomes. Large, well-designed, and controlled studies have shown that most classes of psychotropic medications appear to be relatively safe for use during pregnancy. Untreated psychiatric disorders during pregnancy have associated risks for both mother and child, and these risks need to be considered in the risk–benefit analysis of using psychiatric medication during pregnancy. Regardless, psychotropic medications should not be precipitously stopped, and a comprehensive evaluation and individualized treatment plan is needed for patients who require psychotropic medications during pregnancy. Ideally, this evaluation and plan would take place prior to pregnancy and every treatment provider should attempt to discuss treatment plans prior to pregnancy when psychotropic medications are initially prescribed and during ongoing care. Future work should focus on the proper management of psychotropic medications during pregnancy including prophylactic dosing strategies and management before and after delivery. Finally, more centralized birth registries with improved data procurement regarding potential confounders are also needed in order to truly address the question of whether exposure in utero to psychotropic medication affects outcomes for the child.

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FDA Rules for Pregnancy and Lactation Labeling and Their Clinical Implications

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For every complex problem, there is a solution that is simple, obvious, and wrong.

Henry Louis Mencken

Mary P. suffered from severe obsessive-compulsive disorder (OCD) that had resulted in two previous hospitalizations. She had been stable for over 7 years on paroxetine, which she credited with "saving my life," and occasional lorazepam. She wished to pursue in vitro fertilization due to male factor infertility, and her reproductive endocrinologist required a letter from her psychiatrist stating that he authorized her use of paroxetine in pregnancy. When Mary arrived in her psychiatrist's office to obtain the letter, he announced that he could not support the use of a category D drug and would no longer prescribe paroxetine. Instead, he would start Mary on vortioxetine, a new drug that carried a category B label but was not FDA approved for OCD, lacked human data about its safety, and had never been used by the patient. Mary switched medications as instructed, became pregnant, and, within 6 weeks, became severely ill. She eventually required an inpatient hospitalization and four different medications, including a switch back to paroxetine, to achieve stability. When she was well again, Mary said, "I wish I had known that staying on paroxetine was an option – I would never have stopped it if I had known."

Several new drugs are introduced annually into the pharmaceutical market, and the majority of their labels show only incipient information about their safety in pregnancy or breastfeeding. However, pregnant and lactating women may have diseases for which pharmacological treatment is essential. Hence, both physician and patient need to ponder the risk of insufficient therapy for the mother, the risk of toxicity to the child, and other important questions related to the use of drugs in the perinatal period [1, 2]. Due to issues relating to embryonic, fetal, and postnatal child safety, the decision to maintain or initiate psychopharmacological therapy during pregnancy or breastfeeding must scrutinize the relationship between potential gains and possible harm to both mother and child. It is a shared medical decision, in which the clinical peculiarities and the autonomy of the patient are considered [3, 4]. The risk of untreated psychiatric episodes, which are associated with a greater likelihood of negative obstetric, maternal, neonatal, and puerperal outcomes, and implications for child development and family relationships, must be acknowledged. Therefore, in the absence of an appropriate therapeutic alterna-

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tive, avoiding the relevant use of psychiatric medication as a means of ensuring a hypothetical risk-free pregnancy or breastfeeding is a contestable strategy [3].

Although there is no risk-free therapeutic decision, the most appropriate choices in each case can be identified. With respect to psychiatric medications, it is fundamental to evaluate with the patient the relevance of the current or probable benefits, in the short and long term, especially when other therapeutic options are unsatisfactory, unavailable, or nonexistent. Individual responses to specific treatments and the intensity of previous and current clinical manifestations are important criteria [4, 5]. Particular attention should be paid to a severe patient who presents an early or misleading aversion to an appropriate proposal for drug treatment during pregnancy or breastfeeding. In this scenario, it is recommended to consider with the patient that the choice not to use a relevant psychotropic drug may have acute and chronic medical consequences of its own. In a clear and complementary way, the possible problems related to the use of the drug should be presented [5, 6].

Although research in the area of perinatal psychopharmacology has progressed, there are no definitive answers to a number of questions for which studies are insufficient or inconclusive. In fact, it is very difficult to sustain scientifically the perfect safety of any substance during the perinatal period. Consequently, complex clinical, ethical, and legal dilemmas arise and require a decision. While perinatal psychiatrists demonstrate a perception of reproductive risk in greater conformity with medical research, other specialists often overestimate the reproductive risk related to neuropsychiatric medications [6].

The 1960s epidemic of fetal malformations due to thalidomide cast a pall over the use of any drugs in pregnancy, and the FDA appropriately moved to revise its labeling standards to create an easy-to-use system to address drug risk in pregnancy. Since the introduction of the FDA pregnancy categories in 1979, American women's use of drugs in pregnancy has altered drastically. First trimester use of medication has increased by 60%, and as of 2008, almost 50% of pregnant women took at least one medication during pregnancy [7]. Among the drugs whose use – and scrutiny thereof – has increased the most are antidepressants.

Assessing the influence of the FDA risk categories on the treatment of mental illness in pregnant and breastfeeding women is a complicated task. Physician prescribing practices are based on training, evidence, and experience, with the contribution of each of these factors not often measured nor made explicit. Similarly, the impact of FDA labels on pharmacists, nurses, therapists, and other health-care providers – and the influence of these professionals in turn on the choices of pregnant or breastfeeding women – remains a thicket difficult to penetrate [8].

Despite this quandary, some broad conclusions about the influence of the old FDA categories are well supported. Beginning with their inception in 1979, the FDA risk category labels had an influence far beyond US borders. They offered a standardized system that, despite their replacement announced in 2008 and effective starting in 2015 [8], continues to be a variable of interest in international research published in 2017 [3–9]. The two other most widely recognized national classification systems, those of Switzerland and Australia, have considerable overlap with the FDA categories (viewed as the most restrictive of the three) and do not offer significantly superior alternatives. Switzerland's system, the first to be released, features the categories A, B (with 3 subgroups), C, and D. The FDA system, 1 year later, did away with subgroups and added category X, and the Australian system, which came out in 1989, took categories from both prior systems, along with their limitations. Despite their commonalities, agreement among them for the same drug is rare: one study found that all three systems assigned the same category to the same drug only one-quarter of the time [10].

The apparent simplicity of the FDA system, which helped promote its use worldwide, was its greatest weakness. In abandoning the categories, the FDA noted that they "were heavily relied upon by clinicians but were often misinterpreted and misused" [8]. The assumption

that the categories were like grades, and described an increasing level of risk, with category B drugs being safer in pregnancy than category C drugs, was widespread and erroneous, as many pointed out [8, 10–15]. The B designation was often assigned to newer drugs that had not yet accumulated evidence from animal or human studies showing adverse effects, allowing them, in effect, to jump the queue of public perception ahead of older drugs that had more time to be better researched, thus "prompting the clinician to incorrectly assume that the absence of adverse data implies safety" [6–12]. Antidepressants of all classes (and different levels of reproductive risk) were assigned the category C rating, with the exception of paroxetine, which was later labeled category D, and bupropion, which was initially classified as category B [11, 16]. As newer antidepressants have come on the market (e.g., vortioxetine), they have often been assigned to category B as well, simply because we lack human data about their use in pregnancy.

Almost from the beginning, frustration over the unintended consequences of the categories as used by both physicians and patients was widespread among perinatal specialists. As early as 1992, the Teratology Society was urging the FDA to drop the ratings labels altogether due to concerns that the system was inadvertently leading patients to seek unnecessary termination of wanted pregnancies after exposure to feared categories of medications [17, 18]. In 2007, the same group noted that, despite apparent agreement over the need for its replacement, the FDA letter rating system was still in place 10 years after a 1997 hearing that "was hoped to be the death knell of the pregnancy labeling categories" [19].

Teratology information services like Motherisk, which was founded in 1985, developed to address the need for more specific advice. Studies of physician inquiries to these services suggest that antidepressants are the most widely asked about class of medications [20–22]. A new term was coined: "psychopharmacoteratophobia," the fear that medical providers have of prescribing psychiatric medications to pregnant women [23]. Several studies suggest that physicians around the world tend to overestimate the teratogenic risk of psychotropics as a class [24, 25].

The tempting simplicity of the FDA categories created dangerous situations when combined with two types of ignorance on the part of many physicians: first, a lack of knowledge among nonpsychiatrists in diagnosing and treating depression, including a lack of knowledge about the risks to mother and child of untreated depression, and, second, a lack of knowledge among general psychiatrists about pregnancy and the unique phenotype and risk factors of mental illness associated with reproduction. These factors, combined with a historical stigma around mental illness that questions the need for antidepressants in the first place, created an environment in which the increasing use of antidepressants in pregnancy continues to be questioned [26, 27]. Arguments for continuing the prior FDA system and even reclassifying all antidepressants as category D are prevalent among those who doubt the efficacy of these medications [28, 29].

Given the inadequate and misleading nature of the FDA categories, and recurrent, yet changing, fears of antidepressants in pregnancy, psychiatrists specializing in the care of perinatal women found that they needed to return to the primary literature to counsel their patients adequately on how to weigh the potential risks of psychiatric medications against the risks of untreated mental illness. The evidence base grew exponentially starting in the 1990s as a result of policy changes at the National Institutes of Health and FDA that encouraged research studies to include pregnant women [30]. The FDA, meanwhile, was working toward a solution, with a Proposed Rule for Pregnancy and Lactation published in 2008 – but the old categories still remained in effect [8].

To meet this need for guidance reflecting current knowledge, in 2009, the American Psychiatric Association and the American College of Obstetricians and Gynecologists produced a joint report entitled "Managing Depression in Pregnancy" [31]. This landmark work attempted to repair the harm done by an overly simplistic reliance on the FDA categories

that left many women dangerously untreated. A team of assembled experts reviewed the primary literature to create guidelines that took into account any evidence for possible harm to the fetus from antidepressant medications and weighed that against harm to the fetus of untreated mental illness, generally recognizing that, for those women with severe mental illness, the benefits of pharmacological treatment frequently outweighed harm.

In general, the authors observed that many studies purporting to find an association between antidepressants and increased risk of fetal harm did not control for depression itself or for other health factors that are increased in depressed women, such as obesity, smoking, or drug use, which may have contributed to the outcome of interest. They also found that these associations revealed a small increased absolute risk if any and that many findings later disappeared after adequate controls were instated. These findings were subsequently reiterated in paper that reviewed new studies available through 2013 [32]. The report mentioned the FDA categories only once, noting that the question "Should women who are being treated with paroxetine prior to conception switch to an alternative SSRI?" is frequently raised because of paroxetine's category D status and recommending that physicians stick with paroxetine if it was the only medicine that had worked [31].

Despite the report's carefully crafted analysis, its dissemination often resulted in a reemphasis of the simplistic advice it sought to supplant. Although the guidelines advised departing from the widespread practice of advising pregnant women with more than mild mental illness to stop or avoid psychiatric medications during pregnancy, the reporting of this sea change was often misleading. A *Wall Street Journal* headline, for example, proclaimed "Therapy Preferred to Drugs for Depression in Pregnancy" [33]. Another 2009 article reported that "women who get pregnant while on antidepressants should consider switching to psychotherapy, especially in mild cases," a digression from the guidelines' intended emphasis, if not a misstatement [34].

Websites promulgating increased perception of risk and potential lawsuits continued to use the categories to bolster their arguments. For example, when searching for "venlafaxine FDA category," the sixth result on Google is a website that offers free case review and claims that "Most doctors prescribe Effexor to patients who are pregnant or may become pregnant with some reluctance since it is a Class C drug per the FDA's pregnancy drug category list…Some doctors, in rare cases, prescribe antidepressants such as Effexor without paying attention to the FDA's black box warning about possible birth defects… If your doctor prescribed venlafaxine without advising you of the known side effects and increased risk of birth defects, the doctor may be liable for damages" [35]. Legal blog headlines such as "With Paxil an FDA Category D, Will Other Antidepressants Follow?" expressed a perception among plaintiff's lawyers that a drug's category demotion was good for business [36].

Women trying to make the difficult risk versus risk decision typically underestimate the risk from illness while overestimating the risk of medications. Almost 70% of women who stopped antidepressants during pregnancy experienced relapse of depression, compared to 26% of women who continued their antidepressants in one small study [37]. For those women with bipolar illness, the rates of relapse with medication discontinuation are even higher: 85% of women who stopped medication in pregnancy became ill compared to 37% who continued medication in another study [38]. Maternal illness is linked to numerous adverse outcomes for the baby: the most significant of which are maternal hospitalization, suicide, and in rare cases infanticide. Depression is frequently associated with comorbidities such as obesity and diabetes; unhealthy behaviors such as smoking, alcohol and drug abuse, and poor nutrition [39]; and less adherence to medical and prenatal care. Untreated depression has been linked to modestly earlier births (by 3–4 days) and lower birth weight [40, 41]. Postpartum, ongoing depression and anxiety can impair infant bonding and parenting and have been associated with lower IQ, slower language development, and behavioral disturbances [41–44].

While frequently under-attributing risk to mental illness, mothers frequently over-attribute risk to medications. One small study that attempted to measure women's perceptions found that pregnant women calling a teratology information service requesting advice on specific exposures identified the risk for major fetal malformations in the general population correctly as approximately 4–7%, yet estimated their own baby's mean risk of major malformations at 22–27%, when the exposure in question was a nonteratogen [45]. Similar to physicians, women also seem routinely to overestimate the teratogenic risks of psychiatric medications compared to other medication classes, such as antibiotics or antiemetics [46]. Given the difficulty of understanding the primary research literature, women frequently rely on physicians to advise them but typically find that general providers (whether obstetricians or psychiatrists) are not adequately informed and that access to perinatal specialists is difficult to obtain [45, 47, 48]. One study found that a majority of women who discontinued antidepressants or benzodiazepines for fear of harm to their fetus did so on advice of their physician and that a majority suffered adverse effects, with a third experiencing suicidal ideation and 10% requiring psychiatric admission [49].

Although there are specialized sources of information to advise clinicians, such as Reprotox or Lactmed, many providers are not aware of them and continue to obtain limited and sometimes misleading information from more general sources. The most widely used prescriber's guide, Stahl's Essential Psychopharmacology, in most recent editions has moved away from reliance on the old FDA categories, but continues to print misleading information concerning risk. The paroxetine entry, for example, states "not generally recommended for use in pregnancy" and cites other risks about which data are controversial (stating "although this is not proven") without mentioning that depression itself is associated with the same risks [50].

Parsing the often contradictory literature requires careful attention not always given by nonspecialists. To give an example, a 2016 article in a clinical journal targeted at family physicians misleadingly reports: "There are safety concerns regarding SSRI use during pregnancy. Although causality has not been established, SSRI use during pregnancy is associated with increased risk of persistent pulmonary hypertension of the newborn, lower Apgar scores, attention-deficit/hyperactivity disorder, and speech delay" [51]. Although technically supported by references, this one sentence, lumping together disparate outcomes with no more specific discussion, conveys a general sense that taking antidepressants in pregnancy is risky. A more careful analysis reveals that the absolute increased risk of persistent pulmonary hypertension with third trimester SSRI exposure increases from 2/1000 to 3/1000 [52]; that Apgar scores in a meta-analysis were lower by 0.37 points at 1 minute and 0.18 points at 5 minutes among infants exposed to antidepressants, arguably a clinically negligible outcome [40]; and that risk of ADHD and speech delay are also independently associated with maternal depression and anxiety [41].

Another common source of information among both providers and knowledgeable consumers, the website for the Centers for Disease Control, provides misleading and outdated information about the risks of antidepressants. The site places information about birth defects first, a strategy that assigns undue emphasis to these rare events. Then, antidepressants get their own section, separate from medications for other chronic health conditions (implying that these medications are different than others). More studies are cited in this section than any other, yet the literature cited is out of date and out of context, highlighting the conclusions of a few individual studies and offering no information about other studies, including recent meta-analyses, with contradictory findings. Finally, only the antidepressant section contains information about how many women use these medications, suggesting again that users of antidepressants are somehow different from women who take medications for other health conditions [53].

The absence of expert advice accessible to the public has left behind a vacuum filled with inac-

curate information. Andrew Solomon's 2015 *New York Times Magazine* essay based on in-depth interviews with two dozen pregnant women notes: "Many have heard that S.S.R.I.s can be terribly harmful from online message boards, from news reports heavily influenced by an individual doctor or from small studies that have been amplified into universal statistics." The sentiment "I never knew that was an option" expressed by one mother about treatment during pregnancy remains prevalent today. The public perception of the dangers of antidepressants is such that numerous online comments in response to Solomon's article advise that women with a diagnosis of depression should either forego having biological children altogether or steel themselves to make it through pregnancy untreated. One commenter expressed her conviction that antidepressants were to be avoided at all costs thus: "I have suffered from hormonally induced depression from puberty through menopause, and…I STILL managed to do what was best for my child, preconception through birth without medication…if a woman so needs strong, brain-altering medication with the potential to alter her unborn child's neurobiology for life, perhaps she is not a good candidate to bear a child" [54].

Persuading mothers, the media, and even physicians that the choice between pregnancy and mental health is a false dichotomy and that every mother merits an individualized risk discussion as the standard of care remains a work in progress. There are not enough perinatal psychiatrists available in the US to see every pregnant woman with mental illness, and psychiatry residency programs are not required to train general adult psychiatrists in this area [55–57]. Furthermore, standardized exams used to assess and credential physicians rarely emphasize knowledge in this area, supporting residency programs' failure to mandate this crucial training.

The FDA's decision to leave behind the lettered risk category labels raises the bar for physicians, who must now understand a complicated and often conflicting body of literature, including the strengths and weaknesses of various study designs, in order to provide informed recommendations to their patients. Given no one-size-fits-all solution, the need for continued training for physicians and other medical providers in the treatment of pregnant women with mental illness will remain high.

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Critical Assessment of Observational Studies and Shared Decision Making in Perinatal Psychiatry

Lauren F. Forrest and Ryan J. Van Lieshout

Introduction

Pregnancy and motherhood represent a time of significant change for women and their families. Lifestyle and role transitions, hormonal fluctuations, and other physiological changes all have the potential to trigger an episode of mental illness, or to exacerbate a pre-existing mental disorder [1]. The perinatal period represents not only an important opportunity to intervene with women but also to minimize its adverse effects on their offspring [2–4].

Depression affects up to 1 in 5 women during pregnancy and the postpartum period [5], and recent research suggests that nearly as many are affected by anxiety disorders in the perinatal period [6]. While fewer women are affected by bipolar disorder during this time, the prevalence is still substantial (2.8%) [7].

Despite relatively high rates of mental health problems in pregnant women and mothers, estimates suggest that as few as 1 in 10 women will receive evidence-based care [7]. Barriers to care can occur at the level of the individual (e.g., stigma, shame), the system (e.g., lack of screening and resources), and the clinician (insufficient knowledge). However, even when physicians, nurses, and midwives are familiar with the most recent literature on the risks and benefits of treatment for perinatal mental disorders (as well as those of no treatment), additional barriers exist in the form of a relative lack of evidence to guide treatment decisions, a lack of clarity in how to interpret this evidence, and delivering this information to women in a way that facilitates informed decision making.

Compared to research in other areas of psychiatry, systematic, empirical study of perinatal mental disorders is in its relative infancy. For a variety of reasons, there remains a relative lack of experimental studies (e.g., randomized controlled trials (RCTs)) studying treatments during pregnancy and lactation, particularly for pharmacologic interventions. Large RCTs offer the highest level of evidence for the efficacy and safety of treatments as they minimize the risk of bias (i.e., systematic error or deviation from the truth) through randomization [8, 9]. As a result, much of the evidence base guiding treatment in pregnancy and the puerperium comes from less rigorous observational studies that struggle to balance important confounding variables (i.e., those that adversely affect the internal validity of a study). Therefore, it is very important for health-care providers to be able to critically appraise observational studies (e.g., cohort, case-control) by assessing them for risk of bias, examining their results, and applying evidence to their own patients when applicable [9].

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In addition to a familiarity with the literature and its quality, sound perinatal psychiatric care also requires careful consideration of the benefits and risks of treatment (or of no treatment) for the mother, as well as for the fetus or infant. This is especially important in cases where the use of medication may be indicated since there may be risks of exposure to medication, but there are also risks associated with exposure to untreated mental illness for the fetus, the infant, women's partners, and the other children in the home. As such, treatment decisions are complex, requiring careful consideration of risks and benefits at a number of levels. This complexity also further highlights just how crucial it is to include the mother in this decision-making process when possible (i.e., in the vast majority of cases).

In this chapter, we aim to provide guidance to health-care providers and the women they provide care to by reviewing the steps involved in clearly defining the clinical issue at hand, finding a study that examines the clinical question, and critically appraising observational research (including cohort and case-control studies), as well as provide a practical framework for discussing complex treatment decisions with patients within a shared decision-making framework.

Case Study

Ms. X is a 32-year-old woman, married, with a 2-year-old son at home and is currently 20 weeks pregnant with her second child. She works full time as a sales manager. She has a history of major depressive disorder and is presenting to a psychiatrist because during pregnancy she has developed symptoms of low mood, fatigue, tearfulness, irritability, and impaired concentration. She is also having problems with sleep, her appetite is poor, and her family physician has noted that she has not been gaining as much weight as advised during this pregnancy. She scored 23 on the Edinburgh Postnatal Depression Scale, but she does not have any suicidal thoughts and no hypomanic, manic, or psychotic symptoms are present now or in the past. Ms. X does have some pregnancy-related worry which started after her mood began to decline. She does not have any obsessive thoughts or compulsions. Ms. X is a lifetime nonsmoker and has not been using alcohol or other recreational substances during the pregnancy.

Ms. X had previously taken sertraline to treat her last major depressive episode which began 3 weeks after her first son was born. She made the decision to come off medication when she and her husband were trying to conceive a second time and was tapered off sertraline prior to conception. She is presenting now wanting additional help and support and to seek treatment for her depressive symptoms as they are interfering with her ability to care for her son and function at work.

Important clinical issues and questions include:

1. What is the diagnosis? What is the prognosis for Ms. X's condition?
2. What treatments are indicated for Ms. X's depression?
3. What are the risks and benefits of using medication to treat depression in the perinatal period?
4. What are the risks and benefits of not being treated in the perinatal period?
5. How would you approach shared decision making with Ms. X?
6. What would you recommend for treatment of Ms. X's depression?
7. What is recommended for mothers who wish to breastfeed on medication?

Critical Appraisal of Observational Studies

Formulating a Clinical Question

It is important for mental health clinicians to have an understanding of how to critically

appraise various modes of research in order to make clinical decisions that are based on the most recent and highest-quality evidence. The first step to providing evidence-based care is formulating a clinical question based on your patient/client that will guide your search for evidence. Then you will need to use an appropriate literature searching tool (e.g., PubMed) to find the most up-to-date and highest-quality evidence required to address this question. The PICOT framework is often used for framing a clinical question and requires that you define the following:

1. *P*: Patient/population of interest
2. *I*: Intervention or exposure of interest. Interventions are used when you are curious about evidence-based treatments. The term exposures applies when you are interested in things like examining risk factors for a particular disease outcome.
3. *C*: Control or comparator. In treatment studies, this refers to the control group to which your treatment is compared (e.g., placebo or existing first-line treatment). In studies examining risk factors, the comparison group will be those not exposed to the risk variable.
4. *O*: Outcome. Specifically, the patient-relevant outcomes you are interested in. In the perinatal population this is complex as it involves multiple outcomes for the identified patient, as well as the fetus/infant.
5. *T*: Time/duration over which you are interested.

The above variables should be synthesized into a specific clinical question to guide your literature search [9]. For example, you may wish to know if maternal antidepressant use during pregnancy is associated with school performance in the offspring at 5 years of age. In this example, the patient population is pregnant women with depression, the intervention is antidepressant medication, the comparison is placebo or no treatment, the outcome is school performance, and the time is 5 years of age. This question could be made more specific by selecting a more specific outcome, such as performance in mathematics.

Searching the Literature

With the vast amount of information available, the task of finding evidence can be daunting. It therefore may be helpful to consult with your academic or clinical institution librarian to determine what resources you have access to. A few common helpful tools are listed below:

1. PubMed
   (a) For searches of individual studies, systematic reviews, and meta-analyses.
   (b) Clinical queries function can be used to determine answer to a clinical question in the PICOT framework.
2. Federated search engines
   (a) ACCESSSS – http://plus.mcmaster.ca/accessss
   (b) Trip – http://tripdatabase.com
   (c) SumSearch – http://sumsearch.org
   (d) Epistemonikos – http://www.epistemonikos.org
3. Pre-appraised research
   (a) Evidence-Based Mental Health (http://ebmh.bmj.com)
4. Literature summaries
   (a) UpToDate
   (b) DynaMed

The interested reader is referred to Guyatt et al.'s *Users Guides to the Medical Literature* (2015 ed.) for further information on conducting a sound literature search [9].

Assessing the Evidence

Two main categories of quantitative studies are relevant in the perinatal psychiatric setting: experimental and observational. Experimental studies such as randomized controlled trials represent the highest-quality evidence from single studies for clinical decision making, as investigators are able to balance the presence of confound-

ing variables between treatment and control groups [9]. Confounding variables are those that are associated with both the exposure and the outcome, but are not involved in the causal pathway between the two. They are an important form of bias that affect the internal validity of studies. For example, in studies of the risks of psychotropic medications during pregnancy or lactation, associations between medications and risks can be confounded by indication (the reason the medication is used in the first place) or severity (since medications are more likely to be used in more ill women).

Observational studies, including cohort studies, case-control studies, and cross-sectional studies, represent a lower level of evidence because confounding variables cannot be balanced by the design of such studies (most commonly because it is unethical to do so) [10]. While such variables can be adjusted for in statistical analyses, causality is impossible to infer because of the presence of unmeasured or incompletely measured confounders.

Experimental studies like randomized controlled trials (RCTs) provide the highest level of available evidence from individual studies since this study design limits bias and focuses on a specific population (Fig. 1). This is superseded by the results of systematic reviews and meta-analyses of RCTs which offer the highest level of evidence as they summarize existing research in a systematic way which can reveal results that may not be apparent in smaller individual studies [9, 11] Guidelines also exist for critical appraisal of systematic reviews and meta-analyses, but since their assessment is beyond the scope of this chapter, we include references to these for interested readers.

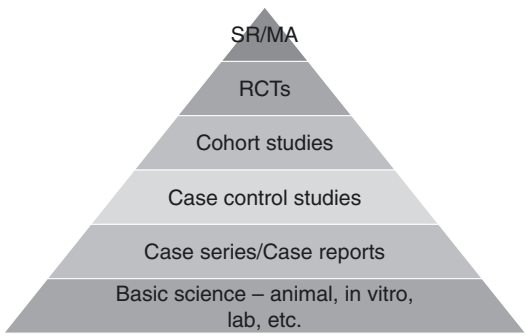

Fig. 1 The evidence pyramid. *SR* systematic review, *MA* meta-analysis, *RCT* randomized controlled trial

1. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health-care interventions: explanation and elaboration [12]
2. Meta-analysis of observational studies in epidemiology: a proposal for reporting [13]

Observational studies represent the next highest level of available evidence and include cohort and case-control studies. This is followed by case series and case reports (both forms of observational research). Evidence lower in the hierarchy includes basic science research involving laboratory or animal models. The hierarchy has been conceptualized as a pyramid (Fig. 1) [11, 14, 15].

Despite their limitations, observational studies are commonly used in studies of women with mental disorders during pregnancy and the postpartum period, and so a knowledge of these study types and their critical appraisal is of importance to clinicians. Cohort studies follow a group of individuals over time and gather information about people and exposures (i.e., risk factors, protective factors, treatments) and later compare groups (cohorts) on the occurrence of outcomes.

Case-control studies examine groups of people with a particular disease outcome (cases) and compare them to individuals without the disease of interest (controls) to examine exposures that impact the risk of the disease outcome. Cross-sectional studies examine individuals in a sample at the same point in time to study the prevalence of disease, risk factors, or exposures [10].

When assessing the quality of observational research, one must understand the study design in order to assess for risk of bias and understand the results [9, 16]. Specific guidelines have been developed that dictate what an observational study should report in the published article to allow the reader to determine the study hypotheses, design, results, and conclusions [17]. This has been outlined in detail in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [10].

Below, we provide an approach to the critical appraisal of an observational study. This includes asking several questions to assess study methods for bias, results for validity and applicability, and finally to apply it to your patient [9]. After describing these questions and their rationale, we will apply them to an example study, one that examined the risk of cardiac defects associated with antidepressant use in pregnancy [18].

Risk of Bias

When using observational research to answer a clinical question or guide a treatment decision, one needs to be aware of the factors that affect the quality of the study by examining the study methods to assess the risk of bias. The risk of bias of a study can be determined by answering the following questions [9]:

A. *What are potential confounding factors? Does the study adequately control for these or use statistical adjustment to minimize their impact on outcome(s)?*

Confounding factors refer to a variable that is associated with both the exposure and the outcome, but are not on the causal pathway between the two. In observational studies, it is often the case that investigators will need to make statistical adjustments to account for these factors because they will tend to be unbalanced at baseline. In a cohort study, groups should be compared on baseline characteristics to ensure similarity and statistical techniques should be used to adjust for confounding variables, particularly if they are unbalanced between groups. In a case-control study, cases should have a similar risk of exposure to controls, which also can be mitigated by statistical adjustment or by the use of matching techniques.

For example, Huybrechts and colleagues (2014) compared SSRI-exposed pregnant women to nonexposed pregnant women for differences in major cardiac defects in offspring [18]. The authors adjusted for possible confounding by maternal depression by conducting a separate statistical analysis restricted to women with that diagnosis. They also adjusted for other known confounders including multiple gestation, chronic maternal medical illness, use of other suspected teratogenic medications, use of other psychotropic medications, use of antidiabetic/antihypertensives, and the number of distinct prescription medications used.

B. *Does the study design use similar methods for detecting outcome or exposure among the groups studied?*

The second question relates to bias introduced in the measurement and assessment of exposures and outcomes. Common sources of bias here include surveillance bias, recall bias, and interviewer bias. Surveillance bias refers to the risk of more vigilant (e.g., frequent, detailed) assessment in patients exposed to a possible risk factor, since this may falsely increase the risk associated with that particular exposure. Recall bias refers to selective memory for an exposure in individuals who have a particular disease outcome. This is higher in retrospective studies like many that use the case-control methodology and can falsely increase the magnitude of the measured association between exposure and outcome. Finally, interviewer bias can falsely introduce increased risk estimates if an interviewer probes cases further for an exposure than they do with a control participant. Interviewers who are blinded to the status of the participant mitigate this type of bias [9].

The work of Huybrechts and colleagues (2014) was based on a population database, and so all the data collected was treated the same way in terms of defining the exposure and outcome of interest [18].

C. *Was follow-up adequate (for cohort studies)?*

Finally, one should assess data regarding follow-up of participants in the study to determine first if the follow-up time is adequate (which will depend on the clinical question) for examining risk of the outcome of interest and, second, to determine if follow-up is different in the control group compared to the exposed group [9]. One would look to make sure the method of

assessment in follow-up is the same in both groups to avoid introducing bias and that the time period of follow-up is the same to ensure that length of time collecting data isn't confounding the results. In the work of Huybrechts and colleagues (2014), the authors used 90 days postpartum as the cutoff date for their outcome, which would be sufficient time to detect a major cardiac malformation in offspring [18].

Interpreting the Results

Once you have examined the study for risk of bias and are satisfied that its methods are sound, you should inspect the study results to determine the size/strength of the association between exposure (i.e., the treatment or risk factor) and outcome (i.e., the odds ratio or relative risk), and by looking at how precise that estimate of risk is (i.e., the confidence interval) [9]. We have chosen to focus on relative proportions (OR, RR) in this chapter given their relevance to clinicians.

A. *Magnitude of effect*: Odds ratios (OR) represent the ratio of the odds of an event in the exposed group of patients/clients compared to the odds of the same event in the unexposed group [9]. Considered another way, the number represents how likely it is that the exposure is associated with the particular outcome. Generally, an odds ratio greater than 2 is considered clinically significant when examining the risk of psychotropic medication exposure in infants [19]. In the study of Huybrechts and colleagues (2014), the unadjusted odds ratio was 1.25 (which became 1.02 when they adjusted for confounding variables) [18]. This means that the associated odds of a major malformation would only be 2% more than women not exposed to an SSRI. Even if these results were statistically significant, they would be of questionable clinical relevance.
B. *Precision of effect*: The confidence interval is an estimate of how precise an effect is and is vital to the interpretation of study results. Most frequently expressed as a 95% confidence interval (95% CI), this represents a range of values within which the true value (e.g., OR) lies 95% of the time [9]. When a CI for a proportion (e.g., OR, relative risk) includes the value of 1.00, it is not statistically significant.

In the work of Huybrechts and colleagues (2014), a 95% CI of 0.90–1.15 was reported for the adjusted OR, indicating that the difference between groups for major cardiac malformations in offspring was not statistically significant [18].

C. *Absolute risk and number needed to treat (or harm)*

In order to adequately counsel patients about risk however, in addition to relative proportion, a knowledge of the absolute or incremental risk can also be helpful, particularly in situations where the exposure or outcome is quite rare [9, 16]. Absolute risk increase or decrease refers to the actual percentage change in outcome associated with the exposure of interest. Indeed, simply because an exposure has a twofold increased risk of leading to an outcome does not necessarily make that risk clinically significant or important to a patient. As a result, it is also helpful to consider the absolute risk increase or the number needed to harm (in studies where risk is the focus) or the absolute risk reduction or number needed to treat (where treatment is the exposure) when fully illustrating the risks or benefits of treatments to patients. Number needed to treat or number needed to harm is calculated by dividing 100 by the absolute risk increase percentage (NNH) or absolute risk reduction percentage (NNT).

Absolute risk increases or reductions (ARI/ARR) refer to the percentage difference in risk of outcome between the experimental (or exposure) and control groups. ARR is calculated by subtracting the rate of the outcome in the treatment group from the rate of the outcome in the control group. ARI is calculated by subtracting the rate of the outcome in the control group from the rate of the outcome in the treatment group. Relative risk increase or reduction (RRI/RRR) refers to the proportional change in risk when comparing the experimental/exposure and control groups [9]. In the study of Huybrechts and colleagues (2014), the adjusted relative risk increase was 2%

[18]. This relative risk is still fairly small, and it translates to an even smaller absolute risk increase, which in this study would be 0.0018% (as the rate of any cardiac malformation increased from 72.3/10000 in women on no medication to 90.1/10000 in women on any antidepressant).

Two other helpful metrics that can be used to quantify absolute risk are number needed to treat (NNT) and number needed to harm (NNH). The former is applicable to studies of interventions looking at the beneficial effects of treatments, and the latter to studies that examine adverse outcomes. The NNT refers to the number of patients that would need to be treated with the treatment of interest to result in one good outcome. The NNH refers to the number of patients that need to be treated to result in one additional case of a bad outcome or adverse event [9]. For example, the study of Huybrechts et al. (2014) examined a putative adverse effect of medication (offspring cardiac malformations) [18]. The NNH for their adjusted analysis is 69,000. This means that 69,000 women would need to be treated with an antidepressant to result in one additional case of a major cardiac malformation.

To further illustrate the concepts of OR, CI, and RRI vs. ARI and NNH, we provide another example. In 2014, Grigoriadis and colleagues published a meta-analysis that examined the risk of persistent pulmonary hypertension of the newborn (PPHN) associated with late pregnancy SSRI exposure [20]. In this work, exposure to SSRIs in late pregnancy was associated with an odds ratio of PPHN of 2.50, CI 1.32–4.73, $P = 0.005$ (meaning that SSRI exposure increased the odds of PPHN two and a half times baseline, a finding that was statistically significant). However, the absolute risk was still very low, with PPHN occurring only in 2.9–3.5 out of 1000 exposed babies. This translated to a number needed to harm of 286–351, meaning that around 300 women would need to be treated with an SSRI to result in one additional case of PPHN.

How Can I Apply the Results to Patient Care?

Finally, after assessing the validity of the study methods and whether its findings are statistically significant and clinically important, one needs to examine the ecological validity of the study and apply it to the patient. Ecological validity refers to how well the results can be applied to the general patient population by comparing how closely the conditions of a study match the real-world situation to which the results would be applied [21].

A. *Do the results apply to my patient based on the population studied?*

To understand whether the results of a study are ecologically valid, it is important to look at the demographics of the population of the study (usually found in Table 1 of the manuscript), as well as the inclusion and exclusion criteria that were applied in the study (usually near the beginning of the methods section of a manuscript), and determine if these apply to the patient you are attempting to apply the study's results to [9].

Table 1 Steps required for proper critical appraisal of observational studies

1. Formulate a question using the PICOT framework
2. Search the literature using appropriate search terms and a good database to select a relevant study
3. Critically appraise the study
3.1 Are the results at risk of bias?
A. What are potential confounding factors when comparing the cases and controls? Does the study adequately control for confounders or use statistical adjustment to minimize the impact of confounding factors on outcome?
B. Does the study design use similar methods for detecting outcome or exposure similar among the groups studied?
C. Was follow-up adequate (for cohort studies)?
3.2 Interpreting the results
A. What is the magnitude of the association (i.e., the OR)?
B. What is the precision of the estimate of the association (i.e., the CI)?
C. What is the absolute risk and NNH/NNT?
3.3 How can I apply the results to patient care?
A. Do the results apply to my patient based on the population studied?
B. Do the results match the values and beliefs of my patient?

This table was adapted from the approach described in Guyatt et al.'s Users Guides to the Medical Literature (2015 ed.) [9]

B. *Do the results match the values and beliefs of my patient?*

Separate from examining the evidence to guide decision making in patient care, and even more importantly, one must have an understanding of the goals and values of the patient [9]. This may be especially important in the perinatal setting. As a result, we discuss the topic of shared decision making in detail below.

Shared Decision Making

Medical practice today differs from past models where decisions about medical care were influenced heavily (if not solely) by the physician. Shared decision making is different than models of the past where physicians provide information about treatment options with little discussion about how these might fit with their values and preferences [22]. Shared decision making has been defined as "a process in which clinicians and patients work together to select tests, treatments, management or support packages, based on clinical evidence and the patient's informed preferences; it involves the provision of evidence based information about options, outcomes, and uncertainties, together with decision support counselling and a system for recording and implementing patients' informed preferences" [23].

In a shared decision-making model, any clinical decision must be consistent with the patient's priorities, goals, and values. This approach is especially important when the decision involves a treatment that may have important harms [9]. In perinatal psychiatry decision making is complicated by the lack of rigorous RCTs, as well as the importance of considering the risk/benefit balance to mother, fetus/baby, partner, and other children [24].

Research into patient decision aids and their integration has found that their use instills patients with a sense of being more knowledgeable and informed, reduces decisional conflict, and confers better understanding of the risks and benefits of a particular intervention [25]. However, evidence on improved clinical outcomes with the use of shared decision making in mental health is lacking in quantity and quality, and so no concrete conclusions can yet be drawn about specific benefit to treatment adherence or disease outcomes [22]. Despite this, the aforementioned patient/client benefits and important ethical considerations (respect for patient autonomy, decisions about one's own health care are a basic human right) make shared decision making an important area for clinicians to become familiar with [22].

Shared decision making requires back and forth discussion between the patient and clinician in order to come to a decision about treatment. The clinician is considered the expert on clinical information and provides evidence based on the diagnosis, prognosis, and treatment options, including risks and benefits. The patient is considered the expert on their own illness experience and values [22, 23]. Discussion with the patient about her own preferences and values is critical to guiding further discussion. It is important that the clinician presents information in a way that is understood by the patient and presents a thorough understanding of the risks and benefits, including the uncertainty (i.e., imprecision) that exists. Implicit in this approach is that different patients will want varied involvement, and some may also choose to involve their partner in the decision making as well. Others may ask for the clinician's input on their own values and preferences when making a decision. This should only be done after presentation of the information and empathic exploration of the patient's values and preferences, while considering the degree of the involvement desired by the patient [9].

Women who are experiencing mental illness in the perinatal period often feel shame in the face of stigma from the media, friends, family, and health-care practitioners [26]. Barriers to making a decision about treatment of depression in pregnancy include difficulty weighing maternal versus infant health, a lack of information, negative information received, and emotional reactions to the decision [27]. This can lead to increased rates of refusal of treatment or discontinuation of treatment (particularly psychotropic medications) in pregnancy and the postpartum period [28–30]. Abrupt discontinuation of psy-

chotropic medication can lead to relapse and this has been found in pregnant women with major depressive disorder [31] and in pregnant women with bipolar disorder [32]. Since some women do not wish to take medications at all during the perinatal period, and given that this occurs in areas where evidence-based psychotherapy is scarce, shared decision making is critical when embarking on a discussion about treatment with pregnant or postpartum patients. The goal of shared decision making in this context is to provide evidence-based information in a nonjudgmental and supportive environment that allows the woman to decide on treatment based on her own values, that is free from coercion, and not based on misinformation.

Informed Consent

Once a clinical question has been defined, a relevant study located, and it is determined to be of applicable and of sufficient quality, this information needs to be shared with the patient so that they can understand the risks and benefits of a treatment and risks and benefits of not taking it. Undertaking a comprehensive informed consent discussion is imperative for shared decision making. In the perinatal population, this requires discussion of all the risks and benefits for both the mother and the baby in the least. The decision to take or not take psychotropic medication in pregnancy is particularly difficult because neither decision is without any risk [33].

Modern medical ethics places a high degree of importance on patient autonomy and the right to voluntarily consent or refuse medical treatments or interventions based on knowledge of risks, benefits, and alternative options for treatment [34]. Informed consent requires that a discussion take place that involves information sharing and patient involvement in decision making [34].

Different governing bodies have established guidelines for outlining the components of informed consent (e.g., The Health Care Consent Act 1996 [35], "A Patient's Bill of Rights: The American Hospital Association," 1978 [36]). Generally, informed consent requires that information has been given to the patient regarding diagnosis, prognosis, and an overview of the possible and recommended treatment options.

When specific treatments are being recommended, information regarding the potential risks and benefits of that treatment should be given, in addition to the potential risks and benefits of not taking that treatment. Where alternative treatments are possible, information regarding the alternatives should also be reviewed and shared with the patient.

Another important component of informed consent is ensuring the patient has capacity to be able to understand the information that has been given as well as be able to appreciate the potential consequences of their decision to consent to or not consent to treatment. Capacity refers to the patient's ability to understand the information presented to them about their diagnosis, prognosis, and recommended treatments, including an ability to apply that information to themselves in appreciating the consequences that may stem from the decision [35].

A Framework for Discussing the Decision of Taking Psychotropic Medication During Pregnancy

Beyond the above basic principles, informed consent in maternity care requires a critical appraisal of the available evidence, along with an integration of the patient's individual circumstances, values, and preferences into the discussion of potential treatment options. An additional consideration is that you are essentially recommending a treatment for two patients – the mother and her fetus/infant. Reviewing all of the information can seem like a daunting task, so it is helpful to organize the discussion based on potential risks and benefits of treatment at particular milestones/time points in the pregnancy and postpartum period. A sample framework is provided in Table 2 to help guide these discussions.

The framework in Table 2 can help organize discussions about treatment during the perinatal period and helps to ensure that no particular period or issue is overlooked. Providing infor-

Table 2 Proposed template for framing discussions about treatment of mental illness with medication in the perinatal period

1. Review of diagnosis and prognosis
2. Review proposed treatment (i.e., specific pharmacotherapy, psychotherapy, etc.)
3. Review of potential risks of treatment, tailored to when the patient is presenting to you for care
   (a) First trimester risks: e.g., growth, physical development, long-term development
   (b) Second trimester risks: e.g., miscarriage, preterm birth, long-term development
   (c) Third trimester risks: e.g., poor neonatal adaptation syndrome, persistent pulmonary hypertension, long-term development
   (d) Risks during lactation: e.g., passage of medication through breast milk
4. Discussion of risk of untreated mental illness
   (a) First trimester risks: e.g., growth
   (b) Second trimester risks: e.g., miscarriage, preterm birth
   (c) Third trimester risks: e.g., growth, preterm birth, still birth
   (d) Postpartum risks: e.g., disrupted attachment, interpersonal problems with other children or partner, may have long-term impact on child mental health
5. Potential benefits of treatment
6. Provide opportunity for patient/partner to ask questions and engage in discussion to elicit patient values and preferences
7. At the end of the discussion, a decision can be made or deferred (time permitting) if the patient desires further information or discussion with others in their lives

mation in this way can help women feel more knowledgeable about the decision they are faced with as well as more supported in making that decision [33, 37]. When discussing this decision, it is also necessary to consider the woman's values and even to take time to elicit these values to aid them in deciding between difficult options [33].

It is also helpful in nonurgent cases to allow the woman time to think about the decision on her own, discuss it with others (if she wishes), and come back for follow-up to permit additional discussion [33]. As mentioned above, women should be presented with numbers for absolute and relative risk when available to help objectively frame the level of risk given the research showing women tend to overestimate the risk of psychotropic medication use on infants [26, 38]. Women should also be afforded the opportunity to include their partner in the decision making if desired and provided reliable external sources of information from which to draw to aid their decision [24, 33, 37].

Case Study

By way of reminder, after meeting Ms. X, the following important clinical issues and questions arose:

Questions

1. What is the diagnosis? What is the prognosis for Ms. X's condition?
2. What treatments are indicated for Ms. X's depression?
3. What are the risks and benefits of using medication to treat depression in the perinatal period?
4. What are the risks and benefits of not being treated in the perinatal period?
5. How would you approach shared decision making with Ms. X?
6. What would you recommend for treatment of Ms. X's depression?
7. What is recommended for mothers who wish to breastfeed on medication?

Answers

1. The psychiatrist discusses Ms. X's diagnosis, major depressive disorder, recurrent, severe, with peripartum onset, and advises her that it may not respond rapidly (or completely) with psychotherapy alone given its severity.
2. You then discuss with her that first-line treatment for severe depression includes medication (sertraline, escitalopram, citalopram) or medication combined with psychotherapy (cognitive behavioral therapy or interpersonal psychotherapy) [39].
3. The psychiatrist also discusses the possible risks of the use of medication at the current point in pregnancy. Ms. X is past the point of organogenesis where teratogenesis would be of major concern, but there is potentially a small increased risk

of miscarriage (relative risk between 1.45 and 1.87) [40], though conflicting evidence exists, and that the absolute risk increase might only be 0.6% [41]. There is also a 15–30% risk of poor neonatal adaptation syndrome that is characterized by infant jitteriness, irritability, tremor, respiratory distress, and excessive crying that typically resolves within a few days, with a maximum up to 2 weeks [42]. Finally, the use of antidepressant medication during pregnancy has been associated with a small increased risk of persistent pulmonary hypertension of the newborn occurring in 2.9–3.5 infants out of 1000 who are exposed to antidepressant medication (compared to a risk of 2 in 1000 in the general population) [20]. It is also shared that there is a paucity of conclusive, high-quality data examining the long-term effects of in utero exposure to antidepressants [43].

4. You advise her about the risks of remaining untreated including continued depression for her, as well as the potential risks to the fetus (increased rates of poor obstetrical outcomes, impaired bonding, infant sleep difficulty, as well as longer-term cognitive, behavioral, and emotional problems) [3]. You comment that it may also affect her relationship with her partner and with her 2-year-old son.
5. After providing detailed information about the risks and benefits of medication use in pregnancy, the psychiatrist begins a conversation with the patient, allowing her to ask questions about the information, while also gently exploring Ms. X's thoughts about the information presented and about the important components of this decision. Ms. X notes that she mainly discontinued the antidepressant due to concerns about malformations in the baby as well as miscarriage. She expresses some relief that the risks are not as high as she initially thought and has requested more information about specific medication that would be recommended. She asks you about what side effects she might experience on the medication and you talk to her about common side effects that occur (headaches, stomach upset, dry mouth, blurred vision, and sleep disturbance) and that if experienced, they often improve after a couple of weeks on medication. You discuss the possibility of sexual dysfunction as well which is not likely to abate off medication. You also talk to her about serious side effect such as serotonin syndrome if too much is used or there is an interaction with another medication. She requests some time to think about the decision and talk it over with her husband.
6. You explain to her that your first-line recommendation in her case is to restart her previous antidepressant – sertraline – and you provide her with a patient information sheet on SSRIs and the number for Motherisk so she can call for further information. Ultimately, Ms. X considers the information provided and decides to restart her previous antidepressant – sertraline. Her symptoms remit at a dose of 100 mg daily and she delivers a healthy male infant at term.
7. She again presents to her psychiatrist at 2 weeks postpartum with questions about what to do with her antidepressant medication now that she is breastfeeding. She knows that medication can pass into her breast milk and then on to her baby and she would like more information about what the risks are and what she should be watching for. You advise her that a small proportion of this medication (0.4–2.2% of the maternal dose) can pass to her baby through breast milk, and this concentration is so low that the actual impact on the baby is minimal. Sertraline is considered safe for breastfeeding with minimal clinically significant effects for her baby in

the short term and to watch for sedation, irritability, difficulty feeding, and appropriate weight gain [44]. There are very limited data regarding the long-term effects on the infant with use of antidepressants during breastfeeding [45]. You also advise Ms. X that she is at risk of relapsing again with discontinuation of her antidepressant medication which could lead to impaired bonding and attachment, as well as cognitive, emotional, and behavioral problems later [46, 47]. After discussing the information again with her husband and with Motherisk, Ms. X decides to continue on her current dose of sertraline.

Conclusion

Mental illness in the perinatal period is an all too common problem that affects mothers and families, and that can have adverse effects on the long-term health and development of children [2–4]. The extant literature examining the treatment of mental illness in the perinatal period is both sparse and methodologically limited. In order to understand the known risks and benefits of existing treatment options and to communicate these effectively to patients, it is important to have an understanding of how to critically appraise observational research [9].

However, adequate informed consent also requires that the clinician helps women to understand their illness, the prognosis, available treatment options, and risks and benefits of taking treatment and not taking treatment [34]. This is a complex decision as women are often misinformed by sources of non-evidence-based information [26], and given that no decision is without any risk [24, 33], it is important for clinicians to offer a supportive environment and be able to provide information on the possible risks and benefits in an organized way that allows the patient to actively participate in the decision-making process [16, 34].

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