Società Italiana di Psichiatria

Evidence based Psychiatric Care
Journal of the Italian Society of Psychiatry

Depression and gender: towards tailored medicine

Claudio Mencacci

Claudio Mencacci[1], Paola Landi[2]

[1] Dipartimento Salute Mentale Dipendenze e Neuroscienze, ASST Fatebenefratelli-Sacco, Milano Italy; [2] Asst Fatebenefratelli-Sacco, Milano Italy

Summary

Since puberty, depressive disorder is about 2 times more frequent in women. the gender prevalence gap begins in adolescence, decline and remain stable in adulthodd and then recurred in later life with a second peak in perimenopausal period. Moreover depression in women has clinical and course peculiarities. A general consensus sees a multifactorial etiology for gender differences in depression. Sociological studies emphasize the role of poverty, violence and gender inequality. Biological theories focus on genetic predisposing factors and hormonal status. The most widely accepted model is the "stress and vulnerabilty" model according to which genetic vulnerability (biological factor) influences temperament (affective vulnerabilty) which shoul lead to negative cognitive styles (cognitive vulnerability) increasing the risk of depression. Finally, there are known gender differences in drug pharmacokinetics as well as specific drug response profiles based on gender.

Key words: depression, gender, etiopathogenetic hypotheses, life stages in women

Introduction

A World Health Organization study on "depression and other mental disorders" published in 2017 revealed that around 300 million people worldwide are suffering from depression, with an increase of over 18% between 2005 and 2015 [1]. In fact, WHO classified depression as the world's leading cause of disability after cardiovascular disease.

Epidemiological studies on samples from different countries show that, since puberty, depressive disorder is about 2 times more frequent in women [2]. In a review by Ferrari AJ et al., the global 12-month prevalence of major depression was 5.8% in women and 3.5% in males [3]. In Italy 5.5% of the population suffers from major depression, with a clear female prevalence in a 2:1 ratio [4]. According to the recent ESEMeD (European Study of the Epidemiology of Mental Disorders) study, in Italy the lifetime prevalence of MD and dysthymia is 11.2% (14.9% in women and 7.2% in men). In the 1970s, Myrna Weissman was the first to review the evidence for differing rates of depression between the sexes [5]. In an article, Hankin et al. [6] noticed that gender difference in depression first began to emerge between the ages of 13 and 15 and then become even more significant between ages 15 and 18. Salk et al. (2017) [7] conducted two meta-analyses, each including more than 1.7 million subjects, taking into consideration not only the categorical diagnosis of major depression but also the dimension of "depression symptoms". The estimate of the weighted mean effect size for the gender difference in major depression was OR = 1.95, whereas the estimate for the gender difference in depression symptoms was Cohen's d = 0.27. The

How to cite this article: Mencacci C, Landi P. Depression and gender: towards tailored medicine. Evidence-based Psychiatric Care 2020;6:126-131. https://doi.org/10.36180/2421-4469-2020-21

Correspondence:
Claudio Mencacci
claudio.mencacci@gmail.com

Conflict of interest
The Authors declare no conflict of interest.

study also confirmed that the gender prevalence gap begins in adolescence, earlier than previously reported in the literature (OR = 2.37 at age 12). The gap then declined and remained stable in adulthood, and then recurred in later life with a second peak in the perimenopausal period.
A general consensus sees a multifactorial etiology for gender differences in depression [8], but the difficulty in defining precise pathophysiological mechanisms can be partly attributed to the heterogeneity of clinical samples. Generally, the sample is recruited taking into account DSM or ICD diagnostic criteria. According to DSM 5, the diagnosis of major depressive disorder (MDD) requires the presence of at least 5 of 9 possible symptoms during the same 2-week period and includes: 1) anhedonia; or 2) depressed mood, or both. Other criterion symptoms include: 3) insomnia or hypersomnia; 4) changes in appetite or weight; 5) changes in psychomotor status; 6) fatigue or loss of energy; 7) worthlessness or guilt; 8) diminished concentration or indecisiveness; or 9) suicidal thoughts or behaviors. Using these criteria, it is possible to have an extremely high number of combinations (up to 227), configuring clinical pictures which are also very different from each other but equally diagnosed as MDD [9]. This sample heterogeneity can explain, at least in part, sometimes inconclusive or contradictory results from different studies.
This review aims to report the most recent literature data on the possible causal factors underlying the different gender prevalence of depression, the different clinical presentation and response to drug therapy in the perspective of precision medicine.

Materials and methods

A systematic search of articles on Pubmed, using as sarch terms “gender and depression” “gender and treatment response” “epidemiology of gender and depression”, has been carried out from 1977 to today. We selected articles that recruited a sample of patients defined as depressed according to DSM and ICD 10 classifications, with or without comorbidities.

Etiopathogenetic hypotheses

Sociological theories

Sociological studies emphasize the role of poverty, violence and gender inequality [10]. The woman is often in a disadvantaged socio-working position, with even lower incomes on equal working conditions. It is most often exposed to violence and mistreatment, often in the domestic environment, which negatively affect not only mental health, but also physical health in a global sense. It has been estimated that complicances deriving from abuse are greater than those deriving from diabetes or hypertension. The lifetime prevalence of violence against women fluctuates between 16 and 50%; one in five women are subjected to an attempted rape or to a rape during lifetime.
Another fact is the higher frequency of mobbing phenomena reported by women with respect to men [11]. A possible explanation could be that women tend to live social and work relationships with greater affective and emotional participation than men, thus increasing their exposition to reasons of suffering. Interestingly, married women are more affected by depression than men, who are more vulnerable in a single condition (WHO 2002). A study that included 18 countries in the WHO World Mental HEalth Surveys [12] found no significant gender gap in major depression in high or medium-low income countries, suggesting that economic development does not explain the variability of cross-national gender differences [4]. Instead, Salk et al. [7] showed larger gender differences in depression in wealthier countries (OR = 2.00) compared to low- to middle-income countries (OR = 1.82). According to some authors there is a basic bias, which consists in the greater aptitude of women to ask for help, thus explaining the finding of higher prevalence of depression in the female sex. However, in the light of scientific evidence, such hypothesis alone cannot justify this epidemiological difference [13].
Hyde JS et al. support the “stress and vulnerability” model, which seems to be the most widely accepted interpretation [8]. It integrates biological, cognitive and affective factors and tries to provide a model for understanding the gender differences in depression observed in childhood. Simplifying, genetic vulnerability (biological factor) is presumed to influence temperament (affective vulnerability), which in turn should lead to negative cognitive styles (cognitive vulnerability), causing an increased risk of depression in adulthood.

Biological theories

Biological vulnerability includes both genetic predisposing factors and hormonal factors.
As for genetic factors, recent studies have analyzed gene expression, finding that over 6,500 genes are expressed differently in men and women in several tissues and organs, and most of them are not directly related to reproduction and sexuality [14]. As expected, the differences in expression were very marked in breast, musculoskeletal and subcutaneous adipose tissues. But what happens in depression? a significant gender difference was found in the role of the serotonin transporter in modulating affective disorders. The s allele of 5-HTTLPR seems to be differently associated with an increased risk of depression, depressive symptoms, anxiety traits and symptoms (instead, in men the same allelic pattern appears to be associated with aggressiveness and conduct disorders). These differences begin in adolescence and are not consistent among the elderly, suggesting a modulatory role of hormonal fluctuations [15]. The polymorphism of the

promoter region of the 5-HT transporter gene ("short", s allele - and "long", l allele) leads to a different functioning of the serotonin transporter and to a different response of ACTH to stress.
A metanalytic study [16] was carried out on gene expression of depression across 3 specific brain regions: dorsolateral prefrontal cortex, subgenual anterior cingulate cortex and basolateral amygdala. In the comparison of differential gene expression in men and women with major depression, 633 of 706 transcripts were present only in men and 809 of 882 only in women. Only 73 genes (21+ 52) were expressed differently in depressed patients (compared to healthy controls), men and women. Of these, however, 52 were expressed in the opposite direction (up/down regulated) in males and females. Therefore, only 21 genes were implicated with the same "polarity" in male and female depressed patients.
Regarding the influence of hormonal profile, the correlation between fluctuations of female sex hormones and windows of vulnerability for depression is evident [17]. The woman has windows of vulnerability for depression in puberty, in the premenstrual phase, in the postpartum and in perimenopause, assuming a critical role of sex hormones. The brain is one of the major targets of sex hormones. Estrogens, in particular, play a complex role at CNS level: they modify the permeability of the blood brain barrier, selectively increase brain flow and the availability of glucose and oxygen, act on neurotransmitter synthesis and release, on the expression of receptors and stimulate neuronal plasticity [18,19].
The hippocampus, for example, has a central role in mood regulation and higher cognitive functions, and shows a high expression of estrogen and progesterone receptors. The administration of these hormones increases the density of dendridic spines and modulates the activity of a series of neurotransmitters through various mechanisms: interactions with receptors, transporters and enzymes involved in their synthesis [17]. Among the various interactions we can mention, for example, the upregulation of the expression of AMPA and NMDA receptors, the reduced function of the 5-HT1A receptor, and the reduced expression and activity of SERT [18]. These interactions are important, because the activity of excitatory synapses in the hippocampus is associated with depression, and is in turn influenced by the action of antidepressants and serotonergic signaling [20].
The prefrontal cortex (PFC) is the area responsible for cognitive processing of impulses: it affects the emotional tone and the reward circuit, as well as the ability to control a stressor or the pleasantness of a stimulus [21]. Estrogen levels are related to the activation of PFC and the modulation of emotional processing and fear extinction. For example, estrogen therapy used in menopause increases PFC activation [22].
The nucleus accumbens (NA) is a key area in the etiology of depression and regulates the reward circuitry. Depressed patients have reduced volume in NA and impaired ability to activate the reward circuitry [23]. Gender dimorphism was found in this area. The dendridic spine density remains homogeneous along the rostral/caudal part of NA in males, whereas in females there is a gradient with an increase in spine synapse density in the more caudal regions [24]. In general, dopaminergic tone is chronically higher in males and this leads to a downregulation of its activity: therefore, when the release of dopamine is stimulated, the relative increase is less in males than in females. In addition, in males there is a greater expression of DA-ergic receptor at the mesolimbic level. In fact, estrogens cause a downregulation of D2 receptor in female striatum [25].

Role of life stages in women

As further confirmation of the influence of hormonal fluctuations on mood in the woman's life stages, **pregnancy**, **childbirth**, **puerperium** and perimenopause are high risk factors for the onset of affective disorders, as shown by several scientific studies. In many women the severity of depressive symptoms worsens in the premenstrual phase [26]. In the STAR*D study, 66% of women reported worsening symptoms at this stage [27]. In addition, this was associated with longer depressive episodes and shorter relapse latency. It is estimated that in our country over 90,000 women suffer from depressive disorders and anxiety in the perinatal period (pregnancy, puerperium and the twelve months following childbirth). About 16% of women are affected in the period of maternity, from 10-16% to 14-23% in pregnancy, and from 10-15% to 20-40% in the postpartum period. These are very rough estimates, because symptoms are frequently underestimated by both patients and clinicians and only in about half of the cases the disorder is recognized and given adequate treatment.
Cohen et al. [28] examined the impact of the transition to menopause on depressive symptoms in 460 women without a history of major depression in the age range 36-45. During the three years of follow-up, the menopause group, especially women with hot flashes, was twice as likely to develop significant depressive symptoms as women who remained premenopausal; mood disorders occurred in 9.5% of pre-menopausal women and in 16.6% of perimenopausal women. All these studies have used rigorous, standardized criteria to make psychiatric diagnoses, and their results lend strong support to the hypothesis of an increasing vulnerability for a major depressive episode that occurs at the time of menopause.
In addition to the onset of "de novo" depression, perimenopause is a risky phase also for depression relapses. In this stage of life, mood disorders and insomnia are reported in about 75% of women and this is associated with an increase in suicidality.
A recent branch of research has focused attention on inflammatory and autoimmune processes in women as vulnerability factors for depression and themselves as phenomena with a clear female prevalence [29]. Talking about inflammation leads to talking about immunity and

autoimmunity. In women there is a greater population of innate immune system cells and a more intense response to inflammatory processes, with greater production of pro-inflammatory cytokines. This is associated with a lower incidence of bacterial infections and greater response to vaccines. Various published studies demonstrate the correlation between proinflammatory cytokines and depression. The hypothesis supported for example by Rainville [30] is that a stronger immune reaction in females leads to a higher incidence of autoimmune diseases. At the same time, a correlation was found between autoimmune diseases and mood disorders in females.
Furthermore, there are a series of biological effects induced by gender difference, which include: the effects of genes located on sex chromosomes, of gonadal steroids during development, of sex hormone exposure during life, as well as the effect of parental stress before birth [31,32]. All these effects have an impact on the subsequent development of depressive symptoms and the different regulation of stress in males and females.

Clinical aspects of depression as a function of gender

In addition to the evidence of higher prevalence, depression in women has clinical and course peculiarities which make specific etiopathogenetic factors plausible [33]. Atypical symptoms such as hypersomnia, hyperphagia and mood hyperreactivity are more frequent, as well as greater vulnerability to stress and longer duration of episodes, higher relapse and chronicity rates [34,35]. Seasonality also seems more frequent. Regarding the age of onset, some studies report an earlier onset of depression in women [36]. Compared to men, suicide attempts are more frequent, but are less lethal [37]. Comorbidity with anxiety disorders is very frequent, whereas men more often experience substance and/or alcohol abuse [38,39]. In womens, somatic symptoms, asthenia/fatigue, symptoms of pain and changes in sleep profile and appetite are more represented. Hyperphagia and craving for carbohydrates can be seen as strategies for emotional regulation and stimulation of endogenous endorphin system [40]. With regards to coping strategies, women tend to have internalizing modalities, men externalizing modalities. Rumination, chronic negative circumstances or strain, and a low sense of mastery have each been found to be more common in women [41]. Finally, there is a greater inheritance for MDD in women, suggesting greater genetic vulnerability [42].

Different response to drug treatment

There are known gender differences in drug pharmacokinetics (absorption, bioavailability, distribution and elimination), but generally no particular dosage adjustments are required between males and females. However, there are some variables that need attention. An example is the greater percentage of adipose tissue in women: given their lipophilic nature, antidepressants have affinity for adipose tissue and therefore have greater volume of distribution in women [43]. Women have less acid secretion and slower gastric emptying. Gastric motility is often slowed down by female sex hormones, reducing the clearance of antidepressants. The physiological changes that occur during the menstrual cycle can influence gastric emptying, reduce acid secretion and transit time, thus influencing drug absorption and elimination. For example, during premenstrual phase a reduction in circulating levels of antidepressants such as desipramine, trazodone and nortriptyline has been demonstrated [44]. During pregnancy, liver metabolism increases, protein binding decreases and intestinal motility increases, therefore it is necessary to increase antidepressant dosage, especially in the second trimester. Furthermore, oral contraceptives can alter liver circulation, affect metabolism and plasma levels of some drugs. Estrogens have an inhibitory effect on some microsomal enzymes, increasing blood levels of the drugs metabolized by these enzymes.
Concerning the different response to drug therapy, the hypothesis of a gender difference in the response to imipramine was postulated a few decades ago [45]. A meta-analysis of 35 studies published between 1957 and 1991 confirmed that men respond better to imipramine than women [46]. Another study found that women, especially with atypical depression and panic disorder, respond better to IMAO, whereas men respond better to tricyclics (TCA) [47]. Kornestein et al. [36] showed a better response of women to sertraline than imipramine, and vice versa for men. In addition, men responded to imipramine much faster than women (8 weeks vs 10 weeks). Another interesting observation was that premenopausal women responded more to sertraline than imipramine, while in postmenopause the response was similar. Furthermore, dropouts were greater in women during treatment with imipramine and in men with sertraline. Another study in favor of SSRI *vs* TCA in women [48] showed a better response to paroxetine than imipramine. An explanatory hypothesis of these evidences could be that women more frequently have atypical forms of depression and comorbidity with anxiety disorders, and therefore have better responses to SSRi or IMAO, whereas men have a prevalent neurovegetative component, that responds more to TCA [49]. Another hypothesis is that female sex hormones interfere with the drug response: in fact, various studies demonstrated the interaction between estrogens and serotonergic activity [50]. A double-blind study carried out in 2,045 patients with depression investigated the different response to SSRIs or venlafaxine based on age and gender. Overall, the 8-week response was higher for venlafaxine than SSRi, probably for the dual mechanism; no gender difference in response was identified. Likewise, no significant gender difference was seen for SSRi. A subsequent analysis took into consideration the group of female patients by dividing the sample based on age (greater or less than 50 years as an approximate indicator

Tabella I. Factors that may contribute to gender differences in antidepressant efficacy [52].

• Liver metabolism
• Physiological and hormone level changes during puberty, menstrual cycle and menopause
• Body fat and volume of distribution
• Gastric emptying, acid production and splanchnic blood flow
• Plasma volume, protein binding and enzymatic activity
• Drug clearance
• Adherence
• Side effect profile
• Interactive effects of estrogen and serotonin on brain
• Function of brain monoamines

of pre- and post-menopausal phase). The results showed that younger women responded better to SSRi than older women, whereas venlafaxine was more effective in older women [51]. The effect of hormone replacement therapy (HRT) on the response to antidepressant therapy was also studied: it was found that HRT did not increase the response to venlafaxine, while improving the response to SSRI (remission rate of 35% in those treated with both SSRI + HRT, compared to 27% in those treated with SSRI alone) (Tab. I).

Conclusions

Despite the evidence reported above, there are still significant difficulties in changing clinical practice and particularly in influencing health policies, even if the panorama was enriched last year of the birth of the first women's Macedonio Melloni hospital in Milan.

Much has moved in recent years to study health topics and issues that mainly concern women (oncological, cardiological, neurodegenerative, autoimmune, sexual, reproductive, climacteric, metabolic and psychic diseases). Foundations such as ONDA (the Health Observatory of Women and Gender) continue to develop, raise awareness of and promote gender health culture, as well as to stimulate scientific and clinical research.

In this context, our experience of the Study Center for the Prevention and Treatment of Depressive Disorders in Women, started over 15 years ago, has allowed us to develop a unique and experienced model of prevention of perinatal depression with a newly-establishing Mother-Baby unit. The Center is also active in the areas of Premenstrual Syndrome, Premenstrual Dysphoric Disorder and Perimenopause, as well as of depressive and anxiety disorders.

In the field of clinical diagnostics and treatment, much still remains to be done to ensure that therapies are highly individualized and personalized (tailored), overcoming the tendency, also present in psychiatry, of overly standardized therapeutic settings, not really inclined to the complexity and articulation of specific factors of the disorders.

It is necessary to collect more and more specific clinical and treatment data and promote the research and awareness of health workers, institutions and population to give a boost to this indispensable and unavoidable cultural change, that will allow greater recognition of the effectiveness of treatments in the perspective of improving health.

References

1 WHO. Depression and other common mental disorders: global health estimates. Geneva: World Health Organization 2017.

2 Brody DJ, Pratt LA, Hughes JP. Prevalence of depression among adults aged 20 and over: United States, 2013-2016. NCHS Data Brief 2018;(303):1-8.

3 Ferrari AJ, Somerville AJ, Baxter AJ, et al.. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. Psychol Med 2013;43:471-81.

4 Bromet E, Andrade LH, Hwang I, et al. Cross-national epidemiology of DSM-IV major depressive episode. BMC Med 2011;9:90.

5 Weissman MM, Klerman GL. Sex differences and the epidemiology of depression. Arch Gen Psychiatry 1977;34:98-111.

6 Hankin BL, Abramson LY, Moffitt TE, et al. Development of depression from preadolescence to young adulthood: emerging gender differences in a 10-year longitudinal study. J Abnorm Psychol 1998;107:128-40.

7 Salk RH, Hyde JS, Abramson LY. Gender differences in depression in representative national samples: meta-analyses of diagnoses and symptoms. Psychol Bull 2017;143:783-822.

8 Hyde JS, Mezulis AH, Abramson LY. The ABCs of depression: integrating affective, biological, and cognitive models to explain the emergence of the gender difference in depression. Psychol Rev 2008;115:291-313.

9 Zimmerman M EW, Young D, Chelminski I, et al. How many different ways do patients meet the diagnostic criteria for major depressive disorder? Compr Psychiatry 2015;56:29-34.

10 Reiss F. Socioeconomic inequalities and mental health problems in children and adolescents: a systematic review. Soc Sci Med 2013;90:24-31.

11 Acquadro Maran D, Bernardelli S, Varetto A. Mobbing (bullying at work) in Italy: characteristics of successful court cases. J Inj Violence Res 2018;10:17-24.

12 Kessler RC, Ustun TB. A re-evaluation of the yield from national surveys of mental health. Int Psychiatry 2008;5:18-20.

13 Parker G, Brotchie H. Gender differences in depression. Int Rev Psychiatry 2010;22:429-36.

14 Gershoni M, Pietrokovski S. The landscape of sex-differential transcriptome and its consequent selection in human adults. BMC Biol 2017;15:7.

15 Gressier F, Calati R, Serretti A. 5-HTTLPR and gender differences in affective disorders: a systematic review. J Affect Disord 2016;190:193-207.

[16] Seney ML, Huo Z, Cahill K, et al. Opposite molecular signatures of depression in men and Women. Biol Psychiatry 2018;84:18-27.

[17] Barth C, Villringer A, Sacher J. Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. Front Neurosci 2015;9:37.

[18] Borrow AP, Cameron NM. Estrogenic mediation of serotonergic and neurotrophic systems: implications for female mood disorders. Prog Neuropsychopharmacol Biol Psychiatry 2014;54:13-25.

[19] Saito K, Cui H. Emerging roles of estrogen-related receptors in the brain: potential interactions with estrogen signaling. Int J Mol Sci 2018;19:1091.

[20] Thompson SM, Kallarackal AJ, Kvarta MD, et al. An excitatory synapse hypothesis of depression. Trends Neurosci 2015;38:279-94.

[21] Berridge KC, Kringelbach ML. Neuroscience of affect: brain mechanisms of pleasure and displeasure. Curr Opin Neurobiol 2013;23:294-303.

[22] Zeidan MA, Igoe SA, Linnman C, et al. Estradiol modulates medial prefrontal cortex and amygdala activity during fear extinction in women and female rats. Biol Psychiatry 2011;70:920-27.

[23] Wacker J, Dillon DG, Pizzagalli DA. The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. Neuroimage 2009;46:327-37.

[24] Wissman AM, May RM, Woolley CS. Ultrastructural analysis of sex differences in nucleus accumbens synaptic connectivity. Brain Struct Funct 2012;217:181-90.

[25] Andersen SL, Rutstein M, Benzo JM, et al. Sex differences in dopamine receptor overproduction and elimination. Neuroreport 1997;8:1495-8.

[26] Hartlage SA, Brandenburg DL, Kravitz HM. Premenstrual exacerbation of depressive disorders in a community-based sample in the United States. Psychosom Med 2004;66:698-706.

[27] Haley CL, Sung SC, Rush AJ, et al. The clinical relevance of self-reported premenstrual worsening of depressive symptoms in the management of depressed outpatients: a STAR*D report. J Womens Health (Larchmt) 2013;22:219-29.

[28] Cohen LS, Soares CN, Vitonis AF, et al. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Arch Gen Psychiatry 2006;63:385-90.

[29] Galecki P, Talarowska M. Inflammatory theory of depression. Psychiatr Pol 2018;52:437-47.

[30] Rainville JR, Tsyglakova M, Hodes GE. Deciphering sex differences in the immune system and depression. Front Neuroendocrinol 2018;50:67-90.

[31] Osborne S, Biaggi A, Chua TE, et al. Antenatal depression programs cortisol stress reactivity in offspring through increased maternal inflammation and cortisol in pregnancy: The Psychiatry Research and Motherhood - Depression (PRAM-D) Study. Psychoneuroendocrinology 2018;98:211-21.

[32] Fatima M, Srivastav S, Mondal AC. Prenatal stress and depression associated neuronal development in neonates. Int J Dev Neurosci 2017;60:1-7.

[33] Mencacci C. Le patologie psichiatriche delle donne. In: Collana Editoriale di Psichiatria. Ed. Medicina 2007.

[34] Marcus SM, Kerber KB, Rush AJ, et al. Sex differences in depression symptoms in treatment-seeking adults: confirmatory analyses from the sequenced treatment alternatives to relieve depression study. Compr Psychiatry 2008;49:238-46.

[35] Marcus SM, Young EA, Kerber KB, et al. Gender differences in depression: findings from the STAR*D study. J Affect Disord 2005;87:141-50.

[36] Kornstein SG, Schatzberg AF, Thase ME, et al. Gender differences in treatment response to sertraline versus imipramine in chronic depression. Am J Psychiatry 2000;157:1445-52.

[37] Weissman MM, Bland RC, Canino GJ, et al. Prevalence of suicide ideation and suicide attempts in nine countries. Psychol Med 1999;29:9-17.

[38] Hildebrandt MG, Stage KB, Kragh-Soerensen P, et al. Gender differences in severity, symptomatology and distribution of melancholia in major depression. Psychopathology 2003;36:204-12.

[39] Parker G, Fletcher K, Paterson A, et al. Gender differences in depression severity and symptoms across depressive sub-types. J Affect Disord 2014;167:351-7.

[40] van Strien T, Winkens L, Toft MB, et al. The mediation effect of emotional eating between depression and body mass index in the two European countries Denmark and Spain. Appetite 2016;105:500-8.

[41] Shors TJ, Millon EM, Chang HY, et al. Do sex differences in rumination explain sex differences in depression? J Neurosci Res 2017;95:711-8.

[42] Kendler KS, Thornton LM, Prescott CA. Gender differences in the rates of exposure to stressful life events and sensitivity to their depressogenic effects. Am J Psychiatry 2001;158:587-93.

[43] Yonkers KA, Brawman-Mintzer O. The pharmacologic treatment of depression: is gender a critical factor? J Clin Psychiatry 2002;63:610-5.

[44] Jensvold MF, Jarrett DB, Hamilton JA. Menstrual cycle-related depressive symptoms treated with variable antidepressant dosage. J Womens Health 2012;1.

[45] Raskin A. Age-sex differences in response to antidepressant drugs. J Nerv Ment Dis 1974;159:120-30.

[46] Hamilton JA, Jensvold MF. Sex and treatment of depression, in Psychopharmacology and Women. In: Sex, Gender, and Hormones. American Psychiatric Association Press 1996, pp. 241-60.

[47] Davidson J, Pelton S. Forms of atypical depression and their response to antidepressant drugs. Psychiatry Res 1986;17:87-95.

[48] Steiner M, Kreider MS, Bushnell WD. Antidepressant response to paroxetine by gender. 1993 Annual Meeting New Research Program and Abstracts. Washington, DC: American Psychiatric Association 1990:176

[49] Pande AC, Birkett M, Fechner-Bates S, et al. Fluoxetine versus phenelzine in atypical depression. Biol Psychiatry 1996;40:1017-20.

[50] Keers R, Aitchison KJ. Gender differences in antidepressant drug response. Int Rev Psychiatry 2010;22:485-500.

[51] Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Br J Psychiatry 2001;178:234-41.

[52] Sramek JJ, Murphy MF, Cutler NR. Sex differences in the psychopharmacological treatment of depression. Dialogues Clin Neurosci 2016;18:447-57.