

Gender Differences in Depression

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ABSTRACT

Depression is twice as common in women as in men, although some concern has been raised in terms of misdiagnosing depression in men. The incidence of depression in women varies during the life span. The peak incidence during childbearing years appears to be associated with cyclic hormonal changes. Women also present with reproductive-specific mood disorders: pre-menstrual dysphoric disorder (PMDD), depression in pregnancy, postpartal mood disorder (PDD) and perimenopausal depressive disorder. Gender differences were repeatedly observed in response to antidepressant medication. Premenopausal women appear to respond poorly and to show low tolerability to TCAs, but they tend to show greater responsiveness to the SSRIs. In contrast, men and postmenopausal women can respond equally to the TCAs and SSRIs. These differences are contributed to gender differences in pharmacokinetics of antidepressants and to the influence of menstrual cycle. These findings suggest the need for a gender-specific approach to the evaluation and management of depression.

Introduction

The interest in gender differences in depression is relatively new. This is largely the result of the exclusion of women from clinical trials in the past and the lack of data analysis by gender in the studies that did include women¹.

Exclusion of women from clinical trials was due to thalidomide tragedy. However, the assumption of similarity between men and women was wrong. The findings of the past studies suggested differences not only in prevalence and clinical presentation of depression but also

the differences in response to various treatments. In 1993 FDA encouraged the inclusion of both women and men in clinical trials and the analysis of drug data separately for men and women (Federal Registry, July 1993). Thus, information regarding sex differences in psychopharmacology will increase in the coming years.

Here we present what is known about sex differences in epidemiology, hormonal influences, differences in pharmacokinetics of antidepressants and in treatment response. The aim of our paper was to es-

establish gender-specific approach to the evaluation and treatment of depression.

Gender Differences in Epidemiology of Depression

Women have a significantly higher risk for developing depressive disorders than men. At first, several epidemiological studies showed approximately a 2:1 ratio of women to men for major depressive disorder^{2,3}. This ratio has been found consistently across ethnic groups and in cross-national studies.

Rates of dystimia are also twice as common in women⁴. Moreover, nearly 80% of individuals with seasonal affective disorder are women⁵. Bipolar affective disorder is an exception. Men and women have an equal lifetime risk for bipolar affective disorder of approximately 1%².

The second important issue is that this difference in prevalence of depression varies during the life-span. Boys and girls have the same incidence of depression⁶, and in elderly the rate is also similar between the men and women. The difference begins in adolescence⁶ and persists until midlife^{2,7}, corresponding roughly to the childbearing years in women. Major depression is an essential disorder of childbearing age. The peak incidence is between the age 20 and 40.

Although reasons for these differences are not fully understood, hormonal and psychosocial influences have direct or indirect effect on mood. The new identities formation in adolescence⁸, an unhappy marriage⁹, the presence of young children at home¹⁰, increased likelihood of experiencing victimization or abuse¹¹, and more frequent help-seeking behavior¹² were all found to make women more vulnerable to depression compared to men.

Not only women are at greater risk for depression, but also once depressed, the

symptom presentation in women may differ from that in men.

In general, the symptoms are similar in men and women, but women are more likely to present with atypical symptoms, such as increased appetite and weight gain and tend to report more anxiety and somatic symptoms. Men typically exhibit classic symptoms of depression, such as insomnia and weight loss^{13,14}.

However, there is yet unresolved puzzle regarding the relationship between depression and suicide. Depression is the main precursor of suicide, and depression is twice as common in women. However, suicide is three times more common in men^{15–18}. Men also tend to use more violent methods of suicide, such as guns and hanging, which along with less help-seeking behavior may explain their higher suicide completion rate¹⁵. The depression in males may manifest itself in ways unrecognized by current diagnostic system. The male pattern is characterized by irritability, aggressiveness, an acting-out behavior, a lowered stress tolerance, and alcohol abuse. In general, it is yet to be determined whether an overrepresentation of depression in women is simply an artifact because alcoholism and antisocial behavior mask depression in men¹⁸.

In terms of comorbidity, women appear to have higher rates of comorbid disorders, the most common being anxiety and eating disorders^{3,18}. In contrast, depressed men have higher rates of comorbid alcohol and substance abuse and dependence¹⁴.

Course of illness has also been evaluated. Some studies have found a younger age of onset of depression in women¹⁴. Women also tend to have a longer duration of episodes¹⁹, as well as a greater risk for chronicity and recurrence²⁰. While men and women have similar incidence of bipolar disorder², they differ in its course. Namely, women are more likely to de-

velop the rapid cycling form of the illness and may also suffer from more episodes of depression²¹.

The Influence of Reproductive Cycle to Depression in Women

When evaluating a female patient, it is always important to consider the influence of the menstrual cycle to her depression²². Periods of increased vulnerability in women are premenstrual period, pregnancy, postpartal period, and perimenopausal years²³. All those periods can trigger a new depressive episode in women with a history of depression, or generate a period of vulnerability for developing a first episode of depression²². Worsening of depression in the premenstrual phase of the cycle is a rule rather than an exception. Even 80% of depressed women reported worsening of their depression prior to menses. On the other hand, 2–8% of women does have the criteria for premenstrual dysphoric disorder (PMDD)²⁴.

Pregnancy is usually considered to be the time of emotional well being. However, the risk of depression in pregnancy is estimated to be around 10%^{25,26}. Not only women are not protected from depression during pregnancy, but also the infant is not protected from maternal depression. Depression in pregnancy carries the risk of preterm delivery²⁷. Furthermore, infants of depressed mothers have, in terms of behavioral^{28,29} and EEG finding^{30,31}, have brains, as they are depressed themselves. It is unknown whether those striking findings will extend to childhood.

The incidence of postpartum depression between 5% and 10% is the same as in non-puerperal, age-matched women³². This period is characterized by rapid shifts in hormone concentration. Particularly women with bipolar disorder who discontinue lithium treatment³³ or have a history of postpartal depression³⁴ or ma-

lor depression³⁵ appear to be at highest risk for postpartum mood disturbance.

There are some groups of women for whom there is an increased risk for depression in perimenopause^{2,36}. Middle-aged women presenting with affective liability should be evaluated for perimenopause-related depression. Perimenopause-related depression is a hormonally mediated, phase-specific mood disorder, likely to respond to estrogen replacement alone³⁷. It should be differentiated from the major depression in perimenopause, that requires treatment with antidepressants. Women in menopause, on the other hand, were not found to be in an increased risk of depression. Characteristics of reproductive-associated mood disorders are presented in Table 1.

The marked sex differences in rates of depression that begin with reproductive age suggest hormonal factors to play a role in this difference. The onset of puberty, rather than chronological age, is linked to the increase in rates of depression in women⁴¹. In puberty, female brain is exposed to estrogen, and hormone levels in women fluctuate cyclically over a much larger range than in men⁴². At female menopause, ovarian secretion shuts down. In men of the same age, however, testes continue to produce testosterone, which is partially converted to estradiol in the brain⁴². Men, on the other hand, seem to be spared from rapid hormone fluctuations.

Increased incidence of depression in women in reproductive age is not caused by specific hormone abnormalities, and measuring serum FSH and estrogen levels has very limited diagnostic value^{20,43}. However, an abnormal response to normal cyclic hormone fluctuations, at the synapse level and at the receptor level^{38,44,45} is supposed to be involved in the etiology of depression in vulnerable women, through the neuromodulatory role of estrogen on the serotonergic system³⁸,

TABLE 1
REPRODUCTIVE-ASSOCIATED MOOD DISORDERS^{38–40}

Disorder	Endocrine environment	Special issues
PMDD	<ul style="list-style-type: none"> • Cyclic changes in gonadal hormone concentrations • Also occurs in anovulatory cycles and in the absence of luteal phase 	<ul style="list-style-type: none"> • Serotonergic antidepressants work better than noradrenergic • Response to SSRIs is very fast, within the hours
Depression in pregnancy	<ul style="list-style-type: none"> • Very gradual rise in estrogen levels 	<ul style="list-style-type: none"> • Risk of preterm delivery • Infants may have depressed patterns
Postpartum depressive disorder (PDD)	<ul style="list-style-type: none"> • Sudden and dramatic decline in estrogen concentrations • Supersensitive dopamine receptors after sharp reduction of antidopaminergic effect of estrogen 	<ul style="list-style-type: none"> • Thyroid status should be checked, while thyroid dysfunction is an associated factor • In women with a previous episode of PDD antidepressants within the first 24 hours may prevent recurrence
Perimenopause-related depression	<ul style="list-style-type: none"> • Variable decline in estrogen concentrations, estrogen unopposed by progesterone due to anovulatory cycles 	<ul style="list-style-type: none"> • Estrogen replacement therapy is the first line of treatment

which is supposed to play a key role in the etiology of depression. Animal studies demonstrated that ovariectomy causes decreases in 5-HT₁ binding, 5-HT_{2A} binding and expression and 5-HT transporter binding and expression⁴⁴, the points in serotonin transmission that are all reported to be altered in depression⁴⁶. In humans, women were found to have decreased 5-HT₂ receptor binding capacity when compared to men⁴⁷. The augmentation of serotonergic activity in postmenopausal women with estrogen replacement therapy⁴⁸ supports the evidence of the relation between estrogen and serotonergic system in humans. Gender-related differences were also found in the rate of serotonin synthesis, which has been found to be as much as 52% greater in males than in females⁴⁹. The reason for this remarkable difference is not clear. All subjects were in age from 18 to 35 years, without

personal or family psychiatric history. The authors presumed early serotonergic events in serotonin synthesis in the brain organization, or effects of circulating gonadal hormones. This is one of the largest differences observed to date between the brains of the healthy men and women, which is not related to hormone-binding sites⁴⁹. Regarding peripheral serotonergic markers, healthy women were consistently found to have lower platelet serotonin levels than healthy men^{50–52}. Depressed drug-free women were also found to have decreased platelet serotonin concentration when compared to depressed men⁵⁰. These data suggest that women in their childbearing years, either healthy or depressed, may have decreased serotonergic function, associated with physiological fluctuations in gonadal hormone concentrations. Tryptophan, a serotonin precursor, is converted to serotonin

in the brain, or, alternatively, to kynurenine in liver. Estrogen enhances the kynurenine pathway in the liver. Therefore, the availability of tryptophan may be lower, and may eventually decrease serotonin content in the brain⁵³. Given that stress plays a major role in the onset of depression, gender differences in the response to stress could increase women's vulnerability to depression⁵⁴. Interesting finding is that decreased cortisol suppression to dexamethasone was found during luteal phase when compared to the follicular phase in the same healthy women⁵⁵. This change is believed to be related to either increased estradiol or progesterone, or their interaction, during the luteal phase. The worsening of depression in premenstrual phase could be attributed to increased resistance to glucocorticoids induced by these hormonal changes. Similarly, oral contraceptives, particularly with a high progestin content, may induce depression⁵³.

In contrast to changing hormonal milieu during reproductive age, postmenopausal women have low estrogen and progesterone levels. The decline in rate of depression in this age group² suggests that estrogen deficiency is not a risk factor for depression. This finding reinforces the hypothesis that it is the change in estrogen that may be the critical hormonal risk factor in reproductive-endocrine-associated depression³⁸.

Gender Differences in Pharmacokinetics of Antidepressants

The differences in pharmacokinetics have been demonstrated in all of the areas of absorption, distribution, metabolism and elimination⁵⁶. However, data are limited until recently, due to previously mentioned exclusions of women from clinical trials. This is unfortunate, because women are significantly more

likely than men to be prescribed antidepressants. When compared to men, women were found to have slower gastric emptying time, lower gastric acid secretion, lower body weight, lower blood volume, higher percentage of body fat, lower plasma protein binding, higher cerebral blood flow, lower hepatic biotransformation and lower renal clearance⁵⁷.

The possible application of these findings is that women tend to have higher plasma levels of antidepressants and higher incidence of adverse events thereafter. However, the menstrual cycle may affect pharmacokinetics in a different manner. Specifically, the late luteal or premenstrual phase has been associated with possible sodium retention and increased total body water, possible increase in hepatic metabolism and possible increase in creatinin clearance⁵⁷. The consequence of these changes is the decrease in antidepressant blood concentrations. These findings seem not to be applied to fluoxetine, due to its long half-life¹.

Gender Differences in Treatment Response

Gender differences were also observed in terms of treatment response to antidepressant drugs. Imipramine was the first antidepressant widely used and has long been the gold standard against which newer agents have been compared. It may not be equally effective in men and women, however. That women may be less responsive than men to imipramine was notified as long as several decades ago. The first study to demonstrate this difference was the Raskin study⁵⁸, when women and men were stratified by gender and age (younger than 40 years, and 40 years or older). In men, imipramine response rates for both groups did not differ and were significantly better than placebo. Response rate in women, however, differed by age group. While women in

the age of 40 years or older showed a responsiveness to imipramine similar to that of men, younger women were no more responsive to imipramine than to placebo⁵⁸. These findings are consistent with the study carried out 25 years later.

In meta-analysis of 35 studies by Hamilton, response rates to imipramine were reported separately by gender⁵⁹. Overall response rates to imipramine differed by 11% between men and women. Women showed lower response to imipramine than men, despite higher plasma concentrations.

The old age interest group⁶⁰ in Britain has found that women taking dothiepine were more likely to experience a recurrence of depression, than men were. Furthermore, women taking placebo were also significantly more likely to suffer recurrence of depression compared with men taking placebo. These findings suggest that women have a worse prognosis in terms of a risk of recurrence of depression.

Really interesting and important findings were found in comparison between imipramine and sertraline⁶¹. Men responded significantly better to imipramine. Women in general responded to sertraline better than to imipramine. However, when data were analyzed separately due to menopausal status, it was found that premenopausal women responded better to sertraline, whereas response rates of postmenopausal women were similar in both drugs!

The authors suggested that female ovarian hormones may enhance response to SSRIs, or inhibit the response to TCAs. The reason for this difference may be also related to sex differences in depressive subtypes, i.e. more atypical depression in women¹. The difference disappears in menopause. In this study gender difference in drug-tolerability was also noted. Women taking imipramine were more likely to drop out from the study than

that taking sertraline. Premenopausal women were more than 3 times as likely to drop out of imipramine treatment than postmenopausal women⁶¹.

When comparing imipramine and paroxetine in outpatients⁶², women responded significantly better to paroxetine than to imipramine, but women responded better to both active treatments compared with placebo. It is noteworthy that in men, however, because of high placebo response rates, there were no significant differences among the three treatment regimens. Women had lower placebo response than men in this study.

In contrast to previous two studies that demonstrated better response to SSRIs paroxetine and sertraline than to imipramine in women, this difference was not found for fluoxetine⁶². Women responded equally to both fluoxetine and imipramine. Unfortunately, there were no comparison data given for placebo or for men. In this study fluoxetine was better tolerated than imipramine⁶³. A recent study, however, demonstrated that depressed women younger than 44 years responded significantly better to fluoxetine than to noradrenergic agent, maprotiline⁶⁴. The men had similar response across different age groups. While women are reported to tolerate better imipramine than sertraline⁶¹, the whole SSRI group seems to be tolerated similar in males and females⁶⁵.

There was also a meta-analysis of 8 placebo-controlled studies of citalopram in women and men with depression⁶⁶. Women treated with either citalopram or placebo showed a significantly greater response to treatment than men, although drug-placebo difference was the same in both men and women⁶⁶. Why do premenopausal women respond better to SSRIs than to other classes of antidepressants? We hypothesize that SSRI treatment could reverse lower serotonergic function^{50–53},

associated with cyclic changes in gonadal hormone levels.

Gender differences were also observed in augmentation studies. As long as several decades ago, a trend for greater efficacy in women using T3 augmentation of antidepressant treatment^{67,68} was noted. More specifically, addition of T3 to imipramine regimen was found to accelerate the recovery of the women but not the men, beginning as early as the third day of treatment⁶⁸. However, clinical improvement may be attributed rather to the correction of mild thyroid dysfunction⁶⁹, since women have ten times the incidence of thyroid disease as men⁵³. On the other hand, a trend for greater efficacy of either T3 or T4 antidepressant augmentation was reported, in women with no difference in baseline serum T3, free T4 and TSH levels in responders and non-responders⁷⁰.

While the efficacy of lithium augmentation of antidepressant response has been documented since the early 1980s, the data were reported by gender in only 2 studies^{71,72}, when lithium was added to different classes of antidepressants. In both studies, significantly better response rate was achieved in women. However, the recent literature analysis indicated similar response rates for lithium in bipolar and related affective disorders⁷³.

Estrogen was suggested to play a permissive role in imipramine-induced changes in serotonergic receptor binding, with possible clinical significance for patients with ovarian hormone deficiency. Preliminary studies suggest that estrogen replacement therapy (ERT) given in conventional doses (high-0.05 and low-0.025 mg) to antidepressant treatment may enhance mood in postmenopausal women^{48,74}. However, the lack of double-blind studies limits any conclusion from currently available data.

No specific relationship between lower testosterone levels and depression in men has been established⁷⁵. Recent data, however, suggest the possibility that testosterone deficiency leads to late life mild depression⁷⁶. Unlike in women, it is not clear whether aging men experience »andropause«, whether there is the testosterone »threshold« associated with CNS effects and/or whether are some men particularly vulnerable to testosterone-mediated depression⁷⁶. Anecdotal reports and uncontrolled data suggest that in some men with hypogonadism comorbid major depression remits with testosterone replacement⁷⁶.

In terms of electroconvulsive treatment (ECT), the data suggest that women have a lower seizure threshold⁷⁷, a more favorable response rate and less severe side effects men⁷⁸. However, data regarding efficacy by gender are inconsistent¹. The inability to provide treatment in double-blind fashion is a consistent confounding factor in interpreting the importance of those findings¹.

Conclusion

Although research on gender effects in depression has been limited, existing literature shows clear evidence of sex-related differences⁷⁹. In general, younger premenopausal women appear to respond poorly and show low tolerability to TCAs, but tend to show greater responsiveness to the SSRIs. In contrast, men and postmenopausal women can respond equally well or better to the TCAs.

Because of pharmacokinetic differences and increased sensitivity to side effects, women may require a lower dosage of some medications.

Because of a possible risk of recurrence of depression among women, a long-term treatment may be required. Menopausal status may be an important consideration not only in choosing an antide-

pressant agent, but also in deterring augmentation strategies. Similarly, the menstrual cycle may affect pharmacokinetics of antidepressant agents of women. Increasing the dosage of SSRIs premenstrual can result in a very rapid response.

The preliminary nature of these conclusions suggests need for future research. Clearly, more data are needed to understand the feature.

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RAZLIČITOST DEPRESIJE U ŽENA I MUŠKARACA

SAŽETAK

Depresija se javlja dvostruko češće u žena, premda postoji podatak da se ona često kod muškaraca previdi i rjeđe dijagnosticira. Incidencija depresije u žena razlikuje se obzirom na dob. S najvećom učestalošću javlja se tijekom fertile dobi, što se tumači cikličkim djelovanjem hormona. Razlikujemo četiri poremećaja specifična za reproduktivno razdoblje: premenstrualni disforični poremećaj, depresija u trudnoći, postpartalna depresija, te depresivni poremećaj u perimenopauzi. Razlike obzirom na spol opažene su također u odgovoru na antidepresivnu terapiju. Dok je u žena u fertile dobi imipramin slabije učinkovit i podnošljiv, za razliku od selektivnih inhibitora ponovne pohrane serotonina (SSRI), u žena u menopauzi i muškaraca ta se razlika ne nalazi. Razlika se nastoji protumačiti razlikama u farmakokinetici antidepresiva te utjecaju hormona. Sukladno spomenutim navodima, smatramo da je prilikom dijagnosticiranja i liječenja depresije važno uzeti u obzir i spol bolesnika.