Annals of Clinical Psychiatry, 19[4]:247–255, 2007

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230701653294

informa
healthcare

Gender Issues in Depression

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Background. *Gender differences in depression have been documented for many years and thought to be insignificant to treatment selection until recently.*

Methods. *This article reviews gender differences in the prevalence, presentation, etiology, and antidepressant treatment of depressive disorders.*

Results. *The high female to male sex ratio in the prevalence of depression, especially during the reproductive years, is one of the most replicated findings in epidemiology. Women more often have a seasonal component, anxious and atypical depression. Explanations for the differences include psychological, neurochemical, anatomic, hormonal, genetic, and personality factors. Gender differences in antidepressant treatment response have not been found consistently. Hormonal status may be an important variable in addition to the effects of the menstrual cycle, pregnancy, perimenopause and menopause.*

Conclusions. *Women have higher rates of depression and can often present differently than do men. Further research can ascertain which combination of factors increase women's risk. The effect of pregnancy and the impact of the menstrual cycle on the course of all depressive disorders need increased attention. Large prospective randomized controlled trials with gender differences in treatment response as the primary endpoint are necessary in order to answer the now controversial question of gender differences in antidepressant treatment response.*

Keywords Gender differences, Depression, Antidepressant treatment

INTRODUCTION

This article reviews gender differences in the prevalence, presentation, etiology, and treatment of depressive disorders. Although the high female to male sex ratio in the prevalence of depression, especially during the reproductive years, is one of the most replicated findings in epidemiology (1), the explanation remains uncertain. It is important to understand what is now thought to be a group of disorders (2) because of their recurrence, potential for chronicity and the substantial disability associated with them (3). For example, Major Depressive Disorder (MDD) has been identified as a leading source of disability in developed countries with direct and indirect costs as well as negative economic consequences (4). In women, MD is already the second leading cause of disease burden in women in the United States (5). Work productivity aside, depression also has profound emotional effects on both the individual and the family. Understanding gender differences is especially important because maternal depression is known to affect child development and is associated with children's disorders (6). Although gender issues had been described, widespread interest is recent and there is a growing body of literature. No significant gender differences have been found in the risk of such sequelae of depression as early school leaving, having a child at a young age, marrying very early or being unemployed. Early childbearing, however, when it does occur, leads to more severe consequences in women than in men (7).

Dr. Grigoriadis is supported by the Ontario Mental Health Foundation, New Investigator Fellowship, The Canadian Institutes of Health RCT Mentoring Program and the C.R. Younger Foundation.

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EPIDEMIOLOGY OF DEPRESSION

Prior to puberty, there are few differences in the prevalence of depression in males and females (8). By contrast, during their reproductive years, women show approximately twice the male

frequency of depression. Large national studies of prevalence of MDD carried out in the 80s (9) and 90s (10) have found higher rates when DSM-IIIR criteria were used than when using DSM-III. Using DSM-IV criteria, the National Epidemiological Survey on Alcoholism and Related Conditions (11) found even higher levels. The 12-month prevalence rate for women was 6.87% versus 3.56% for men and the lifetime prevalence rates were 17.10% versus 9.01% respectively. The odds ratio remained females to males 2.0 to 1.0. The preponderance of female depression has been found throughout the world, although the exact female/male ratios vary somewhat. It is not clear whether this increase in prevalence is real or due to changing diagnostic criteria.

Women are two to four times more likely than men to present with a seasonal component (12) or atypical features (with psychomotor retardation, an increased appetite and weight gain), and higher levels of somatic symptoms, ruminations, feelings of worthlessness and guilt (13). Chronicity of depression appears to affect women more seriously than men, as manifested by greater symptom reporting, poorer social adjustment and poorer quality of life (14). As the number of symptoms increases, so does the female/male prevalence ratio. This ratio has, at times, been attributed to a variety of artifacts including: women being more willing to talk about feelings; women coming more readily for help; and women's symptoms being more readily diagnosed as depression. Community surveys, however, have confirmed that the gender difference is found when the bias arising from help seeking is eliminated (10,15). This difference cannot be explained away, as some have speculated, by depressed men self-medicating with alcohol or drugs and, therefore, being diagnosed with substance abuse instead of a mood disorder.

ETIOLOGICAL THEORIES OF DEPRESSION

Psychosocial Factors

Beginning at an early age, various psychosocial factors influence the occurrence of depression in women. Women are more likely to be sexually abused as children and abused children are more likely to become depressed as adults (16). Prolonged separation from parents at an early age greatly increases the risk of depression in adult women but this is also true for men. Women have a higher rate of victimization than men and victimized women have high rates of depression. In the NCS data, however, Kessler (17) controlled for 24 types of life trauma and found that the sex ratio for depression was identical for those with and without previous trauma. Nevertheless, women are more likely to become depressed following stressful life events.

As adults, women frequently struggle with role overload, the majority of women working full-time as well as doing 70% of the house and child care. Women are more likely to be depressed if they have young children at home, work outside the home (especially if they would rather stay at home), experience role conflict, or have trouble finding childcare (18,19). These factors may contribute to the finding that marriage is not protective for women; married women are more likely to be depressed than married men or single women, the risk increasing further in unhappily married women. The explanation may lie in the fact that women are socialized to look after others, dismissing or minimizing their own needs. They are expected to handle things quietly without resorting to anger and, as a consequence, turn their feelings inward, which results in depression (20). As well, women are more often financially disadvantaged and there is a particularly strong relationship between poverty in women and depression (21).

Neurochemical and Anatomic Factors

Recent research has focused on the neurochemical and anatomic changes accompanying major depressive disorder (22). Initially centred on the brain monoamine system, more recently studies have looked at the role of cyclic adenosine monophosphate (cAMP) signal transduction cascade and its response element binding protein (CREB) (23). Brain derived neurotrophic factor (BDNF), which protects against stress, appears to be an important gene product regulated by CREB (24). Clinical antidepressant efficacy mirrors the extent of expression of BDNF (24).

Activation of the hypothalamic-pituitary-adrenal (HPA) axis is commonly seen in depressed patients. There is evidence for elevated cortisol and corticotropin-releasing hormone (CRH) levels, nonsuppression on the dexamethasone suppression test, and a blunted adrenocorticotropic hormone (ACTH) response to CRH. HPA axis activation appears to have prognostic value and is associated with increased risk of depression relapse and even suicide (25). CRH appears to modulate the general stress response as well as depression-related behaviors including appetite and sleep alterations and behavioral despair (26). Early life stress appears to produce long lasting changes in the regulation of CRH neurons and may, therefore, result in a biological vulnerability to the subsequent development of depression, either directly or by means of increased reaction to stressors later in life. Patients with depression have been found to have volume reductions or other abnormalities in the prefrontal cortex and hippocampus, areas connected to the regulation of mood (27). The lateralization of brain function is also important in depression (28). Depression appears to be associated with increased activity in the left ventral prefrontal cortex, whereas mania appears to be associated with reduced activity on the right side. Research findings in animal models of depression have corroborated the profound effects of stress on intracellular signal transduction and on the expression of genes that drive fundamental neurotropic and neurotoxic processes, thereby demonstrating the link among environmental stressors, anatomical and neurochemical processes, and depression.

Hormonal Factors

Womens gonadal steroid hormones are thought to play an important role in the development of mood disorders (29).

Mood often appears to fluctuate with the change of hormones. Times of low estrogen, such as the premenstrual and postpartum periods, are times of increased risk for mood disorder (30). It is possible that monthly cycling may trigger ongoing mood changes. We know that the brain is a major target organ for gonadal hormones. A complex interaction exists between gonadal hormones and neurotransmitters such as glutamate, gama-aminobutyric acid, acetylcholine, serotonin, dopamine, noradrenaline, adrenaline and neuropeptides. Gonadal steroid hormones can affect the synthesis and release of these neurotransmitters, the expression of their receptors and the membrane permeability of neurons (30). Over the course of life, the risk of thyroid disease in women is four times higher than in men. Although thyroid abnormalities seen in depressed patients are probably transitory and stress-induced, subclinical hypothyroidism always needs to be ruled out in depressed women (31).

Genetic Factors

Although genetic factors play a large role in the vulnerability to mood disorders, they do not totally account for the occurrence of depression. Kendler and colleagues (32) found an estimated heritability for the liability to develop a major depressive disorder over a one year period to be 41–46%; the lifetime estimated heritability was 70%. This research group postulates that what is inherited is a tendency to overreact to stressful life events. Individuals who have one or two copies of the S allele in the serotonin promoter region of the gene, in the context of life stress, have an increased risk of developing depression during their lifetime over people who carry two L alleles (33). There is no evidence that men and women have a different genetic basis for unipolar depression, however, specific genetic risk factors may vary between men and women. For instance, specific genetic factors may be present in some women that predispose toward premenstrual mood disorder.

Personality Factors

Specific personality traits have been hypothesized as factors in the high prevalence of depression in women. Female gender role socialization has been thought to result in a variety of maladaptive styles of coping with life stresses or characteristics such as low self-esteem, low perceived control, pessimistic attributional styles, dependency and expressivity (i.e., orientation and concern for others); factors which might result in depression or in being erroneously labeled as depressed. Low self-esteem, more common in women, clearly appears to be a vulnerability factor for developing depression although the mechanism is not clear. Reviews of a substantial body of research have not found a consistent relationship between depression and the trait of expressivity (34). Less perceived life control was thought to be associated with increased depressive symptomatology in women in that, as women more often develop "learned helplessness," they are more likely to develop pessimistic explanatory styles (35). However, more recent studies that carefully controlled for a previous history of depression found that there was no significant association between these personality factors and depression (13). Duggan and colleagues (36), however, found that neuroticism was associated with both a one year risk and a lifetime risk of depression and postulated that neuroticism predisposes to depression. More recently, Goodwin and Gotlib (37) found that gender roles, and specifically neuroticism, may indeed play a key role. Because neuroticism is a very broad concept, it may be that these studies identified not so much personality factors as alterations in the response to stress, a probable determinant of vulnerability in women predisposed to depression.

Nolen-Hoeksema (38) has hypothesized an interesting relationship between women's coping styles and subsequent depression. She found that women are more likely than men to display a self-focused ruminative style of coping with feelings of sadness. Men's style of distracting themselves rather than ruminating appears, in Nolen-Hoeksema's studies, to be a more effective way of warding off depression.

COMORBIDITY

Depressive and anxiety disorders often occur together. The distinction between these two types of disorders may be an artificial one. Medical historian Shorter and psychiatrist Tyrer suggest that the distinction originated with the development of the DSM-III by the American Psychiatric Association (39). Prior to that time, anxiety had been considered an integral part of depression but, with the arrival of the new diagnostic classification, the two became separate diagnoses. Despite the results of a nationwide household survey in the United Kingdom that showed mixed anxiety-depression to be the commonest form of affective disorder (40), the presence of a mixed syndrome is now viewed instead as comorbidity. The National Epidemiologic Survey on Alcoholism and Related Conditions (11) found that 41.4% of those with a lifetime history of MDD had a comorbid anxiety disorder. The specific comorbidities included: panic disorder with and without agoraphobia, 3.1% and 10.8% respectively; social phobia 12.8%; specific phobia 20.4% and generalized anxiety 15.0%. The STAR*D trial of depressed outpatients found that 25.6% of patients suffered from one comorbid disorder, 16.1% suffered two and 20.2% had three or more comorbid conditions (41). The most common were social anxiety disorder (29.3%), generalized anxiety disorder (20.8%) and posttraumatic stress disorder (18.8%). Although the co-mingling of depression and anxiety is true for both sexes, comorbid anxiety disorder is more likely in depressed women than in depressed men (42). The AMSTEL study of women ages 65–84 found that women were six times more likely than men to have mixed anxiety-depression (43). As well, the association between an increase

of comorbidity with increased severity is twice as strong in women as in men (43).

A review of the relationship between major depression and personality disorders found a comorbidity rate of 20–50% for inpatients and 50–85% in outpatients (44). Ekselius et al. (45) found 60% of depressed females had a personality disorder, the most common being those in cluster C (50.3%). The highest individual comorbidities were with paranoid (27.1%), borderline (21.2%), avoidant (35.8%) and obsessive-compulsive (24.0%). Hasin et al. (11) found that in those with a lifetime history of MDD, over 30% had a comorbid personality disorder with obsessive-compulsive (16.4% and paranoid (10.0%) personalities being the most common. Rogers et al. (46) have suggested that the depressions in those with or without a borderline personality disorder are qualitatively different. It is not clear whether the personality disorder is the result of the depression, predisposes the individual to depression, is an attenuated manifestation of the disease which underlies the depression or whether both disorders are independent.

Hasin et al. (11) also found that 40.5% of those with a lifetime history of MDD had an alcohol use disorder and 17.2% had a drug use disorder. Depression is a strong predictor of suicidal behavior in both sexes. Although men account for 65% of completed suicides, women are three times more likely to attempt suicide (47). Women are more likely to be receiving treatment and have told someone before their attempt (48) and to choose less violent means such as overdoses. Depressed women, more than men, also suffer from comorbid thyroid disorders (49), fibromyalgia (50) and migraines (51).

TREATMENT OF DEPRESSIVE DISORDERS

Pharmacology and Gender

Treatment of depressive disorders may require medication, psychotherapy or a combination of these modalities and an in depth review of psychotherapy or combination treatments is beyond the scope of this paper. Nevertheless however, in general, the effects for gender in psychotherapy trials have been weak and interpreted to have little or no clinical significance (52–54). In considering medication in women, it is important to remember that pharmacokinetic differences (in absorption, bioavailability, distribution, and elimination) have been described for many years (55,56) and attributed to differences in body weight and body size (i.e., different ratio of fat to muscle). The result of these pharmacokinetic effects are typically negligible and do not require dose adjustments compared to doses given to men. The physiological changes across the menstrual cycle are significant and can influence gastric emptying, reduce acid secretion and gastrointestinal transit time which, in turn, affects the absorption and elimination of drugs (55,56). The effects of the menstrual cycle can be clinically important. For example, there have been case reports that there tends to be a premenstrual or late luteal phase decrease in drug levels predominantly because of the above (57,58). Exogenous hormones such as Oral contraceptives (OCs) are also known to alter hepatic blood flow, affecting hepatic metabolism and plasma levels of antidepressants significantly metabolized by the liver. Estrogen has an inhibitory effect on some hepatic microsomal enzymes, decreasing the rates of hepatic metabolism with consequent elevation of plasma levels for those drugs that require these enzymes for their metabolism (59). Alternatively estrogen can induce other conjugative enzymes, decreasing drug levels (60). Pregnancy and the associated change in hormone levels affects pharmacokinetics resulting in a change in dose requirements across pregnancy (increase in the second trimester) (61). Lastly, there are sociocultural reported gender differences which affect patterns of medication use and reactions to side effects (55,56). Women seek medical intervention but also complain of increased side effects compared to men (women may have more side effects from TCAs than men potentially because of higher bioavailability and slower renal clearance). They are, therefore, more likely to discontinue treatment with TCAs than with SSRIs) (62). It is likely that a combination and synergy of the above pharmacokinetic and pharmacodynamic effects would contribute to gender differences in treatment. The extent of the clinical relevance of these differences has been the subject of much debate.

Gender and Treatment Interaction

Although the possibility of gender differences in antidepressant treatment response was suspected almost half a century ago, supporting data did not emerge until several decades later when Raskin reported a gender-based differential response rate to imipramine and phenelzine (63). Moreover, there was also a differential effect of age on imipramine response in women, but not in men. Subsequent studies supported the gender difference finding (64,65) and a meta-analysis of imipramine studies showed a small but statistically significant difference in men responding better to imipramine than women (66). Claims for a gender and age effect have been subsequently supported by Kornstein and colleagues who reported significant differences between pre- and postmenopausal women in the rate of response to sertraline and imipramine (62). Since Kornstein's paper, there has been a plethora of reports to both support and refute the notion that gender and age are salient factors moderating the response to antidepressants; the evidence is now mixed and the area controversial. Table 1 summarizes the studies published on gender differences and Table 2, studies that have taken menopausal status (or older aged women) into account. Aging is associated with decreased albumin, decreased lean body mass, lower hepatic blood flow, decreased activity of hydroxylation or conjugation, decreased renal excretion and elimination (66). All these effects would potentially lead to increased blood levels and half lives of most of the antidepressants and should apply equally to both men and women (87). However, in pre- and post-menopausal women

Table 1 Gender Differences in Treatment Response: Recent Findings

Treatment	Sample Size	Findings
Gender Differences Significant		
Sertraline, imipramine (62)	635	Women had a superior response to sertraline, men to imipramine
Fluoxetine, maprotiline (67)	105	Women were more responsive to fluoxetine than maprotiline. No difference in men
TCA's, MAOI's, fluoxetine (68)	1746	Women had superior response to MAOI
SSRI, venlafaxine, Mirtazepine, bupropion (69)	157	Men achieved remission more often and faster than women
SSRI and SNRI (70)	323	Women had a greater response than men to SSRI
Fluoxetine, nortriptyline (71)	154	Women had a superior response to fluoxetine than nortriptyline but not men
Sertraline, imipramine (72)	239	Women had a superior response to sertraline than to imipramine, men responded similarly to both drugs
No Gender Differences		
Venlafaxine, SSRIs (73)	2045	No gender differences
TCA, SSRI (74)	346	No gender differences
TCA, SSRI, MAOI (75)	292	No gender differences
TCA's (76)	3886	No gender differences
Fluoxetine (77)	320	No gender differences
SSRI (78)	301	No gender differences
Sertraline (79)	5454	No gender differences
Duloxetine (80)	1622	No gender differences

Table 2 Response to Antidepressants: Menopausal Status or Age Effects

Treatment	Sample Size	Main Findings
Menopausal Status Is Significant		
Imipramine, sertraline (62)	635	Premenopausal women showed a superior response to sertraline than to imipramine
Fluoxetine, maprotiline (67)	105	Fluoxetine was more efficacious in younger women than maprotiline
Venlafaxine, SSRIs (81)	2045	Younger women responded better to SSRIs than older women
SSRI, nefazodone, venlafaxine (82)	115	Younger women - lower HAM-D endpoint scores, higher rates of remission than older women
TCA's, fluoxetine (68)	1746	TCA's more efficacious in older women
Venlafaxine, SSRI (83)	1599	Older women – poorer response to SSRI, Hormone replacement therapy eliminated the effect. Older women not on HRT showed superior remission to venlafaxine
SSRI (78)	301	Menopausal women – poorer SSRI response than non-menopausal women
Fluoxetine, nortriptyline (84)	113	Younger (<25) women with melancholic depression had superior response to fluoxetine than nortriptyline; older men (>40) with melancholia showed superior response to nortriptyline than fluoxetine
Menopausal Status Is Not Significant		
Fluoxetine (74)	320	No difference between younger and older women
TCA's (76)	2331	No difference between younger and older women
Desipramine (85)	156	No significant differences although there was a trend for better response in older women
Venlafaxine, SSRIs (81)	2045	Venlafaxine was more efficacious than SSRIs in younger and older women
TCA's, fluoxetine (68)	1746	Fluoxetine – no significant difference in younger or older women
Fluoxetine (86)	184	No difference in response and remission among pre-, peri-, and postmenopausal women
Sertraline (79)	5454	No difference in younger or older women or men
Age Regardless of Gender Is Significant		
TCA, SSRI (74)	346	Older age – superior TCA response, Younger age – superior SSRI response, for both men and women
SSRI, venlafaxine, mirtazepine, bupropion (69)	157	Younger patients responded best to treatment regardless of gender
Fluoxetine, nortriptyline (71)	154	Younger patients (<25) had poorer response to nortriptyline than older patients (>25)

difference in drug response may be accounted for by the action of ovarian hormones. One hypothesis suggests that the differences are a result of the modulation in the density of serotonin receptors in the hypothalamus, cortex and nucleus accumbens as well as because of the enhancement of the antidepressant-induced down regulation of these receptors (88). Alternative explanations include the potential differential efficacy of various antidepressants in treating subtypes of depression (i.e.,

atypical features which are commonly seen in women versus melancholic) (74).

To date, most analyses have relied upon data sets often pooled, derived from randomized controlled trials where gender differences were not predicted a priori; post hoc analyses can be confounded. Moreover, many of the trials had few female participants, especially in the postmenopausal groups, and thus the analysis would be underpowered to detect modest differences. There has not been a prospective study conducted to determine if gender differences exist to the authors knowledge. Prospective studies with large numbers of patients, randomly assigned to antidepressants from various classes, with the primary question being that of determining if gender differences exist would need to be conducted for definitive answers.

There have been mixed reports regarding the use of exogenous female sex hormones in the treatment of MDD in women (89). In perimenopausal women with depressive disorders, estrogen alone appears to be an effective treatment (90–93) but not for postmenopausal women (90,94,95). Results from studies using estrogen to augment SSRIs in women resistant to SSRI therapy alone are also not consistent (83,96–99). It may be that estrogen augmentation accelerates the antidepressant response rate in postmenopausal women (100). Concerns about the risks associated with hormone replacement therapy or estrogen replacement therapy may limit use of estrogen to cases of refractory depression or for perimenopausal women for a limited time period.

SUMMARY AND FUTURE DIRECTIONS

During their reproductive years women are twice as likely as men to suffer from major depressive episodes. They also have more seasonal affective disorders, anxious and atypical depressions. There are also gender differences in the presentation and courses of these depressions. Genetic, psychosocial, hormonal, neurochemical and anatomic factors have all been implicated in the etiology of depression. Further research is necessary to ascertain the combination of factors which increases women's risk of developing depression. The effect of pregnancy on the course of all depressive disorders needs increased attention. Further information is needed about the impact of the menstrual cycle on the course of depression and on the metabolism of psychotropic medications. Large prospective randomized controlled trials need to be conducted with gender differences in treatment response as the primary endpoint in order to answer the now controversial question of gender differences in treatment response.

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