Recent research indicates that subtle differences may exist in the symptom profile of male and female depression. The aim of this review is to examine male/female differences in depressive psychopathology in light of the latest research findings and discuss whether these differences might suggest the need for gender specific treatments. Multiple searches using Medline (1985–2008) were carried out. Additional searches were made using the reference lists of published papers and chapters from books. Differences exist in the clinical profile and comorbidity of male and female individuals with depression. Subtle genetic differences, the role of hormones, the role of preexisting anxiety, and personality differences are some of the factors responsible for these findings. These differences imply that different treatment options should be available for males and females suffering from depression. The available data suggest that clinically relevant differences in depressive symptom profile and the underlying pathophysiology between genders in depression do exist. The identification of distinct endophenotypes for major depression, will not only improve our understanding of the disease, but will also contribute to more specific treatment strategies.

**Key words:** Depression, gender phenotype, psychopathology.
Introduction

Although it is widely held that there are no significant differences between men and women in terms of the symptoms they experience during depressive episodes, recent research suggests that subtle differences in symptom profile may indeed exist. These differences may suggest fundamental gender differences in the pathophysiology of depressive states.

Men are about half as likely as women to suffer from major depressive disorder (MDD) during their lifetime1 and a number of studies have found that depressed females tend to exhibit more “atypical” depressive symptoms (excessive fatigue, overeating and oversleeping, more anxiety and somatisation) than men. However men commit suicide, an act associated closely with severe depression, more often than women.3

Apart from the scientific research on this matter which is not widespread, the general public seems to assume the matter is settled. A quick search on the web reveals thousands of sites referring to male depression. The majority of them seem to take for granted that male depression is different from female depression. These sites aim to advertise and offer information on therapists and therapies, private or public related enterprises, that claim to be gender sensitive and gender specific. The majority of these sites are based in the US. The prevailing assumption is that homosexual orientation is somehow related with greater vulnerability to depression. This however is not supported by the scientific literature. It seems that in the general public there are issues of information and education.

This article reviews the literature on gender differences in depression and whether the roles of genetic and environmental risk factors for MDD differ in men and women, whether the genetic risk factors for MDD operative in men and women are the same.

Method

Multiple literature searches using Medline (1985–2008) were carried out, using the search terms: male, female, major depression, depressive symptoms, treatment, sex differences, gender differences, atypical depression, and combinations.

Additional searches were made using the reference lists of published papers and chapters. All abstracts found were studied. When there was indication that a paper might contain relevant information it was obtained. All papers studied were in English.

Findings

Findings can be organised under two separate headings. First the ones associated with the differences in phenomenology and secondly findings associated with the aetiology of these differences. A third heading could be added regarding the different response to treatment between the genders.

Phenomenological differences in male and female depression

General characteristics

Compared to males, females reported earlier age-at-onset of depression (defined as age at first onset of functional impairment due to depression, median 24 years versus 30 years), a higher median number of depressive episodes (mean 4 versus 3), and a higher mean number of atypical depressive symptoms during their worst ever depressive episode (10,4 versus 9,6). Additionally, the lifetime prevalence of MDD is nearly twofold higher in females than in males.4–6 Compared to men, women also have a much higher rate of 12-month depression, this seems to be largely due to women having a higher risk of first onset compared to males.5

Symptom profile

In both genders, common signs of depression include depressed mood, poor sleep, feelings of guilty and worthless. However, there seems to be significant differences between the sexes for five symptoms. Males reported “initial insomnia”, more frequently and females more frequently reported “diminished libido”, “excessive sleep”, “diurnal variation of mood” and excessive self-reproach. According to other researchers, men more commonly report anger and frustration, violent behaviour, risk taking, such as reckless driving, loss of concentration and isolation from family and friends. Fatigue and loss of interest in work, hobbies and sex are also common as well
as alcohol and substance abuse. Men, in addition, are more often than women unaware that physical symptoms, such as headaches, digestive disorders and chronic pain, can be symptoms of depression.\(^7\)

When compared to women, men report statistically less depressive symptoms.\(^6\) According to the same study, depressed women were more likely to report “increased appetite” (15.5% vs 10.7%), being “often in tears” (82.6% vs 44.0%), have “loss of interest” (86.9% vs 81.1%), and “thoughts of death” (70.3% vs 63.4%). The remaining depressive symptoms tested yielded no significant differences. However, other researchers found no evidence that symptoms of depression tend to be differentially reported between the sexes.\(^9\)

There are reports\(^{10}\) that male depression has a later onset than female (25.5 years, SD=12.56 versus 23 years, SD=10.6). The same researcher also found that men had less frequently some clinical symptoms of depression. These symptoms have also been described as “atypical” ie proneness to fatigue, increased appetite, weight gain and hypersomnia). The diagnosis of atypical depression requires at least two out of the three symptoms: excessive physical fatigue, hypersomnia and hyperphagia. These need to be present during a major depressive episode.\(^{11}\) It was also reported\(^1\) that the prevalence of atypical depression during the worst-ever episode was clearly superior in females, compared to males (31.6% vs 21.1%).

These finding are similar to the findings of Silverstein\(^{12}\) who defined somatic depression as sleep disturbance, fatigue and appetite disturbance for at least 2 weeks and pure depression as “high levels of depression not associated with these other symptoms”. Kessler, data from the National Comorbidity Survey, found that men had half the prevalence of somatic depression (as defined) when both 6-month and lifetime depressive criteria were taken into account, as assessed by the Composite International Diagnostic Interview.\(^{13}\) As a result, he raised the possibility that somatic depression might be a diagnostic category separated from major depression. In the same vein, a study by Wenzel et al,\(^7\) provides partial support for gender differences in somatic depression as assessed by items on the Beck Depression Inventory (BDI-II). In particular change in appetite was sensitive in detecting gender differences even in milder cases of somatic depression. On the other hand, tiredness or fatigue were useful symptoms in detecting gender differences only in moderate to severe cases of somatic depression. The finding that change in appetite was the most consistent symptom to differentiate the genders, raises the possibility that biological factors underlie gender differences in depression.\(^9\)

The scientific literature has up to date, focused on females from a “male perspective”. This can only be done in a “negative way”, i.e. what men do not have (in contrast to women). It was reported\(^6\) that the sex differences in the rate of earlier anxiety disorder play a considerable part in the observed sex difference in MDD. The lower male risk for MDD might be explained in part by the higher rate of anxiety disorders in females than males beginning early in life. In other words, anxiety disorders may be particularly important as a precursor to MDD, but only in women. The same researchers note that any sex differences that might originate in late onset MDD might have little to do with pre-existing anxiety. Apart from the implications of sex differences in MDD, the results emphasize the strong connection between anxiety disorders and subsequent MDD, and they suggest that future research on the nosology of MDD might benefit from distinguishing cases according to previous history of anxiety.

In men, on the contrary, disorders such as alcoholism and drug abuse, which are also genetically influenced may increase the risk of developing MDD.\(^{14–16}\) These hypotheses point to the theory that the developmental pathways toward MDD differ substantially in men and women.

Suicide

Males commit suicide more often than females. In the United States, 80% of all suicides have men as victims (WHO).\(^{17}\) Male suicides by violent means have also more pronounced seasonal variation\(^{18}\) (Christodoulou et al 2008), while male suicide rate at midlife is three times higher than women’s.\(^{19}\) However the issue is not resolved. It is well known that one of the greater predictors of eventual suicide is “parasuicide”, which broadly defined, includes both suicide attempts and deliberate self-harm inflicted
with no intent to die. A review indicated that 30 to 47 per cent of suicide completers had a prior history of parasuicide. All but one studies reviewed by Welch, show consistently lower rates of parasuicide for males. The authors are not aware of any research paper showing whether the suicide attempters that consequently went to commit suicide were or were not mostly male. As mentioned most studies show the highest rates for suicide attempts among women in their teens to early twenties and men in their twenties.

Findings associated with the etiology

Hormonal studies

It has been hypothesized that the lower levels of atypical symptoms in males could reflect a pathophysiological difference between male and female depression. It has been suggested that atypical depression is associated with hypersuppression of the hypothalamic-pituitary-adrenal (HPA) axis, while melancholic depression is associated with HPA overactivity. In particular corticotropin-releasing hormone (CRH), a hypothalamic hormone, seems to be of fundamental importance in depressive illness. Melancholic depressed patients with a syndrome of hyperarousal (anxiety, insomnia, diminished appetite, etc), have increased activity of CRH-producing neurons, while patients with atypical depression, a syndrome of under-arousal (anxiety, insomnia, diminished appetite, etc), have decreased activity of CRH-producing neurons. Besides HPA axis functional changes, distinct alterations of the serotonergic system may also play a critical role for the melancholic and atypical subtypes, namely a reduced restraint via 5-HT-1A autoreceptors in the former and primarily serotonin synthesis in the latter. Gold & Chrousos have also presented data indicating that symptoms of atypical depression are associated with concomitant hypofunctioning of the locus coeruleus-norepinephrine (LC-NE) system.

Female hormones—estrogens in particular exert potent effects on the expression of various forms of psychopathology. Additionally, they have a neuroprotective role regarding neuronal degeneration, growth and susceptibility to toxins. The literature on depression holds female hormones indirectly responsible for the greater prevalence of depression in women. It is not that estrogens directly dampen mood, although progestins may do so, but that the off-and-on binding to intra-nuclear estrogen receptors in the brain, starting in the early teens, somehow renders women vulnerable to stress, probably through glucocorticoid-induced neuronal toxicity. The cyclic nature of estrogen secretion from puberty to menopause and, subsequently its almost total withdrawal may account for the special vulnerability of young women to depression. Recurrent estrogen withdrawal may interfere with estrogen’s ability to neutralize the effects of glucocorticoids released during stress. According to the same author, this explanation, speculative as it is, fits the epidemiologic evidence that the high prevalence of depression in women is evident only after puberty.

Further support to the hormonal hypothesis is added by. They suggested that increased risk of depression is related to high organizational testosterone. Additionally Manning suggested that finger length ratio (2D:4D) index to ring finger is associated with a trait depression subscale in males and Bailey found that depression in men is associated with more feminine length ratios.

Twin studies

A slightly greater correlation in liability to MDD in the female+- female (FF) versus the male+- male (MM) pairs has been reported. However, the best fitting model suggested equal heritability for MDD in the two sexes.

It has been argued, that using broader but not narrower definitions of illness, genetic factors play a smaller role in the aetiology of MDD in men than in women. The genes that influence risk for MDD in the two sexes are correlated but might not be entirely the same. This raises the possibility that, in linkage and association studies, the impact of some loci on risk for MDD will differ in men and women.

Given that the most sensible interpretation of all available data is that men and women share some but not all the genes for MDD, two hypotheses have been advanced. The first, suggests that such a pattern might be due to susceptibility genes for MDD located on the X chromosome. The pattern of correlations in liability observed for sibling and
parent-offspring pairs does not fit that predicted for an X-linked trait. The second hypothesis suggests that some proportion of the genetic risk factors for MDD in women might reflect the sensitivity to the “depressogenic” effects of menstrual and/or pregnancy-related hormonal changes that do not appear in men. Thus, males and females may react differently to similar life experiences, but there may also be different genetic and molecular mechanisms behind female and male psychopathology. Many studies on the neurotransmitter systems like the ones on polymorphisms of the promoter serotonin transporter gene, or in HPA – axis or in the CREB1 gene which has synergistic interactions with the female sex hormones (estrogens and progesterone) have confirmed this hypothesis. These findings may provide the mechanisms on how sex-specific patterns of gene expression could be facilitated. These can manifest themselves in the sex-specificity of the susceptibility locus for Mood Disorders. Concordant with this hypotheses, is the finding by Kendler who establishes that genetic risk factors for premenstrual symptoms accounted for nearly 17% of the genetic risk factors for lifetime MDD in female twins.

Personality differences

We are now increasingly aware that both biological and psychological sex variables shape personality. Investigators have looked for personality factors associated with the sex role that are capable of explaining women’s special vulnerability to depression. Women, to a greater degree than men, invest their emotions in interpersonal relationships, consequently they suffer from the impact of life events that take place not only in their own lives but also in the lives of their network of friends and relatives. However this hypothesis is not supported by the evidence which suggests, to the contrary, that strong social networks more prevalent among women, protect against depression. Another reported personality difference, widely accepted though difficult to prove empirically, is that women internalize their feelings to a greater degree than men and blame themselves for incompetence or failure which leads to depression, while men blame others which leads to anger.

Conflicting and changing social expectations of women and the higher rates of sexual abuse of girls during childhood and adolescence have also been considered as possible explanations for high rates of depression in women.

What is the practical significance of these findings?

Treatment implications: It has been reported that female patients respond better to selective serotonin reuptake inhibitors (SSRIs) than tricyclic antidepressants (TCAs). This might be associated with the side effects profile of the SSRIs. Male depressed patients have on the other side been reported to respond better to TCAs. Interestingly the female predominance among patients seem to be restricted to the atypical subtype. Other studies also mention that TCAs are not particularly effective in the treatment of atypical depression. Atypical depression is related to a decrease of CRH secretion and TCAs also decrease CRH production. Kier reported that treatment with the monoamine oxidase inhibitor (MAO-I) phenelzine, in mice, could reverse the psychiatric symptoms of glucocorticoid deficiency in atypical depression, results that confirm those of Stewart seems that chronic phenelzine treatment induces sustained increases in glucocorticoids by impairing glucocorticoid feedback, increasing adrenocortical responsiveness to ACTH, and increasing glucocorticoid independent stimulation of hypothalamic-pituitary activity. The reported hypofunctioning of the HPA and LC-NE system indicate the need for research on a different therapeutic strategy for this subtype of MDD & Chrousos, 2002.

Conclusion

Overall, the clinical presentation of MDD in males and females is not the same. There are differences in presenting depressive psychopathology and comorbidity. Sex modifies clinical features of depression and an earlier onset of depression and atypical symptoms seems to occur more frequently in women while more aggressive symptoms (against themselves or others) occur more frequently in men. The genetic risk factors for MDD, also appear to have minor differences. There also seem to be different
hormonal dynamics, different influences on the preexisting anxiety and various personality traits between the sexes. These differences though are not pronounced.

We have now reached a stage where we should probably talk about endophenotypes of depression. This suggests that studies of depression should examine each endophenotype separately. Future studies on gender differences in genetic risk factors for depression will determine the way men and women respond to environmental risk factors and will affect the profile of depressive symptoms resulting from these interactions.

Furthermore, regarding the effects of antidepressants in MDD, psychiatrists may need to pay close attention to gender differences and the profile of depressive symptoms before and after antidepressant therapy. The literature reviewed indicates the need for research on a different therapeutic strategy than the one currently used for the treatment of depression. Findings suggest that each subtype of major depression may be associated with its own unique repertoire of presenting symptoms and long-term medical consequences. Gender might be an important parameter that needs to be taken into account.

References
38. Kier A, Han J, Jacobson L. Chronic treatment with the monoamine oxidase inhibitor phenelzine increases hypothalamic-pituitary-adrenocortical activity in male C57BL/6 mice: relevance to atypical depression. Endocrinology 2005, 146:1338–1347

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