Sex differences in the psychopharmacological treatment of depression

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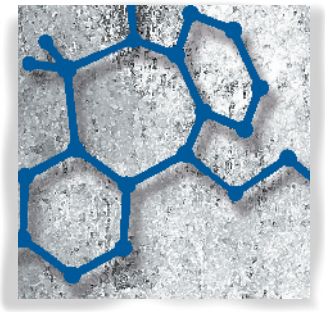

Although a number of studies have observed that females respond better to serotonergic antidepressants than males and that postmenopausal females have a diminished response to antidepressants compared with younger females, there are also studies that conflict with both of these findings, making any generalizations regarding sex differences difficult to make. Sex variance in antidepressant efficacy and pharmacokinetics profiles have been attributed to sex-based physiological differences, behavioral differences, related disorders, and sex-specific conditions, including pregnancy and menopause. This paper will review the history and current research on sex effects of antidepressant treatment.

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Introduction

There is extensive literature on the topic of sex differences in antidepressant treatment.[1] Sex differences in antidepressant efficacy have been linked to sex-related physiological differences, behavioral characteristics, comorbid diseases, menopause, pregnancy, and adherence, among other factors. Although conclusions are tempered by the variability existing in levels and durations of exposure to antidepressants, these data do provide a spectrum of intrinsic factors that are considered to be prognostically important. For example, variance in body fat, hormone levels, and liver metabolism between sexes have been shown to affect the pharmacokinetics of a drug when orally administered. Sex-specific factors have been identified in the clinical presentation, prevalence, and resiliency of depression. This paper will review the clinical literature and research on sex-related differences in the efficacy and pharmacokinetics of antidepressants, including female-specific variables, and how these differences can affect the outcome of antidepressant treatment.

Sex differences in the pathogenesis of depression

The incidence of depression in women is nearly double that in men.[2,3] This is independent of diagnostic nomenclature, including atypical depression, unipolar depression, dysthymia, and seasonal affective disorder.[4-6] These

differences have been found across all age groups.[7] The lifetime risk of major depression in the United States is 21% in females versus 13% in males.[8] Symptom presentation is generally more severe in women. Depressed females typically experience prolonged or recurrent depression more than depressed males, with a younger onset age and lower quality of life.[9] Depressed females generally experience greater weight gain, anxiety, and physical manifestations of their disease than depressed men.[10-13]

The causes of these differences in clinical presentation and response to pharmacotherapy between sexes are unknown, but several theories exist. Sex differences in the incidence of depression generally materialize during adolescence, which has led to suggestions that female susceptibility may be linked to surges in reproductive hormones (estrogen and progesterone) during puberty.[14] The incidence of depression in women after menopause (when reproductive hormones stabilize) appears to be similar to that in men.[15] Levels of estradiol (E2) have also been reported to be lowered in depressed premenopausal and perimenopausal women.[16,17] Estrogen and serotonin appear to interact in significant ways. In animals, estrogen induces changes in brain serotonin transmission, binding, and metabolism.[18]

Sex-related differences in the prevalence of depression may also be affected by differential monoamine functioning between sexes. Monoamine tryptophan depletion results in a temporary decrease in serotonin transmission, and this increased depressive symptoms in females significantly more than males.[19] Likewise, positron emission tomography (PET) demonstrated decreased serotonin synthesis in females compared with males after tryptophan was depleted.[20] Elevated levels of serotonin, as well as the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), were found in women compared with men,[21] which may be related to a greater availability of the serotonin transporter in females.[22] The serotonin 5-HT_{1A} receptor subtype demonstrates decreased binding potential with age in men but not in women, and this receptor subtype is associated with depression pathogenesis.[23] Brain levels of serotonin and norepinephrine show greater age-related changes in females than in males.[24] A study of 75 healthy volunteers of different ages (21 to 80) and sexes (40 females, 35 males) found platelet monoamine oxidase manifested a significant increase in females compared with males ($P<0.05$).[25] The dopaminergic system may also be involved in depression pathology. Through neuroimaging studies, women have been shown to possess a higher concentration of synaptic dopamine in the striatum than men do, and age decreases synaptic dopamine levels in men more than women.[26] Additionally, female hormones seem to increase the turnover rate of presynaptic dopamine in preclinical investigations.[27,28] Women show a greater reduction in striatal dopamine release in response to amphetamines than men.[29] Thus, across monoaminergic systems implicated in the pathogenesis of depression (serotonin, dopamine, and norepinephrine), there is suggestive evidence both in preclinical and clinical studies in support of a pathophysiological basis for differential presentation and response based upon sex.

Sex differences in response to antidepressants

There is still no clear consensus on whether there are sex-related efficacy differences in antidepressant treatment, despite decades of research on this topic. Part of this lack of consensus is related to the diverse diagnostic and trial methodology that has been employed across studies, introducing significant confounds in interpretation. Studies have shown sex differences in antidepressant efficacy while attempting to accommodate differences in medication, dose, regimen, and compliance (see *Table I* for a list of factors that may contribute to sex differences in antidepressant efficacy). See *Table II*[30-38] for a list of studies where females respond better to antidepressants than males and *Table III*[10,31,39-41] for a list of studies where

Body fat and weight distribution
Liver metabolism rates
Changes in physiology and hormone levels during puberty, menstruation, and menopause
Gastric emptying, acid production, and splanchnic blood flow
Plasma volume, protein levels, and enzyme activity
Drug transport and clearance rates
Adherence
Side-effect profile differences
Interactions between estrogen and serotonin in the brain
Brain monoamine functioning

Table I. Factors that may contribute to sex differences in antidepressant efficacy.

males respond better to antidepressants than females. A significantly greater therapeutic response has been shown for males than females for the tricyclic antidepressant (TCA) imipramine.[10,31,40,41] These differences existed even when possible differences in antidepressant type and use patterns, including compliance, were considered.

A number of studies suggest women may respond better to selective serotonin reuptake inhibitors (SSRIs) than men,[30,31,34,35,37,38,42] although the results of one of these studies has been disputed.[43] The greater efficacy results for females than males (studies cited in *Table II*[30-38]) remain variable. For example, examining several of the more recent studies, which employed the HAM-D (Hamilton Depression Rating Scale) as the primary efficacy assessment for SSRI treatment, females had a 15%, 23%, and 40% greater improvement than males.[31,34,35] Younger females exposed to the SSRI fluvoxamine showed greater response than males and older females as well (>44 years old).[36] In a naturalistic

Reference	Drug type	Study type	Subjects	Results
Haykal and Akiskal,[30] 1999	SSRIs, TCAs	TCA-type antidepressants or fluoxetine	25 Male and 17 female primary dysthymic patients	Females responded better than males to SSRIs
Kornstein et al,[31] 2000	SSRIs, TCAs	12-Wk double-blind trial with sertraline or imipramine	235 Male and 400 female outpatients with chronic major depression or double depression	Females responded better to SSRI sertraline; differences observed primarily in premenopausal females
Martenyi et al,[32] 2001	SSRIs, TCAs	6-Wk, double-blind trial of SSRI (fluoxetine) and a norepinephrinergic TCA (maprotiline)	105 Male and female depressed patients	Females in their reproductive period were more responsive to SSRIs than norepinephrinergic TCAs
Quitkin et al,[33] 2002	TCAs, MAOIs, SSRIs	20-Y review of 8 placebo-controlled antidepressant trials and 1 open-label study	1746 Depressed patients aged between 18 and 65 y	Older females had superior response to TCAs than younger females; females had statistically superior response to MAOIs than males
Khan et al,[34] 2005	SSRIs, SNRIs	Review of 15 randomized, placebo-controlled trials for sex differences in antidepressant efficacy	323 Depressed patients	Females had a significantly greater response than males to SSRI and (to a lesser extent) SNRI treatment
Berlanga and Flores-Ramos,[35] 2006	SSRIs, SNRIs	8-Wk, double-blind clinical trial for sex differences with SSRI citalopram and SNRI reboxetine	86 Depressed patients (48 females, 38 males) aged18 to 40 y	Premenopausal females responded better than males to serotonergic antidepressants
Naito et al,[36] 2007	SSRIs, SNRIs	6-Wk study of the clinical effects of fluvoxamine and milnacipran in Japanese major depressive patients	103 Patients with MDD (66 females, 37 males)	Fluvoxamine was more effective in younger female patients than older female patients and male patients
Young et al,[37] 2009	SSRI	12- to 14-Wk study of citalopram	1043 Male and 1833 female patients with single or recurrent nonpsychotic MDD	Females had a better response to the SSRI citalopram than males
Yang et al,[38] 2011	Variety of antidepressants	12-Wk naturalistic study	723 Depressive patients (535 females, 188 males)	Females had a better response to antidepressant treatment than males

Table II. Studies finding greater antidepressant efficacy in females than in males.

study of 138 depressed patients, Vermeiden et al reported a differential sex response based on the antidepressant used; males responded significantly better to imipramine than premenopausal females, but the females responded better to fluvoxamine than the males.[44] An atypical depression study produced mixed findings: whereas monoamine oxidase inhibitors (MAOIs) demonstrated superiority over TCAs in females, the opposite was true in males.[45]

On the other hand, many studies have not detected sex differences in the efficacy of antidepressants (see *Table IV*[33,42,46-55]). The serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine and SSRIs were both shown to produce comparable responses in males and females.[47] Likewise, TCAs, MAOIs, and the SSRI fluoxetine showed no sex differences in drug efficacy in a large, retrospective study.[33] Other studies have shown females do not respond preferentially to SSRIs,[51] nor do males respond preferentially to TCAs.[49] Furthermore, Hildebrandt et al showed no sex effect on the efficacy of the TCA clomipramine, the SSRIs citalopram and paroxetine, and the MAOI moclobemide.[48]

Meta-analyses perform a service by aggregating clinical trial data into an analysis that may help resolve inconsistent conclusions. A meta-analysis of 30 randomized placebo-controlled trials of imipramine or amitriptyline as an example found no effect of sex on TCA efficacy.[50] A more compelling comprehensive analysis using contemporaneous techniques created an "individual patient data" meta-analysis with the primary data of 1766 patients from 14 eligible randomized trials, comparing cognitive behavior therapy (CBT) with pharmacotherapy, and comparing either CBT or pharmacotherapy with pill placebo. This study is additionally noteworthy in that pharmacotherapy, as well as other recognized therapeutic modalities such as CBT, were examined. No sex-modulating effects on treatment were detected regardless of therapeutic intervention.[55] A 2010 analysis by Kornstein et al pooled nine clinical trials of outpatients aged 18 years or older with major depressive disorder (MDD; 1108 males and 1805 females) who received desvenlafaxine or placebo for 8 weeks. They found that desvenlafaxine generally improved depressive symptoms regardless of sex.[53] In 2014, Kornstein et al performed a secondary analysis of a multiphase, multicenter, double-blind study in which adult outpatients (670 females and 377 males) with recurrent MDD were randomly assigned to 10 weeks of acute phase venlafaxine extended release or fluoxetine. They found no observed sex difference in the response to treatment.[54]

Although no definite explanation exists for the many contradictions in this data, numerous issues of methodology might offer a rationale. Such differences

Reference	Drug type	Study type	Subjects	Results
Kornstein et al,[31] 2000	SSRIs, TCAs	12-Wk double-blind trial with sertraline or imipramine	235 Male and 400 female outpatients with chronic major depression or double depression	Males responded better to TCA imipramine than females
Hamilton et al,[39] 1996	TCAs	Meta-analysis of 35 studies that reported imipramine response rates	342 Males and 711 females with depression	Imipramine response rates were significantly better for males than females
Old Age Depression Interest Group,[40] 1993	TCAs	24-Mo, double-blind placebo-controlled study of continuation/prophylaxis therapy with dothiepin	19 Males and 50 females with major depression	Males taking dothiepine were less likely to experience a recurrence of depression than females
Frank et al,[10] 1988	TCAs	16-Wk trial with imipramine and interpersonal psychotherapy	50 Males and 180 females with recurrent major depression	Males showed a more rapid and sustained clinical response to imipramine than females
Raskin,[41] 1974	TCAs and MAOIs	3-Wk trial with chlorpromazine, imipramine, diazepam, phenelzine, or placebo	268 Males and 612 females with moderate depression	Older males responded more positively to active drug than older females

Table III. Studies finding greater antidepressant efficacy in males than in females.

may arise between demographics or due to the nature of diagnostic nosology, class of therapeutic agent, and various parameters related to amount, regimen, and duration of exposure. Additionally, the criteria for determining a significant response to treatment varied considerably between studies. One study used a paired

Reference	Drug type	Study type	Subjects	Results
Himmelhoch et al,[46] 1991	MAOIs, TCAs	Controlled, double-blind comparison: tranylcypromine vs imipramine	56 Outpatients who met operationalized criteria for anergic bipolar depression	Males and females responded comparably to both drugs
Entsuah et al,[47] 2001	SSRIs, SNRIs	Meta-analysis of 8 comparable double-blind, active-controlled, randomized SSRI or venlafaxine clinical trials	2045 Patients with major depression or MDD, aged 18-83 y	Males and females have comparable responses to SSRIs and SNRIs across various age groups
Quitkin et al,[33] 2002	SSRIs, TCAs, MAOIs	Retrospective analysis of patients treated with TCAs, MAOIs, fluoxetine, or placebo	1746 Depressed patients aged 18-65 y	No sex- or menopausal status–based difference in drug efficacy
Hildebrandt et al,[48] 2003	SSRIs, TCAs, MAOIs	Review of 3 Danish double-blind randomized, controlled trials	292 Inpatients (96 males, 196 females) with major and predominantly melancholic depression	No relationship between plasma concentrations, sex, and therapeutic outcome
Parker et al,[49] 2003	SSRIs, TCAs	Review of retrospective and prospective naturalistic uncontrolled studies	Patients with melancholic and nonmelancholic depression	No sex difference in response to either drug class
Baca et al,[42] 2004	SSRIs, TCAs	8-Wk, multicenter, randomized, open-label, parallel group comparative trial of sertraline vs imipramine	234 Patients with major depression or dysthymia (50 males, 184 females)	Overall, statistically significant differences in effectiveness between men and women were not found
Wohlfarth et al,[50] 2004	TCAs	Review of 30 randomized, placebo-controlled trials of antidepressant efficacy	3886 Patients (1555 males, 2331 females) with depression	TCA response is independent of sex
Thiels et al,[51] 2005	SSRIs	Review of data from a 6-mo prospective sertraline utilization observation study	1594 Male and 3858 female depressed patients	No sex difference in side-effects, treatment termination, or treatment response to SSRI
Pinto-Meza et al,[52] 2006	SSRIs	6-Mo follow-up study of antidepressant treatment with a SSRI (citalopram, fluoxetine, paroxetine, or sertraline)	242 Females (95 in menopause) and 59 males with major depression	No sex differences were observed in treatment response, depression severity, and symptomatology
Kornstein et al,[53] 2010	SNRIs	Review of 9 studies comparing desvenlafaxine or placebo for 8 weeks	2913 Outpatients (1108 males, 1805 females) with MDD	Desvenlafaxine generally improved depressive symptoms across sex subgroups
Kornstein et al,[54] 2014	SSRIs, SNRIs	Follow-up review of a 2-y study of acute-phase venlafaxine extended release or fluoxetine	670 Female (168 in menopause) and 377 male outpatients with recurrent MDD	No sex differences were observed in treatment response
Cuijpers et al,[55] 2014	SSRIs, TCAs, other antidepressants	Meta-analysis of 14 eligible randomized trials comparing CBT with pharm, and comparing CBT or pharm with pill placebo	1202 females and 564 males with depression, subjects from 14 eligible randomized trials	No sex differences were observed in treatment response

Table IV. Studies finding no sex-based efficacy differences with antidepressants.

t-test to compare total HAM-D17 (17-item HAM-D) baseline scores with scores after treatment,[32] equating differences on this parameter as potentially clinically important provided they were statistically significant. Another study declared a clinically significant response after a 50% or greater decrease in HAM-D21 (21-item HAM-D) scores.[47] Age variation between female patients in these studies may also influence their outcomes, as levels of female sex hormones change with age and menopause and may affect the efficacy and metabolism of antidepressants. More potential variables include clinical presentation (ie, typical versus atypical), previous antidepressant treatment, differing drugs and dosages, patient adherence to treatment plans, and the type of study conducted (prospective or meta-analysis of large data pools).

Side effects of antidepressants can also detract from overall efficacy, particularly if they lead to early discontinuation. Most of the literature reviewed above regarding sex differences in antidepressant efficacy fail to take adverse events into account. Deleterious effects on sexual drive and satisfaction, but sometimes improvement, have been reported in women taking SSRIs, and weight gain may be more problematic in women because of societal expectations, but further research needs to be done in this area to determine whether true sex differences exist.[56] One study found depressed females to have greater sexual dysfunction than depressed males, yet female sexual dysfunction actually improved with SSRI treatment, whereas male sexual dysfunction worsened with the same treatment.[57] The improvement in sexual function for females may be due to the fact that any negative sexual side effects of SSRIs in women are overshadowed by the drug's positive effects on ameliorating depressive symptoms. As various antidepressants have different adverse event profiles, the clinician can switch to another class of antidepressant if such side effects prove problematic.[58] For example, Shen and Hsu recommended bupropion as an appropriate substitution for SSRIs in patients looking to reduce sexual side effects caused by their antidepressant regimen.[59]

A clinician must also keep in mind that many atypical antipsychotic drugs are used today as adjunctive treatment for depression and can even be employed as stand-alone treatment,[60] in which case the potential for sex differences in either pharmacokinetics or pharmacodynamics must also be considered. In the use of atypical antipsychotics for psychotic disorders, sex differences in efficacy have generally not been found, although this is an area that deserves further study.[61,62] Most of the literature regarding sex differences with antipsychotics relates to side effects experienced during treatment. There is general agreement in the literature on women's increased susceptibility to weight gain, diabetes, metabolic syndrome, and specific cardiovascular risks of antipsychotics compared with men.[63,64] Atypical antipsychotics can raise prolactin levels, resulting in more pronounced symptoms in women than men, including galactorrhea, atrophic changes in the urethra and vaginal mucosa, reduced vaginal lubrication, dyspareunia, decreased libido, ovarian dysfunction, infertility, oligomenorrhea, and amenorrhea.[65] Not all atypical antipsychotics produce the same prolactin-elevating effects. For example, in a study by Wu et al, ziprasidone was associated with greater changes in prolactin levels in women than olanzapine.[66] Hyperprolactinemia appears to be more common with conventional antipsychotics and risperidone than with clozapine, olanzapine, and quetiapine.[67] In a study by Findling et al of risperidone use in children and adolescents aged 5 to 15 years old, serum prolactin levels rose in the first months of treatment before decreasing by week 13. In females, elevated prolactin levels were associated with galactorrhea, menstrual disturbances, and decreases in bone marrow density.[68] Amisulpride, an atypical antipsychotic that has been used to treat dysthymia, appears to elevate plasma prolactin to a greater degree than other atypicals, which can lead to galactorrhea, gynecomastia, and sexual dysfunction.[69]

Pharmacokinetic differences

Different pharmacokinetic profiles exist between men and women for several antidepressants. Possible sources of these differences include differences in body weight, volume of plasma, gastric emptying and acid production, splanchnic blood flow, plasma protein levels, enzyme activity, as well as drug transport and clearance rate differences between sexes. Higher plasma levels[39,70] and lower clearance of TCAs have been found in females.[71] The higher percentage of adipose tissue and body fat in women than in men may be a source of these differences. Due to their lipophilic nature, antidepressants have an affinity for adipose tissue, often producing greater drug distribution in women.[72,73] Women also typically have lower gastric acid secretion and slower

stomach emptying than men. Gastric motility is often slowed in the presence of female sex hormones, decreasing the clearance of antidepressants.[37,74]

The complexity of determining sex effects is further highlighted by similar studies of the same antidepressant that utilized different study methodology. Unterecker et al examined a large therapeutic drug–monitoring database to determine the influence of sex on serum levels of venlafaxine and its metabolite *O*-desmethylvenlafaxine in patients treated with venlafaxine under naturalistic conditions. They found that women had about 30% higher dose-corrected serum levels of venlafaxine and *O*-desmethylvenlafaxine than men ($P<0.01$).[75] Despite this finding, the clinical report by Kornstein et al found no sex difference between males and females treated with venlafaxine.[54] Another cross-sectional study of a large therapeutic drug–monitoring database looked at sex differences in venlafaxine treatment given to elderly patients versus their younger counterparts, and found that the difference between age groups was independent of sex.[76]

Another factor to bear in mind is that antidepressants are noted to cause weight gain, which is variable between men and women. This is important because changing the weight gain and distribution of fat can affect the pharmacokinetics of the antidepressant drugs being administered. Noordam et al examined the association between antidepressant use and change in body mass index from the pharmacy records of 7269 participants and found weight gain was observed only in women (not men) who had been treated for at least 90 days with SSRIs.[77]

The enzyme superfamily cytochrome P450 (CYP450) is a major drug-metabolizing pathway in humans. Several CYP450 variants show sex differences that may affect exposure and pharmacokinetic profiles for antidepressants. Cytochrome P450 3A4 (CYP3A4) is a highly expressed liver enzyme that helps metabolize many drugs, including several SSRIs (sertraline, citalopram, fluoxetine, escitalopram, etc) and TCAs (amitriptyline, imipramine, clomipramine, etc). Drug substrates of CYP3A4 often clear faster in women than in men,[78] potentially caused by increased CYP3A4 enzymatic activity in females compared with males.[79,80] Contrary to this, drug substrates of cytochrome P450 2D6 (CYP2D6), a major metabolizer of xenobiotics, including desipramine and mirtazapine,[81,82] often clear faster in males than females.[83] Likewise, cytochrome P450 1A2 (CYP1A2) substrates have been found to clear faster in males than females,[84-86] although this has been disputed.[87] CYP1A2 may metabolize escitalopram to S-desmethylcitalopram and S-didesmethylcitalopram.[88] Also, a study found that race/ethnic differences in cytochrome P450 2B6 (CYP2B6) genotype and phenotype were observed only in women.[89] CYP2B6 is important for the metabolism of bupropion to its active metabolite hydroxybupropion.

The task of deconstructing how sex-based differences in metabolic enzymes affect the breakdown and distribution of antidepressants is confounded by the many classes of antidepressants, each affected by different enzymes. A complete picture of this interaction may require knowledge of the class and structure of each antidepressant, as well as the duration and repetition of exposure, and even concomitant medications.

Adherence differences

Some studies have also found significant sex differences noted in adherence to antidepressant treatment. Adherence is defined as compliance with dosage and regimen as prescribed for a duration considered sufficiently adequate for therapeutic response. A historical cohort study of 310 994 individuals who filled antidepressant prescriptions during a 4-year period found adherence was significantly higher for males aged 20 to 40 years than for females of that age, but this relationship reversed later in life for those aged 50 to 70 years.[90] A historic cohort study of three Italian local health units of 88 755 patients with a prescription for antidepressants found that female sex was a predictor of better adherence.[91] On the other hand, a sample of 3684 patients with long-term prescription of antidepressants found compliance rates across sexes were similar, with 21.4% compliance for males and 22.4% compliance for females.[92]

Female reproductive hormones

Estrogen is believed to be involved in both the pathogenesis of depression and the effectiveness of antidepressants. In vitro studies have shown that estrogen facilitates the formation of dendritic spines and also influences neurotrophic factors.[93] Progesterone has also been shown to decrease gastric emptying, which has the potential to modify an antidepressant's phar-

macokinetics.[73] Estrogen interacts with the serotonergic system, which is the target of SSRIs. In a challenge study employing the serotonin agonist meta-chlorophenylpiperazine, cortisol and prolactin responses were increased in postmenopausal women who were placed on 1 month of estrogen replacement therapy.[94] Eighty-six depressed male and premenopausal females (18 to 40 years old) were given the SSRI citalopram and the SNRI reboxetine in a blinded, 8-week clinical trial. Premenopausal females were shown to have a better response than males to serotonergic antidepressants, implying that female hormones may improve the efficacy of antidepressants.[35]

These observations were corroborated by studies in depressed postmenopausal women receiving estrogen replacement therapy combined with an SSRI. Depressed postmenopausal females on supplemental estrogen plus SSRIs demonstrated improved response compared with depressed postmenopausal females who received only an SSRI.[95] An open-label, naturalistic, 6-week study examined how premenopausal and postmenopausal females with depression respond to several antidepressants, including TCAs, SNRIs, and SSRIs. This study demonstrated that postmenopausal females had a poorer response to antidepressants than premenopausal females. This inferior response was associated with elevated follicle-stimulating hormone levels.[96]

Naturalistic studies of antidepressants in menopause also support the hypothesis that reproductive hormones may improve the efficacy of antidepressants. One naturalistic study examined 242 females (95 postmenopausal) and 59 males with depression, who began treatment using an SSRI (citalopram, fluoxetine, paroxetine, or sertraline) at primary care centers during a 6-month period. Menopause appeared to produce a poorer response to SSRI treatment in depressed females.[52] Another study looked at 115 depressed female outpatients (separated by menopause status) and 86 age-matched male outpatients who underwent an 8-week treatment taking either the SSRI nefazodone or venlafaxine. Premenopausal females demonstrated a better response to SSRI treatment that postmenopausal females.[97]

Harvey et al reasoned that acute worsening of depression would be found more frequently in females who were postmenopausal than in both premenopausal females and males.[98] However, after reviewing HAM-D scores in 554 patients over 3582 clinic visits, these investigators found the opposite was true—more episodes of worsening depression occurred in premenopausal females and males than in postmenopausal females. Complicating matters further, a secondary analysis by Kornstein et al of a 10-week double-blind study of 670 female and 377 male outpatients with recurrent MDD found no difference between venlafaxine extended release or fluoxetine on the basis of menopausal status in the treatment of major depression.[54]

Even estrogen's mechanism of action in ameliorating depression is unclear. For example, estrogen may play a role as a mood enhancer, separate from any specific role in enhancing antidepressant efficacy. Supporting this notion, estrogen given to perimenopausal females who were not taking antidepressants still proved to be effective at treating depression.[99] In addition, stopping estrogen replacement therapy in females over 40 years old who had previous recurrent episodes of depression rapidly induced a new depressive episode.[100] In contrast, several studies have found no elevated risk for depression in females during their postmenopausal period, when reproductive hormones such as estrogen decrease dramatically.[101,102] Another study found that estrogen alone did not relieve depression in most postmenopausal females.[103]

Low luteinizing hormone (LH) levels may also predict improved response to antidepressant therapy in postmenopausal females.[104] Levels of serotonin appear to vary inversely with LH levels.[105] Therefore, lower LH levels suggest higher baseline serotonin levels for antidepressants to work upon. A correlation has been shown between lower LH levels and hypothalamic-pituitary-adrenal (HPA) axis hyperactivity.[106,107] Normal HPA activity has been found to be disrupted in MDD,[108] and antidepressants have been shown to reduce HPA activity. Low LH levels may therefore indicate a hyperactive HPA axis and identify potentially good responders to antidepressant treatment.[109,110]

In young females, the menstrual cycle itself may also modulate the effectiveness of antidepressants. The menstrual cycle may alter gastric contractions and fluid retention, resulting in a dilution of antidepressant levels in plasma.[73]

Conclusion

Although the evidence is not conclusive, there are two observations that may be made at this time. First, a number of studies suggest that females respond better

to serotonergic antidepressants than males. Secondly, postmenopausal females appear to have a diminished response to antidepressants compared with younger females. All the issues reviewed in this paper are thought to play a role in producing sex-specific differences in response to antidepressant therapy, although the discrete role of any one variable is far from clear. In those situations where differences in response related to sex have been suggested, the magnitude of that difference is of questionable clinical importance. Published studies on the same class of antidepressants have produced conflicting results regarding sex effects. Conflicting results may stem from various sources, including study-related methodological differences and variance in the measurement of treatment responses.

Clearer data exists regarding sex differences in antidepressant metabolism, related to absorption, distribution, and elimination. Sex-specific variance has been identified in numerous biological functions influencing pharmacokinetic determinations, including plasma levels, production of gastric acid, gastric emptying times, levels of plasma protein, enzyme activity, and drug transport and clearance rates. However, it is not clear that such differences translate into clinical practice guidelines, as our earlier example of venlafaxine indicates.

A better understanding of the interactions between these many complex systems is probably required to understand sex differences in depression prevalence and treatment response. At the present time, no specific guidelines can be offered, thus the clinician must remain vigilant to the possibility of sex effects either on the levels of exposure achieved with therapeutic dosing or on the clinical efficacy when treating depressed patients. As is true across many types of pharmacotherapy for psychiatric disorders, available guidance provides only a framework for the use of antidepressant pharmacotherapy for the practicing clinician rather than a codified set of instructions applicable to practice. ❑

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