One of the elusive goals of pharmacotherapy is the ability to identify the relevant characteristics of a patient with a particular disorder in such a way as to permit selection of the best pharmacological agent: the medication with the greatest likelihood of effectiveness and the least likelihood of adverse or undesirable effects. Despite the considerable number of treatments in our psychotherapeutic armamentarium, any individual treatment applied to a group of persons with a given disorder will leave an unacceptably high percentage nonresponsive, again consequent to lack of efficacy or inability to tolerate the treatment. To increase the odds of therapeutic success, it is incumbent on clinicians to consider the multitude of factors that may influence response to a particular medication, eg, prior response to that medication, family history of response, family history of psychiatric disorders, tolerance of side effects, personality style, historical factors (eg, history of hypomania or suicide attempts), symptom constellation (eg, atypical symptoms), and coincident medical problems (eg, hepatic dysfunction). An additional factor that increasingly may inform treatment decisions is sex. The following article will review both the theoretical evidence for, and the practical demonstrations of, the impact of gender and sex steroids on the response to treatment.

**The sexually dimorphic brain**

Two papers in the 1950s and 1960s were critical in demonstrating that the brain, like the gonads, was sexually dimorphic. First, Phoenix et al showed that prenatal exposure of a female guinea pig to testosterone resulted in masculinization and defeminization of behavior upon reexposure to testosterone in adulthood. This ability of gonadal steroids, when administered perinatally, to change the repertoire of adult behavioral response to the same steroid—a process Phoenix et al called “organization”—
showed that the parts of the brain mediating sex-specific behavior were both developmentally plastic and distinct (ie, different across sexes). The existence of sex-dependent structural differences in the brain was subsequently confirmed by Pfaff, who showed both gross and cellular differences between sexes, with the dimorphisms altered by perinatal castration.2 There followed a number of papers in the 1970s amplifying these findings.3-6 In addition to the neuroanatomical differences (size of brain nuclei, neuritic arborization patterns, and synapse formation), sexual differences were observed in the response to stimuli, with Rainbow et al7 demonstrating more robust progesterone receptor induction by estrogen in the brains of females. Two processes, then, appear to underlie sexual dimorphisms in the response to pharmacological agents: the neuromodulatory actions of gonadal steroids; and sex-dependent differences that are independent of ambient gonadal steroid levels.

**Neuromodulatory effects**

The intracytoplasmic/intranuclear receptors for gonadal steroids are transcription factors that bind to enhancer elements to regulate the transcription of a wide range of genes. These receptors, when activated by gonadal steroids, can also interact with coregulatory proteins called cointegrators (eg, CBP [cAMP response element binding protein–binding protein]/GRIP [glucocorticoid receptor–interacting protein]), permitting the gonadal steroids to regulate genes that possess certain enhancer elements (eg, AP1 [activator protein–1]) even in the absence of classical hormone response elements. By these means, gonadal steroids modify the expression of neurotransmitters/neuropeptides (eg, serotonin [5-hydroxytryptamine, 5-HT] by affecting tryptophan hydroxylase; γ-aminobutyric acid [GABA] by affecting glutamic acid decarboxylase; acetylcholine by affecting choline acetyltransferase; endorphin; and oxytocin), their receptors (eg, 5-HT1A, 5-HT2A, endorphin receptor, and oxytocin receptor), receptor conformation (eg, GABA receptor), neurotransmitter reuptake (eg, serotonin transporter [SERT]), and postreceptor signal transduction (eg, Gαi). In addition to these “genomic” mechanisms (in which the activated hormone receptor plays a direct role in the modification of genomic activity), gonadal steroids exert what has been found to be an ever-increasing number of “nongenomic” actions, effects that occur in seconds to minutes (compared with the much longer times required for genomic effects) and that, in many instances, are initiated at the cell membrane without the requirement for diffusion of the hormone into the cell. These nongenomic effects include modulation of ion channels (eg, calcium, potassium) and activation of signal transduction cascades (eg, ERK [extracellular signal–regulated kinase] or Akt [protein kinase B]). As virtually all psychotropic drugs act via modulation of neurotransmitter-gated ion channels or signal transduction systems, sex-related differences in gonadal steroid levels would be expected to produce different responses to the same psychotropic agents. (Early support for this hypothesis was provided by Kendall et al,8 who showed that one of the expected neuromodulatory effects of imipramine—downregulation of the 5-HT2 receptor—occurred in vitro only in the presence of estradiol.)

**Gonadal steroid–independent, sex-dependent differences in response**

While it is tempting to assume that sex-related differences in response simply reflect exposure to different levels of gonadal steroids, both in vivo and in vitro studies suggest the inadequacy of this inference. Following up their demonstration of dimorphisms in estrogen-induced progesterone receptors,7 McEwen and colleagues8 demonstrated that estradiol increased choline acetyltransferase activity in the diagonal band of castrated females and decreased it in castrated males. While there are some sex-related differences in the distribution of estradiol and gonadal steroid receptors, these cannot explain the large differences in response observed in this study. Consequently, the authors suggested that sex may alter the response to the same biological stimulus. Additionally, in vitro studies have shown similar sex-dependent differences in the responses of cells in culture (and hence isolated from circulating steroid levels). These differences include a greater response seen in one sex,
the presence of response in one sex only, or opposite effects across sexes.\textsuperscript{10,11} (Zhang et al, unpublished data). It appears, therefore, that at a cellular level, the response to a pharmacological stimulus may differ in males and females, even when there are no differences in the levels of gonadal steroids to which they are exposed.

\textbf{Sexual dimorphisms in pharmacokinetics and metabolism}

A patient may not respond to a medication for multiple reasons: the levels are too low, the levels are too high (either falling outside of a therapeutic window or causing side effects that compromise tolerance of the medication or compliance), or the biochemical changes induced by the medication are ineffective. Sex may contribute to each of these reasons by modifying pharmacokinetics (reasons one and two) or pharmacodynamics (reason three).

\textbf{Pharmacokinetics}

In order for a drug to work, it must be available at the relevant site of action, a process that involves absorption from the portal of entry and regulation of the concentration of the active moiety in the relevant tissue by binding proteins, volume of distribution, and metabolism. Potentially, each of these may be modified by sex.

\textbf{Absorption}

The absorption of a drug depends on multiple factors related to the characteristics of the drug and the gastrointestinal (GI) environment. These include the lipophilicity, $pK_a$, and molecular weight of the drug, and the acidity of and transit time in the stomach and intestine. Sex differences in both gastric acidity and GI transit time have been reported. Several studies\textsuperscript{12-15} observed decreased gastric acid secretion in women compared with men, although other and more recent studies failed to observe these differences.\textsuperscript{16-18} While the positive studies, in general, had larger sample sizes, they are also notable for having been conducted outside of the USA and may, therefore, also reflect ethnic differences. The consequence of decreased acidity, if it occurs, would be to alter (usually increase) the efficiency of the absorption of drugs, as a function of their $pK_a$, and to decrease their degradation. In general, GI transit time is reported as slower in women,\textsuperscript{19,20} albeit inconsistently.\textsuperscript{21} While longer GI transit time would be expected to increase drug absorption by slowing transit in the small bowel where most drug absorption occurs,\textsuperscript{22} increased (longer) GI transit time (particularly for solids) has most consistently been observed in the stomach in women.\textsuperscript{19,20,23-32} which would decrease absorption (consequent to increased degradation). (In fact, the majority of studies do not find sex-related differences in the small intestine transit time.) Similarly, while observed sex differences in gastric acidity would increase drug absorption in women, differences in GI transit should decrease drug absorption. This introduces what is perhaps the major confound in efforts to determine the effect of sex on drug absorption in particular and pharmacokinetics in general, namely the often opposing actions of sex on the multiple physiological steps that determine circulating plasma concentrations of a drug.

\textbf{Distribution}

\textbf{Binding proteins}

The extent to which a drug is bound to carrier proteins can influence its disposition within the body, such that lower unbound (free) drug levels lead to more restricted distribution outside the plasma space and potentially decreased drug effectiveness.\textsuperscript{33} Albumin, one of the major drug transport proteins, is not affected by either sex or gonadal steroids.\textsuperscript{34} However, at least one binding protein, $\alpha_1$-acid glycoprotein (AAG), may be lower in women\textsuperscript{35-37} (but see also reference 38) and is decreased by estradiol,\textsuperscript{35,39} an effect which should increase the proportion of free drug.\textsuperscript{34,40} Drugs bound by AAG include amitriptyline, chlorpromazine, desipramine, imipramine, doxepin, nortriptiline, olanzepine, reboxetine, thioridazine, and triazolam.\textsuperscript{41} Disagreement regarding the existence of a sex difference in circulating AAG levels could be a result of the small numbers of subjects studied and the failure to control for menopause or for menstrual cycle phase. However, comparable free (active) levels of probe drugs have been observed among individuals with different levels of AAG, suggesting that these differences may have minimal clinical impact.\textsuperscript{32-41}

\textbf{Volume of distribution}

As with absorption and protein binding, the volume of distribution will be determined by both drug-dependent and drug-independent factors, the former including the
Pharmacological aspects

PKₐ and lipophilicity of the drug, and the latter including vascular and tissue volumes and the proportion of body fat. Women have an increased fat-to-lean body mass ratio⁴⁶-⁴⁷ and hence show a greater distribution of fat-soluble drugs⁴⁸ (eg, diazepam). Once again, the clinical impact of the dimorphism in fat content is far from easy to predict. While blood levels of a drug may decrease due to increased volume of distribution, the half-life of the drug may be prolonged due to increased retention in body fat, which effectively serves as a drug reservoir. Additionally, the proportion of body fat tends to increase with age and increases disproportionately (faster and greater) in women, suggesting that some sex-related differences in drug distribution would increase with age. Sex differences in body weight also need to be considered when conducting studies on sex differences in pharmacokinetics. Since males tend to weigh more than females and have larger bodies, some apparent sex differences might actually be due to size differences. This is especially relevant for studies that administer the same dose of a drug to all subjects. Many past pharmacokinetic studies failed to control for body weight; consequently, reported sex differences must be examined critically, as they may be artifactual.

Metabolism

As the oxidation and reduction of most drugs is carried out by the cytochrome P450 (CYP) enzymes, sexual dimorphisms in the activities (or levels) of these enzymes could underlie sexual dimorphisms in the plasma levels of drugs achieved following a given dose of medication. Five isoymes from three families of CYP enzymes are the most widely studied and the most relevant for the metabolism of drugs in the psychiatric armamentarium: CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP1A2. The by now familiar confounds loom large in the assessment of the effects of sex on the activities of these enzymes. For example, the clearance of theophylline and caffeine, substrates for CYP1A2, is slower in young women than in men, suggesting increased activity in men.⁴⁰-⁵⁶ However, theophylline and caffeine, like most drugs, are metabolized by multiple enzymes.⁵⁷ Thus, studies using a “probe” drug to assess the activity of the CYP isoenzyme may yield spurious results due to the multiplicity of enzymatic pathways that may be involved in a drug’s metabolism. Further, while there is indirect evidence for an effect of gonadal steroids on CYP1A2 activity (because the levels of caffeine and theophylline decrease during pregnancy and with oral contraceptive [OC] use⁴⁰,⁵¹,⁵² [but not during the menstrual cycle]),⁵³ smoking has a more prominent effect,⁴⁰,⁵¹,⁵³,⁵⁶ with possible greater induction of activity in males than females.⁵⁶ Thus, sex effects may be conveyed through modulation of other influences on enzyme activity (eg, smoking or aging), as well as through direct effects of gonadal steroids. Ethnicity, in particular, plays a key role in explaining the large interindividual variation in drug metabolism, because polymorphisms in the genes for the CYP isoenzymes are expressed in varying frequencies among different ethnic populations. These polymorphic variants have been used to define three types of drug metabolizers: (i) extensive metabolizers (EM), who are homozygous or heterozygous for the wild-type gene and make up the majority of the population; (ii) poor metabolizers (PMs), who are homozygous for the mutant gene and have lower CYP enzyme expression; and (iii) ultrarapid metabolizers (UM), who have multiple copies of the wild-type gene and have significantly increased CYP enzyme expression.⁵⁶ CYP2D6 has an additional subgroup, the intermediate metabolizers (IM), who have more activity than the PMs, but less than the EMs.⁵⁶ Besides sex differences in the activity of the CYP isoenzymes, the polymorphic variants may themselves display sex-dependent differences in prevalence.

• CYP3A4. This, the most abundant hepatic CYP450 enzyme and metabolizer of 50% of all drugs, shows increased activity in women for some but not all substrates (see reference 63). On average, women have 20% to 50% greater CYP3A4 activity than men.⁵⁴,⁶⁵ Additionally, age and sex interact, so that the declining activity of CYP3A4 with age is seen more in men than in women.⁶⁵ This effect, combined with increased fat proportion in aging women and decreased oxidation in aging men,⁴⁴ suggests that older women should have markedly lower benzodiazepine levels than older men at a comparable dose (all else being equal, which, of course, it is not, eg, glomerular filtration rate [GFR] is proportional to weight and men are larger than women, thus increasing clearance in men).⁴⁴ All of the aforementioned confounds (multiple enzymatic processing of probe drugs, ethnic effects, and age) plus small sample sizes and concurrent disease apply to inferences about the effects of sex on CYP3A4 activity. When examining the possible influence of sex on CYP3A4 activity, it is important to control for ethnicity, as CYP3A4 activity is higher in Caucasians than in African-Americans,⁴⁴ and Asian women also have
lower CYP3A4 activity than Caucasian women. Finally, although sex affects CYP3A4 activity, sex steroid levels do not appear to be responsible for the observed sex difference.

**CYP1A2.** This major metabolizer of olanzapine and clomipramine is induced by smoking (as mentioned above) and ingestion of cruciferous vegetables, and is also influenced by ethnicity. African-Americans are reported to have lower CYP1A2 activity than Caucasians, and Chinese women have nonsignificantly lower activity than Caucasians. Studies are fairly consistent in demonstrating higher CYP1A2 activity in males at least in Caucasians and Chinese). Finally, while OCs clearly inhibit CYP1A2, the failure of CYP1A2 activity to change over the menstrual cycle makes the role of sex steroids in the observed sexual dimorphism in CYP1A2 activity uncertain.

**CYP2D6.** This metabolizes many psychotropic drugs of relevance to psychiatry, including most antidepressants, haloperidol, and analgesics. As noted above, in enzymes with polymorphic alleles, sex differences may occur in the proportion of PMs, as well as in the relative activity of the enzyme. No sex differences have been identified in the incidence of CYP2D6 PMs. Studies with the probe dextromethorphan found CYP2D6 activity to be higher in female EMs than among male EMs, although one study found no sex difference. Because CYP2D6 activity is increased during pregnancy, it would be expected that female sex steroids influence CYP2D6 activity. Studies across the menstrual cycle, however, do not support this hypothesis; only one study found increased CYP2D6 activity during the luteal phase using debrisoquine as the probe, while two other small studies using dextromethorphan found no changes in CYP2D6 activity over the menstrual cycle. OC use does not appear to affect CYP2D6 activity, further bolstering the argument that sex steroids are not responsible for the observed sex difference.

**CYP2C19.** This is responsible for the metabolism of an assortment of drugs, including amitriptyline, citalopram, clomipramine, phenytoin, topiramate, valproic acid, and imipramine. Age and ethnicity are factors that could potentially confound sex effects, because there is some evidence that CYP2C19 activity declines with age and Asians have a higher percentage of CYP2C19 PMs than seen among people from Europe or the Middle East. Findings from studies on sex and CYP2C19 activity are quite inconsistent, due in part to ethnic differences as well as the inclusion of users of OCs, which inhibit CYP2C19 activity.

**CYP2C9.** This accounts for about 20% of hepatic CYP enzyme activity and contributes to the metabolism of medications like phenytoin, imipramine, diazepam, and amitriptyline. While ethnicity plays a significant role in explaining observed interindividual variation in CYP2C9 metabolism, sex does not nor are there sex differences in the frequency of PMs. To summarize, multiple confounds (ethnic and age effects, smoking, body size, multiple enzymatic processing of probes, small sample sizes, etc) notwithstanding, it appears that the activity of CYP3A4 and CYP2D6 are increased in women, CYP1A2 activity is increased in men, and CYP2C9 and CYP2C19 are unaffected by sex.

**Elimination**

Following metabolic transformation, drugs are eliminated from the body via the kidneys. A few studies found lower GFR and renal blood flow in women, although the authors noted that this sex difference can be partly explained by increased muscle mass in men. Other researchers found no sex differences in GFR and renal blood flow, including two studies that controlled for weight differences. Nonetheless, the data appear to suggest slightly elevated renal function in males, leading to increased renal secretion of drugs.

In short, the myriad factors affecting drug kinetics in the body make it impossible to come to any simple conclusions about sex and pharmacokinetics and, more importantly, about the effects of sex on drug plasma levels and efficacy.

**Pharmacokinetics of psychotropic medications**

While sex can affect virtually any aspect of medication processing, there is surprisingly little evidence that sex has a major impact on actual blood levels of most psychotropic drugs. What follows is a summary of studied sex effects for benzodiazepines, antidepressants, and antipsychotics.

**Benzodiazepines**

Despite several examples of increased benzodiazepine absorption in women, almost all studies of benzodiazepine pharmacokinetics found no sex differences in
absorption. It appears, then, that sex has little, if any, influence on the absorption of benzodiazepines and is not of general clinical relevance. With distribution, the results are less clear as to whether a sex difference exists. Benzodiazepines are highly lipophilic drugs and are, therefore, preferably distributed in adipose tissue. As such, observed sex differences in drug distribution are thought to be the result of sex differences in body composition. Nonetheless, the majority of studies on benzodiazepine pharmacokinetics reveal no sex differences in distribution. The most notable exception to this observation is diazepam, studies of which have consistently found increased volume of distribution in women. Apart from diazepam, then, sex and reproductive steroids, both exogenous and endogenous, have little effect on the distribution of benzodiazepines.

While elimination was clearly not sexually dimorphic for many benzodiazepines, several studies showed mixed results, with some researchers finding sex differences in elimination rates for a particular medication and other researchers finding none. With the exception of alprazolam, which was found in one study to have faster elimination in women, most benzodiazepines are not affected by sex or have a weak tendency toward slower elimination in women. Sex also does not significantly contribute to the observed free (unbound) fraction of many benzodiazepines, but several reports suggest higher plasma levels of diazepam in women, although, again, other reports failed to observe sex dimorphisms in the free fraction of diazepam. In conclusion then, sex and sex steroid levels do not significantly affect the pharmacokinetics of most benzodiazepines. For the most part, any observed differences due to sex, menstrual cycle, or OCs are inconsistent and do not appear to be clinically significant. Finally, studies on benzodiazepine pharmacokinetics tend to be compromised by the small number of subjects studied and by the failure to control for menopausal status, smoking, and the use of other medications.

Antidepressants

For most antidepressants, there are no reported sex differences in absorption, particularly after adjustment for body weight and surface area. Similarly, most antidepressant studies do not exhibit sex-related differences in distribution, although dothiepin, trazodone, and buproprion may have increased volumes of distribution in women, suggesting that women would experience lower plasma levels when given the same dose by weight. Elimination appears unaffected by sex for many antidepressants (eg, nefazodone) and where sex differences are reported, they are usually only in one variable, ie, clearance or elimination half-life, but not both. Elimination half-life does appear to be increased in women for sertraline and, less consistently, for bupropion. When one examines the clinically relevant measure—plasma levels—most evidence suggests that sex does not influence circulating antidepressant levels (eg, nortriptyline, fluvoxamine, moclobemide, maprotiline, and trazodone). Nonetheless, several studies do suggest that women experience higher plasma levels of the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and sertraline.

Antipsychotics

Few studies have examined the effect of sex on neuroleptic pharmacokinetics. While increased absorption or higher peak concentrations have been observed in women on ziprasidone, sertindole, and fluphenazine, confounds, such as OC use, inclusion of outliers, and age-dependent phenomena compromise the generalizability of the findings. The metabolism and elimination of some antipsychotic medications (thiothixene, olanzapine, and clozapine) occur more slowly in females than in males, possibly leading to higher drug levels for a given dose, while the elimination of sertindole and ziprasidone is not sexually dimorphic. While sex differences were identified in sertindole pharmacokinetics, the authors concluded that these were not clinically relevant. Plasma levels of most neuroleptics are similar for men and women when dosed according to efficacy. An exception, however, is clozapine, the blood levels of which are 30% to 35% higher in women than in men when dosed by efficacy. Neuroleptic blood levels also do not appear to differ in men and women even at the same dose. Nonetheless, exceptions include higher olanzapine plasma levels in women, even after controlling for body mass index, and higher mean plasma levels of sertindole, which the authors attributed to a higher dose per weight, better absorption, and slower metabolism in women.

In conclusion, for neuroleptics as for antidepressants and benzodiazepines, with several notable exceptions (eg, clozapine and olanzapine), plasma levels are similar in men and women.
Pharmacodynamics

While sexual dimorphisms in pharmacokinetics alter the exposure of a tissue to the medication administered, a considerable degree of variance in the observed effect potentially resides in differences in the response of the tissue, ie, identical drug exposure of a tissue to a drug may elicit very different responses across individuals. Differences in tissue response—the pharmacodynamics—may be quite dramatic, seen, for example, in different profiles of side effects or mood destabilization induced by identical levels of gonadal steroids in different subpopulations of women.147

Antidepressants

Most studies of the effect of sex on the efficacy of antidepressants have many more female subjects than male subjects, and thus are not adequately powered. Nonetheless, although there is the possibility of reporting bias (ie, selectively publishing studies demonstrating sex differences), substantial evidence suggests that males respond better to tricyclic antidepressants (TCAs) than females. An early study of 250 depressed patients by the Medical Research Council reported that imipramine is more effective in men than in women.45 A study of 60 depressed inpatients also found that men responded better to imipramine,148 as did a 4-week study of 55 depressed inpatients treated with imipramine149 and a large study of 200 patients on imipramine.150 More recently, a study of 230 depressed patients also described imipramine therapy as more effective in men.151 However, not surprisingly, some studies failed to observe sex differences in response to TCA treatment. An 8-week, double-blind clinical trial of imipramine efficacy in 80 depressed patients found clinical improvement was not significantly related to sex152; a 6-week clinical trial of imipramine and phenelzine efficacy found no sex difference in imipramine response rate153; a study of 29 depressed inpatients found no sex difference in response after 2 weeks of nortriptyline treatment144; an open-label trial of desipramine in 118 dysthymic patients found equal numbers of men and women responded to treatment after 10 weeks156; and a 4-week study of 66 depressed inpatients found no sex difference in treatment response to imipramine.156 Several studies also suggest that women have a superior response to SSRIs. The largest study with positive findings, a double-blind clinical trial comparing response rates to sertraline or imipramine after 12 weeks of treatment in 635 depressed patients, found women responded better to sertraline, while men responded better to imipramine. Researchers also noted a sex effect in dropout rates: men were more likely to withdraw from the study if randomly assigned sertraline, while women were more likely to drop out if given imipramine.157 Similarly, while a study of 195 depressed outpatients comparing response to fluoxetine versus nortriptyline found no sex difference in study completers, an intention-to-treat analysis revealed that fluoxetine treatment led to superior results for women (due to lower drop-out rates), while men were significantly more likely to drop out of the study if randomly assigned to fluoxetine.158 A third paper presented a retrospective meta-analysis of 11 double-blind studies, which compared the efficacy of fluoxetine with that of a variety of TCAs (amitriptyline, desipramine, doxepin, imipramine, or nortriptyline) in female patients. The authors found no significant difference in the effectiveness of TCAs and fluoxetine in the treatment of depressed women, but more women completed the trial if assigned to fluoxetine.159 Finally, in a double-blind study comparing the response to imipramine versus sertraline and permitting nonresponders to switch treatment groups after 12 weeks, researchers found women tended to be overrepresented in the group that switched from imipramine to sertraline.160 From these studies, it appears that women are more likely to discontinue treatment if given a TCA, due to either increased side effects or lack of response or both, and are more likely to continue treatment if given an SSRI.

Support for the existence of sex-related differences in response to antidepressants is found in several studies showing that younger women (a presumed proxy for reproductive status) respond better to fluoxetine, while older women respond better to imipramine or maprotiline.150,153,157,161,162 Nonetheless, substantial evidence exists for the absence of sex-differences in antidepressant response,163 including two large meta-analyses,164,165 the most recent of which found no differences between men, premenopausal women, and postmenopausal women in their response to TCAs and fluoxetine.165 Despite these impressive negative findings, it is nonetheless striking how rarely we see data in the opposite direction, ie, superior response to fluoxetine in men or to TCAs in (younger) women.
While subject to limited study, it appears that women have a more favorable response to monoamine oxidase inhibitors (MAOIs). MAOIs were noted to more effectively treat atypical depression in women than in men.166 While women are more likely to report atypical symptoms,157,167 female sex was a predictor of response to MAOI treatment, while atypical depressive symptoms were not.168 A meta-analysis of numerous antidepressant studies similarly found women have a better response to MAOIs than do men.169 In contrast, however, a clinical trial comparing the efficacy of imipramine versus phenelzine in the treatment of 100 depressed patients found significantly more men than women responded to phenelzine treatment.153

The literature on the possible effects of sex on the treatment of bipolar disorder is not as extensive as that seen for treatment of depression. Sex is not a valid predictor of response to lithium treatment of bipolar disorder,169 and a retrospective study of 1548 bipolar patients treated with lithium found no sex difference in treatment response rate.170 Another study of 360 bipolar patients reported a nonsignificant superior response in women despite lower mean plasma levels of lithium.171 Data, then, while exiguous, do not suggest a meaningful difference in pharmacodynamic response to bipolar pharmacotherapy in men and women.

**Neuroleptics**

Underlying sex differences in the age of onset, course, and symptomatology of schizophrenia present difficulties when studying potential sex differences in treatment response to neuroleptic medications. Nonetheless, many studies have examined sex differences in treatment response to neuroleptics. After initial observational studies noted that females responded better to neuroleptic treatment,172 clinical trials of neuroleptic efficacy were conducted, and most confirmed that females respond better to neuroleptic treatment than do males173-181 despite comparable drug plasma levels.182 However, many of these studies were compromised by their failure to sufficiently control for sex differences in smoking, dose, weight, and severity and type of symptomatology. Several more recent studies found no sex differences in treatment response to neuroleptic medication,183-186 and two studies of neuroleptic-refractory patients showed a trend for males to respond better to clozapine treatment than females187,188 (although results from studies of neuroleptic-refractory patients might not be generalizable). The inconsistency in results regarding sex differences in treatment response to antipsychotic medication may be due to differences in choice of neuroleptic and dose. For example, in a study of 50 schizophrenic patients, females responded significantly better to clozapine treatment at 100 mg/day, but there were no sex differences in response among schizophrenic subjects randomly assigned daily doses of 300 or 600 mg/day.189 Some studies claim that female schizophrenic patients require lower doses of neuroleptics (after accounting for weight differences) than male schizophrenic patients190,191 while other studies find no significant sex difference in neuroleptic dose requirements.192-194 This contradiction could reflect differences in neuroleptics used. A study comparing chlorpromazine and fluspirilene, for example, found no sex difference in the chlorpromazine dose required to ameliorate symptoms, but males needed a significantly higher dose of fluspirilene.195 Because estrogen is hypothesized to have a neuroleptic-like effect through its modulation of dopamine receptors, a protective effect of estrogens has been invoked to explain why female schizophrenic patients have better social adjustment, fewer and less severe symptoms, and better treatment response.196 If estrogen impacts neuroleptic response, it would be expected that female response to neuroleptics would decline after menopause. A study examining this possibility found that the daily neuroleptic dose for female schizophrenia patients remained constant from age 20 to 59, with no decline in efficacy corresponding to menopause.197 In a conflicting study, however, females under age 40 were on lower neuroleptic doses than their male peers, but after age 40, the trend was reversed and female patients required higher doses than male patients over age 40.198 The overall prevalence of schizophrenia is not sexually dimorphic, but the age of onset is 3 to 6 years earlier in men than in women.199 This raises the possibility that any observed sex differences in response to neuroleptics may reflect differences in the evolution of the illness expressed at a tissue level.

**Conclusions**

There are myriad sex differences in neurobiology, affecting diverse processes from signal transduction to receptor distribution and receptor function to response to stressors. Not surprisingly, multiple effects of sex on pharmacokinetics have also been identified.200 Given the multiple steps
involved in the translation of a dose of ingested medica-
tion to its steady state plasma level, one might imagine that
the effects of sex could either summate to produce dra-
matic sex differences or balance to result in negligible dif-
ferences. While considerably more work could and should
be done to determine the role played by sex in the phar-
macokinetics of psychotropic drugs, the data collected to
date suggest that the effect is not likely to be large for most
classes of psychotropic agents. While pharmacodynamic differences are also likely to
eXist, data to date are exiguous and far from impressive.
As befits the complexity of the brain, there are likely few
instances in which sex alone comprises a large part of the
variance in the response to psychotropic medications.

Nonetheless, the practitioner must realize that, under the
right circumstances, sex may strongly influence the
response to medication, just as the serotonin transporter
genotype (5-HTTLPR) and past history of adverse life
events combine to predict depression, despite the low
predictive value of either of these factors in isolation.201
One size, undoubtedly, does not fit all, and factors related
to sex will provide the attentive careful clinician with pos-
sible explanations for an unsatisfactory therapeutic
response.

The authors gratefully acknowledge the assistance of Kristen Dancer in the
preparation of this manuscript.

REFERENCES

1. Phoenix CH, Goy RW, Gerall AA, Young WC. Organizing action of pre-
nataIy administered testosterone propionate on the tissues mediating mat-
ing behavior in the female guinea pig. Endocrinology. 1959;65:369-382.
2. Pfaff DW. Morphological changes in the brains of adult male rats after
neonatal castration. J Endocrinol. 1966;36:415-416.
3. Nottebohm F, Arnold AP. Sexual dimorphism in vocal control areas of the
songbird brain. Science. 1976;194:211-213.
4. Raisman G, Field PM. Sexual dimorphism in the preoptic area of the rat.
Science. 1971;173:731-733.
5. Raisman G, Field PM. Sexual dimorphism in the neuropil of the preoptic
area of the rat and its dependence on neonatal androgen. Brain Res.
1973;54:1-29.
6. Gorski RA, Gordon JH, Shryne JE, Southam AM. Evidence for a morpho-
logical sex difference within the medial preoptic area of the rat brain. Brain
Res. 1978;148:333-346.
7. Rainbow TC, Parsons B, McEwen BS. Sex differences in rat brain oestro-
gen and progestin receptors. Nature. 1980;300:648-649.
8. Kendall DA, Stancel GM, Enna SJ. Imipramine: effect of ovarian steroids
on modifications in serotonin receptor binding. Science. 1981;211:1183-1185.
9. Luine VN, McEwen BS. Sex differences in cholinergic enzymes of diagonal
band nuclei in the rat preoptic area. Neuroendocrinology. 1983;36:475-482.
CYP2C19 polymorphism in a North-eastern Thai population.

82. Bertilsson L. Geographical/interracial differences in polymorphic drug metabolism and drug interactions in the elderly. Eur J Clin Pharmacol. 1996;21:129-138.

83. Scripture C, Pieper J. Clinical pharmacokinetics of fluvasistan. Clin Pharmacokinet. 2001;40:263-281.

84. Tabrizi AR, Zehnbauer BA, Borecki IB, et al. The frequency and effects of cytochrome P450 (CYP) 2C9 polymorphisms in patients receiving warfarin. J Am Coll Surg. 2002;194:267-273.

85. Wesson LG. Renal hemodynamics in physiological states. Physiology of the Human Kidney. New York, NY, Grune and Stratton; 1968:96-108.

86. James GD, Sealey JE, Alderman M, et al. A longitudinal study of urinary creatinine and creatinine clearance in normal subjects. Race, sex, and age differences. Am J Hypertens. 1988;1:124-131.

87. Slack TK, Wilson DM. Normal renal function: CIN and CPAH in healthy donors before and after nephrectomy. Mayo Clin Proc. 1976;51:296-300.

88. Finney H, Newman DJ, Price CP. Adult reference ranges for serum cystatin C, creatinine and predicted creatinine clearance. Ann Clin Biochem. 2000;37:49-59.

89. Masarei JRL. Validity of corrections for creatinine excretion and creatinine clearance. N Z Med J. 1975;82:197-198.

90. Holazo AA, Winkler MB, Patel IH. Effects of age, gender and oral contraceptives on intramuscular midazolam pharmacokinetics. J Clin Pharmacol. 1988;28:1040-1045.

91. Baumgartner MG, Cautreels W, Langenbahn H. Biotransformation and pharmacokinetics of tetrazepam in man. Arzneimittelforschung Drug Res. 1984;34:724-729.

92. Kristjansson E, Thorsteinsson SB. Disposition of alprazolam in human volunteers. Differences between genders. Acta Pharm Nord. 1991;3:249-250.

93. van Steveninck AL, Wallnofer AE, Schoemaker RC, et al. A study of the effects of long-term use on individual sensitivity to temazepam and lorazepam in a clinical population. Br J Clin Pharmacol. 1997;44:267-275.

94. Smith RB, Divoll M, Gillespie WR, Greenblatt DJ. Effect of subject age and gender on the pharmacokinetics of oral triazolam and temazepam. J Clin Psychopharmacol. 1983;3:172-176.

95. Shader RI, Greenblatt DJ, Ciraulo DA, et al. Effect of age and sex on disposition of desmethyldiazepam formed from its precursor clorazepate. Psychopharmacology. 1981;75:193-197.

96. Divoll M, Greenblatt DJ, Ochs HR, Shader RI. Absolute bioavailability of oral and intramuscular diazepam: effects of age and sex. Anesth Analg. 1983;62:1-8.

97. Ochs HR, Otten H, Greenblatt DJ, Dengler HJ. Diazepam absorption: effects of age, sex, and Billroth gastrectomy. Dig Dis Sci. 1982;27:225-230.

98. Greenblatt DJ, Divoll MK, Abernethy DR, et al. Age and gender effects on chloridiazepoxide kinetics: relation to antipyrine disposition. Pharmacology. 1989;38:327-334.

99. Divoll M, Greenblatt DJ, Harmatz JS, Shader RI. Effects of age and gender on disposition of temazepam. J Pharm Sci. 1981;70:1104-1107.

100. Greenblatt DJ, Harmatz JS, Von Moltke LL, et al. Comparative kinetics and response to the benzodiazepine agonists triazolam and zolpidem: evaluation of sex-dependent differences. J Pharmacol Exp Ther. 2000;293:435-443.

101. Greenblatt DJ, Divoll M, Harmatz JS, Shader RI. Oxazepam kinetics: effects of age and sex. J Pharmacol Exp Ther. 1980;215:86-91.

102. Greenblatt DJ, Abernethy DR, Locianski A, et al. Age, Sex, and nitrazepam kinetics: relation to antipyrine disposition. Clin Pharmacol Ther. 1985;38:697-703.

103. Ochs HR, Greenblatt DJ, Friedman H, et al. Bromazepam pharmacokinetics: influence of age, gender, oral contraceptives, cimetidine, and propranolol. Clin Pharmacol Ther. 1987;41:562-570.

104. Ochs HR, Greenblatt DJ, Otten H. Disposition of oxazepam in relation to age, sex, and cigarette smoking. Klin Wochenschr. 1981;59:899-903.

105. Yeates LA, Laufen H, Rader K, Leitold M. Preliminary study of the pharmacokinetics of desmethyldiazepam administered as drops or tablets. Arzneimittelforshung. 1986;36:138-140.

106. Greenblatt DJ, Abernethy DR, Locianski A, et al. Effect of age, gender, and obesity on midazolam kinetics. Anesthesiology. 1984;61:27-35.

107. Divoll M, Greenblatt DJ. Effect of age and sex on lorazepam protein binding. J Pharm Pharm Sci. 1982;34:122-123.

108. Greenblatt DJ, Allen MD, Harmatz JS, Shader RI. Diazepam disposition determinants. Clin Pharmacol Ther. 1980;27:301-312.

109. Giles HG, Sellers EM, Naranjo CA, Frecker RC, Greenblatt DJ. Disposition of intravenous diazepam in young men and women. Eur J Clin Pharmacol. 1981;20:207-213.
110. MacLeod SM, Giles HG, Bengert B, Liu FF, Sellers EM. Age- and gender-related differences in diazepam pharmacokinetics. J Clin Pharmacol. 1979;19:15-19.

111. Kirkwood C, Moore A, Hayes P, Devane CL, Pelonero A. Influence of menstrual cycle and gender on alprazolam pharmacokinetics. Clin Pharmacol Ther. 1991;50:504-512.

112. Greenblatt DJ, Shadr RJ, Franke K, et al. Kinetics of intravenous chlorzoxepoxide: sex differences in drug distribution. Clin Pharmacol Ther. 1977;22:893-903.

113. Roberts RK, Desmond PV, Wilkinson GR, Schenker S. Disposition of chlorzoxepoxide: sex differences and effects of oral contraceptives. Clin Pharmacol Ther. 1979;25:826-831.

114. Routledge PA, Stargell WW, Kitchell BB, Barchowsky A, Shand DG. Sex-related differences in the plasma protein binding of lignocaine and diazepam. Br J Clin Pharmacol. 1981;11:245-250.

115. Giles HG, Roberts EA, Orrego H, Sellers EM. Disposition of intravenous propylthiouracil. J Clin Pharmacol. 1981;21:466-471.

116. Stoehr GP, Cosenza PD, Juhl RP, et al. Effect of oral contraceptives on triazolam, temazepam, alprazolam, and lorazepam kinetics. Clin Pharmacol Ther. 1984;36:683-690.

117. Kroboth PD, Smith RB, Stoehr GP, Juhl RP. Pharmacodynamic evaluation of the benzodiazepine/oral contraceptive interaction. Clin Pharmacol Ther. 1985;38:525-532.

118. McAuley JW, Friedman CI. Influence of endogenous progesterone on age- and gender-related differences in the plasma protein binding of lignocaine and diazepam. Pharmacol Ther. 1985;38:525-532.

119. Rukstalis M, de Wit H. Effects of triazolam at three phases of the men- strual cycle. Clin Pharmacol Ther. 1999;19:450-458.

120. Kamimori GH, Sirisuth N, Greenblatt DJ, Eddington ND. The influence of the menstrual cycle on triazolam and indocyanine green pharmacokinetics. J Clin Pharmacol. 2000,40:739-744.

121. Bayliss PF, Case DE. Blood level studies with viloxazine hydrochloride in man. Br J Clin Pharmacol. 1975;2:209-214.

122. Maguire KP, Norman TR, McIntyre I, Burrows GD. Clinical pharmacokinetics of dothiepin single-dose kinetics in patients and prediction of steady-state concentrations. Clin Pharmacokinet. 1983;8:179-185.

123. Barbhaiya RH, Shukla UA, Natarajan CS, et al. Single- and multiple-dose pharmacokinetics of nefazodone in patients with hepatic cirrhosis. Clin Pharmacol Ther. 1995;58:390-398.

124. Greenblatt DJ, Friedman H, Burstein ES, et al. Trazodone kinetics: effect of age, gender, and obesity. Clin Pharmacol Ther. 1987;42:193-200.

125. lacharte G, Piva C, Riche C, et al. Single-dose pharmacokinetics of amineptine and of its main metabolite in healthy young adults. Fundam Clin Pharmacol. 1989;3:19-26.

126. Vandel B, Vandel S, Jounet JM, Blum D. Pharmacokinetics of viloxazine and its main metabolite in healthy young adults. Eur J Drug Metab Pharmacokinet. 1989;3:19-26.

127. Stewart JJ, Berkel HJ, Parish RC, et al. Single-dose pharmacokinetics of bupropion in adolescents: effects of smoking status and gender. J Clin Pharmacol. 2001;41:770-778.

128. Barbhaiya RH, Shukla UA, Greene DS. Single-dose pharmacokinetics of nefazodone in healthy young and elderly subjects and in subjects with renal or hepatic impairment. Eur J Clin Pharmacol. 1995;49:221-228.

129. Barbhaiya RH, Buch AB, Greene DS. A study of the effect of age and gender on the pharmacokinetics of nefazodone after single and multiple doses. J Clin Pharmacol. 1996;16:19-25.

130. Ronfeld RA, Tremaine LM, Wilner KD. Pharmacokinetics of sertraline and its N-demethyl metabolite in elderly and young male and female volun-teers. Clin Pharmacokinet. 1997;32:22-30.

131. Winer KD, Tensfeldt TG, Baris B, et al. Single- and multiple-dose pharmacokinetics of ziprasidone in healthy young and elderly volunteers. Br J Clin Pharmacol. 2000;49:155-205.

132. Simpson GM, Yadalam KG, Levinson DF, et al. Single-dose pharmacokinetics of fluphenazine after fluphenazine decanoate administration. J Clin Psychopharmacol. 1990;10:417-421.

133. Wong SL, Cao G, Mack RJ, Gramman GM. Pharmacokinetics of sertin-dole in healthy young and elderly male and female subjects. Clin Pharmacol Ther. 1997;62:157-164.

134. Kelly DL, Conley RR, Taminga CA. Differential olanzapine plasma concentrations by sex in a fixed-dose study. Schizophr Res. 1999;40:101-104.

135. Jerling M, Merle Y, Mentre F, Mallet A. Population pharmacokinetics of clozapine evaluated with the nonparametric maximum likelihood method. Br J Clin Pharmacol. 1997;44:447-453.

136. Ereshefsky L, Saklad SR, Watanabe MD, Davis CM, Jann MW. Thiothixene pharmacokinetic interactions: a study of hepatic enzyme inducers, clearance inhibitors, and demographic variables. J Clin Psychopharmacol. 1999;37:306-311.

137. Callaghan JT, Bergstrom RF, Ptak LR, Beasley CM. Olanzapine. Pharmacokinetic and pharmacodynamic profile. Clin Pharmacokinet. 1999;37:177-193.

138. Lane HY, Chang YC, Chang WH, et al. Effects of gender and age on plasma levels of clozapine and its metabolites: analyzed by critical statistics. J Clin Psychiatry. 1999;60:36-40.

139. Haring C, Meele U, Humpel C, et al. Dose-related plasma levels of cloza-pine: influence of smoking behaviour, sex and age. Psychopharmacology (Berl). 1989;99(suppl):S38-S40.

140. Jann MW, Crabtree BL, Pitts WM, Lam YWF, Carter JG. Plasma alpha-one acid glycoprotein and haloperidol concentrations in schizophrenic patients. Neuropsychobiology. 1997;36:32-36.

141. Fabrazzo M, Esposito G, Fusco R, Maj M. Effect of treatment on plasma levels of clozapine and N-desmethyloclozapine in men and women. Psychopharmacology, 1996;124:197-200.

142. Kelly SJ, Ostrowski NL, Wilson MA. Gender differences in brain and behavior: hormonal and neural bases. Pharmacol Biochem Behav. 1999;64:655-664.

143. Schmidt PJ, Nieman LK, Danaceau MA, Adams LF, Rubinow DR. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. N Engl J Med. 1998;338:209-216.

144. Glassman AH, Perel JM, Shostak M, Kantor SJ, Fleis J. Clinical implications of imipramine plasma levels for depressive illness. Arch Gen Psychiatry. 1977;34:197-204.

145. Wilson IC, Rabon AM, Buffalo WJ. Imipramine therapy in depressive syn-dromes: prediction of therapeutic outcome. Psychosomatics. 1967;8:203-207.

146. Raskin A. Age-sex differences in response to antidepressant drugs. J Nerv Ment Dis. 1974;159:120-130.

147. Fischel JS. Rodent study of age-related differences in hippocampal binding and morphine antagonism by octapeptide analogs of somatostatin. Neuropharmacology. 1964;6:472-474.

148. Asberg M, Cronholm B, Sjoqvist F, Tuck D. Relationship between plasma concentrations by sex in a fixed-dose study. J Clin Psychopharmacol. 1993;99(suppl):S38-S40.

149. Resiby N, Gram LF, Bøch P, et al. Imipramine: clinical effects and phar-macokinetic variability. Eur J Clin Pharmacol. 1999;40:101-104.

150. Resiby N, Gram LF, Bøch P, et al. Imipramine: clinical effects and phar-macokinetic variability. Psychopharmacology. 1977;54:263-272.

151. Kernstine SG, Schatzberg AF, Thase ME, et al. Gender differences in treatment response to sertraline versus imipramine in chronic depression. Am J Psychiatry. 2000;157:1445-1452.

152. Joyce PR, Mulder RL, Luty SE, et al. Patterns and predictors of remis-sion, response and recovery in major depression treated with fluoxetine or nortriptyline. Aust N Z J Psychiatry. 2002;36:384-391.

153. Lewis-Hall FC, Wilson MG, Tepner RG, Koke SC. Fluoxetine vs tricyclic antidepressants in women with major depressive disorder. J Womens Health. 1997;6:337-343.
160. Thase ME, Rush AJ, Howland RH, et al. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. Arch Gen Psychiatry. 2002;59:233-239.

161. Frank E, Thase ME, Spanier CA, Reynolds CF, III, Kupfer DJ. Gender-specific response to depression treatment. J Geriatr Spec Med. 1999;2:40-44.

162. Martenyi J, Dossenbach M, Mraz K, Metcalfe S. Gender differences in the efficacy of fluoxetine and maprotiline in depressed patients: a double-blind trial of antidepressants with serotonergic or norepinephrine reuptake inhibition profile. Eur Neuropsychopharmacol. 2001;11:227-232.

163. Burns RA, Lock T, Edwards DR, et al. Predictors of response to amine-specific antidepressants. J Affect Disord. 1995;35:97-105.

164. Etsuah AR, Huang H, Thase ME. Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo. J Clin Psychiatry. 2001;62:869-877.

165. Quitkin FM, Stewart JW, McGrath PJ, et al. Are there differences between women's and men's antidepressant responses? Am J Psychiatry. 2002;159:1848-1854.

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

167. Morales AJ, Nolan JJ, Nelson JC, Yen SSC. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. J Clin Endocrinol Metab. 1994;78:1360-1367.

168. Davidson JR, Giller EL, Zisook S, Helms MJ. Predictors of response to monoamine oxidase inhibitors: do they exist? Eur Arch Psychiatry Clin Neurosci. 1991;241:181-186.

169. Secunda SK, Katz MM, Swann A, et al. Mania. Diagnosis, state measurement and prediction of treatment response. J Affect Disord. 1985;8:113-121.

170. Vigueria AC, Tondo L, Baldessarini RJ. Sex differences in response to lithium treatment. Am J Psychiatry. 2000;157:1509-1511.

171. Vigueria AC, Baldessarini RJ, Tondo L. Response to lithium maintenance treatment in bipolar disorders: comparison of women and men. Bipolar Disord. 2001;3:245-252.

172. Denber HCB, Bird EG. Chlorpromazine in the treatment of mental illness. IV: final results with analysis of data on 1523 patients. Am J Psychiatry. 1957;113:972-978.

173. Chouinard G, Annable L. Pimozide in the treatment of newly admitted schizophrenic patients. Psychopharmacology. 1982;76:13-19.

174. Hogarty GE, Goldberg SC, Scholler NR. Drug and sociotherapy in the aftercare of schizophrenic patients. III. Adjustment of nonrelapsed patients. Arch Gen Psychiatry. 1974;31:609-618.

175. Goldberg SC, Scholler NR, Davidson EM, Kayce MM. Sex and race differences in response to drug treatment among schizophrenics. Psychopharmacologia. 1966;9:31-47.

176. Kolakowska T, Williams AO, Jambor K, Ardern M. Schizophrenia with good and poor outcome. Ill. Neurological "soft" signs, cognitive impairment and their clinical significance. Br J Psychiatry. 1985;146:348-357.

177. Meltzer HY, Busch DA, Fang VS. Serum neuroleptic and prolactin levels in schizophrenic patients and clinical response. Psychiatry Res. 1983;9:271-283.

178. Robinson DG, Woerner MG, Alvir JM, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. Am J Psychiatry. 1999;156:544-549.

179. Goldstein JM, Cohen LS, Horton NJ, et al. Sex differences in clinical response to olanzapine compared with haloperidol. Psychiatry Res. 2002;110:27-37.

180. Goldstein MJ, Rodnick EH, Evans JR, May PR, Steinberg MR. Drug and family therapy in the aftercare of acute schizophrenics. Arch Gen Psychiatry. 1978;35:1169-1177.

181. Lieberman J, Jody D, Geisler S, et al. Time course and biologic correlates of treatment response in first-episode schizophrenia. Arch Gen Psychiatry. 1993;50:369-376.

182. Szymanski S, Lieberman JA, Alvir JM, et al. Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic-patients. Am J Psychiatry. 1995;152:698-703.

183. Glick M, Mazure CM, Bowers MB, Zigler E. Premorbid social competence and the effectiveness of early neuroleptic treatment. Compr Psychiatry. 1993;34:396-401.

184. Pinals DA, Malhotra AK, Missar CD, Pickard D, Breier A. Lack of gender differences in neuroleptic response in patients with schizophrenia. Schizophr Res. 1996;22:215-222.

185. Labelle A, Light M, Dunbar F. Risperidone treatment of outpatients with schizophrenia: no evidence of sex differences in treatment response. Can J Psychiatry. 2001;46:534-541.

186. Jeste DV, Linnoila M, Wagner RL, Wyatt RJ. Serum neuroleptic concentrations and tardive dyskinesia. Psychopharmacology. 1982;76:377-380.

187. Szymanski S, Lieberman J, Pollack S, et al. Gender differences in neuroleptic nonresponsive clozapine-treated schizophrenics. Biol Psychiatry. 1996;39:249-254.

188. Lieberman JA, Kane JM, Safferman AZ, et al. Predictors of response to clozapine. J Clin Psychiatry. 1994;55:126-128.

189. Simpson GM, Josiassen RC, Stanila JK, et al. Double-blind study of clozapine dose response in chronic schizophrenia. Am J Psychiatry. 1999;156:1744-1750.

190. Young MA, Meltzer HY. The relationship of demographic, clinical, and outcome variables to neuroleptic treatment requirements. Schizophr Bull. 1980;6:88-101.

191. Perry PJ, Lund BC, Sanger T, Beasley C. Olanzapine plasma concentrations and clinical response: acute phase results of the North American Olanzapine Trial. J Clin Psychopharmacol. 2001;21:14-20.

192. Zito JM, Craig TJ, Wandling J, Siegel C. Pharmacoepidemiology in 136 hospitalized schizophrenic patients. Am J Psychiatry. 1987;144:778-782.

193. Maghauri W, Goff DC, Amico E. Relationship of gender and menstrual status to symptoms and medication side effects in patients with schizophrenia. Psychiatry Res. 1998;77:159-166.

194. Jeste DV, Lindamer LA, Evans J, Lacro JP. Relationship of ethnicity and gender to schizophrenia and pharmacology of neuroleptics. Psychopharmacol Bull. 1996;32:243-251.

195. Chouinard G, Annable L, Steinberg S. A controlled clinical trial of fluspirilene, a long-acting injectable neuroleptic, in schizophrenic patients with acute exacerbation. J Clin Psychopharmacol. 1986;6:21-26.

196. Riecher-Rossler A, Hafner H. Schizophrenia and oestrogens—is there an association? Eur Arch Psychiatry Clin Neurosci. 1993;242:323-328.

197. Salokangas RK. Gender and the use of neuroleptics in schizophrenia. Further testing of the oestrogen hypothesis. Schizophr Res. 1995;16:7-16.

198. Seeman MV. Interaction of sex, age and neuroleptic dose. Compr Psychiatry. 1983;24:125-128.

199. Riecher-Rossler A, Hafner H. Gender aspects in schizophrenia: bridging the border between social and biological psychiatry. Acta Psychiatr Scand Suppl. 2000;102:58-62.

200. Committee on Understanding the Biology of Sex and Gender Differences. Exploring the Biological Contributions to Human Health: Does Sex Matter? Washington, DC: National Academy Press; 2001:1-8.

201. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 2003;301:291-293.