Sex-dependent modulation of treatment response

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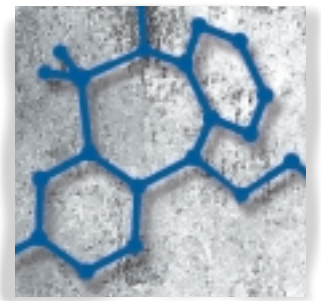

The response to a psychotropic medication reflects characteristics of both the medication and the substrate, ie, the individual receiving the medication. Sex is an individual characteristic that influences all elements of the pharmacokinetic process—absorption, distribution, metabolism, and elimination. The effects of sex on these components of the pharmacokinetic process often counterbalance one another to yield minimal or varying sexual differences in blood levels achieved. However, sex also appears to influence pharmacodynamics, the tissue response to a given level of medication. Consideration by the practitioner of sex as a possible contributing factor to treatment nonresponse will enhance the efficacy and precision of clinical interventions.

© 2004, LLS SAS *Dialogues Clin Neurosci*. 2004;6:39-51.

Keywords: *sex; psychotropic drug; pharmacokinetics; antidepressant; neuroleptic; pharmacodynamics*

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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[1] 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"—

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Selected abbreviations and acronyms

AAG	*α_1-acid glycoprotein*
CYP	*cytochrome P450*
EM	*extensive metabolizer*
GFR	*glomerular filtration rate*
MAOI	*monoamine oxidase inhibitor*
OC	*oral contraceptive*
PM	*poor metabolizer*
SSRI	*selective serotonin reuptake inhibitor*
TCA	*tricyclic antidepressant*

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 al[7] 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-HT_{1A}, 5-HT_{2A}, endorphin receptor, and oxytocin receptor), receptor conformation (eg, $GABA_A$ receptor), neurotransmitter reuptake (eg, serotonin transporter [SERT]), and postreceptor signal transduction (eg, $G_{\propto i}$). 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-HT_2 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 colleagues[9] 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[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.

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).

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.

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[12-15] observed decreased gastric acid secretion in women compared with men, although other and more recent studies failed to observe these differences.[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,[19,20] albeit inconsistently.[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,[22] increased (longer) GI transit time (particularly for solids) has most consistently been observed in the stomach in women,[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.

Distribution

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.[33] Albumin, one of the major drug transport proteins, is not affected by either sex or gonadal steroids.[34] However, at least one binding protein, α_1-acid glycoprotein (AAG), may be lower in women[35-37] (but see also reference 38) and is decreased by estradiol,[35,39] an effect which should increase the proportion of free drug.[34,40] Drugs bound by AAG include amitriptyline, chlorpromazine, desipramine, imipramine, doxepin, nortriptyline, olanzepine, reboxetine, thioridazine, and triazolam.[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.[42-44]

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

pK_a 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 ratio[45-47] and hence show a greater distribution of fat-soluble drugs[48] (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 isozymes 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.[49-56] 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] use[49,51,52] [but not during the menstrual cycle]),[58] smoking has a more prominent effect,[49,51,53,59-62] with possible greater induction of activity in males than females.[54] 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.[63] CYP2D6 has an additional subgroup, the intermediate metabolizers (IM), who have more activity than the PMs, but less than the EMs.[64] 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.[63,65] 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,[34] 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).[34] 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.[66] Finally, although sex affects CYP3A4 activity, sex steroid levels do not appear to be responsible for the observed sex difference.[67-69]

- *CYP1A2*. This major metabolizer of olanzapine and clomipramine is induced by smoking[59,60] (as mentioned above) and ingestion of cruciferous vegetables,[51] and is also influenced by ethnicity. African-Americans are reported to have lower CYP1A2 activity than Caucasians,[50] and Chinese women have nonsignificantly lower activity than Caucasians.[70] Studies are fairly consistent in demonstrating higher CYP1A2 activity in males[49,52] (at least in Caucasians and Chinese). Finally, while OCs clearly inhibit CYP1A2,[49,51-53,62,71,72] the failure of CYP1A2 activity to change over the menstrual cycle[58,68] 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.[65] As noted above, in enzymes with polymorphic allelles, 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,[73-75] although one study found no sex difference.[68] Because CYP2D6 activity is increased during pregnancy,[76] 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,[77] while two other small studies using dextromethorphan found no changes in CYP2D6 activity over the menstrual cycle.[68,73] OC use does not appear to affect CYP2D6 activity,[78] 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.[63] Age and ethnicity are factors that could potentially confound sex effects, because there is some evidence that CYP2C19 activity declines with age[79] and Asians have a higher percentage of CYP2C19 PMs than seen among people from Europe or the Middle East.[80-82] 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.[74,75]
- *CYP2C9*. This accounts for about 20% of hepatic CYP enzyme activity and contributes to the metabolism of medications like phenytoin, imipramine, diazepam, and amitriptyline.[63] While ethnicity plays a significant role in explaining observed interindividual variation in CYP2C9 metabolism, sex does not,[63,83] nor are there sex differences in the frequency of PMs.[84]

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,[85,86] 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,[87] including two studies that controlled for weight differences.[88,89] 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.[90-100] 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.[90-92,94,99,101-107] The most notable exception to this observation is diazepam, studies of which have consistently found increased volume of distribution in women.[96,97,108] 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.[90-92,94,99-101,103-107,109-113] With the exception of alprazolam, which was found in one study to have faster elimination in women,[92] 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,[104,114] although, again, other reports failed to observe sex dimorphisms in the free fraction of diazepam.[108,115] 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.[69,90,103,111,116-120] 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.[121-127] Similarly, most antidepressant studies do not exhibit sex-related differences in distribution, although dothiepin,[122] trazodone,[124] and bupropion[128] 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[129]) and where sex differences are reported, they are usually only in one variable, ie, clearance or elimination half-life, but not both.[130] Elimination half-life does appear to be increased in women for sertraline[131,132] and, less consistently, for bupropion.[128,133] 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.[132,134]

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,[135-137] 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.[135,137-141] While sex differences were identified in sertindole pharmacokinetics, the authors concluded that these were not clinically relevant.[137] 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.[142-145] 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,[146] and higher mean plasma levels of sertindole, which the authors attributed to a higher dose per weight, better absorption, and slower metabolism in women.[137]

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 imipramine[149] 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 sex[152]; a 6-week clinical trial of imipramine and phenelzine efficacy found no sex difference in imipramine response rate[153]; a study of 29 depressed inpatients found no sex difference in response after 2 weeks of nortriptyline treatment[154]; an open-label trial of desipramine in 118 dysthymic patients found equal numbers of men and women responded to treatment after 10 weeks[155]; 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.[165] 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 males,[173-181] 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 females[187,188] (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 patients,[190,191] 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 medication to its steady state plasma level, one might imagine that the effects of sex could either summate to produce dramatic sex differences or balance to result in negligible differences. While considerably more work could and should be done to determine the role played by sex in the pharmacokinetics 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 possible explanations for an unsatisfactory therapeutic response. ❑

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

La modulación de la respuesta al tratamiento dependiente del sexo

La respuesta a los fármacos psicotrópicos refleja las características tanto de la medicación como del sustrato, es decir, del sujeto que recibe el fármaco. El sexo es una característica individual que influye en todos los elementos del proceso farmacocinético: absorción, distribución, metabolización y eliminación. Los efectos del sexo en estos componentes del proceso farmacocinético a menudo se compensan unos con otros produciendose diferencias mínimas o variables entre los dos sexos en los niveles plasmáticos alcanzados. Sin embargo, el sexo también parece influir en la farmacodinámica, la respuesta del tejido a una determinada concentración del fármaco. El hecho que el clínico considere el sexo como un posible factor que contribuye a la falta de respuesta terapéutica, aumentará la eficacia y precisión de las intervenciones clínicas.

Modulation sexe-dépendante de la réponse au traitement

La réponse à un médicament psychotrope reflète les caractéristiques du médicament et du substrat, c'est-à-dire le sujet recevant le médicament. Le sexe est une caractéristique individuelle qui influe sur tous les éléments du processus pharmacocinétique – absorption, distribution, métabolisme et élimination. Les effets du sexe sur ces composantes du processus pharmacocinétique s'équilibrent souvent l'un l'autre et n'entraînent de ce fait que des différences liées au sexe minimales ou variables dans les concentrations sanguines obtenues. Cependant, le sexe semble aussi influer sur la pharmacodynamique, la réponse tissulaire à une concentration donnée de médicament. La prise en compte du sexe par le médecin en tant que facteur pouvant contribuer à la non-réponse au traitement augmentera l'efficacité et la précision des interventions cliniques.

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