CME

The Pharmacologic Treatment of Depression: Is Gender a Critical Factor?

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Background: In the medical literature, there is a lack of sex-specific information regarding the efficacy, metabolism, and side effects associated with psychopharmacologic treatment. In part, this lack results from the historic underinclusion of women in clinical trials during early drug development, but it also occurs because investigators of treatment and metabolic studies do not routinely analyze results according to sex. In 1993, the U.S. Food and Drug Administration (FDA) announced changes that encourage the inclusion of women in early pharmacokinetic studies and emphasize the need for subset analyses using sex and age parameters. In conjunction with advances in basic science regarding drug metabolism, these modifications have led to modest increases in information regarding sex differences in drug metabolism and efficacy. In this article, current information regarding potential sex differences in the pharmacotherapy of major depressive disorder is reviewed.

Data Sources: A MEDLINE search was conducted using the terms *antidepressants, sex-factors, gender differences,* and *women* for the years 1966 to 2000.

Data Synthesis and Conclusions: There are data supporting sex differences in the activity of various antidepressant-metabolizing enzymes. However, there is a paucity of investigation regarding how these differences might translate into differences in clinical efficacy. Notably, there is little work using existing databases to perform the subgroup analyses recommended by the FDA. The widespread dissemination of such work is needed, and, if conducted, investigations in this area have the potential to enhance psychopharmacologic treatment for both men and women.

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In a landmark report presented 20 years ago, Kinney and colleagues[1] reviewed articles published in 3 premier pharmacology journals during the prior year. Their survey indicated that only 12% of phase 1 and 21% of phase 2 studies included women. The authors elegantly stated the problem: because many compounds are not adequately tested in women during the early stages of development, "the most accurate and complete information about how best to use drugs in women will not be available."[1(p498)] In essence, the authors were concerned that some medications might not be as useful in women as in men or that the dosages necessary for optimal efficacy in women might not be determined if the majority of early research were conducted on men. Concern about the inclusion of both women and men in clinical trials was also found in a 1985 Public Health Service Task Force Report that acknowledged disparities in the inclusion of women in clinical research and made recommendations to correct the inequities.[2]

Findings from reviews conducted by the U.S. General Accounting Office years later documented continuing problems: representation among women and men was equal in clinical trials, although women may have been overrepresented in some categories and underrepresented in others[2,3]; among phase 2 and 3 trials for drugs approved between 1988 and 1991, subset analyses by gender were conducted in only 50% of applications. In 1993, the U.S. Food and Drug Administration (FDA) attempted to broaden the inclusion of women in early medication testing by announcing new guidelines for applicants of new drug applications. These guidelines eliminated the recommended exclusion of women with childbearing potential from participation in phase 1 and early phase 2 trials and, in a reversal, encouraged the inclusion of women in earlier pharmacokinetic studies. Guidelines also specifically encouraged applicants to conduct subset analyses by sex and age, theoretically increasing knowledge regarding gender-specific effects.[2] Congress mandated that the National Institutes of Health introduce similar changes for government-sponsored studies.[4]

Given the historical problem of including women in the early stages of drug testing and the lack of post hoc analyses to evaluate sex differences in medication efficacy, it is reasonable to wonder whether more information is available 7 years after the changes in FDA guidelines. With this as context, we take the example of depression

and examine what is known regarding sex differences in the pharmacokinetics and pharmacodynamics (including therapeutic efficacy) of antidepressant agents. We gathered this information by conducting a MEDLINE search using the terms *antidepressants, sex-factors, gender differences,* and *women* for the years 1966 to 2000. Our choice of this medical area is appropriate because major depressive disorder (MDD) is an illness that is common in women, and thus women comprise the majority of the target population. Approximately 21% of women, compared with 13% of men, will suffer an episode of MDD at some point in their lives.[5] However, we caution that advances in some areas of medicine may not be found in the area of mood disorders. Similarly, there may be issues concerning nonpsychotropic medications that are not relevant for the majority of psychotropic agents.

POTENTIAL CONTRIBUTORS TO SEX DIFFERENCES IN DEPRESSION TREATMENT

Much of treatment research has been based on the assumption that if a medication works for a man, then it is efficacious for a woman and vice versa. This assumption appears to hold true in the majority of instances, but, as noted below, there are instances where gender strongly influences therapeutic outcome. In these cases, the importance of gender could be due to a number of factors including (1) unique biological processes underlying the depressive disorder that render either men or women more treatment resistant; (2) variations in the way a drug is absorbed, distributed, or metabolized that lead to sex differences in the amount of drug arriving at the site of action; and (3) pharmacodynamic effects occurring in a sex-specific environment, e.g., endogenous hormones influencing neurotransmitter receptor properties.

SEXUAL DIMORPHISM AND THE BIOLOGY OF THE UNDERLYING MDD SUBTYPE

Although sex-related differences in the pathophysiology of depressive disorders have not been identified, the subtype of MDD known as "atypical depression," characterized by dysphoria and pronounced anxiety, predominates in clinical samples of women.[6] This condition shows preferential response to monoamine oxidase inhibitors (MAOIs).[7,8] It follows that if individuals with MDD were treated with a tricyclic antidepressant (TCA) or an MAOI, and women were more likely to have atypical depression, then women would be more likely to respond to the MAOI than the TCA. Preliminary support for this hypothesis was shown in one database reanalysis,[9] thus illustrating how depression subtype and gender can interact, even though the exact mechanism is unknown.

A role for unique gender-related pathophysiologic processes is suggested by preliminary work treating MDD with a postpartum onset. Although the connection has not been definitively shown, postpartum depressive disorders have been linked theoretically to a withdrawal of gonadal steroids. In a study testing this hypothesis, investigators administered high-dose β-estradiol or placebo to 64 women with an onset of MDD within 12 months of parturition.[10] By the first month of treatment, β-estradiol was superior to placebo and this difference remained throughout the subsequent 6 months. These results support the success of an earlier open study that entailed administering β-estradiol to women with recurrent postpartum psychosis,[11] again in an attempt to replace the putative agent whose withdrawal triggered the psychiatric illness. Similarly, several recent studies[12,13] show that minor and major depressive disorders occurring during the perimenopause have a preferential response to β-estradiol over placebo. This supports a gender-specific pathophysiologic trigger related to the deficiency of estrogen.[12,13] As noted below, the effects of estrogen on the serotonin system are intriguing in that estradiol has some properties similar to those of antidepressant agents.[14]

SEX DIFFERENCES IN PHARMACOKINETICS OF ANTIDEPRESSANT AGENTS

Differential therapeutics for psychotropic agents may also be related to sex differences in plasma levels of drug and the metabolism of medication. There have been several recent reviews of sex-related differences in the pharmacokinetics of psychotropic agents,[15–21] and the authors concur that the extant literature is sparse. However, a growing number of reports address potential sex-related differences. What follows is a brief presentation of data regarding sex differences in the pharmacokinetics of antidepressant agents.

An antidepressant agent is taken orally, and after the drug is absorbed it is distributed throughout the body and to its site of action. The degree to which the drug is absorbed depends on its acid-base properties, the acidity of gastrointestinal tract, the amount of food in the gut, and its vulnerability to metabolism at the villous brush border of the gut. After absorption, the medication enters systemic circulation and is delivered to the liver, where a proportion may be immediately metabolized, and the residua is distributed to various compartments in the body. In the gastrointestinal tract, liver, and perhaps other compartments (including brain), the medication may be metabolized via oxidation, reduction, or conjugation. Oxidative and reductive reactions are largely driven by cytochrome P450 (CYP) enzymes. Research continues to determine and refine the structure and activity of the various metabolizing enzymes. Conventions have been established to name these enzymes according to their amino acid structure: an Arabic numeral is assigned to a family, which has 36% homology; a capital letter is assigned

to compounds within the same family that share 70% homology; and an Arabic numeral identifies the gene associated with the enzyme.[22]

Advances in the identification of various CYP enzymes have facilitated research, and investigators have begun to address potential sex differences in the activities of CYP enzymes.[15,19,20,23] Some,[19,20,24,25] but not all,[26] studies have found that CYP3A activity is higher in women compared with men. On the other hand, several reports find higher plasma levels of drugs metabolized by CYP1A2 in women,[27,28] suggesting sexual dimorphism for this isoenzyme, but in the opposite direction. CYP2D6 is another isoenzyme commonly involved in the metabolism of antidepressant medication. Less evidence supports sex differences in the activity of this enzyme, although CYP2D6 activity is largely dependent on the genetic polymorphism, and this contribution may have obscured a gender effect. A recent report finds that both enzyme genotype and gender largely accounted for variability in plasma levels of nortriptyline.[29] In sum, given the evidence for an influence of biological sex on several hepatic enzymes involved in antidepressant medication metabolism, it is possible that blood levels of drug will differ in men and women and that this may influence response and side effect profiles.

Empirical Data on Plasma Levels and Clearance of Antidepressant Agents

Several older studies found that women have higher plasma levels of the tertiary amines, imipramine,[30] amitriptyline,[31] and clomipramine,[32] although not all studies concur.[33] The inconsistencies in the older treatment literature are consistent with the previously mentioned findings[29] that both genetic polymorphisms and gender play a role in determining the clearance of drugs metabolized by CYP2D6, with genetic polymorphisms playing a more important role than gender.

The data regarding potential sexual dimorphism in the metabolism of clomipramine may be stronger than for other tricyclic compounds, since there are now 2 reports that suggest sex differences in metabolism of this compound.[32,34] Clomipramine is both demethylated and hydroxylated, but dissection of the various metabolites suggests that the hydroxylation step is less active in women compared with men. This example nicely illustrates how inconsistencies in the data regarding sex differences in the metabolism of tertiary amines could be due to the fact that, in addition to CYP2D6, other enzymes are involved in the metabolism of TCAs.[35] In the case of clomipramine, the fact that CYP2C, in addition to CYP2D6, is implicated in the metabolism of the drug is particularly relevant since at least CYP2C19 activity may be higher in men than in women. Men clear methyl phenobarbital, a compound metabolized by CYP2C19, approximately 1.3 times faster than women.[36]

Similarly, CYP1A2 is an enzyme involved in the metabolism of tertiary amines. The role of this protein may be informative in terms of the issue of sex differences. CYP1A2 enzyme activity is inhibited by gonadal steroids,[37–39] potentially leading to lower concentration of metabolites synthesized via this pathway in women; reciprocally, compounds eliminated via this pathway could accumulate in women. What also follows is that compared with men, oral contraceptive–using women would have lower apparent clearance for medications metabolized by CYP1A2. In fact, even small "replacement-level" dosages of estrogen can influence plasma levels for compounds metabolized by CYP1A2.[39]

Clearance for the secondary amines desipramine and nortriptyline is reported to be lower in women compared with men.[29,40] One caveat is that these studies failed to include a correction for body weight that could potentially neutralize sex differences.

Of the newer antidepressant agents, several investigations show possible sexual dimorphism in the metabolism of the selective serotonin reuptake inhibitor (SSRI) sertraline.[41,42] It is not clear whether CYP3A or CYP2D6 isoenzymes are the dominant metabolic enzymes for clearance of sertraline,[42] but plasma levels can be 27% lower in young men compared with older women, younger women, and older men. Another unknown is whether this difference is clinically meaningful (see below), since there appears to be no dose-response relationship between sertraline levels and therapeutic response. Interestingly, there appear to be differences in treatment response between females and males (see below), but whether this is related to plasma levels is not yet known.

The antidepressant nefazodone blocks the reuptake of serotonin and binds to postsynaptic serotonin-2 (5-HT_2) receptors. It is putatively metabolized by CYP3A.[43] As with sertraline, single-dose and steady-state nefazodone and hydroxynefazodone levels are highest in elderly women.[43] There are no significant differences in plasma levels of drug in young men or women, although, numerically, young women have higher plasma levels than young men after single-dose administration. The authors implicate an age-related decline in CYP3A activity for the age-related differences; a similar explanation may be evoked for the age-related findings for sertraline noted above.

Gender and Adverse Events

An important factor to consider is that higher plasma levels of drug may lead to more side effects even though efficacy may not change for differing levels. For example, between men and women treated with the cholinesterase inhibitor tacrine, women have higher plasma levels of drug, and plasma levels are highly correlated with the incidence of adverse effects.[28] In a study comparing the efficacy of sertraline and imipramine for chronic MDD, women were significantly more likely to discontinue imipramine be-

cause of side effects. Data regarding the contribution of plasma levels have not yet been analyzed.[44] Other databases exploring a broader set of prescribed medications find a higher rate of adverse events in women. Domecq et al.[45] found that female inpatients were more likely than male inpatients to have adverse drug reactions and that in the majority of instances, these side effects were dose related. In another study, the higher rate of adverse events in women compared with men was replicated.[46] The authors conclude that medication overdose is not responsible for these events, although their analysis does not rule out the possibility that "therapeutic doses" resulted in higher plasma levels and thus adverse events in women.

TREATMENT OUTCOMES RESULTING FROM PHARMACODYNAMIC EFFECTS

As part of the guideline revisions, the FDA encouraged subgroup analyses to explore possible sex-related differences in drug response. Mandates such as this may have aided in the finding that the 5-HT_3 antagonist alosetron, a recently approved but now unavailable compound for the treatment of irritable bowel syndrome, is effective in women but not men.[47] The plasma levels for this compound are 30% to 50% higher in women, possibly because of slower metabolism in women.[48] However, simple pharmacokinetics do not adequately explain the differences in efficacy, since higher doses that would produce equivalent plasma levels in men are no more effective in men than lower doses.[47] Rather, it is hypothesized that sex differences in response may have a pharmacodynamic basis grounded in other differences such as variations in endogenous levels of serotonin.[49]

It is possible that similar pharmacodynamic explanations may be responsible for the sex differences found for some antidepressant agents. An early study explored whether age or sex influenced depression treatment response.[50] Data analyzed included results from several studies in which patients were treated with imipramine, chlorpromazine, phenelzine, diazepam, or placebo. The response to imipramine and phenelzine was analyzed in the context of patient age and sex. Results showed that imipramine was no better than placebo for young women, although imipramine was efficacious for men and older women. On the other hand, the MAOI phenelzine was more effective in young women than placebo. The authors did not evaluate the type of depression experienced by men and women but rather hypothesized that the difference in response among younger and older women could be linked to age-related or hormonal factors.

The relatively weaker response women have to TCAs is seen in several other reports. Hamilton et al.[51] conducted a meta-analysis of all published imipramine trials that presented outcome by sex (35 studies including 342 men and 711 women). Results showed that 62% of men but only 51% of women ($p < .001$) were considered imipramine responders. A large database reanalysis of SmithKline Beecham trials comparing paroxetine with imipramine was presented in poster form but never published. This analysis shows that paroxetine was more effective than imipramine for women with MDD.[52] Similarly, in a large study comparing the SSRI sertraline with the TCA imipramine for treatment of chronic MDD,[44] a sex-by-treatment interaction was found. This study of 235 men and 400 women showed that women were 10% more likely to respond to sertraline than to a TCA, whereas men were 12% more likely to respond to the TCA. Interestingly, the difference in response between TCAs and sertraline disappeared in the 74 women who were postmenopausal, suggesting that endogenous gonadal hormones may have some role in the preferential response young women have to the SSRI.

This sex-related differential response for some SSRIs in comparison to TCAs also appears to hold for the chronic mild depressive disorder dysthymic disorder. In a study that included 266 women and 144 men, response rates were 20% higher in women than men among those treated with the SSRI (64% in women and 42% in men; $p = .02$) (K.A.Y., unpublished data, May 1998). The only SSRI study not consistent with this picture found that women's response to fluoxetine and a TCA was equivalent. Unfortunately, this analysis did not include men, so there was no comparison of women's response to the SSRI and TCA vis-à-vis men's response.[53]

While it is difficult to account for the variations in response suggested by the above data, it is possible that sex-specific features play a role in the different outcomes. A clue is the differential response noted above between premenopausal and postmenopausal women[44] and by several other reports showing that older women who take hormone replacement therapy (HRT) are more likely to be responsive to serotonin reuptake inhibitor treatment for depression than women not undergoing HRT.[54,55] For these women, it is possible that estrogen, when present, changes the biochemical milieu or changes receptor characteristics such that the efficacy of selective antidepressant agents is improved. For example, it may be that indolamine synthesis is lower in young men compared with young women[49] and that serotonin reuptake inhibitors, but not most TCAs, are able to augment serotonin levels in critical brain regions. Exogenous gonadal steroids may also be able to alter serotonin content or receptor activity in selected brain regions contributing to such an effect. Numerous reports in the preclinical literature find that gonadal steroids modulate serotonin receptors and function (see DeBattista[14] for a review). For example, preclinical data suggest that the acute administration of estradiol increases the expression of 5-HT_2 and decreases 5-HT_1 receptors.[56,57] Estradiol also appears to influence the activity of the serotonin transporter by increasing serotonin

reuptake.[58,59] On the other hand, progesterone has independent and similar effects on serotonin receptors, and progesterone and serotonin receptors are colocalized in the midbrain.[60–62] Progesterone can partially reverse the effects of estrogen in certain brain regions and can decrease serotonin accumulation if it is given after estrogen.[63]

The influence of hormonal milieu on specific neurotransmitter systems is found elsewhere. It has been shown that cognitive impairment is greater in women who are coadministered the benzodiazepine triazolam with progesterone compared with women who are administered triazolam alone; plasma levels of triazolam are not appreciably changed by coadministration of progesterone even though the cognitive effects are modified.[64–66]

There are many unanswered questions regarding sex differences in treatment response for MDD, and provocative issues are raised. Early pharmacokinetic trials that include men and women may be able to address some questions, but the results of such studies will require dissemination rather than sequestration in a new drug application file. To include both men and women in early pharmacokinetic studies, sample sizes need to be enlarged and physiologic factors unique to women such as reproductive status and menstrual cycle phase need to be addressed. Differences in reproductive status or menstrual cycle phase and their influence on pharmacokinetic factors can be "controlled" for by including women only at a particular phase of the menstrual cycle or assays can be repeated at several times of the cycle so that a much broader base of information on the metabolism of drugs in women is available.

A second arena that needs to be addressed is the optimal utilization of extant data. Pharmaceutical companies and independent researchers have datasets that include large numbers of men and women who have already undergone study. Subgroup analyses using sex as a variable can help identify meaningful differences. One of the issues confronting researchers using these databases is that large numbers of men and women are needed so that the power is adequate to address hypotheses regarding potential gender effects. In instances where data are suggestive of a gender effect but sample sizes are inadequate, follow-up studies can be designed and conducted with enough power to confirm or refute such findings.

Optimally, the dissemination of subgroup analyses on existing databases and postmarketing studies will further enhance information regarding potential sex differences in antidepressant drug response and adverse effects. There may be a general reluctance on the part of pharmaceutical companies to publish such information, since these sorts of data suggest differential efficacy for their compounds. However, it is incumbent on academic and pharmaceutical industry researchers to clarify the optimal utilization of their compounds. Such explorations will lead to improved pharmacotherapy for both women and men.

Drug names: amitriptyline (Elavil and others), chlorpromazine (Thorazine and others), desipramine (Norpramin and others), diazepam (Valium and others), fluoxetine (Prozac and others), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), phenobarbital (Nembutal and others), sertraline (Zoloft), tacrine (Cognex), triazolam (Halcion).

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