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Dr. Marsh: Pharmacokinetic considerations of antidepressant use during pregnancy

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Sex-related differences in antidepressant response: When to adjust treatment

How pharmacodynamic, pharmacokinetic, and hormonal factors impact prescribing

With a history of panic disorder, perfectionistic tendencies, and depression, Ms. C, age 32, presents 29 weeks into her first pregnancy with a chief complaint that "the Zoloft is not working; my sadness and anxiety are increased and I feel dizzy, like when I miss a dose." For the past 7 years, she has done well on sertraline, 50 mg/d; she has had no depressive symptoms and experienced minimal to manageable anxiety. Ms. C has found psychotherapy helpful for the last 2 years, including during her pregnancy.

After discussion with her obstetrician, Ms. C remained on sertraline through her early pregnancy. She did well until several weeks ago, when she noticed a return of sadness and incessant worry. She resumed an old habit of excessively cleaning her home. Ms. C denies missing doses but states she has the physical feeling as if she were—a lightheadedness that she clearly distinguishes from pregnancy symptoms.

Both men and women respond well to antidepressants, yet there are notable differences between the 2. Understanding why men and women may differ in response to antidepressants helps clinicians better tailor their treatment choice and dosing.

This article outlines some of differences—and lack thereof—in response rates to antidepressants. Our discussion of why these differences may occur is framed in the context of pharmacokinetics, pharmacodynamics, and the influence of gonadal hormones on antidepressant-related neurotransmitter systems. The second section focuses on major reproductive phases of adult

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Antidepressants in women

Clinical Point

Hormone-related changes associated with the menstrual cycle may affect antidepressant absorption and distribution

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Table 1

Sex differences in antidepressant response

Class	Response: Male vs female
Monoamine oxidase inhibitors	M<F
Serotonin-norepinephrine reuptake inhibitors	M=F
Selective serotonin reuptake inhibitors	Age <50: M< F Age ≥50: M=F
Tricyclic antidepressants	M=F

Source: References 1-12

women (the menstrual cycle, pregnancy, postpartum, and menopause) and how antidepressant response rates can influence clinical decision making, such as antidepressant timing, dose, and choice of potential adjunct treatments.

What the evidence says

Most studies look at sex differences in response to a single antidepressant, but several comparing sex differences among classes have produced fascinating results ***(Table 1)***. One of the most robust and replicated findings—although not universally reproduced[1]—is that compared with men, women are more likely to respond to selective serotonin reuptake inhibitors (SSRIs) than to tricyclic antidepressants (TCAs).[2-4] Because of this and the fact that SSRIs are so commonly used, this article primarily will address SSRIs in women.

Initially, however, in reviewing non-SSRI antidepressants, monoamine oxidase inhibitors (MAOIs) are reported to produce a superior response in women than in men.[5] Women are more likely to have atypical depression symptoms, which MAOIs often treat better than other antidepressants. In contrast, a recent meta-analysis of TCAs[6] found no sex response difference within the class. However, 1 study reported women may be slower to respond to TCAs than men.[2]

Studies on the newer and more frequently prescribed antidepressants reveal some interesting sex differences. Although smaller studies initially did not find a sex difference in SSRIs,[5,7] when response rates to citalopram were compared in 2,876 subjects in Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, women were more likely to reach remission and response than men.[8] Younger women—generally those age <50—respond better to SSRIs than women age ≥50.[2,3,9]

There are less data concerning newer non-SSRI antidepressants. In the second stage of the STAR*D trial, when subjects who did not respond to citalopram were randomly assigned venlafaxine, bupropion, or sertraline, there was no sex difference in response.[10] Pooled analysis of randomized controlled trials specifically looking at remission rates between the sexes for venlafaxine,[9] bupropion,[11] or duloxetine[12] found no difference between men and women, regardless of age. No published sex differences in antidepressant response were found for mirtazapine.

Numerous studies have detailed sex differences in antidepressant pharmacokinetics (***Box 1***) and pharmacodynamics (***Box 2, page 28***), as well as human sexual dimorphism of the serotonergic system. Estrogen's influence on the serotonergic system (***Box 3, page 28***) may be a component of men and women's different responses to antidepressants, particularly across reproductive phases.

Change across reproductive phases

In contrast to men, women's estrogen and progesterone status varies widely across a woman's reproductive lifecycle (menstrual cycle, pregnancy, postpartum, premenopause vs postmenopause). In men and women, androgen levels—including testosterone—tend to remain at steady levels, and then slowly decline with age.

Menstrual cycle. Hormone-related changes associated with the menstrual cycle may affect antidepressant absorption and distribution. During the luteal phase—second half of the menstrual cycle post-ovulation—and pregnancy, increased progesterone concentrations are associated with slowed gastrointestinal transit time[13,14]

Box 1

Sex differences in antidepressant pharmacokinetics

Medical literature has documented gender differences in antidepressant absorption, distribution, metabolism, and elimination.[a-c] Compared with men, women—especially premenopausal women—have slower gastric emptying[d] and small bowel and colonic transit times.[e,f] Also, because antidepressants generally are lipophilic,[a,g] a lower ratio of lean muscle to adipose tissue in women compared with men may result in a greater volume of drug distribution (Vd).

Sex differences also have been reported in hepatic enzyme activity and may affect clinical response. Most medications, including antidepressants, undergo phase I metabolism, commonly via the cytochrome P450 (CYP450) pathway, and/or phase II conjugation reactions. Generally, phase I oxidative metabolism appears to be greater in women than in men; in contrast, phase II conjugation activity appears to be greater in men than in women.[h]

Lower CYP1A2 activity in women[i] along with gonadal steroid inhibition of CYP1A2[j,k] may explain why clomipramine metabolic clearance is reduced in young women[l] and mean steady state plasma levels of fluvoxamine are almost double in women than in men for the same dose.[m] In theory, greater CYP3A4 activity in women[i] has the potential to accelerate metabolism and/or decrease plasma levels of some commonly used antidepressants metabolized via CYP3A4, such as nefazodone and (to some extent) sertraline and citalopram. In contrast, CYP2D6 and CYP2C9 do not show sex differences in metabolism.

Differences in antidepressant blood levels, however, are difficult to base solely on CYP metabolic route differences. Sex differences in plasma antidepressant levels likely reflect a summation of several sex-associated pharmacokinetic processes and may impact one of many factors that contribute to the small observed difference in antidepressant efficacy between men and women.

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compared with the follicular phase (preovulation).

Premenstrually, at the end of luteal phase, reduced serum antidepressant levels have been associated with breakthrough depressive symptoms.[15,16] In these case reports, serum antidepressant levels returned to baseline and depressive symptoms resolved after menses ended. It is possible that women may be at increased risk of symptom recurrence before menses because of hormonally driven changes in drug absorption, distribution, and metabolism. Increased dosing of sertraline in the luteal phase has helped reduce premenstrual exacerbation of depression.[17]

Pregnancy. Dose requirements for the SSRIs citalopram, escitalopram, and sertraline,[18] the serotonin-norepinephrine reuptake inhibitor venlafaxine,[19] and the TCAs nortriptyline, clomipramine, and imipramine[20] increase during the second half of pregnancy. This appears to be the result of increased drug metabolism. Altered cytochrome P450 (CYP450) enzymatic activity in pregnancy—likely mediated by elevated estrogen and progesterone—may have clinical effects on drug levels and treatment response. Studies indicate that CYP3A4—and possibly CYP2D6—are induced during pregnancy.[21,22] Dose increases are necessary in two-thirds of pregnant women on antidepressant monotherapy, typically after 20 weeks gestation[18,20,23] to treat symptom recurrence or maintain euthymia.

During pregnancy, drug elimination may increase because of higher renal blood flow and glomerular filtration rate (GFR).[24] This could reduce blood levels of water-soluble active metabolites of some TCAs. Pregnancy-associated reductions in intestinal motility and gastric pH alone do not change medication bioavailability. Increased body fat could increase the volume of drug distribution for antidepressants, and, in theory, create a dilutional drop in free drug concentration, but this likely would have only a minor effect.

The range of antidepressant effectiveness among pregnant patients is wide, which reflects individual differences in pharmacokinetics and pharmacodynamics.[25] Because we cannot predict which women will require dose changes during pregnancy or postpartum, patients should be monitored frequently for depressive symptom recurrence. Dose adjustments may be necessary to prevent re-

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Dose increases are necessary in two-thirds of pregnant women on antidepressant monotherapy

To read more about depression in women, see **"Is it a mood disorder or menopause?"** page 56

Box 2

Sex differences in antidepressant pharmacodynamics

Sexual dimorphisms in the localization and concentration of endogenous neurotransmitters such as serotonin and dopamine and their degradative enzymes and transporters have the potential to clinically affect antidepressant pharmacodynamics (eg, drug-receptor interactions).

Recent investigations report sex differences in some key monoaminergic enzymes in the brain, notably monoamine oxidase-A (MAO)[a,b] and catechol-O-methyltransferase (COMT).[c-e]

For example, estrogen has been found to inhibit MAO,[f] which is potentially clinically relevant in light of the finding that women respond better than men to MAO inhibitors. COMT—which is responsible for metabolism of norepinephrine, epinephrine, and dopamine—is down regulated by estradiol[e,g] likely accounting for some sex effects. Recently, the sexually dimorphic effect of a COMT polymorphism was associated with a poorer fluoxetine response in men treated for major depression.[h]

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Box 3

Brain dimorphisms and estrogen's influence

Human sexual dimorphism of the serotonergic system has been described for many years,[a,b] including estrogen's sexually dimorphic effects on the brain.[c] Sex steroid receptors are found in mood-processing brain regions in men and women[d] and may influence sex differences in antidepressant response.

Estrogen has been found to augment serotonergic activity[e] by increasing serotonin synthesis and decreasing serotonin reuptake[f] as well as increasing serotonin 5-HT2A binding sites.[g] Estrogen therapy has been shown to increase the number of sites available for active transport of 5-HT into brain cells.[h]

Source: For reference citations, see this article at CurrentPsychiatry.com

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Long-term data on prenatal exposure to antidepressants are limited

lapse (eg, when net metabolism is increased) or pronounced side effects (eg, when net metabolism is reduced).[18,26]

When prescribing antidepressants for pregnant women, a personalized discussion of the risks and benefits with each patient in the context of her psychiatric history, the developing fetus, and her value system is warranted. The potential consequences of antidepressant effect on patient and fetus, or lack there of, continues to be an evolving area; long-term data on prenatal exposure are limited.

Postpartum. The postpartum period—when depression can hit 10% to 15% of new mothers[27]—entails rapid shifts in many factors that may influence antidepressant response. Levels of gonadal hormones such as estrogen and progesterone decline, plasma volume contracts, and hepatic enzymatic metabolism and GFR return to pre-pregnancy levels. Together these changes may result in increased antidepressant blood levels postpartum, especially when the dosage used during pregnancy is held constant.[19]

The postpartum period is associated with a high risk for depression onset or worsening and is a time of great hormonal and pharmacokinetic change. Accordingly, a postpartum woman should be followed closely for changes in response and adverse effects, and her antidepressant dosage adjusted. Breast-feeding is a critical consideration in the postpartum. Meltzer-Brody et al[28] provide a discussion of postpartum depression and what to tell patients who breast-feed.

Menopause. Despite evidence that reproductive-age women may respond better to SSRIs than men, the same findings have not been reproduced in postmenopausal women. For example, compared with men, postmenopausal women had no significant difference in SSRI treatment response in primary care clinics. In contrast, the same postmenopausal women had a significantly worse treatment response than premenopausal women.[29]

In considering why SSRI response among women would differ depending on reproductive stage or hormonal status, researchers examined the effect of estrogen on antidepressant response with the use of

estrogen therapy (ET). As detailed in ***Box 3***, estrogen has many serotonergic-enhancing properties. Early studies with TCAs and a retrospective analysis of SSRIs did not demonstrate improved antidepressant effect with the addition of ET in depressed women.[30,31] In contrast, recent studies have demonstrated better SSRI response—regardless of which medication was used—in postmenopausal women on ET or ET with progesterone, compared with postmenopausal women taking placebo.[32,33] Perhaps explaining the discrepancy, in a randomized, placebo-controlled trial, Rasgon et al[34] found transdermal estrogen shortened time to response to sertraline in postmenopausal women, although it did not improve end response rate.

CASE CONTINUED

Dosage increase

After a detailed discussion with her psychiatrist about the potential benefits, known risks, and possible alternatives to using and increasing sertraline in pregnancy, Ms. C agrees to a dosage increase to 75 mg/d. Within 2 weeks she reports decreased anxiety and depression. Her depression remits for the remainder of the pregnancy and she gives birth to a full-term healthy infant. Ms. C's sertraline dose is held at 75 mg/d during the early postpartum period, as she experienced no side effects at that dose, then reduced to 50 mg/d after a period of sustained euthymia.

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continued

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Multiple rapid physiologic changes may impact antidepressant drug levels in the postpartum period

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Studies have shown better SSRI response in postmenopausal women receiving estrogen therapy compared with placebo

Related Resources

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Drug Brand Names

Bupropion • Wellbutrin
Citalopram • Celexa
Clomipramine • Anafranil
Duloxetine • Cymbalta
Escitalopram • Lexapro
Estradiol • Estrace, Climara, others
Fluoxetine • Prozac
Fluvoxamine • Luvox
Imipramine • Tofranil
Mirtazapine • Remeron
Nefazodone • Serzone
Nortriptyline • Pamelor
Sertraline • Zoloft
Venlafaxine • Effexor

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Bottom Line

Pharmacodynamic, pharmacokinetic, and hormonal factors account for why women may respond differently to antidepressants than men. Consider these changes when prescribing antidepressants during different reproductive phases.

Box 1

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Box 2

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Box 3

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