

## The Safety of Duloxetine During Pregnancy and Lactation

Chittaranjan Andrade, MD



Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, India (candrade@psychiatrist.com).

### ABSTRACT

Depression is common in women, especially during pregnancy and the postpartum period. Untreated depression is associated with many adverse gestational outcomes. It is therefore important to know about the safety of different antidepressant drugs during pregnancy and lactation so that informed decisions can be made regarding treatment. This article summarizes published literature on the subject with regard to duloxetine, an antidepressant with serotonin-norepinephrine reuptake inhibition properties. In general, it appears that the use of duloxetine during pregnancy is associated with an increase in the risk of spontaneous abortion, but no increase in other adverse outcomes, such as major fetal malformations. Late-pregnancy exposure to duloxetine may be associated with poor neonatal adaptation syndrome, but the magnitude of this risk is not known. Infant exposure to duloxetine in breast milk is less than 1% of the maternal weight-adjusted dose, suggesting that duloxetine can be safely administered to a woman who is breastfeeding her infant. In general, the very limited data available on the subject do not uncover a signal that the use of duloxetine during pregnancy or lactation increases the risk of adverse outcomes.

*J Clin Psychiatry* 2014;75(12):e1423–e1427  
(doi:10.4088/JCP14f09631).

© Copyright 2014 Physicians Postgraduate Press, Inc.

### Clinical Problem

Ms K is a 29-year-old woman with a 7-year history of recurrent depressive illness. She has been euthymic on duloxetine (80 mg/d) for the past 18 months. She wishes to conceive. She recognizes that duloxetine has stabilized her life. She knows that she is at increased risk of relapse into depression during pregnancy and the postpartum period and that continuation of duloxetine could protect her against relapse. However, she is concerned about the possible adverse effects of duloxetine on her child. What information is available on the subject?

### Introduction

Pregnancy is associated with a unique combination of physical, physiologic, and psychological stresses, and women are at increased risk of depression during pregnancy and the postpartum period<sup>1–3</sup>; this is especially so if they have a previous history of depression and if they discontinue effective antidepressant treatment before conceiving or after discovering that they are pregnant.<sup>4</sup>

Depression is associated with neuroendocrinologic changes, immunologic impairments, abnormal eating patterns, nutritional disorders, neglect of health, poor adherence to medical regimens, smoking and drinking, impulsive behavior, deliberate self-harm, and other behaviors, all of which can harm not only the mother but also the unborn child. These factors may explain why untreated depression during pregnancy is associated with several adverse maternal and offspring outcomes, including preterm birth, low birth weight, perinatal complications, decreased initiation of breastfeeding, poor mother-child bonding, etc.<sup>3,5–7</sup> There is therefore an increasing trend to advocate the continuation of effective antidepressant treatment during pregnancy and lactation, especially in women with more severe forms of illness,<sup>8–10</sup> and this is reflected by an increasing prevalence of antidepressant use during pregnancy.<sup>11–13</sup>

In a single case report,<sup>14</sup> umbilical cord serum concentration of duloxetine was found to be only 12% of that in maternal serum, and the ratio of duloxetine in infant plasma to maternal plasma was just 0.81% during lactation. If these findings can be generalized, they suggest that fetal and neonatal exposure to duloxetine is low when this drug is used during pregnancy and lactation. Case reports, however, are not evidence. This article therefore examines what is known about the use of duloxetine during pregnancy and lactation. The contents of this article are based on a PubMed search conducted on November 2, 2014, with the search terms *duloxetine* combined singly with *pregnancy*, *malformations*, *teratogenicity*, *lactation*, *breastfeeding*, and *milk*. Searches were also conducted for duloxetine paired with specific adverse pregnancy outcomes.

### Duloxetine and Pregnancy Outcomes

Duloxetine is a serotonin-norepinephrine reuptake inhibitor that is classified as a Pregnancy Category C drug by the US Food and Drug Administration (FDA)<sup>15</sup>; that is, there are no adequate and well-controlled studies of duloxetine in pregnant women. What do the available data show?

- The use of duloxetine during pregnancy is associated with an increased risk of spontaneous abortion and with no known increase in the risk of other adverse outcomes, such as major fetal malformations.
- Late-pregnancy exposure to duloxetine may be associated with poor neonatal adaptation syndrome, but the magnitude of this risk is not known.
- Infant exposure to duloxetine in breast milk is less than 1% of the maternal weight-adjusted dose, implying that a woman receiving duloxetine can probably safely breastfeed her infant.

In a multicenter, prospective, observational study, Einarson et al<sup>16</sup> followed 208 women who had directly or through their health care providers inquired about the safety of duloxetine during pregnancy. Of these, 206 women (99.0%) took duloxetine before conception and during early pregnancy, 51 (24.5%) used it all through pregnancy, and 2 took it only during the second or third trimesters. These women were compared with 208 randomly selected women who had inquired about the use of other antidepressants during pregnancy and 208 women who had inquired about the use of substances not considered to be teratogenic. The 3 groups were matched for age and for alcohol and tobacco use. There were 165 live births and 3 (1.8%) major malformations (clubfoot, hydronephrosis, kidney agenesis) in the duloxetine group. The rate of major malformations did not differ significantly across the 3 groups ( $P = .99$ ). Although the sample was underpowered for confident conclusions, it is reassuring that the malformation rate was not elevated above the 2%–3% rate that is expected in the general population. Readers may note that to identify a doubling of malformation risk from 3% to 6%, a sample of 750 women would have been required in each of the groups. Other pregnancy outcomes were not reported in this study.<sup>16</sup>

Hoog et al<sup>17</sup> reported on 400 cases of duloxetine exposure during pregnancy for which pregnancy outcome information was available. These cases were identified from the Eli Lilly Safety System database. There were 233 prospectively recorded cases, of which 170 were spontaneous reports, 58 were from clinical trials, and 5 were from postmarketing studies. The mean age of the women was 32 years. Most (74%) women had received duloxetine for the indication of depression. There were 41 (18%) spontaneous abortions, 19 (8%) premature births, 25 (13%) perinatal or postnatal conditions (not further described), 6 (3%) congenital malformations, 3 (1%) ectopic pregnancies, 3 (1%) intrauterine deaths or stillbirths, and 1 postterm delivery. Relative to women with normal pregnancy outcomes ( $n = 140$ ; 61%), women with abnormal outcomes ( $n = 90$ ; 39%) were more likely to have used potentially unsafe medications such as benzodiazepines, nonsteroidal anti-inflammatory drugs, and anticonvulsants during pregnancy (13% vs 26%, respectively;  $P = .02$ ). Also, relative to women with normal outcomes, women with abnormal outcomes were more likely to have had a past or current history of

medical issues such as miscarriage, smoking, and substance abuse (17% vs 30%, respectively;  $P = .03$ ). It is therefore uncertain whether the abnormal outcomes recorded were due to duloxetine use, the depression, the medical issues, the concurrent medications, or combinations of these factors. In any case, with the possible exception of spontaneous abortion, the rates of adverse outcomes were largely similar to those in the general population.

Hoog et al<sup>17</sup> noted that the Eli Lilly database also contained 167 retrospectively reported cases, which included 120 (72%) abnormal outcomes. These outcomes were not further described by the authors, perhaps because retrospective identification is known to be biased toward adverse findings. Finally, Hoog et al<sup>17</sup> observed that analysis of data from the FDA Adverse Event Reporting System database did not demonstrate disproportionality of adverse outcomes (congenital anomaly, spontaneous abortion, induced abortion, ectopic pregnancy, and stillbirth) in women treated with duloxetine as compared with all other drugs or with selected antidepressants.

In an analysis of data from population-based registries, Kjaersgaard et al<sup>18</sup> reported that exposure to duloxetine during pregnancy was associated with a trebled risk of spontaneous abortion (relative risk = 3.12; 95% CI, 1.55–6.31) in women diagnosed with depression.

No information is available about duloxetine and other pregnancy outcomes such as preterm delivery, low birth weight, persistent pulmonary hypertension of the newborn, and other perinatal complications.

### Duloxetine, Poor Neonatal Adaptation Syndrome, and Other Infant Outcomes

Late-pregnancy exposure to antidepressant drugs has been associated with the development of the poor neonatal adaptation syndrome (PNAS), also known as the neonatal behavioral syndrome. The clinical features of PNAS include 1 or more of the following: lethargy, hypoactivity, shaking, shivering, tremors, excessive crying, jitteriness, irritability, agitation, poor feeding, excessive weight loss, rapid respiration, respiratory distress, hypothermia, hypoglycemia, increased or decreased muscle tone, and seizures.<sup>6,19</sup>

The odds of PNAS are 5 times as high in antidepressant-exposed infants as in unexposed infants.<sup>19</sup> The clinical features of PNAS develop hours to days after birth and resolve days to (rarely) weeks later.<sup>6</sup> It is unclear to what extent PNAS is due to antidepressant withdrawal and to what extent it is due to antidepressant toxicity resulting from an inability of the neonate to capably metabolize the drug that is present in the circulation at birth.<sup>19</sup>

Poor neonatal adaptation syndrome, including probable seizures, was reported in a child born at 38 weeks after late-pregnancy exposure to duloxetine (90 mg/d). However, at a 2-year follow-up, the child was healthy with consistently normal neurobehavioral development.<sup>20</sup> Another case of neonatal withdrawal syndrome was described after late-pregnancy exposure to duloxetine (90 mg/d) in a woman who was receiving insulin for gestational diabetes; because

the woman was also receiving lamotrigine (100 mg/d) and quetiapine (800 mg/d), it is uncertain to what extent duloxetine contributed to the PNAS.<sup>21</sup>

Bellantuono et al<sup>22</sup> described a 42-year-old woman with a past history of major depressive illness and comorbid panic disorder who received duloxetine (60 mg/d) throughout pregnancy; she delivered a healthy baby at 37 weeks of gestation. There was no malformation, perinatal complication, or abnormal neurobehavioral outcome in the child on prospective follow-up to age 9 months. Briggs et al<sup>23</sup> and Boyce et al<sup>14</sup> also described completely uneventful exposure to duloxetine (60 mg/d) during the second half of pregnancy and all through pregnancy, respectively.

Other than the case reports described above, there is no published information about duloxetine exposure during pregnancy and long-term neurobehavioral outcomes.

### Transfer of Duloxetine Across the Placenta

At least 2 case reports have presented duloxetine levels in cord blood, which is a proxy measure of transplacental transfer of the drug. Briggs et al<sup>23</sup> found that, in a woman who received duloxetine (60 mg/d) during the latter half of pregnancy, the concentration of the drug in cord plasma was 65 µg/L; the sample was obtained 14 hours after a 60-mg extended-release dose. A corresponding maternal plasma sample was not obtained. However, the concentration of duloxetine in maternal plasma was slightly lower, at 53 µg/L, on the same dose and with sampling conducted 32 days after delivery, with the blood sample drawn 6 hours after dosing.

Boyce et al<sup>14</sup> found that the concentration of duloxetine in cord serum was 18 µg/L and that the corresponding concentration of the drug in maternal serum was 151 µg/L. The transplacental transfer ratio, therefore, was just 0.12 (12%).

### Transfer of Duloxetine Into Breast Milk

Briggs et al<sup>23</sup> studied a breastfed infant whose mother was receiving duloxetine (60 mg/d). They found that the peak concentration of duloxetine in milk was double that of the trough concentration (64 vs 31 µg/L, respectively) and that the milk-to-plasma ratios at the milk peak and milk trough were 1.21 and 1.29, respectively. The theoretical infant dose was calculated to be 7.1 µg/d, corresponding to a relative infant dose that was just 0.82% that of the mother's weight-adjusted dose. Duloxetine was not detected in the infant's plasma with a limit of detection of 1 µg/L.

Boyce et al<sup>14</sup> found that, with duloxetine dosed at 60 mg/d, the average concentration of duloxetine in milk was 51 µg/L across a 24-hour period. Thus, an infant consuming 150 mL of milk daily would receive 7.7 µg of duloxetine per day. When the dose of duloxetine was adjusted for body weight, the relative infant dose was estimated at 0.81% of the maternal dose. The concentrations of duloxetine in infant and maternal plasma, assessed 7.6 hours after the morning dose of the drug, were 2 and 245 µg/L, respectively; the infant concentration was 0.82% that of the maternal

concentration. The concentration of duloxetine in hindmilk was 1.4 to 2.0 times that in foremilk, depending on the time of sampling.

Lobo et al<sup>24</sup> administered duloxetine 40 mg twice daily to 6 healthy women who were weaning their infants and who stopped nursing during the course of the study. All women were at least 12 weeks postpartum. Paired milk and blood samples were obtained at steady state. The mean concentration of duloxetine in milk was in the 10–20 µg/L range, while the mean concentration of the drug in maternal plasma was in the 30–60 µg/L range. The ratio of duloxetine in milk to plasma was 0.25 (95% CI, 0.18–0.35) for the 12-hour area under the curve. The mean quantity of duloxetine in breast milk was 7.4 (range, 4–15) µg/d. The predicted infant exposure was 1.7 (range, 0.6–3.1) µg/kg/d, which was 0.14% (range, 0.06%–0.25%) of the maternal weight-adjusted dose.

These findings are reassuring, given that infant exposure that is < 10% of the maternal dose is generally considered acceptable.<sup>25</sup>

### General Conclusions

There is only a small body of information available on the safety of duloxetine in pregnancy and lactation. From the literature that has been reviewed, the following broad conclusions can be drawn:

1. The use of duloxetine during pregnancy is associated with an increase in the risk of spontaneous abortion. One study<sup>17</sup> suggested an absolute risk of 18%, and another<sup>18</sup> suggested a trebled relative risk.
2. Two small studies<sup>16,17</sup> with a pooled sample of 441 cases found that, after duloxetine exposure during pregnancy, the risk of major fetal malformations was similar to that in the general population (2%–3%).
3. There are 2 case reports<sup>20,21</sup> describing PNAS after late-pregnancy exposure to duloxetine. There are also 3 case reports<sup>14,22,23</sup> describing a normal and uneventful perinatal course. The magnitude of the risk of PNAS with duloxetine is not known.
4. There are no data on the risk of other adverse outcomes such as preterm birth, low birth weight, persistent pulmonary hypertension of the newborn, neurodevelopmental delays, and neurobehavioral syndromes.
5. Infant exposure to duloxetine in breast milk is < 1% of the maternal weight-adjusted dose.
6. In general, from the very limited data available on the subject and with the exception of the increased risk of spontaneous abortion, there does not seem to be a signal that the use of duloxetine during pregnancy or lactation increases the risk of adverse outcomes.

### Practical Notes About Dosing

Here are some practical suggestions for dosing duloxetine during pregnancy. These suggestions are based on clinical

knowledge of pharmacodynamics and pharmacokinetics, rather than on specific evidence.

1. If duloxetine is required to be administered during early pregnancy, it may be best to administer the drug in 2 to 3 divided doses rather than in a single daily dose. This way, there will be 2 or 3 small peaks in blood levels across the course of a day rather than a single large peak. Given that the adverse effects of a drug depend on the extent to which blood levels cross the threshold for adverse effects, a single large peak at any time of day is more likely to occasion adverse effects, including adverse fetal effects (such as damage to cells during critical periods of development) than several small peaks spaced several hours apart.
2. To reduce the risk of PNAS, a possible strategy is to lower the dose of the drug a week or so before term and to stop the drug completely, if possible, for 1–2 days before planned or expected delivery. The medication can be resumed in the regular dose immediately after delivery. It is unlikely that such a short period of dose taper and drug discontinuation would be associated with a risk of relapse. An important limitation of this strategy is that it assumes that the date of delivery can be pinpointed. If delivery is unexpectedly early, as may occur in antidepressant-treated women,<sup>26,27</sup> this strategy may not be implementable, and if delivery is delayed for any reason, prolongation of a low-dose or a drug-free period may risk relapse of depressive illness, which defeats the purpose of having exposed the offspring to the drug during pregnancy. The taper-and-transiently-discontinue strategy is intuitively appealing, and a register-based study by Warburton et al<sup>28</sup> indeed found that respiratory distress and convulsions were each less likely to occur in neonates who had not been exposed to selective serotonin reuptake inhibitors in the 2 weeks before delivery ( $n = 2,122$ ) relative to those who were exposed ( $n = 1,605$ ); however, this finding disappeared in a propensity-matched analysis ( $n = 239$  per group), implying that maternal illness characteristics may also drive the clinical features of PNAS. Therefore, some authors<sup>6,29</sup> do not consider this a viable dosing strategy. However, a limitation of the Warburton et al study<sup>28</sup> is that the propensity-matched analysis was seriously underpowered for the low frequency categorical outcomes that it examined, and so firm conclusions cannot be drawn either way.
3. Many standard texts, particularly the older ones, recommend that if psychotropic drugs are administered during pregnancy, they are best prescribed in the “lowest historically effective dose.” This is a curious recommendation given that even without medication some patients can remain well for months to years; so for how long should

that historically lowest effective dose have been administered to qualify for efficacy? Furthermore, if a patient was well for a long spell, chances are that the period was characterized by low levels of stress, good adaptation, or both. Pregnancy, in contrast, is characterized by unique physical, physiologic, and psychological stresses. It therefore does not make sense to expose the fetus to a psychotropic drug in a potentially ineffective dose. It probably does not make sense, either, to use a low dose and titrate to efficacy only if the woman shows signs of decompensation or relapse, because it can be more difficult to pull a patient out of a relapse than to prevent that relapse in the first place. The most sensible option, therefore, is that if a drug is being prescribed, it is best prescribed in the dose that is most likely to be effective.

4. In middle to late pregnancy, the volume of the fluid compartment increases and certain metabolic enzymes are up-regulated. This can result in dilution of drugs such as lithium or faster clearance of drugs such as lamotrigine.<sup>30</sup> Duloxetine is metabolized by cytochrome P450 (CYP)1A2 and CYP2D6<sup>31</sup>; the activity of the former is down-regulated and that of the latter is up-regulated during pregnancy,<sup>30</sup> so it is possible that duloxetine dosing may not need to be changed during pregnancy. Unfortunately, there are no data on duloxetine pharmacokinetics during pregnancy,<sup>30</sup> but plasma levels of the drug in healthy lactating women are comparable with those in healthy adults.<sup>24</sup>

It needs to be recognized that although 60 mg/d is the standard antidepressant dose for duloxetine, some patients may require higher doses. In this context, Waldschmitt et al<sup>32</sup> found that depressed patients who were very much improved with duloxetine had higher serum levels of the drug than those with moderate, minimal, or no improvement (mean, 93 vs 47 ng/mL, respectively); however, daily doses of duloxetine did not differ significantly between duloxetine responders and nonresponders (mean, 76 vs 83 mg/d, respectively). It is difficult to know what to make of these findings, but whereas the dose could have been unnecessarily high in the responders, it was clearly inadequate in the nonresponders with low serum levels. In other words, patients who fail to respond to approved doses of duloxetine may require higher-than-approved doses to bring their serum duloxetine levels within a more therapeutic range.

For a more general discussion of recommendations regarding the use of antidepressants in pregnancy and lactation, readers are referred to available reviews on the subject.<sup>6,10,33</sup>

#### Afternotes

1. The major metabolites of duloxetine are biologically inactive.<sup>34</sup> This, therefore, simplifies the conduct

and evaluation of studies on duloxetine in pregnancy and lactation. In contrast, drugs such as fluoxetine and venlafaxine have active metabolites, the effects of which will also need to be considered when evaluating the use of the parent drug in women who are pregnant and those who breastfeed their infants.

- Duloxetine is marketed as an enteric-coated formulation because it rapidly degrades to naphthol in acidic environments such as the stomach.<sup>35</sup> A breastfed infant ingests duloxetine directly, without the protection of enteric coating. Might the infant be harmed? It is unlikely, if only because the magnitude of exposure is in micrograms (< 10 µg spread across the course of a day, by all available estimates).
- Some women develop stress urinary incontinence (SUI) during or after pregnancy.<sup>36,37</sup> In a recent meta-analysis of 10 randomized controlled trials (pooled N = 5,738), duloxetine was found to be superior to placebo in the treatment of SUI.<sup>38</sup> Duloxetine (80 mg/d) is an approved treatment for SUI in the European Union but not in the United States.<sup>39</sup> The benefits of duloxetine for symptoms of SUI might be a bonus in women who receive the drug to treat or prevent depression during pregnancy and the postpartum period.

#### REFERENCES

- Bennett HA, Einarson A, Taddio A, et al. Prevalence of depression during pregnancy: systematic review. *Obstet Gynecol.* 2004;103(4):698–709.
- Gavin NI, Gaynes BN, Lohr KN, et al. Perinatal depression: a systematic review of prevalence and incidence. *Obstet Gynecol.* 2005;106(5 pt 1):1071–1083.
- Davalos DB, Yadon CA, Tregellas HC. Untreated prenatal maternal depression and the potential risks to offspring: a review. *Arch Women Ment Health.* 2012;15(1):1–14.
- Cohen LS, Althshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA.* 2006;295(5):499–507.
- Grote NK, Bridge JA, Gavin AR, et al. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Arch Gen Psychiatry.* 2010;67(10):1012–1024.
- Byatt N, Deligiannidis KM, Freeman MP. Antidepressant use in pregnancy: a critical review focused on risks and controversies. *Acta Psychiatr Scand.* 2013;127(2):94–114.
- Grigoriadis S, VonderPorten EH, Mamisashvili L, et al. The impact of maternal depression during pregnancy on perinatal outcomes: a systematic review and meta-analysis. *J Clin Psychiatry.* 2013;74(4):e321–e341.
- Parry BL. Assessing risk and benefit: to treat or not to treat major depression during pregnancy with antidepressant medication. *Am J Psychiatry.* 2009;166(5):512–514.
- Koren G, Nordeng H. Antidepressant use during pregnancy: the benefit-risk ratio. *Am J Obstet Gynecol.* 2012;207(3):157–163.
- Sie SD, Wennink JM, van Driel JJ, et al. Maternal use of SSRIs, SNRIs and NaSSAs: practical recommendations during pregnancy and lactation. *Arch Dis Child Fetal Neonatal Ed.* 2012;97(6):F476–F476.
- Cooper WO, Willy ME, Pont SJ, et al. Increasing use of antidepressants in pregnancy. *Am J Obstet Gynecol.* 2007;196(6):e1–e5.
- Huybrechts KF, Palmsten K, Mogun H, et al. National trends in antidepressant medication treatment among publicly insured pregnant women. *Gen Hosp Psychiatry.* 2013;35(3):265–271.
- Jimenez-Solem E. Exposure to antidepressants during pregnancy—prevalences and outcomes. *Dan Med J.* 2014;61(9):B4916.
- Boyce PM, Hackett LP, Ilett KF. Duloxetine transfer across the placenta during pregnancy and into milk during lactation. *Arch Women Ment Health.* 2011;14(2):169–172.
- Khan AY, Macaluso M. Duloxetine for the treatment of generalized anxiety disorder: a review. *Neuropsychiatr Dis Treat.* 2009;5:23–31.
- Einarson A, Smart K, Vial T, et al. Rates of major malformations in infants following exposure to duloxetine during pregnancy: a preliminary report. *J Clin Psychiatry.* 2012;73(11):1471.
- Hoog SL, Cheng Y, Elpers J, et al. Duloxetine and pregnancy outcomes: safety surveillance findings. *Int J Med Sci.* 2013;10(4):413–419.
- Kjaersgaard MI, Parner ET, Vestergaard M, et al. Prenatal antidepressant exposure and risk of spontaneous abortion: a population-based study. *PLoS ONE.* 2013;8(8):e72095.
- Grigoriadis S, VonderPorten EH, Mamisashvili L, et al. The effect of prenatal antidepressant exposure on neonatal adaptation: a systematic review and meta-analysis. *J Clin Psychiatry.* 2013;74(4):e309–e320.
- Eyal R, Yaeger D. Poor neonatal adaptation after in utero exposure to duloxetine. *Am J Psychiatry.* 2008;165(5):651.
- Abdy NA, Gerhart K. Duloxetine withdrawal syndrome in a newborn. *Clin Pediatr (Phila).* 2013;52(10):976–977.
- Bellantuono C, Marini A, Lucarelli C. Infant health and neurodevelopmental outcomes following prenatal exposure to duloxetine. *Clin Drug Investig.* 2013;33(9):685–688.
- Briggs GG, Ambrose PJ, Ilett KF, et al. Use of duloxetine in pregnancy and lactation. *Ann Pharmacother.* 2009;43(11):1898–1902.
- Lobo ED, Loghini C, Knadler MP, et al. Pharmacokinetics of duloxetine in breast milk and plasma of healthy postpartum women. *Clin Pharmacokinet.* 2008;47(2):103–109.
- Sachs HC; Committee On Drugs. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. *Pediatrics.* 2013;132(3):e796–e809.
- Andrade C. Antenatal exposure to selective serotonin reuptake inhibitors and duration of gestation. *J Clin Psychiatry.* 2013;74(7):e633–e635.
- Huybrechts KF, Sanghani RS, Avorn J, et al. Preterm birth and antidepressant medication use during pregnancy: a systematic review and meta-analysis. *PLoS ONE.* 2014;9(3):e92778.
- Warburton W, Hertzman C, Oberlander TF. A register study of the impact of stopping third trimester selective serotonin reuptake inhibitor exposure on neonatal health. *Acta Psychiatr Scand.* 2010;121(6):471–479.
- Udechuku A, Nguyen T, Hill R, et al. Antidepressants in pregnancy: a systematic review. *Aust N Z J Psychiatry.* 2010;44(11):978–996.
- Deligiannidis KM, Byatt N, Freeman MP. Pharmacotherapy for mood disorders in pregnancy: a review of pharmacokinetic changes and clinical recommendations for therapeutic drug monitoring. *J Clin Psychopharmacol.* 2014;34(2):244–255.
- Knadler MP, Lobo E, Chappell J, et al. Duloxetine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet.* 2011;50(5):281–294.
- Waldschmitt C, Vogel F, Pfuhlmann B, et al. Duloxetine serum concentrations and clinical effects. Data from a therapeutic drug monitoring (TDM) survey. *Pharmacopsychiatry.* 2009;42(5):189–193.
- Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Obstet Gynecol.* 2009;114(3):703–713.
- Carter NJ, McCormack PL. Duloxetine: a review of its use in the treatment of generalized anxiety disorder. *CNS Drugs.* 2009;23(6):523–541.
- Kumar N, Sangeetha D, Reddy PS, et al. Development and validation of a dissolution test for delayed release capsule formulation of duloxetine hydrochloride. *Curr Pharmaceutical Anal.* 2012;8(3):236–246.
- Fritel X, Ringa V, Quiboef E, et al. Female urinary incontinence, from pregnancy to menopause: a review of epidemiological and pathophysiological findings. *Acta Obstet Gynecol Scand.* 2012;91(8):901–910.
- Sangsawang B. Risk factors for the development of stress urinary incontinence during pregnancy in primigravidae: a review of the literature. *Eur J Obstet Gynecol Reprod Biol.* 2014;178:27–34.
- Li J, Yang L, Pu C, et al. The role of duloxetine in stress urinary incontinence: a systematic review and meta-analysis. *Int Urol Nephrol.* 2013;45(3):679–686.
- Smith AL, Wein AJ. Urinary incontinence: pharmacotherapy options. *Ann Med.* 2011;43(6):461–476.

JOIN THE ONLINE DISCUSSION of this article at

**PSYCHIATRIST.COM** Enter Keyword **PRACTICAL**