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LEARNING OBJECTIVES

Upon successful completion of this lesson, you should be able to:

1. describe the risks associated with undertreating depressive disorders during pregnancy
2. apply the available data regarding the likelihood of adverse fetal outcomes related to exposure to antidepressant medications during pregnancy
3. explain the optimal treatment approaches in selected clinical situations for depression during pregnancy
4. discuss the implications of taking antidepressant medication while breastfeeding
5. outline the role of the pharmacist in assisting in the management of depression during pregnancy

INSTRUCTIONS

1. After carefully reading this lesson, study each question in the post-test and select the one option you believe is the best answer. Although more than one option may be considered acceptable, only one option is the *best* answer.
2. To pass this lesson, a grade of at least 70% (14 out of 20) is required. If you pass, your CEU(s) will be recorded with the relevant provincial authority(ies). (Note: some provinces require individual pharmacists to notify them.)

ANSWERING OPTIONS

- A. For immediate results, answer online at www.pharmacygateway.ca.
- B. Mail or fax the printed answer card to (416) 764-3937. Your reply card will be marked and you will be advised of your results within six to eight weeks in a letter from *Pharmacy Practice*.

The use of antidepressants in pregnancy: an update

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Depressive disorders are among the most common disorders encountered in health care. More than one million Canadians suffer from some form of depressive illness at any given time.¹ Precise prevalence is unknown as less than half of depressed adults actually seek treatment. The estimated lifetime prevalence of major depression has been found to be 20.4% in women and 9.6% in men.²

Individuals undergoing a major depressive episode may experience some, many or all of the symptoms listed in Table 1. As a consequence of these symptoms, patients may find moderate to severe difficulty keeping up their job or schooling, social relationships and/or self-care and hygiene. The goals of treatment are to avoid or to minimize the functional losses related to depressive illness. Antidepressant medications play a major part in the treatment of depression, achieving maximal recovery, reducing the likelihood of depressive relapse, and maximizing quality of life.³

The avoidance of nonessential medications during pregnancy is clearly desirable. Maintaining prescribed anti-

depressant therapy may, however, reduce the risk of a depressive episode in susceptible women who are pregnant. When pregnant women experience a major depressive episode, both maternal and fetal outcomes are adversely affected.^{4,5}

The prevalence of depressive disorders during pregnancy has been estimated at approximately 10–20%.^{6,7} For women with a history of recurrent major depression, stopping antidepressant therapy during pregnancy has been correlated with relapse

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table 1

Symptoms (warning signs) of depression^{*55}

- persistent sad, anxious, “empty” mood
- feelings of hopelessness, pessimism
- feelings of guilt, worthlessness, helplessness
- loss of interest or pleasure in hobbies and activities that were once enjoyed, including sex
- decreased energy, fatigue; being “slowed down”
- difficulty concentrating, remembering, making decisions
- insomnia, early-morning awakening or oversleeping
- appetite and/or weight loss, or overeating and weight gain
- thoughts of death or suicide; suicide attempts
- restlessness, irritability
- persistent physical symptoms (e.g., headaches, digestive disorders, chronic pain) that do not respond to treatment

***Not everyone who is depressed experiences all symptoms. Some people experience only a few symptoms, some many symptoms. Severity of symptoms varies with individuals and also varies over time.**

rates as high as 70%.⁸ Estimating the risk of a depressive episode (either initial or recurrent) for an individual patient is an inexact science, at best.

A woman’s initial episode of depression may occur during pregnancy or in the postpartum period.⁹ The precise incidence of this phenomenon is unknown. For women with a history of depression who stop their medication near the time of conception, the risk of relapse is particularly high during the first trimester.³ For women experiencing a depressive episode at the time of delivery, at least half will suffer from postpartum depression, as well.⁹ The adverse impacts of untreated depression are well-documented.^{6,9} In order to help patients and practitioners make an informed decision regarding the use of antidepressants during pregnancy, it is vital to consider the evidence with respect to the relative risks and benefits of these drugs.

There is evidence supporting the safety and effectiveness of antidepressant use during pregnancy, however it is incomplete.¹⁰ Randomized prospective controlled trials in pregnancy are difficult to justify on ethical grounds. Matching a control group exactly is extremely challenging. The data we do have consist largely of retrospective epidemiological studies. Separating the adverse outcomes related to medication versus undertreatment versus the effect of depression, itself, is extremely problematic. These factors limit the ability to make firm recommendations about the

use of drugs in pregnancy.¹¹

This lesson will discuss the consequences of untreated depression during pregnancy, as well as focus on the potential risks to the fetus/neonate of selected antidepressants. In particular, the latter will examine effects related to fetal development (teratogenicity), late-term exposure (toxicities), and long-term effects (neurobehavioural). Breastfeeding will be briefly addressed and a list of resources for the pharmacist will be provided.

Consequences of untreated depression during pregnancy

Individuals with a history of major depression (especially those currently experiencing a depressive episode), place themselves at risk of exacerbation when antidepressant medication is diminished or discontinued. An exacerbation of depression can have a detrimental impact on the behaviour, emotions and functional status of a woman who is pregnant.⁴ The abrupt discontinuation of antidepressant medication is to be avoided whenever possible. At a minimum, such action is very likely to lead to uncomfortable symptoms for the patient. Rapid escalation of depressive symptoms and/or suicidality may also result from abrupt cessation of therapy.^{1,3,9}

The risks of discontinuing effective antidepressant therapy due to pregnancy were highlighted by a recent study. This study examined a cohort of women with a history of depression who had been

euthymic (mood disorder in remission) for at least three months prior to their last menstrual period. All had been taking antidepressant medication prior to conception. In this study, women who stopped their antidepressant medication near the time of conception were almost three times more likely to have a relapse of depression during pregnancy than women who continued their pharmacologic therapy (68% vs. 26%).⁸

Depression can contribute to poor prenatal care and to inadequate nutrition of mother and neonate. It may also lead to an increased risk of drug and alcohol use, and suicidal ideation.¹² Should a depressive state be present near the time of delivery, the probability it will persist or worsen postpartum is extremely high.¹³ A consensus statement from the U.S. National Depressive and Manic-Depressive Association concludes that 15% of women who do not treat an active depressive episode during pregnancy will attempt suicide, while 50–62% will continue to suffer from depression in the postpartum period.¹⁴

Uncontrolled depression during pregnancy has been associated with other important adverse outcomes, including perinatal and birth complications, bleeding during gestation, preeclampsia, spontaneous abortion, preterm deliveries, increased uterine artery resistance, spontaneous early labour, low infant birth weight, low Apgar scores, admission to a neonatal care unit, neonatal growth retardation and disturbances in mother-child interactions.^{9,14}

Adverse outcomes for infants born to depressed mothers may be correlated with unfavourable maternal/infant biochemical profiles. Both depressed women and their newborn infants often have elevated cortisol and norepinephrine levels and reduced dopamine and serotonin levels compared to controls.¹⁵ Elevated cortisol levels also result from high levels of anxiety.¹⁵

An association has been made between maternal anxiety and/or depression and increased uterine artery resistance leading to reduced blood flow to the fetus. This phenomenon appears to be mediated by elevated maternal cortisol and norepinephrine levels, and may explain the increased risks of delayed growth, premature birth,

and reduced birth weight noted in infants born to depressed mothers.¹⁵

Some combination of the abnormalities in cortisol, norepinephrine, dopamine, and serotonin levels may also account for the increased occurrences of elevated frontal EEG activation, elevated physical activity and lower vagal tone found in neonates born to depressed mothers.¹⁵

Biochemical imbalances may affect mother-infant interactions which, in turn, can impair parent-child bonding. The emotional and cognitive development of the child may then be adversely affected.^{4,15}

While sound evidence connecting all these negative outcomes to biochemical changes related to uncontrolled depression may not be available, it is clear that the prevention of depression or depressive relapse during pregnancy offers advantages for mother and child.⁴

Risks associated with antidepressant medications

Virtually no medication can be described as *completely* safe during pregnancy. Most evidence suggests the likelihood of adverse neonatal outcomes related to antidepressant exposure is relatively small.^{10,16} The body of literature which leads to this generalization is substantial, although far from ideal. Additional evidence is needed.

A rational decision regarding the use of antidepressant medication during pregnancy should ideally factor in the mother's perspectives, values, current status and psychiatric history.^{6,12} These considerations may supersede the clinical data available for these medications. A more complete understanding of the implications of available data can help guide and support the decision-making process.

DEVELOPMENTAL EFFECTS

Selective serotonin reuptake inhibitors

Paroxetine

The frequency of congenital cardiac malformations in the U.S. has been estimated at one per cent.^{17,18} The overall baseline frequency of congenital malformations in the general population is considered to be between one and three per cent.^{19,20} An epidemiological study based on Swedish medical birth-registry data found roughly a twofold increased risk of cardiac malformations in infants exposed to paro-

xetine. A total of 20 infants in the paroxetine-exposed group had congenital cardiac defects. Of these 20 infants, 13 had ventricular and/or atrial septal defects.²¹ In the most recent report of this study, the investigators determined a risk ratio (RR) of 1.63 for any cardiac malformation and a RR of 1.81 for septal defects related to paroxetine exposure within the first trimester, when compared to infants not exposed to paroxetine.²¹ (A RR of 1.81 means that infants exposed to paroxetine in the first trimester were found to be 1.81 times more likely to have septal defects than those infants who were not exposed to antidepressants in the first trimester.)

A recent Canadian study which examined the association between congenital cardiac malformations and exposure to paroxetine added an investigation for a dose-response relationship. The investigators included only major cardiac malformations which did not resolve spontaneously, in order to be consistent with World Health Organization criteria. In this study, 10 of 509 (1.96%) paroxetine-exposed infants had cardiac malformations. For infants exposed to other antidepressants, the corresponding numbers were 14 of 817 (1.71%). These investigators determined a RR of 1.38, suggesting a trend toward increased risk of cardiac malformations with first trimester paroxetine exposure compared to exposure with other antidepressants. When apparent paroxetine dosage was considered, an important dose-response relationship was observed. At dosages of 25 mg per day or less, the risk of cardiac malformations was not significantly different from the one per cent value found in the general population (5 of 371 or 1.35%). The authors did find a twofold risk for *any* major malformation (RR = 2.23) and a threefold risk of cardiac malformations (RR = 3.07) with paroxetine exposure at dosages greater than 25 mg per day. The actual occurrence rate observed in this higher-dose group was 3.62% (5 of 138).¹⁷

Other studies have found associations between early paroxetine exposure and increased risk for septal defects in infants.²²⁻²⁴ Studies which have failed to show such an association are also found in the literature.^{25,26}

Further epidemiologic evidence is

needed to more clearly delineate the risk of cardiovascular malformations for infants exposed to paroxetine during the first trimester. The defects implicated are rare and the absolute risks are relatively small. A large proportion of neonatal ventricular septal defects also resolve spontaneously. Pending further evidence it would be prudent to exercise caution in initiating paroxetine during the first trimester or in a patient attempting to become pregnant. For patients established on paroxetine, current evidence is insufficient to justify discontinuation of therapy without regard for the clinical situation. Abrupt discontinuation is to be discouraged. Strategies involving dosage reduction or switching antidepressant agents should be considered only after careful evaluation of patient-specific factors. There will be clinical scenarios in which the use of paroxetine during pregnancy represents the best risk/benefit balance.

Sertraline

The majority of data regarding the safety of sertraline in early pregnancy raises no particular concern.²⁷ One study is discordant with the larger body of data, having found an increased risk of cardiac septal defects and omphalocele (a protrusion at birth of part of the intestine through a defect in the abdominal wall covered only by a thin transparent membrane).²⁴ The overall significance of this study is uncertain. The absolute patient numbers are small and these findings have not been replicated.

Fluoxetine

This medication was the first selective serotonin reuptake inhibitor (SSRI) to reach clinical practice. The available animal and human data with this agent appear to indicate it is not associated with major congenital malformations.²⁸ The additional years and volume of experience with this agent has led to some recommendations that fluoxetine be a preferred antidepressant for initiation of therapy in pregnant women or those who are considering pregnancy. Switching from an effective established antidepressant to fluoxetine is a different situation and usually unnecessary. In particular, the risk of decompensation associated with switching antidepressants is significant.²⁹

Citalopram/escitalopram

A Motherisk study examined the outcomes related to first trimester exposure to citalopram and did not find any adverse association.³⁰ Escitalopram, the S-enantiomer of racemic citalopram, would be expected to be very similar to citalopram and the other SSRIs in terms of risk/benefit regarding use in pregnancy. Caution is advised in the use of escitalopram as the introduction of this isomer is relatively recent.

Fluvoxamine

Exposure to fluvoxamine during the first trimester has not been shown to significantly increase risk of major malformations, prematurity or miscarriage but data are extremely limited.¹⁹

Other Antidepressants

Tricyclic and MAOI antidepressants

Although there were preliminary concerns regarding limb malformations, more than a dozen recognized studies have found no association between tricyclic antidepressants and congenital malformations.^{6,9}

Despite decades of availability, there is a definite lack of data regarding monoamine oxidase inhibitors (MAOIs) in pregnancy. This is the primary reason MAOIs are best avoided in pregnant women.⁹ As well, the potential for hypertensive emergencies related to MAOIs may be small but cannot be overlooked. Contraindications associated with MAOIs (including medications used to prevent preterm labour) are also of concern.⁹

Venlafaxine

A single, published controlled study of venlafaxine use in pregnancy examined the outcomes of 150 women treated with venlafaxine during the first trimester. The authors concluded that the risk for major malformations was similar for both venlafaxine exposure and SSRI exposure.²⁰ In both groups, the results suggest no elevation of risk beyond the baseline rate of one to three per cent for any major malformations. The significance of this study is limited primarily by the small number of subjects. Other studies, having limitations of their own, are consistent with this finding.^{10,16,27}

Mirtazapine

Mirtazapine exposure does not appear to increase the rate of major malformations above the baseline rate of one to three per cent.^{10,31} Animal studies using 17–20 times the maximum recommended human dose have shown no evidence of teratogenicity.³² The evidence currently available is extremely limited.

Bupropion

The prevalence of congenital malformations among infants exposed to bupropion in the first trimester was within the one to three per cent baseline for the general population and comparable to that of infants exposed to other antidepressants in a study of 1,213 bupropion-exposed infants.³³ Concerns regarding malformations raised in some animal models have not been supported in human experience to date.³³

Moclobemide

The use of this medication in pregnant women has not been systematically studied. Current literature consists primarily of case reports.³⁴ While this limited information has raised no major concern, the absence of reliable data renders the use of moclobemide during pregnancy uncertain.

LATE EXPOSURE EFFECTS

Some studies show a small but significant increase in the risk of spontaneous abortion related to antidepressant use during pregnancy.³⁵ Maternal depression has also been associated with this adverse outcome.¹⁴ When control groups adequately reflect a population likely to be considered for antidepressant therapy, a significantly increased risk related to antidepressants has not been replicated.¹⁰ Interpretation of research in this area faces the problem of factoring out the effects of depressive illness from the effects of medications.

Exposure to SSRIs and other serotonergic antidepressants (Table 2) during the third trimester has been associated with a usually mild and self-limiting condition called neonatal adaptation syndrome.³⁶ Symptoms may include jitteriness, irritability, shivering, tremor, constant crying, feeding or sleeping problems, gastrointestinal symptoms, increased tonus, convulsions, tachypnea and/or respiratory

distress.¹⁰ An infant's presentation may be consistent with SSRI withdrawal, serotonergic toxicity or components of both phenomena.^{37,38}

Neonatal adaptation syndrome may become apparent in the newborn almost immediately or may be delayed for a few days. Neonates exposed to highly serotonergic agents near the time of birth should be observed for adverse effects during the first seven to 10 days of life.^{36,37}

Neonates exposed to serotonergic agents near term also have a higher probability of being admitted to special-care nurseries. A study from the Motherisk program examined the outcomes in 55 neonates exposed to paroxetine during the third trimester of gestation. The authors found that 22% of these infants had complications (mainly respiratory distress) requiring more intensive treatment and prolonging hospitalization.³⁹ The rate of similar complications in the control group was six per cent. Respiratory distress and related symptoms from serotonergic medications usually resolve within three to five days. These complications tend to be more problematic for premature infants, likely due to incomplete lung tissue development. All complications reported in this study disappeared within one to two weeks.³⁹

A systematic review of available data found that late exposure to SSRIs increased the risk of respiratory difficulty but pointed out that no deaths attributable to the syndrome had been identified.²⁶ The neurological status of infants experiencing these respiratory effects is expected to be indistinguishable from that of other infants within the first four weeks of life.²⁶

Another study reported an association between maternal use of SSRIs after week 20 of gestation and the presence of persistent pulmonary hypertension of the newborn (PPHN). The researchers reported a relative risk of 6.1 for PPHN related to maternal ingestion of an SSRI during the latter half of pregnancy.⁴⁰ This study has been widely criticized regarding its diagnostic criteria for PPHN. This criticism and extremely low mortality rates in both control and study groups makes the significance of this study uncertain.

Antidepressant drugs available in

table 2

Serotonergic activity of selected antidepressant drugs*56-58		
Drug name	Drug class	Serotonergic activity
citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	SSRI	++++
clomipramine	tricyclic (tertiary amine)	++++
amitriptyline	tricyclic (tertiary amine)	+++
phenelzine, tranylcypromine, moclobemide	MAOI	+++
trazodone	triazolopyridine	+++ (higher doses)
imipramine, trimipramine, doxepin	tricyclic (tertiary amine)	++
desipramine, nortriptyline, protriptyline	tricyclic (secondary amine)	+
bupropion	aminoketone	+

*This table is meant to serve as a general guide to the serotonergic activity of antidepressant medications. It is NOT intended as a definitive pharmacologic reference.
MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor
++++ = high serotonergic activity; + = low serotonergic activity

Canada are chemically quite distinct. In terms of potential benefits and risks related to use during pregnancy, evidence related to one agent may not be accurately attributed to other agents as a “class effect.” Findings related to PPHN, cardiac septal defects, respiratory effects and adaptational symptoms raise valid concerns. The majority of available evidence, however, generally supports the relative safety of antidepressant use during pregnancy.¹⁰

LONG-TERM EFFECTS

The possibility of altered neurocognitive development secondary to antidepressant exposure in utero has been raised by some studies in rodents.⁴¹ Impaired performance or impaired neuronal activity has been found in some rat models but has been absent in others. Dosing on a mg/kg basis has been quite high in some of this research.⁴²

Three studies in human children exposed to tricyclic antidepressants or to fluoxetine in utero have found no significant difference in IQ, language or behaviour.⁴³⁻⁴⁵ Some of this research has followed children to preschool age and beyond. A seven-year followup study of children exposed to fluoxetine during pregnancy found no evidence of adverse behavioural consequences to neonatal drug exposure.⁴⁴ Further research

is needed, especially with other antidepressants, to definitively answer the difficult question of long-term impacts. Current data cannot exclude the possibility of unforeseen long-term neurobehavioural consequences as a result of antidepressant exposure in utero. On the other hand, neurobehavioural dysfunction in children has been associated with maternal depression during pregnancy or in the postpartum period.⁴³

Breastfeeding considerations

For many patients, the use of antidepressant medications in the postpartum period will be of vital importance. The risk of developing postpartum depression ranges from 13–62%, depending on the patient population studied.⁴⁶

All antidepressants will find their way into the breast milk of lactating patients. Plasma levels of these drugs in breastfeeding infants are generally below or just above the limit of detection.⁵ The American Academy of Pediatrics considers a medication compatible with breastfeeding in most situations when the dosage ingested by the infant is < 10% of the weight-adjusted maternal dose.⁴⁷

Citalopram and fluoxetine are more likely than the other SSRIs to result in significant levels in the serum of a breastfeeding infant.

For citalopram, the dose ingested has been calculated at 0.7–5.9%.¹⁶ One breast excretion study estimated the mean daily dose of “fluoxetine equivalents” (a calculation used to account for both fluoxetine and norfluoxetine) to be about 10.8% of the weight-adjusted maternal dose.⁴⁷ In this study, the mothers reported no adverse effects in nursing infants. One review found no published reports of adverse outcomes related to breastfeeding while taking fluvoxamine, paroxetine or sertraline.⁴⁶ In 2001, sertraline was recommended as first-line treatment during breastfeeding, based on multiple case series reports.¹¹ Tricyclic antidepressants do not generally achieve measurable levels in nursing infants.⁴⁶

Existing evidence for bupropion, moclobemide, trazodone, venlafaxine and the nonreversible MAOIs raises no particular concerns related to breastfeeding, but is extremely limited.⁴⁸

In summary, sertraline, fluvoxamine, paroxetine or tricyclic antidepressants would appear to be the safest choices with respect to breastfeeding. Current evidence is, however, generally regarded as insufficient to justify *switching* medications to one of the above for the majority of breastfeeding women who are already taking antidepressant medication. Strategies designed to minimize exposure through breast milk are impractical, and clear benefit has not been demonstrated. In the absence of a patient-physician consultation, stopping antidepressant therapy solely because of a desire to breastfeed is to be strongly discouraged.

Therapeutic considerations

The broad spectrum of depressive disorders dictates that decisions regarding antidepressant therapy must be made on an individual basis. Discontinuing or modifying effective treatment is associated with an increased risk of relapse, a greater severity of illness and increased suicidality.^{6,49} For patients with a history of illness that is less recent, less persistent or less severe (especially where psychosocial supports are adequate or better), the risks associated with altering or stopping medication may be diminished.^{6,16} It is important to note that depression during pregnancy is the most reliable predictor of postpartum

depression.^{14,50} Evidence suggests approximately 25% of postpartum depressions actually begin during pregnancy.⁷

None of the antidepressants currently available in Canada are considered contraindicated in pregnancy.^{51,52} The risk of congenital malformations related to their use appears to be quite low. This risk may be somewhat greater with paroxetine. For initiation during pregnancy, fluoxetine may be advantageous based on greater volume and duration of clinical experience.⁵³ A thorough patient history and assessment of current risk are critical factors in drug treatment decisions.

For women who have maintained a good response to medication during the first and second trimesters, it has been suggested by some that a dose reduction be attempted during the last trimester.⁵⁴ Given the risks associated with postpartum depression and a lack of evidence of clinical benefit (e.g., neonatal adaptation problems have not been found to be dose-related), this practice cannot routinely be encouraged. The patient and physician must weigh the relative merits of minimizing late exposure effects on the neonate against the relative risk of third-trimester or postpartum relapse.

The reduction of stressors through optimizing psychosocial supports, through lifestyle simplification and through support from professional interactions, would intuitively seem beneficial. A reduction of stress and anxiety will likely result in a reduction of serum cortisol and norepinephrine levels in mother and neonate.¹⁵ As noted earlier, such reductions may have advantageous influences on blood flow to the fetus. A reduction of stressors seems likely to contribute to improved maternal and fetal outcomes.

The pharmacist's role

Pharmacists can play a major role in the care of depressed patients. A key factor for pharmacists is to have full appreciation for what they *do* know (reviewing, accessing, interpreting the medical literature), and for what they might *not know* (the patient's history, current status, communication between the patient and her physician).

In terms of adding to information upon which treatment decisions are based, pharmacists can enhance access to credible

drug information. Table 3 lists resources on antidepressants, pregnancy and lactation for pharmacists.


Pharmacists' counselling of and support for patients may be of tremendous value. Pharmacists are uniquely positioned to support the alliance between patient and physician and to support decisions regarding antidepressant use. Care must be taken to avoid providing information that appears contradictory. For all depressed patients, pharmacists can strongly advise against the abrupt discontinuation of antidepressant medication prior to discussion with their physician.

Pharmacists are intuitively sensitive to the value of avoiding undue medication during pregnancy. They need to be fully cognizant of the potential patient/fetus risks of nonadherence with necessary medications. In situations where a decision to stop antidepressants has been made, pharmacists should generally advise tapering these agents as opposed to abrupt discontinuation.^{10,11,29}

Pharmacists may also serve a valuable role in the early detection of depression. This can be accomplished through direct open communication with their patients and by educating the patient regarding recognizing and responding to early warning signs of decompensation (Table 1).

This is particularly important when antidepressant therapy is modified, when adherence may be suspect, during pregnancy or in the postpartum period. Addressing relapse in its earliest stages is a vital component in minimizing associated morbidity and mortality.

Summary

Optimal management of a depressive disorder during pregnancy may vary widely from one individual to another. The principle of minimizing neonatal exposure to all unnecessary medications is a cornerstone of reducing risk. The achievement and maintenance of health and wellness for expectant mothers is also of clear benefit. Decisions regarding antidepressant therapy are best made following a comprehensive review of a variety of factors and in the context of a patient-centred process. Pharmacists can play a key role in the provision of information, in the education and support of the patient and in the monitoring and promotion of overall patient health. 

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table 3

Recommended references for pharmacists and consumers

1. *Depression in Pregnancy*. Public Health Agency Canada. www.phac-aspc.gc.ca/mh-sm/preg_dep_e.html
2. The Motherisk program at The Hospital for Sick Children is a clinical, research and teaching program that provides evidence-based information and guidance about the safety or risk to the developing fetus or infant, of maternal exposure to drugs, chemicals, diseases, radiation and environmental agents. There are two sites—one for professionals and one for laypersons. www.motherisk.org
3. *Is It Safe for My Baby? Risks and Recommendations for the Use of Medication, Alcohol, Tobacco and other Drugs during Pregnancy and Breastfeeding* is a reference for women. Centre for Addiction and Mental Health. www.camh.net/Publications/CAMH_Publications/is_it_safe_my_baby.html
In the "Related Links" on the right-hand side there is a link for live and archived webinars based on the CAMH publication *Exposure to Psychotropic Medication and Other Substances during Pregnancy and Lactation: A Handbook for Health Care Providers*, and a link to information in the reference book *Postpartum Depression: A Guide for Front-Line Health and Social Service Providers*.
4. Drugs and Lactation Database (LactMed) is part of Toxnet from the US National Library of Medicine. It is a peer-reviewed and fully referenced database of drugs to which breastfeeding mothers may be exposed. Among the data included are maternal and infant levels of drugs, possible effects on breastfed infants and on lactation, and alternate drugs to consider. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

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Questions

To answer online, go to www.pharmacygateway.ca, CE section, CE Online, Pharmacy Practice

1 Data about the safety of antidepressants in pregnancy comes primarily from:

- randomized prospective controlled trials
- case-control research
- retrospective epidemiological studies
- none of the above

2 Depressed women who stop their antidepressant during pregnancy increase their risk for postpartum depression.

- true
- false

3 By which of the following mechanisms can maternal depression adversely affect the fetus?

- increased maternal suicidality
- inadequate maternal nutrition
- poor maternal prenatal care
- increased maternal alcohol/substance abuse
- all of the above

4 Increased maternal uterine arterial resistance secondary to neurotransmitter imbalance may explain which of the following adverse neonatal outcomes?

- ventricular septal defects
- limb malformations
- prematute birth
- cleft palate

5 A woman's initial episode of depression can occur:

- prior to conception
- during pregnancy
- in the postpartum period
- a) or b)
- during any of the above

6 Which of the following has not been associated with uncontrolled depression during pregnancy?

- disturbances in mother-child interactions
- major neonatal malformations
- low birth weight
- birth complications

Questions

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7 When is depressive relapse *most likely* to first appear in a woman with a history of depression who discontinues her antidepressant medication near the time of conception?

- a) within 48 hours of stopping medication
- b) within the first trimester
- c) within the second trimester
- d) within the third trimester
- e) during the postpartum period

8 Both maternal depression and the use of antidepressants have been associated with spontaneous abortion.

- a) true
- b) false

9 Within the general population, roughly what percentage of women will experience depression during their pregnancy?

- a) 1 %
- b) 5 %
- c) 15 %
- d) 50 %
- e) 80 %

10 Of all the antidepressants, fluoxetine may be advantageous for initiation of therapy during pregnancy based on its greater volume and duration of clinical experience.

- a) true
- b) false

11 Abrupt discontinuation of an antidepressant can lead to:

- a) uncomfortable symptoms for the patient
- b) rapid escalation of depressive symptoms
- c) suicidal ideas
- d) both a) and b)
- e) all of the above

12 Where there is little therapeutic rationale for the selection of one agent over another, which of the following raises the least concern regarding breastfeeding?

- a) venlafaxine and bupropion
- b) citalopram and mirtazapine
- c) sertraline and fluvoxamine
- d) fluoxetine and paroxetine

13 Within the current literature, it would appear that:

- a) Paroxetine is a poor choice for mothers who are breastfeeding.
- b) For most patients, it is rational and safe to reduce their paroxetine dosage during the third trimester.
- c) Paroxetine may have a higher risk of congenital malformations when compared to the other SSRIs.
- d) Continuing paroxetine during the third trimester

may increase the risk of neonatal adaptation syndrome.

- e) Both c) and d) are true.

14 With regard to venlafaxine, we can confidently state that:

- a) The SSRIs are a safer choice than venlafaxine for all pregnant women.
- b) Although somewhat limited, current information suggests this medication is not a major teratogen.
- c) The first trimester use of venlafaxine is associated with persistent pulmonary hypertension of the newborn (PPHN).
- d) Venlafaxine should not be taken during pregnancy, even if the patient has a superior response to this agent.
- e) Both b) and c) are true.

15 For paroxetine, which of the following statements is/are true?

- a) The association between increased ventricular septal defects and first trimester exposure to paroxetine has been replicated in all studies with this drug.
- b) The ventricular septal defects reported with paroxetine are likely to resolve spontaneously.
- c) According to one study, the risk of cardiac malformations from paroxetine is greater at doses of 12.5 mg/day or more.
- d) Women who are doing well on paroxetine and find out they are pregnant should stop this drug right away to avoid fetal cardiac malformations.
- e) Both b) and d) are true.

16 A patient has managed her depression quite well on clomipramine for the last three years. She is now pregnant. For this patient, which statement(s) is/are true?

- a) Based on evidence pertaining to fetal safety, she should be switched to an SSRI.
- b) She should be made aware of the evidence that shows tricyclic antidepressants are likely to be highly teratogenic.
- c) She can likely continue taking clomipramine at her current dosage after discussing this issue with her doctor.
- d) Patient and doctor should be advised that she cannot continue this medication if she plans on breastfeeding.
- e) Both c) and d) are true.

17 Regarding neonatal adaptation syndrome and respiratory impairment in infants born to women taking a serotonergic antidepressant throughout pregnancy, which of the following statements is/are true?

- a) Symptoms of neonatal adaptation syndrome are related to serotonergic withdrawal only, and tend to appear within six to 12 hours of birth.
- b) Symptoms of neonatal adaptation syndrome are related to serotonergic toxicity only, and are expected to last about seven days.
- c) Respiratory distress related to antidepressant exposure is more likely to be problematic in premature infants.
- d) Both a) and c) are true.
- e) Both b) and c) are true.

18 Which of the following is/are true with respect to long-term neurobehavioural effects in the neonate?

- a) These effects may be associated with maternal depression during pregnancy and/or in the postpartum period.
- b) Animal models have suggested these effects are a possible consequence of maternal antidepressant use.
- c) These effects are more likely to occur in children exposed to fluoxetine in utero.
- d) Both a) and b) are true.
- e) All of the above are true.

19 Regarding antidepressant drug selection for patients who are pregnant, which of the following statements is/are false?

- a) Bupropion may be preferable to moclobemide, based on evidence of major malformations related to moclobemide.
- b) Citalopram may be preferable to paroxetine based on the evidence regarding ventricular septal defects.
- c) Current evidence does not establish an advantage for escitalopram, in comparison to citalopram.
- d) When depression is controlled, switching medication from paroxetine to fluoxetine during pregnancy increases the risk of depressive relapse.
- e) Both a) and d) are false.

20 A newly pregnant patient is not well-controlled on her current antidepressant. The doctor would like to switch her to sertraline and asks the pharmacist if this is a safe antidepressant in pregnancy. The pharmacist should tell the doctor to avoid sertraline in pregnancy due to the risk of:

- a) ventricular septal defects
- b) omphacele
- c) interactions with drugs used to help prevent preterm labour
- d) all of the above
- e) none of the above

ce faculty

THIS MONTH

The use of antidepressants in pregnancy: an update

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All lessons are reviewed by a minimum of six pharmacists for accuracy, currency and relevance to current pharmacy practice.

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