

BRANCH OUT

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A Review: Serotonin Reuptake Inhibitors in Lactation

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For decades healthcare professionals and researchers alike have been promoting breastfeeding as the primary source of infant nutrition in early life. Health Canada recommends exclusive breastfeeding for the first six months postpartum and for another year-and-a-half thereafter in combination with supplemental foods.¹ The benefits of breastfeeding to both mom and baby have been long understood and make breastfeeding a more favourable option. For baby, breast milk offers a balanced mixture of carbohydrate, protein and fats necessary for optimum growth and development; it also provides infants with essential immunological elements that aid in protection against the development of allergies, gastrointestinal diseases, etc. For mother, breastfeeding aids in the return to pre-pregnancy weight, protects against premenopausal breast cancer, and so on.^{1,2,6,7} Despite these advantages, mothers are often faced with concerns regarding medication usage while lactating. Decision making is often based on a risk versus benefit scenario. With a striking 13% of all women developing depression in the postpartum period, the decision to initiate drug therapy during lactation may be one many clinicians and new mothers must consider.^{7,8} Selective serotonin reuptake inhibitors (SSRIs) are frequently recommended as first line agents in the management of postpartum depression.^{5,8} This article will aim to review the safety of SSRIs and venlafaxine in lactation.



A number of factors must be considered when assessing drug safety during lactation including drug transfer, properties promoting transfer, and factors influencing the relative infant dose (RID). The transfer of a medication into breast milk occurs by the process of passive diffusion. Passive diffusion occurs only when a concentration gradient is present (gradient can permit forward or retrograde diffusion) and the medication is in its unionized form and not bound to proteins. Accordingly, the properties of a drug which promote transfer into breast milk include low protein binding, high lipid solubility, and low molecular weight. Other factors that need to be considered in drug transfer are half-life, oral bioavailability and the degree of distribution of active metabolites. Medications with shorter half-lives and poor oral bioavailability tend to accumulate less in breast milk. Additional factors which influence the amount of drug an infant receives include: the amount of milk produced, the composition of the milk, the concentration of drug in breast milk and the extent to which the breast was emptied during the last feeding.^{1,2,3,4}

Methods are available to estimate the amount of medication a nursing infant receives. Hale uses the relative infant dose (RID) in most instances to determine exposure and states that an RID of less than 10% is safe. RID is calculated by

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Presenting.....

CSHP Vision 2010

In August 2006, CSHP Council Members, Branch presidents and presidents-elect, the CSHP executive and staff members met for a planning day. Utilizing a variety of tools and resources, including the results of an online membership survey and the CSHP 2015 document, Vision 2010 was created.

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At the same time, a new mission statement was also developed:

CSHP is the national voice of pharmacists committed to the advancement of safe, effective medication use and patient care in hospitals and related health care settings.

Over the next 3 years, CSHP encourages its members to participate in the strategies that will be created to achieve Vision 2010. This is a challenge to all members to expand the direction of their pharmacy practice to ensure hospital pharmacy continues to grow in the right direction!



Upcoming Events...

- Pharmacy Technician Conference, Sept 14-16, St. John's, NL
- PANL Annual Conference 2007 , Sept 28-30, Corner Brook, NL
- CSHP NL Branch AGM, Saturday , Sept 28, Corner Brook, NL
- CSHP Professional Practice Conference 2008, Feb 2-6, Toronto, ON

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Awards Committee

Congratulations to Jennifer Donovan, *Eastern Health*, on being awarded the Bayer/CSHP NL Branch Travel Grant to the National AGM in Regina!!



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dividing the dose in infants via milk in mg/kg/day by the dose in mother in mg/kg/day.³ The milk to plasma ratio (m/p) has also been used to estimate infant exposure. The m/p is the ratio between drug concentration in maternal milk and plasma. An acceptable ratio should be less than one. Drug clearance from an infant is not considered by either the RID or m/p ratio and is an important component in determining infant exposure.^{3,9} Therefore, all literature reporting these parameters should be reviewed with caution. The presumed clinical safety of SRIs is reported in table 2 below quoting both the LRC and AAP recommendations for medication use in lactation. Lactation risk categories (LRC) have been established for most drugs: L1 (safest), L2 (safer), L3 (moderately safe), L4 (possibly hazardous) and L5 (contraindicated). In addition, the American Academy of Pediatrics (AAP) reviews and reports the safety of drugs in lactation approximately every five years.

Table 1: Comparison of pharmacokinetic properties of SRIs*

SRI	Protein binding (%)	Half-life (hr)	Oral bioavail. (%)	Mol. Weight	Clinically Significant Metabolites
Fluoxetine	94.5	4-6 days**	95	309	yes
Fluvoxamine	80	15.6	53	318	no
Paroxetine	95	21	~50	329	no
Sertraline	99	27	36	306	yes
Citalopram	80	33	>/ 80	324	yes
Venlafaxine	27-30	5	45	314	no

*Adapted from References 2 & 3 (see references section)

**with chronic dosing; norfluoxetine (active metabolite) has $t_{1/2}$ of 4-16 days

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Table 2: Comparison of clinical properties of SRIs

SRI	m/p*	RID (%)*	LRC ^a	AAP ^a
Fluoxetine	0.68	6.5-11	L2***	**
Fluvoxamine	1.34-1.31	1.34-1.38	L2	**
Paroxetine	0.96	1.13-1.25	L2	**
Sertraline	1.93	0.2	L2	**
Citalopram	1.8	4.4-5.1	L3	Not re-viewed
Venlafaxine	2.5-4.8	5.5-7.6	L3	Not re-viewed

*m/p = milk / plasma ratio & RID adapted from data presented in Tables 2 & 3 of Drug Safety 2005

**Drugs whose effect on nursing infants is unknown but may be of concern

***L2 in older infants; L3 if used in neonatal period

a LRC & AAP review as reported by Hale (see reference section)

Determination of the safest SRI in lactation requires that both the pharmacokinetic and clinical findings of a drug be considered (see Tables 1 & 2). Review of these factors suggests that the amount of drug the infant receives through breast milk is invariably small.

Most researchers suggest the use of either sertraline or paroxetine in breastfeeding mothers to treat depression.^{3,4} Both medications have a relatively low RID (2.2 and 2.1 respectively), have strong protein binding capabilities, poor oral bioavailability (decreased absorption in an infant's GIT), high molecular weight and moderate $t_{1/2}$ compared to others in the same class. Sertraline is the most well studied of the group and has proven safety with no immediate adverse effects seen in infants.^{3,6,10} Sertraline, like citalopram and fluoxetine does have an active metabolite. But unlike fluoxetine, the N-methylsertraline metabolite is far less active than the parent compound and has been shown to be of low concentration in breast milk and plasma of infants.³ Paroxetine has not been evaluated as extensively as sertraline, however, the studies that have been conducted consistently report no detectable serum concentrations in nursing infants.^{3,10,11}

Fluoxetine should be avoided if possible. It has an extremely long half-life which can be attributed to its active metabolite (see table 1 above). Both the parent and metabolite permeate breast milk at levels equal to 1/5 to 1/4 of maternal plasma. The most recent Drug Safety review states that fluoxetine and its metabolite have a RID of 6.5-11% and infant plasma concentrations of 28-340 ng/mL and 38-250 ng/mL, respectively. This data is significantly higher than that listed for others within the same class. In addition, infants who were breastfed by mothers receiving fluoxetine have been reported to have reduced postnatal growth.^{3,6,9,10}

Fluvoxamine may offer some promise for use in breastfeeding as its RID is the lowest of those compared above. It also has a short half-life which is favourable. One concern surrounding this drug is that it exhibits moderate protein binding which is significant in comparison to the others in its class.^{2,3} Limitations facing fluvoxamine usage relate to its sedative effect and potential for drug interaction (Cont on page 5)

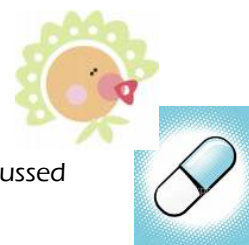
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Citalopram may be considered a second line treatment option when sertraline or paroxetine cannot be used. It is commonly prescribed for the treatment of depression due to a perceived favourable side effect profile. Citalopram's RID has been estimated at an acceptable 3.6%. It does have an active metabolite, desmethylcitalopram which is eight times less active than the parent compound.^{2,10} Drug Safety 2005 reports desmethylcitalopram to have a negligible RID and an infant plasma concentration of 2.2 ng/mL.

While not classified as an SSRI, Venlafaxine does inhibit the reuptake of serotonin in addition to other neurotransmitters. It has been studied only minimally in the lactating population and therefore should only be used when absolutely necessary pending further research.¹⁰ Hale reports it as L3 like citalopram. Its protein binding capabilities are minimal at 30% while its RID is 6.4%. Hence, its RID is higher than that for paroxetine or sertraline, but still below the 10% level.

Antidepressant selection for a lactating mother is not always an easy decision but should be based on the strength of evidence supporting a particular choice. Although the long term neurobehavioural effects of SRIs on infants exposed during lactation has not been determined consideration must be given to the risk of not treating depression when therapy is warranted. Sertraline or paroxetine should be a first line choice in any case for the reasons discussed above. While citalopram may be a reasonable alternative, further studies are warranted.



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It's that time of year again .



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