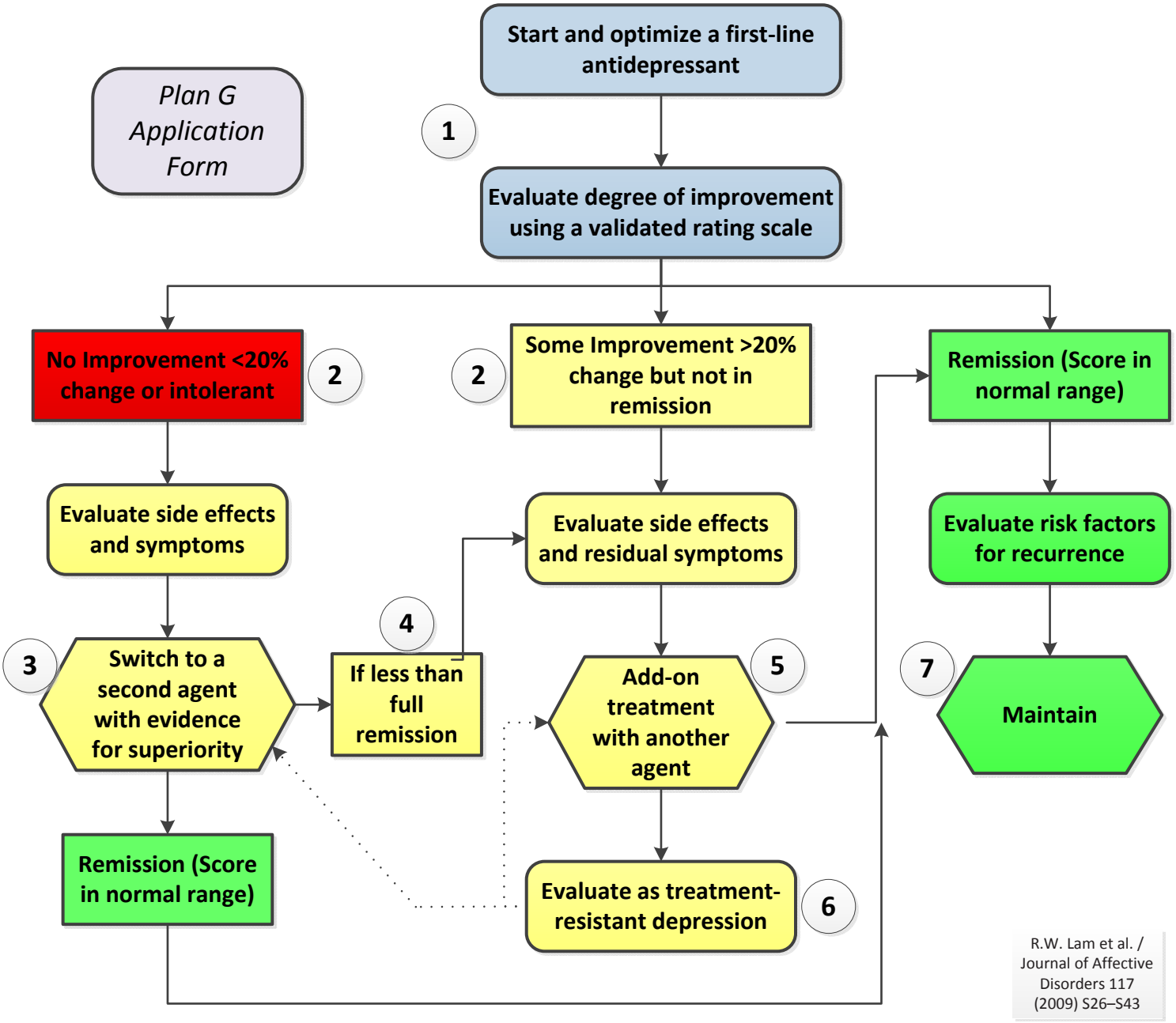

1. Initial improvement (defined as ≥20% reduction in symptom score) to a first-line antidepressant should be apparent within 1–4 weeks of achieving a therapeutic dose. If there is not at least an initial improvement within this time frame, and the drug is well tolerated, the dose should be increased. If there is still limited improvement, there should be a reassessment of diagnosis (especially comorbidity), degree of improvement (such as number and type of residual symptoms), adherence and tolerability.
2. At any step, depending on severity and patient preference, adding an evidence-based, non-pharmacological treatment (e.g., cognitive behavioural therapy, exercise, light therapy, etc.) or switching to a neurostimulation treatment (such as electroconvulsive therapy or transcranial magnetic stimulation) can be considered.
3. If there is no improvement (defined as b20% reduction in symptom score), switch to another antidepressant with evidence for superior efficacy.
4. If tolerability is an issue, switch to an antidepressant with a different side effect profile. 4) If there is no or limited improvement with the second monotherapy, an add-on treatment is recommended.
5. If there is some improvement but remission has not been achieved with the first-line antidepressant, and depending on tolerability, use an add-on treatment (adding another agent to the index antidepressant. The selection of medication for add-on treatment should be individualized depending on efficacy, side effect burden, and residual symptoms.
6. If there is limited response to add-on treatment, consider strategies for treatment-resistant depression (TRD). The pharmacotherapy options include using another add-on agent, or switching to another first-line antidepressant with some evidence for superiority, or to second and third-line antidepressants including TCAs (especially clomipramine), quetiapine, or MAO inhibitors.
7. After achieving full symptom remission, patients should be maintained on antidepressants for at least 6–9 months before stopping. Patients with risk factors for recurrence should have a personalized assessment for maintenance treatment. Most should be maintained on their antidepressant for at least 2 years and some may require lifetime maintenance. The dose of antidepressant for maintenance treatment should be the same as that required for acute treatment.

Antidepressant Medications

First-line	Switch to an agent with evidence for superiority	Duloxetine [Level 2] Escitalopram [Level 1] Milnacipran [Level 2] Mirtazapine [Level 2] Sertraline [Level 1] Venlafaxine [Level 1]
	Add-on another agent	Aripiprazole [Level 1] Lithium [Level 1] Olanzapine [Level 1] Risperidone [Level 2]

Second-line	Add-on another agent	Bupropion [Level 2] Mirtazapine [Level 2] Quetiapine [Level 2] Triiodothyronine [Level 2] Other antidepressant [Level 3]
	Switch to an agent with evidence for superiority, but with side effect limitations	Amitriptyline [Level 2] Clomipramine [Level 2] MAO Inhibitors [Level 2]

Third-line	Add-on another agent	Buspirone [Level 2] Modafinil [Level 2] Stimulants [Level 3] Ziprasidone [Level 3]

Unadjusted frequency of common adverse events as reported in product monographs of some second-generation antidepressants.

	Central nervous system				Anticholinergic				Cardiovascular			Gastrointestinal					Body as a whole		
	Drowsiness, sedation, somnolence	Insomnia	Headache	Tremor	Dry mouth	Blurred vision	Sweating	Delayed micturition	Dizziness/ orthostatic hypotension	Hypertension	Tachycardia, palpitation	GI pain/ distress	Nausea	Vomiting	Diarrhea	Constipation	Nervousness/ anxiety	Fatigue/ aesthenia	Dermatitis, rash
Citalopram	B	*	*	A	B	*	B	*	*	*	*	A	B	A	A	*	A	A	*
Escitalopram	A	A	*	*	A	*	A	*	A	*	*	A	B	*	A	A	A	A	*
Fluoxetine	B	B	*	B	B	*	A	*	*	*	*	A	B	*	*	*	B	*	A
Fluvoxamine	C	B	C	B	B	*	B	A	B	*	*	A	C	*	A	B	C	A	*
Paroxetine	B	B	B	A	B	A	B	A	B	*	*	A	B	A	B	B	A	*	A
Sertraline	B	B	C	B	B	A	A	A	B	*	A	A	C	A	B	A	B	B	A
Agomelatine	A	A	A	*	*	*	A	*	A	*	*	A	A	*	A	A	A	A	*
Bupropion	*	B	*	A	B	A	A	*	A	A	A	A	B	A	*	B	A	*	A
Desvenlafaxine	A	B	B	A	B	A	B	A	B	A	A	*	B	A	B	A	A	A	A
Duloxetine	A	B	A	A	B	A	A	A	A	A	A	A	C	A	A	B	A	A	*
Mianserin [b]																			
Milnacipran [b]																			
Mirtazapine	D	*	*	A	B	*	*	*	A	*	*	*	*	*	*	B	*	A	*
Moclobemide	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Reboxetine [b]																			
Quetiapine [b]																			
Selegiline [a]	A	B	B	*	A	A	*	*	B	A	A	A	*	*	A	*	A	A	C
Tianeptine [b]																			
Trazodone	C	A	A	A	B	A	*	A	B	*	A	B	*	*	*	A	*	B	A
Venlafaxine	B	B	B	A	B	A	B	A	B	A	A	A	C	A	A	B	B	*	A

Controlled release formulations are not listed—frequency of adverse events may be lower for those formulations.
A= 9% or lower, B= 10–29%, C= 30–49%, D= 50% or higher.
* = Lower than the threshold rate for reporting in monograph (usually 5% or less).

[a] Some rates may be equal to, or less than, those reported for placebo.

[b] At the time of publication, product monographs were not available for these agents—an updated table is available at www.canmat.org.

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APPENDIX 2: WOMEN'S MENTAL HEALTH ISSUES

Detailed information on the specific application of these treatment modalities in the perinatal period is in the (1) *Best Practices Guidelines relating to Reproductive Mental Health,* and (2) *Self-Care Program for Women with postpartum depression & anxiety (see Resources). See also the section on non-pharmacological therapies in the Guide.*

Pharmacotherapy in the Perinatal Period

Practice Issues: Antidepressants in Pregnancy and Postpartum

- Sustaining maternal mental health throughout pregnancy is the key to ensuring an optimum outcome for the baby.
- As yet, there is little evidence for the efficacy of psychotherapy in the treatment of moderate to severe depression in pregnant, depressed women.
- Resolution of symptoms for women in this category is best achieved, at present, with antidepressant medications.
- Women with severe depression and with a prior history of depression can be treated with a combination of antidepressant medication and psychotherapy.
- To date, existing evidence suggests that the most commonly used antidepressant medications, such as SSRIs (e.g., Prozac, Paxil, Zoloft, Luvox and Celexa) and SNRIs (e.g., Effexor), have not been associated with major birth defects.
- There is increasing concern regarding transient neonatal adaptation symptoms following prenatal exposure.
- This has led the Health Canada (see Health Canada Advisory below) and the US Food and Drug Administration (FDA) to issue warnings regarding third-trimester SSRI and SNRI use for treating depression during pregnancy.
- The recent concern over the warnings by Health Canada and the US FDA regarding infants exposed to antidepressants in the third trimester, has lead to a clinical dilemma for treating physicians. The evidence for these warnings is:
  - based on case reports and retrospective data.
  - the number of cases studied tends to be small, particularly with newer anti-depressants
- In addition, the presence/absence of symptoms observed in neonates are governed by a complex set of factors including:
  - prematurity
  - maternal mental and physical health
  - use of concomitant substances (e.g., alcohol, cigarettes)
  - polypharmacy
- Characteristics of this Neonatal Poor Adaptation Syndrome include:
  - transient course in the infant
  - resolution within the first few days of life
  - no evidence of long-term consequences in the children.
  - the use of multiple psychotropic medications during pregnancy with an SSRI appears to increase the risk of these symptoms

Neonatal Management Issues

- An infant can be identified as being at risk for transient Neonatal Poor Adaptation Syndrome if the mother is:
  - taking a high dose of any antidepressant medication
  - on more than one medication
  - if the woman is mentally ill and/or under-treated

APPENDIX 2: WOMEN'S MENTAL HEALTH ISSUES

- The infant's behaviour should be monitored closely :
  - by nursing and medical staff
  - if there are signs of abnormal Central Nervous System (CNS) behaviour, avoid early discharge and consider a differential diagnosis
  - obtain infant drug levels if possible where a diagnosis remains unclear
- Supportive neonatal care of symptomatic infants can be provided by using the following approach:
  - provide low level stimulation
  - support breastfeeding
  - provide supportive measures where appropriate
  - follow symptoms closely
- Ensure long-term follow-up for mother and infant.

Pharmacotherapy in the Perinatal Period: Specific Medications

TABLE 3: AMERICAN FOOD AND DRUG ADMINISTRATION RISK CATEGORIES	
a) Pregnancy Risk Categories	
A	Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the developing fetus.
B	Either animal studies show a risk, but human studies do not; or, if no adequate studies have been conducted in pregnant women, then animal studies have not demonstrated a risk.
C	Human studies are lacking, and animal studies have either produced adverse effects or are also lacking. Therefore, the risk of medication exposure in the fetus cannot be ruled out. Medications should be used in pregnancy only when potential benefits outweigh potential risk.
D	Positive evidence of fetal risk has been demonstrated in humans. However, the potential benefits of use in pregnant women may outweigh the potential risks, thus decisions must be made on an individual basis.
X	The medication is contraindicated in women who are or may become pregnant. The fetal risk of medication exposure clearly outweighs any potential benefits to the mother.
b) Lactation Risk Categories The lactation risk classification system has been developed by Hale, and is described in detail in his publication *Medications in Mothers' Milk, 9th edition* (2000). The 5 categories closely follow the pregnancy risk categories of the FDA, and they outline the infants' risk of medication exposure through breast milk.	
L1	The medication has been taken by a large number of breastfeeding mothers without any documented adverse effects in their nursing infants. Controlled studies have been conducted and have not identified an increased risk to infants.
L2	The medication has been studied in a limited number of breastfeeding women, and no adverse effects have been documented in their infants.
L3	No controlled studies of the medication have been conducted in breastfeeding women. The medication should be used only when the potential benefits to the mother outweigh the potential risks of infant exposure.
L4	There is documented evidence of risk to infants exposed to this medication through breast milk. However, the potential benefits of use of the medication in women may outweigh the potential risk to the nursing infants, so the decision must be made on an individual basis.
L5	This medication is contraindicated in mothers who are breastfeeding. Human studies have clearly demonstrated risk to exposed infants, and this risk outweighs any potential benefits.

Pharmacotherapy in the Perinatal Period: Specific Medications

TABLE 4: SSRIs (SELECTIVE SEROTONIN REUPTAKE INHIBITORS) IN THE PERINATAL PERIOD

(from Best Practice Guidelines relating to Reproductive Mental Health. January 2003).

DRUG CLASS	START DAILY DOSE AT (MG)[a]	MAX DAILY DOSE AT (MG)	FDA PREGNANCY RISK CATEGORY [b]	FETAL RISKS[c]	HALE'S LACTATION RISK CATEGORY [d]	BREASTFEEDING[e]
Fluoxetine (Prozac®)	10	80	B	Fluoxetine exposure in pregnancy is not associated with increased teratogenic effects in humans, but perinatal effects of 3rd trimester exposure have been reported. A study of 55 preschool children exposed to fluoxetine *in utero* reported no long-term adverse effects with respect to IQ, language, or behaviour.	L3 for neonates L2 for older infants	Norfluoxetine, the active metabolite of fluoxetine, has a very long half-life that predisposes to accumulation in the infant, particularly neonates. Adverse effects (colic, fussiness, crying, seizure activity, lower weight gain) have been documented.
fluvoxamine (Luvox®)	50	300	C	Use of these SSRIs during pregnancy does not appear to have teratogenic effects, but data is limited. One prospective case series reported 26 exposures to fluvoxamine, 97 to paroxetine, and 147 sertraline in pregnancy. The rates of malformations were similar between all 3 groups, and were not higher than those reported for the control group.	L2	Two small case studies of fluvoxamine exposure through breast milk have reported very low levels in the breast milk, and no adverse events in the infants.
citalopram (Celexa®)	10	60	C	A review of 375 cases of citalopram exposure in early pregnancy found that the rate of congenital anomalies was not higher than that for SSRI exposure or for the general population	L3	20 cases reported. 1 case report of uneasy sleep in the infant, correlated to high serum concentration of citalopram. Symptoms were short-lasting and disappeared after a dose decrease. Data is limited.
Paroxetine (Paxil®)	10	60	B	Transient neonatal withdrawal (?) symptoms have been reported	L2	Paroxetine does not have an active metabolite. It is excreted into breast milk but with generally undetectable serum levels in infants; no adverse effects have been reported.
sertraline (Zoloft®)	50	225	B		L2	Milk levels have been reported for sertraline and its weak metabolite desmethylsertraline, but with low or undetectable serum levels in the infant. There is one report of a nursing infant with 50% of maternal serum levels, but no adverse effects noted.

a *monograph doses are guidelines only. Doses must be individualized for each patient.*
b *adapted from the Food and Drug Administration (FDA, 1979). See Table 3a.*
c *comments adapted from GG Briggs et al., (1998),* Drugs in Pregnancy and Lactation, *5th edition, as well as TW Hale (2000),* Medications in Mothers' Milk, *9th edition.*
d *adapted from TW Hale (2000).* Medications in Mothers' Milk, *9th edition. See Table 3b.*
e *comments adapted from GG Briggs et al., (1998),* Drugs in Pregnancy and Lactation, *5th edition, as well as TW Hale (2000),* Medications in Mothers' Milk, *9th edition.*

Pharmacotherapy in the Perinatal Period: Specific Medications

TABLE 5: ATYPICAL ANTIDEPRESSANTS IN THE PERINATAL PERIOD

(from *Best Practice Guidelines relating to Reproductive Mental Health*. January 2003)

DRUG CLASS	START DAILY DOSE AT (MG)[a]	MAX DAILY DOSE AT (MG)	FDA PREGNANCY RISK CATEGORY[b]	FETAL RISKS[c]	HALE'S LACTATION RISK CATEGORY[d]	BREASTFEEDING[e]
bupropion (Wellbutrin SR®)	100	300	B	Insufficient human data available to ascertain the teratogenicity of these agents. Caution is recommended, and when possible, use an alternate medication with better know effects.	L3	Bupropion and its two metabolites have been measured in milk with reported milk: plasma ratios of up to 8.7, however no adverse effects have been reported.
trazodone (Desyrel®)	75	600	C	No documented teratogenic effects	L2	Trazodone is excreted in milk with peak levels at 2 hours.
venlafaxine (Effexor®)	75	225	C	No documented teratogenic effects.	L3	One case report of high infant venlafaxine levels transferred through breastmilk. No adverse effects reported.

TABLE 6: TRICYCLIC ANTIDEPRESSANTS IN THE PERINATAL PERIOD[f]

(from *Best Practice Guidelines relating to Reproductive Mental Health*. January 2003)

DRUG CLASS	START DAILY DOSE AT (MG)[a]	MAX DAILY DOSE AT (MG)	FDA PREGNANCY RISK CATEGORY[b]	FETAL RISKS[c]	HALE'S LACTATION RISK CATEGORY[d]	BREASTFEEDING[e]
Amitriptyline (Elavil®)	25-75	300	D	Data analysis has shown that TCA exposure in pregnancy does not increase the incidence of teratogenic effect in humans.	L2	All TCAs are excreted into human breast milk in low concentrations. The active metabolite of doxepin has a long half-life (37 hrs) and can be hazardous due to documented high accumulations in nursing infants.
imipramine (Tofranil®)	25-75	300	D	As above	L2	As Above
Clomipramine (Anafranil®)	25-75	300	C	Neonatal withdrawal symptoms have been associated with high doses of clomipramine	L2	As Above

For tables 5 & 6

a monograph doses are guidelines only. Doses must be individualized for each patient.

b adapted from the Food and Drug Administration (FDA, 1979). See Table 3a.

c comments adapted from GG Briggs et al., (1998), Drugs in Pregnancy and Lactation, 5th edition, as well as TW Hale (2000), Medications in Mothers' Milk, 9th edition. .

d adapted from TW Hale (2000). Medications in Mothers' Milk, 9th edition. See Table 3b.

e comments adapted from GG Briggs et al., (1998), Drugs in Pregnancy and Lactation, 5th edition, as well as TW Hale (2000), Medications in Mothers' Milk, 9th edition .

f doses adapted from the Clinical Handbook of Psychotropic Drugs, 10th revised edition (2000). Starting doses of medications are lower for pregnant and postpartum women than for the general adult population. Bezchlibnyk-Butler KZ, Jeffries JJ, Editors. Toronto, Hogrefe & Huber Publishers, 2000.

Pharmacotherapy in the Perinatal Period: Specific Medications

Table 7: Benzodiazepines in the Perinatal Period

(from *Best Practice Guidelines relating to Reproductive Mental Health*. January 2003).

	Start Daily Dose at (mg)[a]	Max Daily Dose at (mg)	FDA Pregnancy Risk Category[b]	Fetal Risk[c]	Hale's Lactation Risk Category[d]	Breastfeeding[e]
Alprazolam (Xanax®)	0.5	4	D	Exposure to benzodiazepines *in utero* has been associated with withdrawal symptoms, including irritability and restlessness. Alprazolam has not been associated with congenital anomalies during human pregnancies, however, caution is urged, as data is limited.	L3	Benzodiazepines are excreted into breast milk. These medications are not ideal during breastfeeding due to relatively long half-lives; chronic exposure may therefore be of concern. Monitor infants closely for sedation. Withdrawal symptoms have been reported in infants exposed to alprazolam through breast milk.
clonazepam (Rivotril®)	0.25	8	C	Clonazepam exposure during pregnancy has been associated with symptoms of newborn toxicity, including apnea, cyanosis, lethargy, and hypotonia. No long-term effects have been reported for clonazepam, although data is limited.	L3	Is preferred by the Reproductive Mental Health program due to intermediate length of action.
Diazepam (Valium®)	5	30	D	Diazepam use in pregnancy has been associated with oral clefts, though the data is conflicting.	L3-acute L4-chronic	Diazepam and its metabolite have long half-lives and tend to accumulate when used for chronic treatment. Diazepam treatment has been associated with withdrawal, lethargy, sedation, and poor suckling in nursing infants.
Lorazepam (Ativan®)	1	6	D	Placental transfer of lorazepam is lower than that of other benzodiazepines, but high doses in pregnancy have been associated with "floppy infant syndrome".	L3	When benzodiazepines are indicated, lorazepam may be preferred over the others, due to its shorter half-life and absence of active metabolites.

a *monograph doses are guidelines only. Doses must be individualized for each patient.*
b *adapted from the Food and Drug Administration (FDA, 1979). See Table 3a.*
c *comments adapted from GG Briggs et al., (1998), Drugs in Pregnancy and Lactation, 5th Edition, as well as TW Hale (2000), Medications in Mothers' Milk, 9th edition.*
d *adapted from TW Hale (2000). Medications in Mothers' Milk, 9th edition. See Table 3b.*
e *comments adapted from GG Briggs et al., (1998), Drugs in Pregnancy and Lactation, 5th Edition, as well as TW Hale (2000), Medications in Mothers' Milk, 9th edition.*

Pharmacotherapy in the Perinatal Period: Specific Medications

TABLE 8: MOOD STABILIZERS AND NEUROLEPTICS IN THE PERINATAL PERIOD[a]

(from *Best Practice Guidelines relating to Reproductive Mental Health*. January 2003)

DRUG CLASS	START DAILY DOSE AT (MG)[b]	MAX DAILY DOSE AT (MG)	PREGNANCY RISK CATEGORY[c]	FETAL RISK[d]	LACTATION RISK CATEGORY[e]	BREASTFEEDING[f]
carbamazepine (Tegretol®)	200	1600	C	Estimated risk of neural tube defects with carbamazepine (CBZ) during pregnancy is 1%. Facial dysmorphism has also been associated with CBZ and VP during pregnancy. Women of childbearing age taking CBZ or VP should take folic acid supplements prior to conception and throughout the pregnancy.	L2	Both carbamazepine and valproate are approved by the American Academy of Pediatrics for use in breastfeeding mothers. Small amounts are secreted into breastmilk and have been measured in infant serum, but neither of these medications have been found to be associated with adverse events in infants.
Valproate (Epival®)	750	3000	D	Estimated risk of neural tube defects 3-8%. Other risks see above (CBZ).	L2	As above.
Lithium carbonate (Lithane®, Carbolith®)	**maint. :** 400 **acute:** 900	1200 2400[g]	D	First trimester exposure to lithium has been associated with a increased risk of fetal cardiovascular anomalies, particularly Ebstein's anomaly (1:1000). Use near term may produce neonatal toxicity.	L4	Lithium is excreted into breastmilk at 30 – 40% of maternal serum concentrations, and therefore is contraindicated during breastfeeding.
Haloperidol (Haldol®)	1.5	6	C	Haloperidol does not have known teratogenic effects based on animal data and limited case reports in humans.	L2	Caution advised, observe infant for sedation.
Loxapine (Loxapine®)	15	250	C	There are no published studies on the use of loxapine in pregnant women. Animal studies with loxapine have shown retarded fetal development.	L4	Loxapine is a potent tranquilizer, and may produce adverse effects in the developing fetus or nursing infant.
Olanzapine (Zyprexa®)	2.5	10	C	A report from the Lilly Worldwide Safety Database on 23 pregnancy outcomes found no increased risk of adverse fetal outcomes.	L3	There is very limited data available on the use of olanzapine during breastfeeding. Caution is advised.
Quetiapine (Seroquel®)	50	600	C	There are no published studies on the use of quetiapine in pregnant women.	L4	No information is available on the use of quetiapine during breastfeeding.
Risperidone (Risperdal®)	1	8	C	There are no published studies on the use of risperidone in pregnant women.	L3	One case report of a nursing infant exposed to risperidone did not indicate any adverse effects.

[a] *doses adapted from the Clinical Handbook of Psychotropic Drugs, 10th revised edition. Starting doses of medications are lower for pregnant and postpartum women than for the general adult population.*

[b] *monograph doses are guidelines only. Doses must be individualized for each patient.*

[c] *adapted from the Food and Drug Administration (FDA, 1979). See Table 3a.*

[d] *comments adapted from GG Briggs et al., (1998), Drugs in Pregnancy and Lactation, 5th edition, as well as TW Hale (2000), Medications in Mothers' Milk, 9th edition.*

[e] *adapted from TW Hale (2000). Medications in Mothers' Milk, 9th edition. See Table 3b.*

[f] *comments adapted from GG Briggs et al., (1998), Drugs in Pregnancy and Lactation, 5th edition, as well as TW Hale (2000), Medications in Mothers' Milk, 9th edition.*

[g] *starting and high doses are higher for mania and adjunct psychotic states than for panic disorder and anxiety.*

MAJOR DEPRESSIVE DISORDER

WASHOUT RECOMMENDATIONS FOR SWITCHING ANTIDEPRESSANTS

Adapted from Guidelines for the Diagnosis and Pharmacological Treatment of Depression. Toronto, ON, Canadian Network for Mood and Anxiety Treatments, 1998.

Switch to →	SSRI	Novel	TCA	RIMA	MAOI
Switch from ↓					
SSRI citalopram fluoxetine fluvoxamine paroxetine sertraline	No washout May have additive serotonergic side effects for 1 week (5 weeks for fluoxetine)	No washout May have additive serotonergic side effects for 1 week (5 weeks for fluoxetine)	No washout Start TCA at a lower dose Some SSRIs can increase serum TCA levels for 1 week (5 weeks for fluoxetine)	1 week (5 weeks for fluoxetine)	1 week (5 weeks for fluoxetine)
NOVEL bupropion-SR mirtazapine venlafaxine-XR	No washout May have additive serotonergic side effects for 1 week	No washout May have additive serotonergic side effects for 1 week	No washout	1 week	1 week
TCA desipramine nortriptyline amitriptyline imipramine others	No washout Serum TCA levels may be increased by some SSRIs for 1 week	No washout	No washout	1 week	1 week
RIMA moclobemide	3 days	3 days	3 days	N/A	3 days
MAOI* phenelzine tranylcypromine	2 weeks	2 weeks	2 weeks	2 weeks	2 weeks