

# Evidence-based Pharmacy Practice (EBPP): Antidepressants in Pregnancy

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## Abstract

Depression is a common chronic and recurrent illness that is the cause of significant morbidity that often requires long-term treatment. Depression is among the most common health disorders in women. The prevalence of depression is approximately twice as great in women as in men and it is more common in the childbearing years. Despite its common occurrence it is frequently undiagnosed and left untreated during pregnancy usually due to concerns about the safety of treating women during pregnancy. Depression itself can have a negative impact on the course of the pregnancy as well as the foetus. All antidepressants cross the placenta and expose the foetus to the effects of these medications. The decision on whether to treat a pregnant woman with depression with pharmacotherapy depends on the severity of the disease, the number and frequency of episodes and the history of response to medication. Whether or not the patient may breastfeed also needs to be taken into consideration when deciding on which antidepressant to prescribe. Psychotherapy may obviate the need for pharmacotherapy in mild to moderate depression and may also be beneficial in patients taking antidepressants. All pregnant patients with depression need to be assessed and treated on an individual basis. Pharmacists can provide patients with general counselling regarding depression and antidepressants and support by identifying any pharmaceutical issues such as interactions, persistent side effects, and adherence. Pharmacists may also identify potential suicide risk which may become apparent when talking with a patient which would require urgent referral.

## Definitions

The terms 'depressive episode', 'major depressive episode', 'unipolar depression', and 'clinical depression' have all been used to define the symptoms that collectively make up the severe and enduring illness of depression.<sup>1</sup>

There are two classification systems used for diagnosing depressive conditions.

1. *ICD-10 Chapter V: Mental and behavioural disorders* part of the International Classification of Diseases produced by the World Health Organization (WHO).<sup>2</sup> This system is used in European countries. The term 'depressive episode' is used.<sup>2</sup>
2. The *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)* published by the American Psychiatric Association.<sup>3</sup> This system is used in the USA and other non-European countries. The term 'major depressive episode' is used.<sup>3</sup>

Both systems have very similar criteria for the diagnosis of a depressive episode; either classified as mild, moderate or severe. The ICD-10 system adds recurrent to 'depressive episode' if there have been multiple episodes without mania.<sup>2</sup> In the DSM-IV system *Major depressive disorder (MDD)* is defined as a depressed mood on a daily basis for a minimum duration of two weeks.<sup>3,4</sup> An episode may be characterised by sadness, indifference, apathy, or irritability and is usually associated with changes in sleep patterns, appetite and weight; motor agitation or retardation; fatigue;

impaired concentration and decision-making; feelings of shame or guilt; and thoughts of death and dying.<sup>4</sup> The coding system used in the DSM-IV is designed to correspond with the codes used in the ICD-10 but not all codes match at all times because the two publications are not revised at the same time.

## Epidemiology

Women suffer from depression twice as often as men.<sup>5</sup> The prevalence of depression is higher during the childbearing years than at any other time.<sup>5,6</sup> Prevalence rates of depression are estimated to vary from 7–15% in economically developed countries to 19–25% in less developed or poorer countries.<sup>6</sup> Peak prevalence is between the ages of 25 and 44.<sup>7</sup> Of pregnant women 10–16% fulfil the DSM-IV diagnostic criteria for major depression.<sup>8</sup> The relapse rate in pregnant women with a history of recurrent mood disorder may be as high as 50%.<sup>6</sup>

## Aetiology/pathophysiology

The aetiology of depression is too complex to be totally explained by a single theory.<sup>9</sup> The original hypothesis of depression 'The Monoamine theory' proposes that depression is due to a deficiency or depletion of one or another of the monoamine transmitters; dopamine, noradrenaline and/or serotonin.<sup>9,10</sup> This theory does not explain all the factors involved in the treatment of depression, the main one being that there is a therapeutic delay of at least two weeks between the pharmacological effects of antidepressants.

sants and the therapeutic effects.<sup>9</sup> It is proposed that the delayed therapeutic action of antidepressants is due to postsynaptic changes in receptor sensitivity.<sup>9</sup> A host of deficiencies in serotonin, noradrenaline, dopamine,  $\gamma$ -aminobutyric acid (GABA), and peptide neurotransmitters or tropic factors such as brain-derived neurotrophic factor, somatostatin and thyroid-related hormones have been proposed as contributing to depression.<sup>11</sup>

Several factors appear to work together to cause or precipitate depression.<sup>9</sup> These factors include genetic disposition, adverse early life experiences, social stress and elevated cortisol levels.<sup>1</sup> Having a chronic illness increases the risk of depression and even some drugs can cause depression. (Refer to Table 1)

### Diagnosis

In the WHO classification of disease, a 'depressive episode' is classified as mild, moderate or severe or recurrent.<sup>2</sup> Refer to Table 2.

### ICD-10 Classification<sup>1,2</sup>

*Mild:* involves having two to three of the symptoms in Table 2. Although the patient will be depressed they will generally be able to continue with ordinary activities.

*Moderate:* involves four or more of the symptoms in Table 2. The patient will be unlikely to be able to carry on with daily activities.

*Severe:* also involves four or more of the symptoms in Table 2 but these are distressing, typically including loss of self-esteem and ideas of worthlessness or guilt. Suicidal thoughts and acts are also common.

*Recurrent:* characterised by repeated episodes of depression without any history of independent episodes of mood elevation and increased energy.

Symptoms associated with pregnancy, such as sleep disturbances, poor appetite and fatigue, may often mask symptoms of depression.<sup>8</sup>

**Table 1: Prescribed drugs that can cause or exacerbate depression<sup>1,12</sup>**

Methyldopa (may be used for hypertension in pregnancy)
Corticosteroids
Benzodiazepines
Levodopa
Some anticonvulsants
Isotretinoin (contraindicated in pregnancy)
Calcium channel blockers e.g. nifedipine
Lipophilic beta-blockers e.g. propranolol
Interferon $\alpha$
Interleukin-2
Mefloquine
Progestogen-releasing implanted contraceptives

Somatic symptoms such as insomnia, pain and gastrointestinal disturbances are common presentations as first symptoms of depression.<sup>12</sup>

Depression should be assessed via use of patient self-report or a clinician-administered depressive symptom rating scale.<sup>13</sup> Documentation of clinical status should include evaluation of patient's depressive symptoms and functional level.<sup>13</sup>

The evaluation can be repeated after intervention to assess response.<sup>13</sup> A self-report form like the 'Inventory to Diagnose Depression' can be used by the patient.<sup>14</sup> The 'Hamilton Rating Scale for Depression' (HAMD)<sup>15</sup> is the clinician-administered scale which is used in clinical trials to rate the severity of depression.<sup>16</sup> The most commonly used screening questionnaire for depression in pregnancy is the Edinburgh Postnatal Depression Score and includes 10 items.<sup>17</sup>

### Clinical approaches to the pregnant patient with depression for the pharmacist

The pharmacist may be able to identify a patient not already diagnosed with depression by asking one of the two following questions<sup>1</sup>:

- During the past month, have you often been bothered by feeling down, depressed or hopeless?<sup>1</sup>
- During the past month, have you often been bothered by having little interest or pleasure in doing things?<sup>1</sup>

A positive answer to either of these two questions suggests a degree of depression and the patient needs to be referred for further medical assessment.<sup>1</sup>

### General counselling points regarding depression

Patients presenting for the first time with depression may have concerns about the associated stigma of being treated for a mental health condition and the pharmacist can reassure the patient by offering the following advice.<sup>12</sup>

- Depression is an illness like asthma, diabetes or heart disease. Taking antidepressants is not a sign of weakness but an important part of treatment for depression.<sup>12</sup>
- All antidepressants take around four to six weeks to have an effect but there may be signs of improvement earlier in some people.<sup>12</sup>

**Table 2: Symptoms of depression<sup>1,2</sup>**

Lowering of mood
Reduction of energy and decreased activity
Loss of interest and enjoyment
Reduced concentration
Disturbed sleep
Disturbed appetite
Reduced self-esteem and self-confidence
Ideas of guilt or worthlessness
Marked psychomotor retardation

- Side effects are common, initial effects such as nausea, anxiety, insomnia and drowsiness usually wear off. Suicidal ideas which may occur on initiation, after dose increase or change of drug require urgent medical attention. Some side effects such as weight gain, sweating and sexual dysfunction may persist and should be discussed with their doctor.<sup>1,12</sup>
- In a first episode of depression, treatment should be continued for at least six months after all the symptoms have resolved to reduce the risk of relapse. A course of two years or longer is indicated when there has been two or more recent depressive episodes.<sup>1,12</sup> Antidepressants are not addictive; they do not cause tolerance or cravings, but should be withdrawn slowly because discontinuation symptoms are possible. Missing even one dose of some antidepressants can cause discontinuation symptoms.<sup>1,12</sup>
- Alcohol should be avoided (especially in pregnancy). It can increase side effects or drowsiness.
- Antidepressants can react with other medications so always check with the doctor or pharmacist before taking any other medication along with antidepressants. This also includes medication that may be bought over the counter (OTC) or herbal preparations such as St Johns' wort.
- If serotonin syndrome is suspected (with symptoms of mild diarrhoea, sweating and tremor, akathisia (restlessness), ataxia, confusion or convulsions) urgent medical attention should be sought.<sup>1,12</sup>

### Practice points for pharmacists

- Identify other medications that a patient may be taking that may cause or aggravate depression.<sup>12</sup> Refer to Table 1.
- Identify any adherence problems and offer advice and/or adherence aids.<sup>12</sup>
- Recognising persistent side effects and offering advice on coping mechanisms or referral.<sup>12</sup>
- Identifying patients at risk of suicide and urgently referring for medical attention. The pharmacist can ask the patient about their plans for the future or if they have any thoughts of harming themselves. Patients should be warned at the start of their treatment that if they experience suicidal thoughts they should contact their doctor or emergency services.<sup>12</sup>

### Available treatment options

1. Non-drug treatments (Psychotherapy)
2. Pharmacotherapy
3. Electroconvulsive therapy (ECT)

### Therapeutic objectives

The obstetrician/gynaecologist should be able to manage a pregnant woman with mild to moderate depression but a pregnant woman who is severely depressed requires skilled decision making by a psychiatrist<sup>7</sup> in consultation with the obstetrician/gynaecologist. There are four possible outcomes for a depressive episode: remission, improvement, continuation at the same symptom level and worsening.<sup>7</sup> Since the degree of maternal depression plays a significant role in child development, the maintenance of euthymic (normal) mood in

the mother during pregnancy and postpartum are the most important goals of treatment.<sup>9</sup>

### Non-pharmacological management

Many patients with mild to moderate depression can be successfully treated by psychosocial approaches including individual and group psychotherapy.<sup>18</sup> This option is preferred by a large percentage of pregnant women who may plan to avoid medication.<sup>17</sup> Psychosocial management strategies should also be used as adjunctive treatment alongside pharmacotherapy in women with severe depression.<sup>18</sup>

### Therapeutic prevention strategies<sup>18</sup>

For patients with mild illness therapeutic prevention strategies such as a healthy diet free of alcohol, nicotine and caffeine may prevent exacerbation.<sup>18</sup> Proper sleep hygiene, stress management and exercise are also good prevention strategies.<sup>18</sup>

### Cognitive-behavioural therapy (CBT)

Cognitive therapy is structured, goal directed, problem focused and time limited.<sup>19,20</sup> Ten to twenty sessions are recommended for depression.<sup>21</sup> This form of therapy shows patients how to change self-defeating and disturbed thought patterns into more positive and productive ways of thinking. The behavioural aspect of this therapy includes training in asserting oneself, practising relaxation techniques, and increasing pleasurable activities. Web and computer based cognitive behavioural therapy may also be an option if the cost or access to behavioural therapists is limited.<sup>18</sup>

### Interpersonal therapy (IPT)

This form of therapy focuses on role transitions and the acquisition of new skills applicable to motherhood.<sup>7</sup>

### Pharmacological treatment

The treatment of any medical condition during pregnancy involves the comparison of exposure to the illness versus exposure to the treatment. The risks and benefits of treatment need to be carefully considered in each individual case.

The toxic effects of foetal exposure to drugs can be organised into five domains<sup>13</sup>:

1. intrauterine death
2. physical malformations
3. growth impairment
4. behavioural teratology
5. neonatal toxicity

All antidepressants studied to date, cross the placenta, are present in amniotic fluid and are excreted into breast milk.<sup>22</sup> Antidepressants are not only used in the treatment of depression but also in the treatment of anxiety disorders, pain and insomnia.

Before initiating pharmacotherapy a thorough history should be taken.<sup>18</sup> All drug and environmental exposures dating back to conception should be recorded.<sup>17</sup> Exposure to alcohol and other drugs (including nonprescription) is common during pregnancy and must

be documented before prescribing antidepressants.<sup>13</sup> Smoking also affects pregnancy outcomes.<sup>13</sup> Careful documentation of a risk benefit discussion regarding medication or other treatment between the patient and prescriber is imperative.<sup>17</sup> This is important to avoid selective implication of the antidepressant if a negative outcome occurs.<sup>13</sup> Informed consent for treatment is essential.<sup>7</sup>

Risks that should be discussed with the patient include<sup>21</sup>:

- teratogenicity
- miscarriage
- low birth weight
- preterm birth
- poor neonatal adaptation/behavioural syndromes
- maternal relapse – if medication ineffective or inadequate dosage
- no treatment vs treatment

Once the decision to use pharmacotherapy is taken the selection of an antidepressant should take the following points into consideration<sup>21</sup>:

- patient's prior response/experience with antidepressant therapy
- family history of response to antidepressant therapy (especially if patient is drug-naïve)
- concurrent medications and risk of interactions
- potential adverse effects to patient and foetus
- intention to breastfeed

If a patient is already taking an antidepressant and she falls pregnant a similar risk benefit discussion needs to be undertaken between the patient and prescriber. If it is decided to discontinue therapy one must take into consideration the risk of relapse. Approximately 75% of women who discontinue an antidepressant due to pregnancy experience a relapse.<sup>23</sup> It is not uncommon for clinicians to reduce the dose of an antidepressant upon learning a patient is pregnant in a well meaning attempt to reduce exposure to the foetus.<sup>13,22</sup> However, like discontinuing a medication, this leaves the woman vulnerable to relapse and increases the likelihood that the foetus will be exposed to maternal depression.<sup>22</sup> In fact dose titration rather than reduction has been shown to be required in the third trimester to maintain both clinical response and therapeutic serum levels.<sup>13,22</sup> This is the case for tricyclic antidepressants and SSRIs.<sup>13</sup>

### **Impact of antidepressant medication on birth outcomes**

Several studies report foetal malformations in association with first trimester antidepressant exposure but there is no specific pattern of defects for individual medications or classes of agents.<sup>17</sup> The increased risk for spontaneous abortion or miscarriage is associated with the use of various antidepressants in

early pregnancy.<sup>17</sup> Low birth weight and preterm delivery has also been associated with antidepressant use in pregnancy.<sup>17</sup> Paroxetine has been associated with cardiac defects and even though the link is not strong it has prompted the FDA to change the status of paroxetine from pregnancy category C (indicating that either studies in animals had demonstrated adverse foetal effects or there are no controlled data from studies in women) to category D (indicating that studies [controlled or observational] in pregnancy have demonstrated a risk to the foetus).<sup>17</sup> Use of SSRIs late in gestation is associated with poor neonatal adaptation (symptoms include tachypnoea, hypoglycaemia, temperature instability, irritability, a weak or absent cry, and seizures) and a low risk

for persistent pulmonary hypertension in the newborn.<sup>17</sup> In utero exposure to TCAs are associated with an increase in perinatal complications which include jitteriness, irritability and rarely convulsions.<sup>17</sup> Withdrawal in the neonate is also a problem but decreasing dose or discontinuing dose prior to delivery is not an option because foetal withdrawal syndromes pose a greater risk to the foetus than extrauterine withdrawal and it also places the woman at greater risk of relapse.<sup>18</sup>

### **Selective serotonin reuptake inhibitors (SSRIs)**

The selective serotonin reuptake inhibitors (SSRIs) i.e. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline are recommended as first-line antidepressants in non-pregnant patients with depression.<sup>1</sup> This is due to their tolerability and safety in overdose when compared to tricyclic antidepressants (TCAs).<sup>1</sup> Generally SSRIs are regarded as a good choice in pregnancy because of their side effect profile and safety in overdose.<sup>24</sup> Fluoxetine is the best studied SSRI in terms of safety and efficacy in pregnancy and lactation.<sup>21</sup> Available animal and human experience indicates that fluoxetine is not related to major congenital malformations.<sup>24</sup> However minor malformations and severe perinatal complications have been observed with fluoxetine.<sup>24</sup> Exposure to fluoxetine in the third trimester may be related to perinatal complications, neurobehaviour disruptions and a withdrawal syndrome.<sup>24</sup> Fluoxetine has a long half-life so it will accumulate in the neonate and it also has a higher rate of transfer to the baby during breastfeeding when compared to other SSRIs.<sup>21</sup> Paroxetine and sertraline do not usually cause detectable concentrations in breastfed infants, whereas fluoxetine has been found to produce the highest proportion (22%) of infant concentrations which exceeds the average maternal concentrations by 10%.<sup>25</sup> Paroxetine has been associated with an increase in congenital heart defects particularly ventricular septal defects so should not be considered as a first-line choice in pregnancy.<sup>21</sup> Its use should be limited to those women who have become pregnant on paroxetine and do not want to discontinue because they

have had a good response.<sup>21</sup> Disruptions in neurobehaviour and a withdrawal syndrome have also been observed after exposure to paroxetine in the third trimester.<sup>24</sup> Withdrawal symptoms have also been reported with the use of sertraline.<sup>24</sup> Escitalopram which is the *s*-enantiomer of racemic citalopram has a long half-life of 27-32 hours.<sup>24</sup> Animal data suggests that the risk to an embryo/foetus is low.<sup>24</sup> The limited animal and human data available on fluvoxamine does not demonstrate a major teratogenic risk from its use in pregnancy.<sup>24</sup>

### Tricyclic antidepressants (TCAs)

TCAs inhibit the neuronal uptake of noradrenaline and serotonin. They also antagonise muscarinic, histamine and  $\alpha$ -1 receptors which leads to associated side effects.

In general, most TCAs do not have a known teratogenic effect in humans.<sup>24</sup> Nortriptyline and desipramine (secondary amine tricyclics) are often the preferred and recommended TCAs for use in pregnancy and lactation in reviews because they have the least sedative action and maternal adverse effects – they tend to cause less orthostatic hypotension, dry mouth and constipation.<sup>18,24</sup> They also have fewer sedative, gastrointestinal, cardiac and hypotensive effects in the foetus.<sup>21</sup> Occasional reports have associated the therapeutic use of TCAs with congenital malformations but the bulk of the evidence indicates that these widely used drugs are relatively safe during pregnancy.<sup>24</sup> They have a proven response but have more side effects so are not as well tolerated as the SSRIs.<sup>18</sup> Side effects include dry mouth, blurred vision, constipation, dizziness, cardiac symptoms, sedation or agitation and weight gain.<sup>18</sup> They can also cause epileptiform seizures.<sup>26</sup> They can be lethal in overdose due to cardiac arrhythmias so are contraindicated in patients with a history of attempted overdose and those who are actively suicidal.<sup>1</sup> Exposure to TCAs may also result in significant, though usually transient withdrawal symptoms in the neonate.<sup>13</sup> Withdrawal symptoms include transient jerky movements and seizures, tachypnoea, tachycardia, irritability, feeding difficulties and profuse sweating.<sup>13</sup> Gastrointestinal stasis and bladder distension due to direct anticholinergic effects have also been reported.<sup>13</sup>

Studies have shown that a rapid acceleration of dose is required to maintain both clinical response and therapeutic serum levels in the third trimester when treating pregnant women with TCAs.<sup>13</sup> The physiological changes that contribute to the increase in dose requirements include increased hepatic metabolism, increased volume of distribution as well as changes in protein binding and gastrointestinal absorption.<sup>13</sup> Doses on average need to be increased 1.6 times what the initial (or pre-pregnancy) TCA dose was.<sup>13,22</sup> The cytochrome P-4502D6 isoenzyme is induced during pregnancy.<sup>13</sup> If a woman has been treated with TCAs during pregnancy, she should take the dose she received when not pregnant in the immediate postpartum period.<sup>13</sup> If this dose is not known then the dose of the TCA needs to be reduced by a third.<sup>13</sup>

### Serotonin-noradrenaline reuptake inhibitors (SNRIs)

#### Venlafaxine

Venlafaxine is a serotonin and noradrenaline reuptake inhibitor otherwise known as a dual reuptake inhibitor.<sup>1</sup> It also weakly inhibits dopamine reuptake.<sup>26</sup> It inhibits serotonin reuptake at any dose but it only inhibits noradrenaline reuptake at doses above 150 mg/day.<sup>1</sup> A significant, dose-related increase in blood pressure has been reported at doses above 200 mg/day.<sup>1</sup>

When discontinuing therapy the dose of venlafaxine needs to be tapered over at least 2 weeks (dependent on dose) in order to avoid discontinuation symptoms.<sup>26</sup>

Venlafaxine does not appear to cause structural malformations but use in the third trimester may result in toxicity in the neonate.<sup>24</sup> Licensed drug information recommends that venlafaxine should not be used during pregnancy unless clearly necessary.<sup>26</sup>

#### Monoamine oxidase inhibitors (MAOIs)

MAOIs irreversibly block the enzyme monoamine oxidase (except for moclobemide which is reversible and selective for MAOA). This action reduces the breakdown of serotonin, noradrenaline and dopamine.<sup>1</sup> MAOIs are not used widely in clinical practice because of the greater hepatic toxicity than newer drugs, the need for a low-tyramine diet, and toxic interactions with other drugs.<sup>13</sup> MAOIs have been associated with growth retardation, congenital anomalies and foetal death in animal and human studies and are contraindicated in pregnancy.<sup>18</sup>

### Other antidepressants

#### Bupropion

Bupropion is the only marketed aminoketone antidepressant.<sup>9</sup> It is also marketed for smoking cessation. It is a dopamine and noradrenaline reuptake inhibitor with minimal effect on re-uptake of serotonin. It may have a role in depressed pregnant women who wish to give up smoking.<sup>17</sup> There appears to be no increased risk for major malformations found to date.<sup>27</sup>

#### Mirtazapine

Mirtazapine is a tetracyclic antidepressant that is chemically unrelated to SSRIs, TCAs and MAOIs.<sup>24</sup> It directly increases noradrenaline and serotonin transmission by  $\alpha_2$ -adrenergic inhibition.<sup>24</sup> It also blocks 5HT<sub>2A</sub> and 5HT<sub>3</sub> receptors as well as potentially inhibiting H<sub>1</sub> receptors.<sup>1,24</sup> Marked sedation often occurs with this agent which can be attributed to the inhibition of H<sub>1</sub> receptors.<sup>1,24</sup> Less nausea, vomiting and sexual dysfunction is seen with mirtazapine than the SSRIs.<sup>1</sup>

In the treatment of depression, it is used if first-line antidepressants have been poorly tolerated or sedation is required.<sup>1</sup>

In the limited reports on the effect of mirtazapine on pregnancy outcomes and perinatal adverse effects no major abnormalities, minor malformations or developmental impairments were observed.<sup>25</sup>

**Reboxetine**

Reboxetine is a noradrenaline reuptake inhibitor that has little effect on other neurotransmitters.<sup>1</sup> Caution is recommended when prescribing in cardiac disease.<sup>1</sup> Tachycardia and palpitations are often reported.<sup>1</sup> There was no data on reboxetine exposure in humans found in the literature. It appears to produce no teratogenic effects in animal studies.<sup>25</sup>

**St John's wort (*Hypericum perforatum*)**

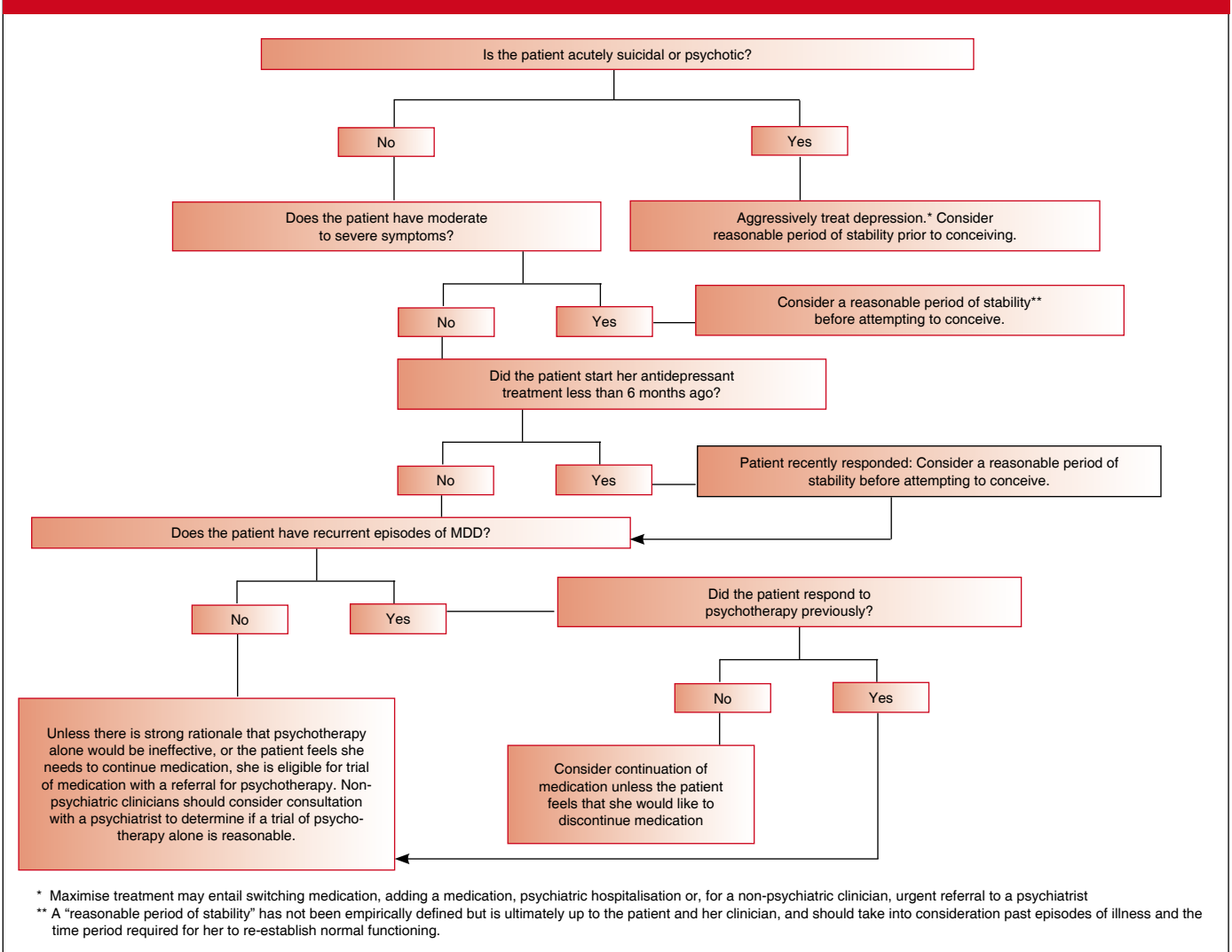
St John's wort is a herbal supplement used for mild depression. As is the case with many dietary herbal supplements, the amount of the active ingredients may vary significantly depending on the source, time of year of harvest, plant component used, and type of preparation.<sup>28</sup> Hypericum extracts are potent inducers of hepatic enzymes. Hypericum has been shown to double the metabolic activity of cytochrome P-450.<sup>29</sup> It may alter the serum concentration of drugs such as digoxin and warfarin. In patients taking SSRIs the concomitant use of hypericum may induce symptoms characteristic of the serotonin syndrome.<sup>30</sup> Photosensitivity has also been reported. St John's wort is not

recommended for use in pregnancy. It is important to remember to inquire about herbal remedies when obtaining a history from a pregnant patient since some women self-medicate with herbal remedies assuming them to be natural and safe therefore failing to consider their potential toxicity in pregnancy and lactation.<sup>18</sup>

**Electroconvulsive therapy (ECT)**

ECT is an effective short-term treatment for severe depression which is resistant to antidepressant drugs or is life-threatening.<sup>1,31</sup> Before administering ECT the patient will receive a short-acting anaesthetic like propofol and a muscle relaxant such as suxamethonium.<sup>1</sup> An electric current is then passed through the brain with the aim of inducing a seizure.<sup>1</sup> ECT is thought to be faster and more effective than antidepressants but the benefits are not long term and ideally an antidepressant should be prescribed to reduce the risk of relapse. Memory loss is experienced in up to one third of patients who undergo ECT. This procedure has been used in all trimesters of pregnancy and is considered safe for the foetus.<sup>24</sup> There is little evidence that ECT is harmful to the woman or the foetus when both are carefully monitored.<sup>17</sup>

**Figure 1: Patient is contemplating pregnancy and is undergoing pharmacological treatment for depression<sup>17</sup>**



Untreated maternal depression during pregnancy may have a harmful effect on both the obstetrical outcome and the later development of the infant.<sup>22</sup> Severe stress and depression during pregnancy may impede foetal growth, lead to smaller head circumferences at delivery, increase risk of complications including preterm delivery and even induce behavioural changes in the offspring.<sup>22</sup> Neonates born to mothers with a depressive disorder have increased risk for irritability, less activity and attentiveness, and fewer facial expressions compared to offspring born to mothers without depression.<sup>17</sup> Many pregnant women discontinue their antidepressant medication abruptly because of the fears of foetal adverse effects.<sup>9</sup> This puts the woman at an increased risk of morbidity, adverse pregnancy and foetal outcomes and relapse of their depression.<sup>8</sup> Risks to the mother when depression is untreated include suicidality; hospitalisation with associated disruption to work and home life; impairment of self care; weight loss; preeclampsia, increased risk of alcohol, cigarette and illegal drug abuse; and postpartum depression.<sup>23</sup>

**Evidence based recommendations**

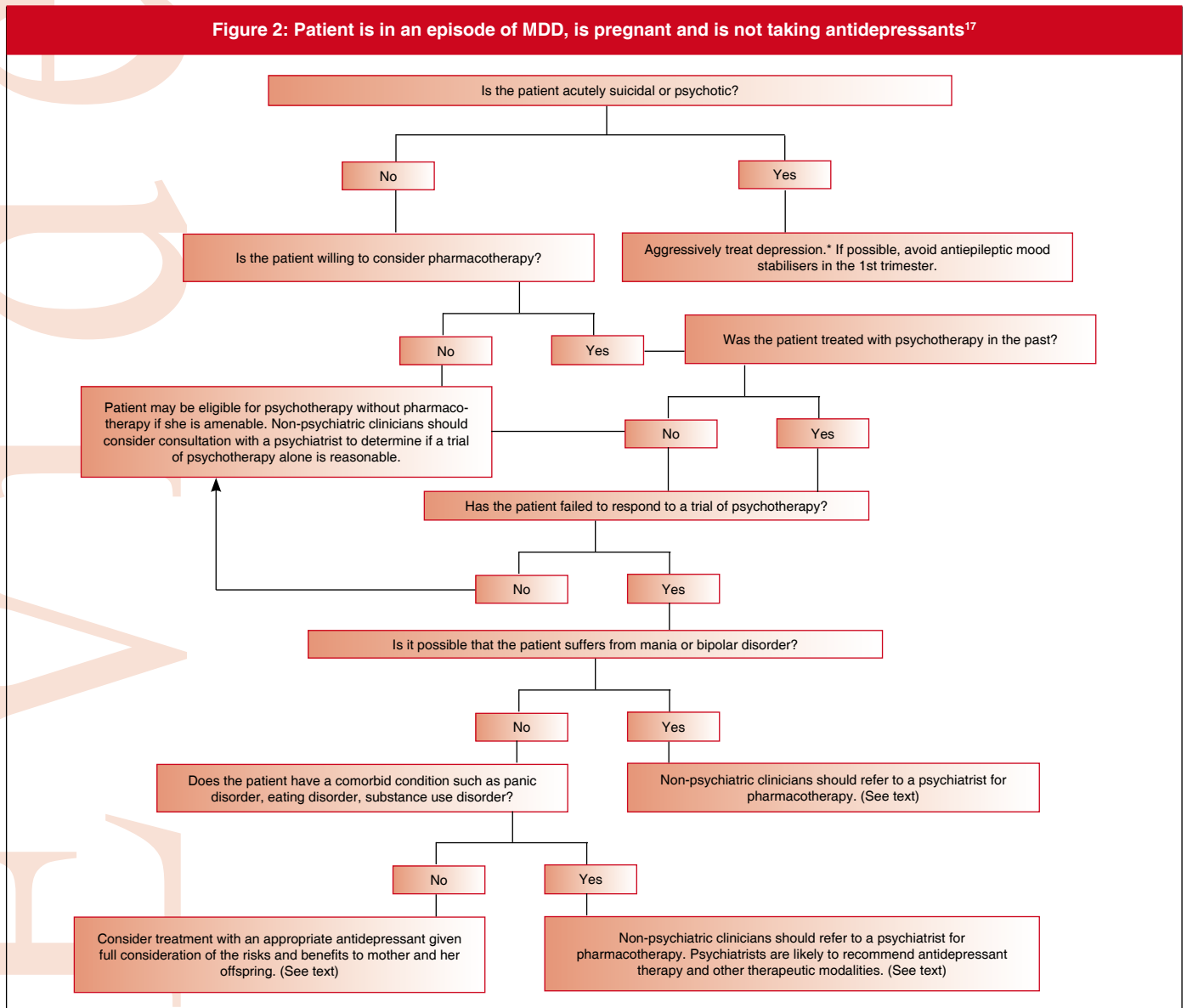
Management of depression during pregnancy should depend on the severity of the disease,<sup>8</sup> the number and frequency of episodes (the higher the number of previous episodes, the more likely a relapse will occur in pregnancy) and the history of response to medication (relapses tend to become progressively harder to treat).<sup>21</sup>

Algorithms 1, 2 and 3 can be used to help decide how to treat patients in different scenarios.

**Women thinking about getting pregnant (Refer to Figure 1)(See previous page)**

For women who are taking medication who have mild or no symptoms for six months or longer, it may be appropriate to taper or discontinue treatment before attempting to get pregnant.<sup>17</sup> The preferable way to taper medication is to reduce the dose by 25% every one to two weeks while being closely monitored for relapse or discontinuation symptoms.<sup>17</sup> It may not be appropriate to discontinue medication in women with a history of severe, recurrent depression

**Figure 2: Patient is in an episode of MDD, is pregnant and is not taking antidepressants<sup>17</sup>**



(or who have psychosis, bipolar disorder, other psychiatric illness requiring medication, or a history of suicide attempts).<sup>17</sup> Women who have suicidal or acute psychotic symptoms should be referred to a psychiatrist for aggressive treatment.<sup>17</sup>

**Pregnant and not currently on medication for depression (Refer to Figure 2)(See previous page)**

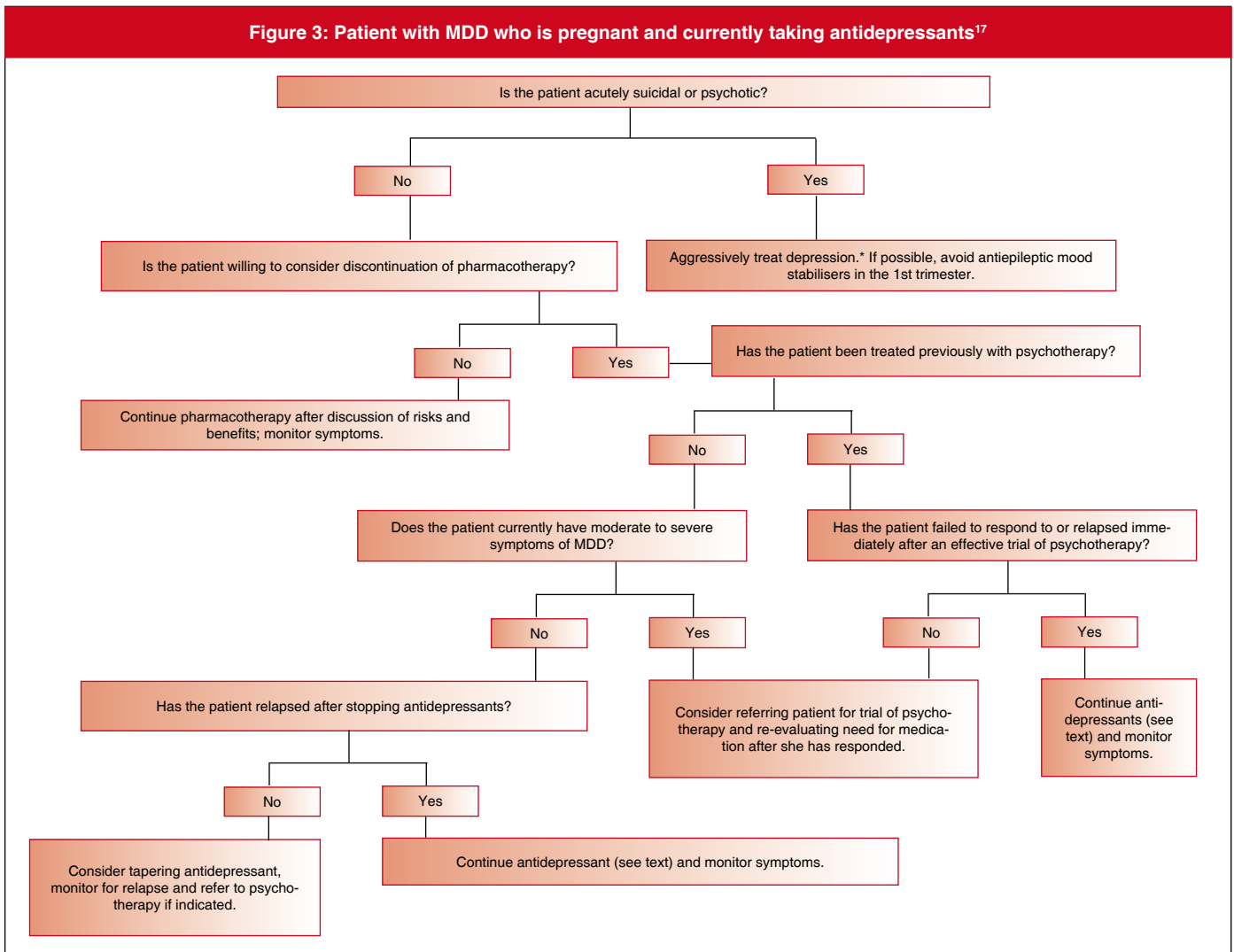
Psychotherapy may be beneficial in women who prefer to avoid antidepressants.<sup>17</sup> If a woman is prepared to consider pharmacotherapy then risks and benefits of treatment choices should be evaluated and discussed.<sup>17</sup> Treatment choice will depend upon the safety profile of the medications, the stage of gestation, the patient’s symptoms, history and therapeutic preferences.<sup>17</sup> Antidepressant agents that are metabolised primarily by cytochrome P450 2D6 or P450 3A4 may require a dose increase in the second half of pregnancy.<sup>17</sup> A patient may require a more sedating antidepressant like a TCA if she has agitated depression.<sup>17</sup> If a woman is having difficulty gaining weight during her pregnancy the TCAs and some SSRIs may increase her appetite.<sup>17</sup> Bupropion may be beneficial in patients who smoke so long as there is no history of seizures or bulimia.<sup>17</sup>

**Pregnant women currently on medication for depression (Refer to Figure 3)**

Women who are psychiatrically stable who wish to stay on antidepressants should have the risks and benefits discussed with them.<sup>17</sup> This discussion should be documented in the patient’s medical records.<sup>17</sup> Women who would like to discontinue antidepressants may be able to attempt medication tapering and discontinuation if they are not experiencing symptoms and they do not have a history of recurrent depression.<sup>17</sup> Women with recurrent depression are at a high risk of relapse if antidepressants are discontinued.<sup>17</sup> Psychotherapy may be able to replace or augment antidepressant therapy in women who have recurrent symptoms despite taking antidepressants.<sup>17</sup> Women with severe depression (suicide attempts, functional incapacitation, or weight loss) should not stop taking antidepressants.<sup>17</sup> In all cases a women with suicidal or psychotic symptoms should be urgently referred to a psychiatrist for treatment.<sup>17</sup>

When choosing an antidepressant for a pregnant woman the risks and benefits need to be considered on an individual basis. (Refer to Table 3)

**Figure 3: Patient with MDD who is pregnant and currently taking antidepressants<sup>17</sup>**



**Table 3: Points to consider when choosing an antidepressant<sup>32</sup>**

TCAs such as amitriptyline, imipramine and nortriptyline, have lower known risks during pregnancy than other antidepressants.

TCAs are more likely to cause death if taken in overdose than selective serotonin reuptake inhibitors.

Fluoxetine is the SSRI with the lowest known risk during pregnancy.

Paroxetine taken in the first trimester may be associated with foetal heart defects.

SSRIs taken after 20 weeks gestation may be associated with an increased risk of persistent pulmonary hypertension in the neonate.

Venlafaxine may be associated with increased risk of high blood pressure at high doses, higher toxicity in overdose than SSRIs and some TCAs, and increased difficulty in withdrawal.

All antidepressants carry the risk of withdrawal or toxicity in neonates – usually mild and self-limiting.

Imipramine, nortriptyline and sertraline are present in breast milk at relatively low levels.

Citalopram and fluoxetine are present in breast milk at relatively high levels.

## Conclusion

The primary clinical goal in treating a pregnant woman with depression is to minimise foetal/neonatal exposure and to help guide the patient and their families to choose which paths of exposure pose the least risk for their situation.<sup>22</sup> When indicated adequate antidepressant therapy should be instituted and maintained (which may also necessitate an increase in dose) during pregnancy and postpartum.<sup>8</sup> The decision to initiate pharmacotherapy is not one to be taken by the prescriber alone and should only be initiated once a risk-benefit decision making discussion has been undertaken between the pregnant woman and the prescriber and informed consent obtained. Pregnant women with depression should be closely monitored every few weeks until symptoms begin to remit.<sup>18</sup> If antidepressant medication is being taken it should be continued for six months following delivery to prevent exacerbation during the postpartum.<sup>18</sup> □

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