INTRODUCTION

Without adequate treatment, depression may assume a recurrent or chronic course, and over time be associated with increasing disability.\(^1\),\(^2\) Antidepressants are indicated for the management of moderate – severe depression; however, as discussed in the previous bulletin, when using an antidepressant, the choice of agent must take into account individual patient needs and medical status.\(^3\) This bulletin addresses frequently asked questions on the use of antidepressants, received by the National Medicines Information Centre (NMIC).

WHAT IS THE CURRENT INFORMATION ON THE CHOICE OF ANTIDEPRESSANT FOR USE DURING PREGNANCY?

In general, the decision to use a drug during pregnancy is a clinical one based on a number of factors including the mother’s condition, the drug used, and the consequences of not treating the condition for both mother and foetus. The choice of agent to use in depression can also depend on whether the woman has been stabilised on a particular antidepressant prior to pregnancy.\(^4\) A patient, already receiving antidepressant therapy, and at high risk of relapse, may be best maintained on an antidepressant during and after pregnancy.\(^4\) If a tricyclic antidepressant (TCA) is used amitriptyline, and imipramine (not currently licensed in Ireland) are considered the agents of choice based on cumulative data on their relative safety.\(^4\),\(^5\) Selective serotonin reuptake inhibitors (SSRIs) are not thought to be major teratogens, however a number of information sources have recently highlighted concerns with the use of these agents during pregnancy.\(^6\) The Irish Medicines Board [IMB] in May 2010 reported on a small increased risk of congenital cardiac defects in association with fluoxetine in early pregnancy, similar to that seen with paroxetine.\(^6\) Results from a meta-analysis of nine studies suggest that fluoxetine is not associated with a risk of non-cardiac defects, and that any increased risk of malformations appears to be driven by a possible excess cardiac risk.\(^7\) The cardiac defects reported in the studies were varied, and ranged in severity from reversible ventricular septal defects to transposition of the great vessels. The background incidence of congenital cardiac defects is approximately 1/100. The meta-analysis results for fluoxetine are consistent with an increased absolute risk of less than 2/100 pregnancies. The mechanism is unknown and there is insufficient data to draw conclusions on the risk of cardiac congenital anomalies with other SSRIs, but the possibility of a class effect cannot be excluded.\(^6\),\(^7\)

In August 2010, the IMB also highlighted the increased risk of persistent pulmonary hypertension in the newborn (PPHN) associated with all SSRIs and potentially SNRIs (Serotonin and Noradrenaline Reuptake Inhibitors). The observed risk was approximately 5/1,000 pregnancies whereas the background rate in the general population is 1-2/1,000 pregnancies.\(^8\) Currently available data suggest, but do not establish conclusively, an increase in the risk of PPHN following maternal exposure in the later stages of pregnancy (after 20 weeks gestation).\(^8\),\(^9\) Close observation of neonates exposed in utero to SSRIs and SNRIs, for signs of PPHN (including tachypnoea, respiratory distress, cyanosis and heart murmur) is recommended after birth.

Other Agents: Information is changing as experience with their usage in clinical practice increases. [The NMIC can provide further information on specific agents.]

WHICH ANTIDEPRESSANT CAN A BREASTFEEDING WOMAN USE?

Postpartum depression affects up to 20% of women.\(^10\),\(^11\) As well as having an impact on the mother it has also been associated with impaired child development.\(^5\),\(^11\),\(^12\) In addition, a woman may have been taking antidepressant therapy during her pregnancy up until delivery.\(^7\) The decision to use an antidepressant in a breastfeeding woman requires an individual risk/benefit assessment, to include (1) assessment of the risk to the mother and child of not treating the depression, (2) the risk of exposing the infant to antidepressants, (3) the benefits of breastfeeding and (4) the availability of psychological therapies.\(^5\),\(^11\),\(^12\) Currently available evidence (mainly from observational studies) suggests that most antidepressants are secreted in breast milk, although serum concentrations vary widely.\(^5\),\(^11\),\(^12\) If an antidepressant is indicated for a breastfeeding mother, one with a lower risk profile for mother and infant should be chosen, it should be used at the lowest
Depression occurs in up to 50% of patients with Parkinson's Disease (PD), with 25% of patients suffering from major depression.4,21-27 It is thought that depression in patients with PD may be related more to the underlying pathology associated with PD itself rather than a reaction to the motor impairment.23-26 There are difficulties in the diagnosis of depression as the clinical features of depression often overlap with the motor features of PD.23-26 In spite of the high frequency of PD-associated depression and the wide range of antidepressants available, pharmacological intervention is poorly understood and the available data are conflicting.22-27 Several reviews have concluded that there is insufficient evidence for the efficacy or safety of antidepressant therapy in PD to make specific recommendations for their use.23-26,29 SSRIs are reported to be the most commonly prescribed antidepressants for patients with PD and depression, and some experts recommend them as first line treatment.27 However, there are concerns about possible worsening of motor function.28-29 The possibility of drug interactions should also be considered (e.g. serotonin syndrome with monoamine oxidase-B inhibitors).23,26,27 TCAs are also used in depressed patients with PD, however they may result in anticholinergic side-effects including orthostatic hypotension, delirium, and memory impairment.4,22,27 They should be used with caution in patients with cognitive impairment.4,32 Recent evidence suggests that TCAs may not be as poorly tolerated and that SSRIs may not be as efficacious as currently perceived in patients with PD.20,51 Other Agents: Limited data are available to evaluate the effectiveness of SNRIs or other agents such as mirtazapine, in treating depression in this patient group.27 Recent evidence suggests that the anti-parkinsonian drug pramipexole may also be effective at reducing depression in patients with PD.5,35 Many antidepressants (including some SSRIs) have antimuscarinic (anticholinergic), mydriatic properties and have the potential to either induce or worsen narrow-angle glaucoma in susceptible patients.5,33 In the more common open-angle glaucoma, the angle between the iris and the cornea is open and cannot be closed by an increase in pupil size.37 Therefore antidepressants with antimuscarinic side effects have no effect on the more common type of glaucoma i.e. open-angle glaucoma.38 Examination by an ophthalmologist is recommended prior to antidepressant therapy in patients with PD suffering with depression needs to be individualised to the patient and should be under specialist control. Considerations should include co-existing morbidity, concomitant medications (and the potential for drug-drug interactions), patient acceptability and the potential adverse effects of the antidepressant. Ideally there should be close cooperation between the psychiatrist and neurologist to optimise treatment in this group of patients.4 There is an urgent need for further research to establish effective and safe treatments for depression in patients with PD.20,24,26

**WHICH ANTIDEPRESSANT SHOULD BE USED IN PATIENTS WITH PARKINSON’S DISEASE?**

Glucoma is classified according to the anatomical status of the anterior chamber angle, as either open or closed. In narrow (or closed)-angle glaucoma, the angle between the iris and the cornea is at least partially closed and drainage of the aqueous fluid is blocked or reduced.5,9 Many antidepressants (including some SSRIs) have antimuscarinic (anticholinergic), mydriatic properties and have the potential to either induce or worsen narrow-angle glaucoma in susceptible patients.5,9 In the more common open-angle glaucoma, the angle between the iris and the cornea is open and cannot be closed by an increase in pupil size.9 Therefore antidepressants with antimuscarinic side effects have no effect on the more common type of glaucoma i.e. open-angle glaucoma.98 Examination by an ophthalmologist is recommended prior to antidepressant therapy in patients at risk of narrow-angle glaucoma.59 There are many risk factors including race (e.g. Asians, Hispanics), older age, female gender, farsightedness, narrow-angle glaucoma in the other eye, a positive family history, small eye or narrow angle, use of any substance that causes pupillary dilatation or the presence of cataracts.39-41 Patients with a narrow anterior chamber angle receiving glaucoma treatment, or those who have had laser treatment, may still be treated cautiously with antidepressants that have antimuscarinic properties.9 Intraocular pressure should be monitored regularly, with ongoing specialist ophthalmology review, the patient should be given information on the symptoms of acute narrow-angle glaucoma (e.g. blurred vision, intense pain, coloured halos around bright lights, red eye, lacrimation) and should be advised to stop the drug.
and seek immediate medical attention should they occur.5

Summary: Prescribing information for antidepressants with antimuscarinic properties may list the general terms “glaucoma” as a contraindication, or “can cause glaucoma” as a caution, without specifying the type of glaucoma.36 However, patients with open-angle or treated narrow-angle glaucoma should not be adversely affected by their use.41

WHICH ANTIDEPRESSANTS CAN BE USED IN PATIENTS WITH EPILEPSY?

Depressive symptoms often occur in people with epilepsy, and may be related, in part to depletion of serotonin; patients with epilepsy who have depressive symptoms occurring independently of seizures may require treatment with antidepressants.4 In addition, some antiepileptic drugs (AEDs) have been associated with depression, including carbamazepine, gabapentin, phenytoin and vigabatrin.4

Many antidepressants can reduce seizure threshold and the risk is dose-related.43 The general advice is that if an antidepressant is required, it should be commenced at the lowest dose which should be gradually increased until a therapeutic dose is achieved.43 SSRIs are considered a good choice if used with caution for the treatment of depression in patients with epilepsy; no clear difference exists between drugs in the class.4,42 They should be avoided if the epilepsy is poorly controlled and discontinued if convulsions develop.4

TCAs are in general epileptogenic and ideally, should be avoided completely.4

SNRIs: Seizures have been reported rarely for duloxetine and venlafaxine (in overdose), therefore care is required if they are prescribed.44,45 There are limited data on use of other agents such as mirtazapine or trazodone.4

There is potential for significant drug-drug interactions between antidepressants and AEDs, primarily mediated via the cytochrome P (CYP) 450 system and this should be taken into account when prescribing an SSRI with an AED. Some SSRIs are weaker inhibitors than others (e.g. citalopram) and some AEDs (e.g. carbamazepine and phenytoin) have a narrow therapeutic index; plasma levels of the AED should be monitored, where appropriate, and dosages adjusted accordingly.4 [The previous NMIC bulletin (2010;16:6) gives full information on the CYP 450 metabolic profile and drug interaction potential of the most commonly prescribed antidepressants.]

WHICH ANTIDEPRESSANT IS LEAST LIKELY TO CAUSE HYPONATRAEMIA?

Hyponatraemia is the fall in the plasma-sodium concentration, usually with a simultaneous fall in plasma osmolality. Risk factors include old age, female sex, low body weight, concomitant drugs (e.g. carbamazepine, diuretics), reduced renal function, and medical co-morbidity e.g. diabetes.4,5 The most common cause of hyponatraemia is dilution. This may result from excessive fluid intake; it may also occur as a result of reduced water excretion, as in renal impairment or the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).46

Hyponatraemia has been reported uncommonly with most antidepressants; some studies have suggested it may be more likely to occur with SSRIs.4,47,48,49 The mechanism of this adverse effect is probably SIADH. Symptoms include muscle cramps, fatigue and confusion, and seizures. The onset is usually within 30 days of starting antidepressant treatment and is probably not dose-related.4 When hyponatraemia is detected, antidepressants should be withdrawn immediately.46 Upon drug withdrawal, sodium usually returns to normal within two weeks.5 Consideration should also be given to the possibility of antidepressant withdrawal symptoms, once the antidepressant has been stopped abruptly.

The Committee on Safety of Medicines in the UK in 2005 estimated the risks of hyponatraemia associated with various antidepressants, based on available clinical trial and spontaneous report data at the time, while noting that under-reporting might occur (See Table 1).3

Table 1: Estimated risk5 of antidepressant-associated hyponatraemia

<table>
<thead>
<tr>
<th>Highest risk (&gt;1% incidence)</th>
<th>citalopram, escitalopram, fluoxetine, sertraline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium risk (0.5%-1% incidence)</td>
<td>amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lorfenamine, moclobemide, paroxetine, venlafaxine</td>
</tr>
<tr>
<td>Lowest risk (&lt;0.5% incidence)</td>
<td>nortriptyline, trazodone, mirtazapine, tranylcypromine, reboxetine, phenelzine</td>
</tr>
</tbody>
</table>

*the current Summary of Product Characteristics for each medicine is available on www.medicines.ie or www.imb.ie

For patients who require the re-introduction of an antidepressant, there have been reports both of recurrence of hyponatraemia, as well as reports of successful re-introduction. Experts currently recommend to reinitiate therapy using an antidepressant from a different class, to start at a low dose, to increase the dose slowly and to monitor closely.44 If hyponatraemia recurs and continued antidepressant use is essential, specialist advice should be sought.
IS THERE AN INTERACTION BETWEEN ANTIDEPRESSANTS AND TAMOXIFEN?

Tamoxifen is a selective oestrogen receptor modulator indicated for breast cancer; it requires conversion to its principal active metabolite (endoxifen) by cytochrome P450 enzymes, the most clinically relevant of which is CYP2D6.60,69 Although information is limited, it is reported that moderate inhibitors of CYP2D6, can alter the metabolism of tamoxifen to its active metabolites. The effect of altered metabolism on the clinical efficacy of tamoxifen remains to be established.60 Several observational studies investigating the effects of SSRIs on tamoxifen have not found an increase in breast cancer recurrence, although one case-control study with CYP2D6 inhibitors did suggest an increased recurrence.68 In addition, one retrospective cohort study reported an increased risk of breast cancer recurrence in patients taking paroxetine with tamoxifen.6

The SSRIs, paroxetine and fluoxetine are moderate inhibitors of CYP2D6; citalopram and escitalopram have minimal effects and sertraline is a dose-related inhibitor of CYP2D6.59 At present, there is insufficient evidence to provide definitive guidelines for the use of SSRIs in patients taking tamoxifen. Despite the lack of conclusive evidence, many commentators suggest that paroxetine (and therefore probably fluoxetine, which has similar CYP2D6 inhibitory potential) should be avoided.69 Since a number of SSRIs (e.g. citalopram, escitalopram, sertraline) have minimal / dose-related effects on CYP2D6, and given the potential seriousness of the proposed interaction, until the risks are established it would seem prudent to use an alternative SSRI to paroxetine and fluoxetine wherever possible.59,60 In November 2010 the IMB highlighted the reduced efficacy of tamoxifen reported with concomitant use of some SSRI antidepressants (e.g. paroxetine) and advised that co-administration of tamoxifen and potent CYP2D6 inhibitors should be avoided whenever possible.59

The SNRI venlafaxine has a low potential for affecting CYP2D6, and may provide an alternative option in some cases.50,52 However, duloxetine is known to have moderate to potent inhibitory effects on CYP2D6 and is best avoided with tamoxifen.52,54 Other Agents: Although direct studies are lacking, mirtazapine is thought to have little or no effect on CYP2D6 and may be suitable for those on tamoxifen therapy.52,54-56 The tricyclic antidepressants are metabolised by several cytochrome enzymes and drug-drug interactions are common; however, they are regarded as having weak CYP2D6 inhibitory activity.1,54

For patients who do not respond to other antidepressants, fluoxetine or paroxetine may be given and, if appropriate, and in conjunction with the specialist oncology team, tamoxifen substituted by an aromatase inhibitor.59,55

WHAT ACTION SHOULD BE TAKEN IF A PATIENT DOES NOT RESPOND TO AN ANTIDEPRESSANT?

As reported in the previous bulletin, it is estimated that at least 20% of patients do not respond to the first antidepressant prescribed.3,4,57-61 There are limited data available to provide guidance on what sequence of subsequent treatments might bring about remission in patients who have failed initial therapy.47 The US STAR*D project undertook a series of studies to examine “next best” treatment steps for over 2,500 patients, the majority of whom had chronic or recurrent major depression.48 Remission of symptoms was reported in approximately 25% of patients, previously unresponsive to, or intolerant of treatment with a SSRI, irrespective of whether they were switched to monotherapy (another SSRI, SNRI, mirtazapine) or combination (augmentation) therapy i.e. addition of another antidepressant to the original SSRI.50,59 [Note: the antidepressant drugs used in combination therapy in this study are not licensed in Ireland]. Patients, who were non-responders to these therapeutic regimens, showed modest remission rates when switched to subsequent therapies (including monotherapy or combination therapy with non-antidepressant agents under specialist use).51,62

MANAGEMENT OF NON-RESPONDERS TO INITIAL ANTIDEPRESSANT THERAPY:

SUMMARY

In the case of no response at 2 weeks to initial therapy:

- The patient should be monitored on a weekly basis for a further two weeks to check for non-adherence, presence of concomitant psychiatric disorders such as anxiety disorders or chronic medical conditions that may impact on the use/efficacy of antidepressants
- At 4 weeks the dose should be gradually increased to the maximum tolerated recommended dose
- If there is no response after 2-4 weeks, or patient is already on maximum dose regimen, the patient should be switched to another antidepressant, which can be from within the same class or another class. The changeover sequence should take into account the potential for serotonin syndrome with the switch and the patient’s response should be monitored as per initial therapy
- Modest responses to subsequent antidepressant therapy, after failure of two prior treatment regimens, have been reported from some studies
- Refractory patients requiring augmentation therapy or those with concomitant psychiatric or complex medical conditions require specialist referral.

List of references available on request. Date of preparation: March 2011

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a drug.
References: Frequently Asked Questions on Pharmacotherapy of Depression in Adults 2011; 17: 1

2. Andrews G, should depression be managed as a chronic disease BMJ 2001; 322: 419-21
17. Clinical Knowledge Summaries (CKS) print review: Depression – antenatal and postnatal. Which antidepressant should I prescribe for a woman who is breastfeeding? Available at http://www.cks.nhs.uk/print_preview?pageid=-297426&pagepath=/depression_antena... Downloaded on 8th Feb 2011
18. Musters C, McDonald E, Jones I, Management of postnatal depression, Clinical review, BMJ 2008;337:399-403
24. SIGN, Diagnosis and pharmacological management of Parkinson’s Disease – a national clinical guideline, January 2010, downloaded from www.sign.ac.uk on 22nd February 2011
42. Clinical Knowledge Summaries: Clinical Topic Depression (Feb 2010) Available online at www.cks.nhs.uk accessed 18th March 2011
56. Mann JJ, The medical management of depression. NEJM 2005; 353: 1819-34
57. Valenstein M. Keeping our eyes on STAR*D. Am J Psychiat 2006; 163: 1484-6
59. Rush AJ et al, Bupropion-SR, Sertraline or Venlafaxine-XR after failure of SSRIs for depression. NEJM 2006; 354: 1231-42
60. Trivedi M et al, Medication augmentation after the failure of SSRIs for depression. NEJM 2006; 354: 1243-52