







FOR PERSONAL USE ONLY. NOT TO BE REPRODUCED WITHOUT PERMISSION OF THE EDITOR

FREQUENTLY ASKED QUESTIONS ON USE OF ANTIDEPRESSANTS IN ADULTS

Topics Include:

-  Use of antidepressants in pregnant and breastfeeding women
-  Choice of antidepressant in patients with specific concomitant medical conditions
-  Frequently asked questions on adverse effects / potential drug interactions with antidepressants
-  Management of patients not responding to initial antidepressant therapy

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. **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. 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.⁵ 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.^{4,5,11,12} **Currently available evidence (mainly from observational studies) suggests that most antidepressants are secreted in breast milk, although serum concentrations vary widely.**^{5,11,13,14} 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

effective dose and concomitant therapy with other sedating drugs should be avoided.^{4,15-17} If a mother has taken a particular antidepressant during pregnancy up until delivery, continuation with the same drug while breast-feeding may be appropriate.^{4,5,11,12} **Infants should be monitored for possible effects of medication such as irritability, sedation and change in feeding patterns.**^{12,18,19} Ideally, premature or low birth weight infants, or those with renal, hepatic, cardiac or neurological impairment, should not be exposed to antidepressants as they may experience greater adverse effects due to drug accumulation.^{4,5,15,17} However the ultimate decision to treat depends on individual circumstances; referral to specialist services should be considered for these patients.

SSRIs and their metabolites pass into breast milk in small amounts, although there are variations within the group: citalopram and fluoxetine are more likely to be present at higher levels (compared to sertraline and paroxetine).¹¹⁻¹⁵ A review of SSRIs concluded that if there were compelling reasons to treat a mother for postpartum depression, the benefits of therapy with SSRIs would most likely outweigh the risks.¹⁴ SSRIs have relatively long half lives and if used, concomitant treatment with other sedating agents should be avoided.¹⁶ **Paroxetine and sertraline are the preferred options while citalopram and fluoxetine are less preferred,** because the latter are more likely to be present at higher levels and have been associated with a relatively higher risk of paediatric adverse events.^{10,12,17,20}

TCAs: The risks of taking TCAs when breastfeeding are better established than those of newer drugs, although the risks of tolerability and risk in overdose remain.^{11,15,19} Amitriptyline and imipramine have been recommended as the preferred TCAs for breastfeeding.⁵ Adverse effects from observational studies have not been reported in breastfed infants with TCAs, apart from doxepin (not authorised), which has a long-acting metabolite that may accumulate in breastfed infants.^{4,5,13-15}

Other Agents: Clinical experience of use during breastfeeding is limited with other antidepressants including venlafaxine, duloxetine, mirtazapine and trazodone; they are not considered as first choice agents.^{13,14,16}

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

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.^{22-27,29-31} 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.^{4,27} However, there are concerns about **possible worsening of motor function;**^{4,28,29} 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.^{26,31}

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.^{33,34}

The pharmacological management of a patient 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.^{22-24,26}

CAN ANTIDEPRESSANTS BE USED IN PATIENTS WITH GLAUCOMA?

Glaucoma 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.^{5,35} 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.^{3,5,36} 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 at risk of narrow-angle glaucoma.**⁵ 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.⁵ 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.^{4,5} 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.^{4,5}

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.^{4,5,42} 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.^{4,43,46,47} 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.**⁴⁸ 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).⁵

Table 1: Estimated risk* of antidepressant-associated hyponatraemia⁵

Highest risk (>1% incidence)	citalopram, escitalopram, fluoxetine, sertraline
Medium risk (0.5%-1% incidence)	amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, moclobemide, paroxetine, venlafaxine
Lowest risk (<0.5% incidence)	nortriptyline, trazodone, mirtazapine, tranylcypromine, reboxetine, phenelzine

*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 reinstitute therapy using an antidepressant from a different class, to start at a low dose, to increase the dose slowly and to monitor closely.^{4,5} **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.^{46,49}

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.⁵⁰ 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.⁵⁰ In addition, one retrospective cohort study reported an increased risk of breast cancer recurrence in patients taking paroxetine with tamoxifen.⁵

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.**⁵⁰ 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.⁵⁰ 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.^{50,52} 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.**⁵³

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.^{52,54,55} 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.^{3,54}

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.^{50,55}

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.^{3,4,56} 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.⁵⁷ 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.^{4,58} 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.^{59,60} [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).^{61,62}

MANAGEMENT OF NON-RESPONDERS TO INITIAL ANTIDEPRESSANT THERAPY: SUMMARY ^{3,4,57-61}

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

1. Moussavi S et al, Depression, chronic diseases, and decrements in health: results from the World Health surveys. *Lancet* 2007; 370: 851-8
2. Andrews G, should depression be managed as a chronic disease *BMJ* 2001; 322: 419-21
3. Pharmacotherapy of depression in adults. *NMIC Bulletin* 2010; Vol 6: 6. Available online at www.nmic.ie. Accessed 18th March 2011
4. The Maudsley Prescribing Guidelines 10th Edition. Eds: D Taylor, C Paton, S Kapur. Publishers Informa Healthcare UK 2009
5. Psychotropic Drug Directory 2010. Ed: Stephen Bazire. Publishers: HEALTHCOM UK Ltd
6. Irish Medicines Board Drug Safety Newsletter, 36th Edition. March 2010. Available online at www.imb.ie. Accessed on 10th January 2011.
7. Fluoxetine – risk of cardiovascular birth defects. Monthly Report of Pharmacovigilance working party (PhVWP) February 2010 Plenary meeting. Document No. EMA/102067/2010. Available online at www.ema.europa.eu. Accessed 16th March 2011
8. SSRIs and SNRIs: risk of persistent pulmonary hypertension in the newborn. Irish Medicines Board publication 3rd August 2010. Available online at www.imb.ie. Accessed 16th March 2011
9. UKTIS. Use of SSRIs during pregnancy and the risk of PPHN. Oct 2010. Available online at www.toxbase.org Accessed 14th February, 2011.
10. Gentile S, Use of Contemporary Antidepressants during Breastfeeding, A Proposal for a Specific Safety Index, *Drug Safety* 2008;30(2):107-121
11. Payne J, Antidepressant use in the postpartum period: practical considerations *Am J Psychiatry* 2007;164:1329-1332
12. Pearlstein T, Perinatal depression: treatment options and dilemmas, *Rev Psychiatr Neurosci* 2008;33(4):302-18
13. Medications and Mothers Milk 2010, Hale T 14th Edition, Publishers: Hale Publishing LP
14. *Drugs in Pregnancy and Lactation*, 8th Edition 2008,Eds: Briggs G, Freeman R, Yaffe S. Publishers
15. NICE clinical guideline 45 – Antenatal and postnatal mental health, February 2007 (reissued April 2007) downloaded from www.nice.org on 8th February 2011
16. Eberhard-Gran M et al, Use of Psychotropic medications in Treating Mood disorders during Lactation. *CNS Drugs* 2006; 20: 187-198
17. Clinical Knowledge Summaries (CKS) print review: Depression – antenatal and postnatal. Which antidepressant should I prescribe for a woman who is breast feeding? 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
19. Whitby D, Smith K, The use of tricyclic antidepressants and selective serotonin reuptake inhibitors in women who are breastfeeding, *Pharmacotherapy* 2005;25(3):411-425
20. Gentile S, The Safety of Newer Antidepressants in Pregnancy and Breastfeeding, *Drug Safety* 2005;28(2):137-152

21. Oguro M et al, Apathy and depression in Parkinson's Disease, *J Geriatr Psychiatry Neurol* 2010;23(1):35-41
22. Wood L et al, Clinical Review of treatment options for select nonmotor symptoms of Parkinson's Disease, *Am J Geriatric Pharmacother* 2010;8(4):294-315
23. The National Collaborating Centre for Chronic Diseases, Parkinson's Disease – National Clinical Guideline for diagnosis and management in primary and secondary care, published by the Royal College of Physicians 2006, downloaded from www.nice.org.uk on 9th February 2011
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
25. Ghazi-Noori S, Chung TH, Deane K, Rickards HE, Clarke CE, Therapies for depression in Parkinson's Disease, *Cochrane Database of Systematic Reviews* 2003, Issue 2. Art. No.: CD003465. DOI: 10.1002/14651858.CD003465
26. Canadian Agency for Drugs and Technologies in Health, Health Technology Inquiry Service, Pharmacological management of depression in Parkinson's Disease: Evidence for antidepressant of choice, 29 January 2009, downloaded from www.cadth.ca
27. Reichmann H, Schneider C, Lohle M, Non-motor features of Parkinson's disease: depression and dementia. *Parkinsonism and Related Disorders* 2009; 15:S87-92
28. Antonini A et al, Randomised study of sertraline and low-dose amitriptyline in patients with Parkinson's Disease and depression: effect on quality of life. *Movement Disorders* 2006;21(8):1119-1122
29. Weintraub D et al, Antidepressant studies in Parkinson's Disease: a review and meta-analysis. *Movement Disorders* 2005;20(9):1161-1169
30. Devos D et al, Comparison of desipramine and citalopram treatments for depression in Parkinson's Disease: a double-blind, randomized, placebo-controlled study. *Movement Disorders* 2008;23(6):850-857
31. Menza M et al, A controlled trial of antidepressants in patients with Parkinson Disease and depression. *Neurology* 2009;72:886-892
32. Park A, Stacy M, Non-motor symptoms in Parkinson's disease. *J Neurol* 2009;256(Suppl3):S293-298
33. Barone P et al, Pramipexole versus sertraline in the treatment of depression in Parkinson's Disease, *J Neurol* 2006;253:601-607
34. Barone P et al, Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease; a randomised, double-blind, placebo-controlled trial, *Lancet Neurol* 2010;9:573-80
35. Eskander O et al, Treatment of overactive bladder (OAB) with anti-cholinergic drugs and the risk of glaucoma. *J Obstet Gynaecol* 2005; 25: 419-21
36. Li et al., Drug-induced ocular disorders. *Drug Safety* 2008; 33: 127-141
37. Clinical Knowledge Summaries (CKS) Glaucoma and ocular hypertension (Sept 2010). Available online at www.cks.nhs.uk accessed 8th February 2011
38. Clarification: Drug risk in patients with glaucoma. *Medical Letter* 2001; 43: 52
39. Razeghinejad M et al, Iatrogenic glaucoma secondary to medications. *The American Journal of Medicine* 2011; 124: 20-25
40. Richa S and Yazbek J-C, Ocular adverse effects of common psychotropic agents: a review. *CNS Drugs* 2010;24: 501-26

41. Subak-Sharpe I et al, Pharmacological and environmental factors in primary angle-closure glaucoma. *British Medical Bulletin* 2010;93:125-143
42. Clinical Knowledge Summaries: Clinical Topic Depression (Feb 2010)
Available online at www.cks.nhs.uk accessed 18th March 2011
43. British National Formulary (BNF):61. Publishers: BMJ Publishing Group, UK. March 2011. (www.bnf.org)
44. SPC Efexor XL®. Available on www.medicines.ie, accessed 20 Jan 2011
45. SPC Cymbalta®. Available on www.medicines.ie, accessed 20 Jan 2011
46. *Martindale: The Complete Drug Reference*. [online] London: Pharmaceutical Press. Available online at <http://medicinescomplete.com/> (Accessed on 9th February 2011)
47. Depression: the treatment and management of depression in adults (CG90). National Institute of Health and Clinical Evidence, UK 2009. Available at www.nice.org.uk. Accessed 7th January 2011
48. Reid S and Barbui C, Long term treatment of depression with selective serotonin reuptake inhibitors and newer antidepressants. *BMJ* 2010; 340: c1468
49. Nolvadex D® 20mg SmPC, revised May 2010. Available online at: www.medicines.ie accessed 15th February 2011
50. Baxter K (Ed), *Stockley's Drug Interactions*. [online] London: Pharmaceutical Press <http://medicinescomplete.com/> (Accessed on 9th February 2011)
51. Kelly C et al, Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. *BMJ* 2010; 340. c693.
52. Tamoxifen *in* Drug Interactions, Analysis and Management. Authors: Hansen and Horn. Publishers: Wolters Kluwer Health (USA) 2010.
53. Tamoxifen – Risk of Reduced Therapeutic Response (IMB November 2010). Available online at: www.imb.ie accessed 9th February 2011
54. Sideras K et al, Co-prescription of tamoxifen and medications that inhibit CYP2D6. *J Clin Oncol* 2010; 28: 2768-76.
55. Desmarais J et al, Interactions between tamoxifen and antidepressants via cytochrome P450 2D6. *J Clin Psychiatr* 2009; 70; 1688-1697
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
58. Trivedi M et al, Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiat* 2006; 163: 28-40
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
61. Nierenberg A et al, A comparison of lithium and T3 augmentation following two failed medication treatments for depression: A STAR*D Report. *Am J Psychiat* 2006; 163: 1519-30
62. McGrath P et al, Tranylcypromine versus venlafaxine plus mirtazepine following three failed antidepressant medication trials for depression: A STAR*D Report. *Am J Psychiat* 2006; 163: 1531-41
63. Depression: Quick Reference guide (NICE clinical guidelines 90 and 91). National Institute for Health and Clinical Excellence 2009. Available online at www.nice.org. Accessed 7th January 2011