WeMeReC
Welsh Medicines Resource Centre
Canolfan Adnoddau Moddion Cymru

Bulletin
"Independent prescribing information for NHS Wales"

Antidepressant therapy in primary care

This bulletin focuses on antidepressant therapy in adults (aged 18 years and over) in primary care, and complements the recent WeMeReC module on the management of depression.

The UK has seen a substantial increase in antidepressant prescribing over the past 20 years. The possible reasons behind this rise have been studied, but are not well understood.[1] Guidelines recommend that antidepressants should not be prescribed routinely for mild depression. However, they may be considered for people with a history of moderate or severe depression; subthreshold depressive symptoms present for at least two years; and mild depression persisting after other interventions, or complicating the care of a chronic physical health problem.[2,3]

Choice of antidepressant

Generally, the more severe the symptoms of depression, the greater the likely benefit from antidepressants. There is strongest evidence for the efficacy of antidepressants in treating depression of at least moderate severity.[4] In this group of patients, approximately 20% will recover with no treatment at all, 30% will respond to placebo, and 50% will respond to antidepressant treatment.[5,6] It should be noted that response in clinical trials is generally an arbitrary dichotomy defined as a 50% reduction in depression rating scale scores. Change measured using continuous scales tends to show smaller mean differences between active treatment and placebo.[5,6]

When selecting therapy, a number of factors must be considered, such as comorbid diseases, existing therapy, the degree of sedation desired, suicide risk, and outcomes of any previous antidepressant therapy. In the absence of previous treatment, a generic selective serotonin re-uptake inhibitor (SSRI) should usually be used first-line.[2]

SSRIs have been shown to be as effective as other classes of antidepressants but are generally better tolerated and are considered safer than tricyclic antidepressants (TCAs) in overdose.[2] There is no evidence of any clinically meaningful difference in efficacy between SSRIs, although their side effect profiles differ.[5] Paroxetine has been associated with more weight gain and a higher incidence of sexual dysfunction, and sertraline with a higher incidence of diarrhoea than the other SSRIs.[5] The risk of drug interactions appears to be lower with citalopram and sertraline. The risk of discontinuation reactions is higher with paroxetine (short half-life) and lower with fluoxetine (long half-life).

The newer serotonin and noradrenaline re-uptake inhibitors (SNRIs), such as venlafaxine and duloxetine, tend to be tolerated less well than SSRIs but better than TCAs. Non-reversible monoamine oxidase inhibitors (MAOIs), e.g. phenelzine, should normally be prescribed only by specialists in mental health. Dosulepin should not be prescribed.[2]

As there is interpersonal variation in tolerability of antidepressants, a flexible approach is usually required to find the right medicine for an individual.[5]

Summary

- Antidepressants should not be prescribed routinely for mild depression.
- A generic SSRI should usually be used first-line.
- Comorbid conditions will influence the choice of agent and, possibly, dose selection.
- Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions.
- SSRIs should not normally be offered to patients taking aspirin or NSAIDs due to the increased risk of bleeding.
- Experience with antidepressants during pregnancy and breastfeeding is growing; up-to-date advice should always be sought.
- Non-response at two to six weeks is a predictor of overall non-response to a specific agent.
- Concomitant use of some antidepressants is contraindicated and, if switching agents, a drug-free interval may be required to avoid interactions.
- The incidence of discontinuation reactions appears to be influenced by dose, duration of therapy, and plasma half-life of the drug.

Welsh Medicines Resource Centre
Academic Centre, University Hospital Llandough,
Penarth, Vale of Glamorgan CF64 2XX

Tel: 029 2071 6117 Web: www.wemerec.org
Email: wemerec@wales.nhs.uk

NHS WALES GIG CYMRU

January 2011

Comorbid conditions

Heart disease: TCAs should be avoided as they have the potential to cause arrhythmias. Although there are limited data, SSRIs do not appear to increase the risk of cardiovascular adverse effects.[3,7] Of the SSRIs, sertraline and citalopram appear to have the lowest interaction potential so should generally be first choice.[7] Mirtazapine is a suitable alternative if SSRIs cannot be used, but it should be used with caution.[7]

Diabetes: SSRIs appear to have a favourable effect on diabetic parameters in type II diabetes and are considered first-line.[5] SNRIs are likely to be safe but there are fewer supporting data. TCAs and MAOIs should be avoided if possible due to their effects on weight, and glucose homeostasis.[5]

Epilepsy: The first consideration should be to check a patient's anticonvulsant regimen for potential drug-induced depression. The patient may benefit from changing to an anticonvulsant with a more favourable effect on mood rather than adding an antidepressant.[8] SSRIs are the preferred choice, but should be avoided if the epilepsy is poorly controlled and discontinued if convulsions develop.[8,9] Citalopram and sertraline are considered less likely than the other SSRIs to interact with anticonvulsant agents.[8]

Hepatic disease: All antidepressants should be avoided in severe disease. In less severe disease sedative agents are unsuitable. Paroxetine and citalopram are suitable choices, although SSRIs should be avoided when the prothrombin time is prolonged. Of the TCAs, there is most clinical experience with imipramine. Lofepramine is contraindicated.[5]

Renal disease: Many antidepressants have active metabolites that are renally excreted and doses may need to be adjusted. No agent is clearly preferred; citalopram or sertraline may be reasonable choices.[5]

In hepatic or renal impairment, treatment should start at low doses and increase slowly as tolerated.

Pregnancy and lactation

As with all medicines, antidepressants should only be prescribed for pregnant or breastfeeding women if the benefits outweigh the risks. A patient already receiving an antidepressant, who is at a high risk of relapse, is probably best maintained on therapy during and after pregnancy.[5] Up-to-date advice should be sought from local medicines information centres regarding the suitability of the medicine in pregnancy and/or breastfeeding. Experience with antidepressants, particularly the newer agents, during pregnancy and breastfeeding is growing and a change in treatment may not be necessary.[5]

All antidepressants carry the risk of withdrawal or toxicity in neonates; in most cases the effects are mild and self-limiting.[10] There are currently far fewer safety data for duloxetine, mirtazapine, moclobemide, reboxetine, or venlafaxine and they should be avoided in pregnancy if possible; TCAs or SSRIs are preferred.[11]

Historically, TCAs have been used in the management of depression in pregnancy, most experience being with amitriptyline and imipramine. However, as adverse effects and toxicity in overdose limit their use,[10,11] most patients are now likely to be taking SSRIs.

SSRIs as a class are not considered to be major teratogens but paroxetine has been associated with foetal heart defects when taken in the first trimester.[5,12] More recently, a small increased risk of congenital heart defects with fluoxetine has been reported. It is not yet known if this is a class effect.[12,13] Data indicate that use of SSRIs beyond 20 weeks gestation may be associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). Should SSRI treatment be required, the lowest effective dose should be used.[14]

Any initiation or continuation of an antidepressant in a woman who is breastfeeding requires that her infant is full-term, healthy, and can be adequately monitored for specific adverse effects (such as sedation), feeding problems, growth, and development. When an infant is premature or low birthweight, specialist advice should be sought. Of the TCAs, imipramine and nortriptyline are preferred in breastfeeding as they are less sedating than other TCAs.[15] Doxepin should not be used. Of the SSRIs, paroxetine and sertraline are preferred as they have shorter half-lives, lowering the risk of drug accumulation in the neonate.[15] Citalopram and fluoxetine are less suitable as they have longer half-lives.[11,15]

Initiating therapy

A starting dose should be prescribed and titrated, where necessary, up to the recognised minimum effective dose. SSRIs, mirtazapine, moclobemide, reboxetine, and venlafaxine are often effective at the starting dose and titration may be unnecessary.[16] Lower starting doses should be considered for elderly patients (see BNF for specific recommendations).[9]

Traditionally, the onset of response to therapy is said to occur within two to three weeks, with a full response often taking at least four to six weeks. Over the past few years, this has been challenged. A number of meta-analyses show statistical separation and the highest rate of improvement during weeks one to two of treatment.[5,17]

Despite this, it is prudent to counsel patients that they may not start to feel better immediately. Initial follow-up should be every one to two weeks, depending on the severity. During this period, it is advisable to prescribe limited quantities of antidepressants and to monitor patients closely for adherence, adverse effects, and suicidal ideation.

Adverse effects

The most common adverse effects associated with SSRIs are dose-related gastrointestinal (GI) effects (nausea, vomiting, abdominal pain, dyspepsia, constipation, and diarrhoea), central nervous system effects (dizziness, agitation, anxiety, insomnia, and tremor), and headache. Sexual dysfunction, which affects up to 70% of people taking SSRIs, can be problematic.[5] Communication regarding this potential effect is often poor.[18]

The most common adverse effects of TCAs are antimuscarinic effects, such as dry mouth, constipation, and blurred vision. However, some tolerance to these adverse effects seems to develop. TCAs can also cause cardiac conduction disturbances, orthostatic hypotension, and weight gain. They are particularly toxic in overdose; lofepramine is associated with the lowest risk of fatality.[5,9] Drowsiness is associated with some TCAs whereas others, e.g. imipramine, lofepramine, and nortriptyline, are considered to be less sedative.[9]

Regular monitoring of blood pressure is recommended for patients taking venlafaxine as dose-related increases in blood pressure have been reported.[6] For patients who experience a sustained increase in blood pressure, either dose reduction or discontinuation should be considered.[19] Venlafaxine should not be used in patients with conditions associated with a high risk of cardiac arrhythmias or those with uncontrolled hypertension.[19]

Increased appetite and weight gain commonly occur in people taking mirtazapine. This should be taken into account before prescribing, particularly for people who are overweight, obese, or who have an eating disorder.[16]

Hyponatraemia

Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant.[20] Hyponatraemia has been associated with all types of antidepressant, but has been reported more frequently with SSRIs. It is a potentially serious adverse effect that warrants careful monitoring and, if necessary, action.

For those patients at high risk of drug-induced hyponatraemia, serum sodium should be determined at baseline, at weeks two and four, and every three months thereafter. Risk factors include:[5]

- Extreme old age (> 80 years)
- History of hyponatraemia
- Concomitant therapy with other medicines known to be associated with hyponatraemia
- Reduced renal function (GFR < 50ml/min)
- Medical comorbidity (e.g. hypothyroidism, hypertension, diabetes, chronic obstructive pulmonary disease, head injury, cerebrovascular accident, various cancers).

Bleeding

An increased risk of upper GI bleeding has been seen in observational studies with antidepressants such as fluoxetine, sertraline, paroxetine, and clomipramine.[21] However, the absolute risk is small; three extra episodes of upper GI bleeding requiring hospitalisation per 1000 patient-years of treatment. This risk is similar to that experienced by users of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).[21] The risk of bleeding is further increased if the patient also takes aspirin or NSAIDs, has had a previous upper GI bleed, or if they are very old.[5,21]

SSRIs should not usually be offered to patients taking NSAIDs or aspirin; a medicine with a lower propensity for, or a different range of, interactions should be considered (e.g. mirtazapine, trazodone, or reboxetine).[3] If there is no suitable alternative to an SSRI, an NSAID may be co-prescribed if a gastroprotective agent (e.g. a proton-pump inhibitor) is also offered.[3] This may reduce, but will not eliminate, the risk of bleeding.[5]

Continuing therapy after remission

If treatment is discontinued at remission there is considerable risk of early relapse. After recovery from a single episode, the effective dose of the antidepressant should be continued for six to nine months.[5] Treatment should not be discontinued if symptoms are still present. Many patients comply poorly once they are feeling better and the benefits of continuing therapy should be discussed with them. Patients who express concerns about prolonged therapy may need reassurance that antidepressants are effective, not known to lose their efficacy over time, and are not addictive.

Maintenance therapy

Of those patients who have one episode of major depression, 50-85% will go on to have a second episode, and 80-90% of these will have a third.[5] Long-term prophylactic therapy may be needed for recurrent depression. The National Institute for Health and Clinical Excellence (NICE) recommends

that patients who have had two or more episodes of depression with significant functional impairment in the recent past should be advised to continue antidepressants for at least two years.[2] Patients should be re-evaluated, taking into account age, co-morbidities, and other risk factors in any decision to continue maintenance therapy beyond that time.[2]

Partial or non-response

Treatment should be continued for at least four weeks at a therapeutic dose (six weeks in elderly patients) before deciding whether it is likely to be successful. If there is some improvement in the patient's condition, treatment should be continued for another two to four weeks before reassessing response.

If a patient has not responded, it is important to check the diagnosis, any concurrent medical or psychiatric conditions, and adherence. Non-adherence rates are estimated to be about 40%.[4] Where there is minimal or no response, a change of dose or antidepressant may be necessary. Although there is limited evidence for increased efficacy after dose escalation, particularly for SSRIs,[5] a dose increase within the SPC recommended range may be a reasonable step as there is wide variability in plasma concentration between individuals.[4] Non-response at two to six weeks is a good predictor of overall non-response to a specific agent.[5]

Switching antidepressants

Approximately one-third of patients treated for major depression do not respond satisfactorily to the first antidepressant prescribed.[6] It should be noted that the evidence for the relative advantages of switching either within or between classes of antidepressants is weak. However, NICE concludes that, overall, switching is worthwhile. Initially, a different SSRI or a better tolerated newer-generation antidepressant should be tried, followed if necessary by a trial of an antidepressant from a different class.[2] The choice of alternative should be guided by the same principles that apply when choosing the initial agent.

When changing from one antidepressant to another, consideration should be given to the possibility of discontinuation reactions, potential loss of antidepressant effect, and the risks of concomitant therapy. Cross-tapering is one method of switching, whereby the dose of the ineffective or poorly tolerated medicine is slowly reduced while the new medicine is slowly introduced. Sometimes, cross-tapering is not necessary or advisable. Concomitant use of some antidepressants is contraindicated and a drug-free interval may be required after cessation to avoid clinically significant interactions and, in the case of serotonergic agents, the potentially lethal **serotonin syndrome**.[5]

Symptoms of this syndrome include cognitive behavioural changes, autonomic dysfunction, and neuromuscular abnormalities. The potential for this syndrome to occur has been noted with some antidepressants when used with other agents, such as triptans, that have serotonergic activity.[22]

Appropriate resources should be consulted for guidance on switching between antidepressants. Specific advice is available from local medicines information centres. All patients should be carefully monitored when switching.[5]

Stopping antidepressants

Discontinuation reactions can occur with all classes of antidepressants and may be triggered by non-adherence as well as intentional cessation.[4] The incidence seems to increase with higher doses, longer durations of therapy, and with agents that have shorter plasma half-lives. For more guidance see the WeMeReC e-notes on stopping antidepressants www.wemerec.org/res_enotes.php.

References

1. Moore M et al. Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database. BMJ 2009; 339: b3999.
2. National Institute for Health and Clinical Excellence. Depression: the treatment and management of depression in adults. NICE Clinical Guideline 90, October 2009. www.nice.org.uk/cg90
3. National Institute for Health and Clinical Excellence. Depression in adults with a chronic physical health problem: treatment and management. NICE Clinical Guideline 91, October 2009. www.nice.org.uk/cg91
4. Anderson IM et al. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2000 British Association for Psychopharmacology guidelines. J Psychopharmacol 2008; 22: 343-396.
5. Taylor D et al. The Maudsley Prescribing Guidelines10th Ed. London: Informa Healthcare, 2009.
6. National Collaborating Centre for Mental Health. Depression in Adults (update). National Clinical Practice Guideline 90, October 2009. www.nice.org.uk
7. UK Medicines Information (UKMi). What is the antidepressant of choice in coronary heart disease? UKMi Medicines Q&A 55.4c. www.nelm.nhs.uk
8. UK Medicines Information (UKMi). What is the most appropriate antidepressant to use in epileptics? UKMi Medicines Q&A 24.4. www.nelm.nhs.uk
9. BNF 60. British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. Pharmaceutical Press, September 2010. www.bnf.org
10. National Institute for Health and Clinical Excellence. Antenatal and postnatal mental health. NICE Clinical Guideline 45, February 2007. www.nice.org.uk/cg45
11. Clinical Knowledge Summaries. Depression-antenatal and postnatal. www.cks.nhs.uk
12. UK Teratology Information Service. Use of SSRIs in pregnancy. October 2010. www.toxbase.org
13. MHRA. Fluoxetine: possible small risk of congenital cardiac defects. Drug Safety Update 2010; 3(8): 4.
14. UK Teratology Information Service. Use of SSRIs during pregnancy and the risk of PPHN. October 2010. www.toxbase.org
15. UK Medicines Information (UKMi). Management of depression in breastfeeding mothers – an overview. UKMi Medicines Q&A 255.1. www.nelm.nhs.uk
16. Clinical Knowledge Summaries. Depression. www.cks.nhs.uk
17. Taylor MJ et al. Early onset of selective serotonin reuptake inhibitor antidepressant action. Arch Gen Psychiatry 2006; 63: 1217-1223.
18. Gigerenzer G et al. Simple tools for understanding risks: from innumeracy to insight. BMJ 2003; 327: 741-4.
19. Duff G. Updated prescribing advice for venlafaxine (Efexor/Efexor XL). CSM May 2006 [letter]. www.mhra.gov.uk
20. UK Medicines Information (UKMi). If antidepressant-induced hyponatraemia has been diagnosed, how should the depression be treated? UKMi Medicines Q&A 137.2. www.nelm.nhs.uk
21. Anon. Do SSRIs cause gastrointestinal bleeding? DTB 2004; 42(3): 17-18.
22. UK Medicines Information (UKMi). Triptans and SSRI antidepressants – is there an interaction? UKMi Medicines Q&A 48.5. www.nelm.nhs.uk