J R Coll Physicians Edinb 2006; 36:27–29

The pros and cons of the SSRI antidepressants

G Masterton
Consultant Psychiatrist, Department of Psychological Medicine, Royal Infirmary of Edinburgh, Edinburgh, Scotland

ABSTRACT The SSRIs have become the most heavily prescribed antidepressant drugs in North America and Europe. However, they have been dogged by controversy about withdrawal effects/drug dependence, heightened suicidal thinking and behaviour, and their use in children and adolescents who are depressed. This paper brings the reader up to date with developments, including opinion and guidance from the MHRA and NICE.

KEYWORDS Antidepressants; benefits; guidance; safety; SSRIs

LIST OF ABBREVIATIONS Committee on the Safety of Medicines (CSM), International Classification of Diseases (ICD), Medicines and Healthcare products Regulatory Agency (MHRA), National Institute for Clinical Excellence (NICE), selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant (TCA)

DECLARATION OF INTERESTS No conflict of interests declared.

Published online ***January 2007***

Correspondence to ***G Masterton, Department of Psychological Medicine, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA***

tel. ***+44(0)131 242 1398***

fax. ***+44 (0)131 242 1393***

e-mail
george.masterton@luht.scot.nhs.uk

INTRODUCTION

Since the SSRI antidepressants were introduced in the late 1980s, they have become heavily prescribed, first-line therapy for depressive illness. Their licensed uses have diversified to include treatment of generalised anxiety, panic disorder, post-traumatic stress disorder, social phobia, obsessive compulsive disorder, and bulimia nervosa. However, the SSRIs have proved controversial and have repeatedly attracted hostile publicity, especially with regard to risks of withdrawal reactions and increased suicidal behaviour. Concern was sufficiently great for the MHRA to convene an expert working group that reviewed the SSRIs, concluding with a report in late 2004.[1] The outcome was reassuring: The MHRA and NICE[2] endorsed continuing use of this group of antidepressants (while restrictions were placed on a related compound, venlafaxine, in response to safety concerns emerging).

Before discussing the pros and cons of SSRIs, it is appropriate to remind readers that depression has a lifetime incidence of 15–20%, and a prevalence of 4–8%. It is a distressing and disabling illness with appreciable mortality that includes a 6% suicide rate. Specific treatment is required when the illness is moderate or severe, with antidepressant medication remaining the mainstay of therapy.

EFFECTIVENESS

The SSRIs are equally effective, with 50–70% of patients responding satisfactorily. Of the newer antidepressants, venlafaxine may be slightly more effective. In meta-analyses, the TCAs also tend to emerge as more effective, especially when the illness is severe. There is no additional benefit gained by increasing the dose of SSRI above the recommended daily dose.[1]

TOLERABILITY

The SSRIs are undoubtedly better tolerated than the TCAs, in so far as patients are less likely to drop out of treatment. There is not much difference between the SSRIs and most of the other newer antidepressants. Among the SSRIs, fluvoxamine is inferior, mainly because of more severe gastrointestinal side effects.

TOXICITY

While the SSRIs are safer and better tolerated than the TCAs, they are not free from either potentially significant side effects or hazards. Gastrointestinal symptoms, sweating and insomnia are well-known side-effects, but there are other important problems regularly encountered with this group of drugs, notably sexual dysfunction, weight change, agitation, and vivid dreams/nightmares.

The propensity for SSRIs to provoke upper GI bleeding through impairment of platelet aggregation has been confirmed, a risk that is clinically important when prescribing for the elderly and patients with a history of previous GI bleeding.[3]

PREGNANCY AND BREAST FEEDING

Mild discontinuation reactions have been reported in the newborn whose mothers were taking SSRIs;[4] paroxetine is most commonly implicated.[5] When SSRIs are taken in late pregnancy, a five-fold increase in the risk of pulmonary hypertension (to around 1%) has been

reported among newborns.[6] Concern has also emerged recently about adverse fetal effects when paroxetine is prescribed during early pregnancy with a doubling of the risk of cardiac abnormality from 1 to 2%.[5] As with any other drug, continuation of therapy during pregnancy needs to be reviewed and discussed with the patient. At present, there is no need to stop SSRIs routinely during pregnancy or prior to conception. Fluoxetine is the SSRI of choice when prescribing in pregnancy.

The issue of breastfeeding when taking SSRIs is encountered frequently when treating a woman with post-natal depression. The SSRIs are fat soluble, so pass to the baby in breast milk, the dose being estimated at 1% of the mother's dose. In general, the risks to mother and baby from untreated depression greatly outweigh this drug-related risk. Longer acting SSRIs such as fluoxetine are best avoided in this setting (unless already being taken with benefit); sertraline and paroxetine are preferred.

DISCONTINUATION REACTIONS

This syndrome, and whether it does or does not define addiction, has been one of the main areas of criticism and concern about SSRIs.

Discontinuation reactions can occur with all classes of antidepressant; indeed they were first recognised with imipramine in the 1950s. The syndrome varies from one type of antidepressant to another, and may figure symptoms that seem unusual in drug withdrawal. For the SSRIs, the most common complaints are dizziness, light-headedness, GI disturbances, anxiety, sleep impairment and headaches. Sensory disturbances – numbness, tingling and electric shock-like spasms – are common and characteristic. Several strands of evidence indicate these reactions occur more often with paroxetine among the SSRIs. The disorder is usually mild and self-limiting. The key elements to management are firstly to warn and reassure patients about this possibility, and secondly to avoid abrupt cessation and to taper the dose when ending treatment, especially if higher doses are being used.[1,2]

The MHRA expert group concluded that the SSRIs were not dependence-forming drugs since, among the six cardinal features of drug dependence, three of which must be present to reach the ICD–10 diagnosis, only an abstinence syndrome was definitely evident.[1] Supporting this conclusion, the only evidence of SSRIs being abused has emerged when the drugs have been prescribed to patients who abused other substances.

LOSS OF EFFECT

Loss of effect is a problem with longer term use of SSRIs. Although less well known than the discontinuation reaction, it is clinically significant, and difficult to recognise and treat. The phenomenon is thought to be due to down regulation of the neuroreceptors, and may occur more often with SSRIs than with other antidepressants. Its importance has not yet been fully appreciated.

SUICIDE AND SELF-HARM

A major benefit of SSRIs is the much-reduced toxicity in overdose compared with TCAs (and venlafaxine), such that their use in depressed patients has been advocated as a key suicide prevention measure. However, paradoxically, suicides, homicides, acts of self-harm and increased suicidal thinking have all been attributed to the SSRIs, stimulating public concern, media criticism and legal actions. This topic has been investigated thoroughly using a variety of research designs. The results have been inconclusive, with studies finding increased, unchanged or reduced risks of suicide, self-harm and suicidal thinking. The MHRA's conclusion reflected this: the mixed picture produced by data obtained from different sources meant that an adverse effect could not be ruled out.[1]

Subsequent research studies have continued to produce contradictory findings.[7–9] Overall, the pendulum may have swung towards acceptance of an increased risk of self-harm and suicidal thinking during the first few weeks of SSRI treatment compared with other drugs. This presents most often in the young but can occur at any age. It appears to be an idiosyncratic response, probably due to the drug's stimulatory action inducing agitation, restlessness, akathisia or hyperarousal. Physicians are advised to check for these features in the early stages of treatment as a cue to assessing risk.[2]

DRUG INTERACTIONS

The SSRIs are metabolised via cytochrome P450 enzymes, and the important interactions are with other drugs that compete for this pathway. Sertraline and citalopram have the lowest potential for drug interactions among the SSRIs, and are to be preferred, along with other classes of antidepressants, in patients taking competitor drugs. Finally, there are potentially hazardous interactions with dopaminergic and serotonergic drugs, resulting in a serotonin syndrome, or crisis in extreme cases.

CHILDREN AND ADOLESCENTS

In June 2003, the CSM in the UK concluded that paroxetine should not be prescribed to treat depression in children and adolescents. Six months later, an extensive CSM review concluded that the balance of risks and benefits for the treatment of depressive disorder in under-18s was judged to be unfavourable for sertraline, citalopram and escitalopram, and unassessable for fluvoxamine.[10] Only fluoxetine has been shown in clinical trials to be effective in treating depression in this age group, so although it might also be associated with an increased risk of self harm and suicidal thinking the benefit

J R Coll Physicians Edinb 2007; **37**:27–29

was judged to outweigh the risk. The MHRA expert group endorsed these recommendations, reinforcing the point that it was lack of antidepressant effect that was the reason these SSRIs were now contraindicated in the under-18s, and advising they could still be prescribed for other licensed indications in this age group.[1]

So what is the current advice for using SSRI antidepressants to treat depression? The National Institute for Health and Clinical Excellence is unequivocal: SSRIs are the recommended first line therapy when antidepressant drug treatment is required to treat moderate or severe depression in adults, and in mild depression that has not responded to other interventions.[2] Their advantages lie in fewer side effects resulting in greater likelihood of treatment completion and less toxicity especially in overdose, rather than greater effectiveness.

KEYPOINTS

- Selective serotonin reuptake inhibitors are equally effective, and as effective as other types of antidepressant drug, in mild to moderate depression. Selective serotonin reuptake inhibitors, with the exception of fluoxetine, should not be prescribed to treat depression in children and adolescents because they are ineffective.
- Selective serotonin reuptake inhibitors are well tolerated compared with TCAs, so compliance is better, and treatment drop-out less frequent. Side-effects are generally mild, but there are potential hazards, such as increased risk of gastrointestinal bleeding in the elderly and in those with a history of this condition. There are also clinically important drug interactions that include precipitation of a serotonergic crisis. There is evidence accumulating of risks to the fetus and newborn when taken during pregnancy.
- Discontinuation reactions ('withdrawal' symptoms) occur in a minority of patients and are usually mild and self-limiting. Patients should stop SSRIs gradually over several weeks rather than abruptly.
- Loss of effect is probably an under-recognised problem with SSRIs, especially when treatment is long-term.
- Selective serotonin reuptake inhibitors have a clear advantage over TCAs in suicidal patients of being much less toxic when taken in overdose.

REFERENCES

1 http://www.mhra.gov.uk/. Report of the CSM Expert Working Group on the safety of selective serotonin reuptake inhibitor antidepressants. Accessed 6 December 2004.

2 Management of depression in primary and secondary care. Clinical Guideline 23. www.nice.org.uk/guidance/CG23 Accessed 6 December 2004.

3 Van Walraven C, Mamdani MM, Wells PS, Williams JI. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. *BMJ* 2001; **323:**655–8.

4 Moses-Kelko EL, Bogen D, Perel J *et al.* Neonatal signs after late *in utero* exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. *JAMA* 2005; **293:**2372–83.

5 National Teratology Information Service, Regional Drug and Therapeutics Centre, Newcastle. Use of paroxetine in pregnancy. Accessed 28 Sept 2005.

6 Chambers CD, Hernandez-Diaz S, Van Marter LJ *et al.* Selective serotonin re-uptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006; **354:**579–87.

7 Cipriani A, Barbui C, Geddes JR. Suicide, depression and antidepressants. Editorial. *BMJ* 2005; **330:**373–4.

8 Simon GE, Savarino J, Operskalski B, Wang PS. Suicide risk during antidepressant treatment. *Am J Psychiatr* 2006; **163:**41–7.

J9 Juurlink DN, DN, Mamdani MM, Kopp A, Redelmeier DA. The risk of suicide with selective serotonin reuptake inhibitors in the elderly. *Am J Psychiatr* 2006; **163:**813–21.

10 Committee on Safety of Medicines. Selective serotonin reuptake inhibitors – use in children and adolescents with major depressive disorder. Accessed 10 December 2003.