Properties and use of SSRIs for depressive disorders

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Steve Chaplin and Dr Rajeev Krishnadas provide an overview of SSRIs – the first-choice medications for the treatment of depressive, obsessive compulsive and anxiety disorders

**KEY POINTS**

- All SSRIs are licensed for the treatment of major depression and some are also licensed for the treatment of OCD, bulimia nervosa, panic disorder, social anxiety disorder, generalised anxiety disorder and post-traumatic stress disorder.
- SSRIs are better tolerated and safer in overdose than other classes of antidepressants.
- There is robust evidence to support the use of SSRIs in moderate to severe depression.
- SSRIs have been associated with suicidal thoughts and behaviour; patients should be closely monitored during early treatment.
- Fluoxetine is the only SSRI licensed for the treatment of depression in children (over eight years old).

**Steve Chaplin**

The selective serotonin reuptake inhibitors (SSRIs) are better tolerated and safer in overdose than other classes of antidepressants and are the drugs of first choice for major depression. All are available as tablets or capsules and, except for fluvoxamine and sertraline, in liquid formulation.

All SSRIs are licensed for the treatment of major depression and some are also licensed for the treatment of obsessive compulsive disorder (OCD; escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), bulimia nervosa (fluoxetine), panic disorder (citalopram, escitalopram, paroxetine, sertraline), social anxiety disorder (escitalopram, paroxetine, sertraline), generalised anxiety disorder (escitalopram, paroxetine) and post-traumatic stress disorder (paroxetine, sertraline).

**Children**

Fluoxetine is the only SSRI licensed for the treatment of depression in children (over eight years old); for other SSRIs, the risks to children outweigh the benefits but specialists may prescribe them under exceptional circumstances. Fluvoxamine and sertraline are licensed for the treatment of OCD in children.

**Dosage**

The dose response relationship for SSRIs is relatively flat so the recommended range of doses is narrow. Nevertheless, treatment should be initiated at the lowest dose and increased if necessary after an interval long enough to determine efficacy. This is usually three to four weeks, despite differences in the elimination half-lives (see Table 1).

The initial dose for elderly patients should be reduced for citalopram and escitalopram and the maximum dose is reduced for all SSRIs except sertraline. Blood levels of escitalopram are increased in individuals who are poor metabolisers with respect to the hepatic enzyme CYP2C19; the initial dose should be halved for the first two weeks in these patients.

**Hepatic and renal impairment**

All the SSRIs undergo hepatic metabolism, sometimes producing active metabolites (see Table 1). Doses should be reduced in patients with impaired hepatic function but no adjustment is recommended for patients with impaired renal function unless it is severe (the exception being sertraline, for which the dose is not affected by renal function).

**Drug interactions**

The SSRIs are associated with a relatively large number of clinically significant drug interactions arising from interference with hepatic metabolism. The risk varies between the SSRIs and should be checked before prescribing.
bearing in mind the long half-lives of these agents when monitoring adverse effects.

Pharmacodynamic interactions are also clinically significant and include an increased risk of bleeding with aspirin, an increased risk of toxicity with lithium, a reduced seizure threshold (as with other antidepressants), an increased risk of arrhythmias with agents that lower potassium or magnesium blood levels, and an increased risk of serotoninergic effects if prescribed with or close to a monoamine oxidase inhibition (MAOIs).

Cautions

There is also a long list of cautions to consider when prescribing an SSRI, including epilepsy, heart disease (sertraline is considered safe in patients with unstable angina or after recent myocardial infarction), diabetes, susceptibility to angle-closure glaucoma, a history of mania (avoid if a patient enters a manic phase) or bleeding disorders, and concurrent electroconvulsive therapy. Hyponatraemia, which usually occurs in older patients and is more frequent with SSRIs than antidepressants, should be considered if drowsiness, confusion or convulsions occur during treatment.

As with other antidepressants, SSRIs have been associated with suicidal thoughts and behaviour; patients should be closely monitored during early treatment and after alterations in dose. They can impair the performance of skilled tasks like driving and operating machinery and can enhance the sedative effects of alcohol. The SSRIs may prolong the QT interval or increase the risk associated with co-prescribed drugs that do so.

Withdrawal symptoms

Antidepressants may be associated with withdrawal symptoms. After abrupt withdrawal of an SSRI or a large dose reduction, these most frequently include gastrointestinal disturbances, headache, anxiety, dizziness, paraesthesia, electric shock sensation in the head, neck and spine, tinnitus, sleep disturbances, fatigue, flu-like symptoms and sweating; palpitations and visual disturbances may also occur.

The risk is said to be greatest with paroxetine (in trials, 30 per cent vs 20 per cent in patients taking placebo) but figures cited for other SSRIs are not dissimilar (12–40 per cent vs 12–20 per cent with placebo). Symptoms can be minimised by tapering the dose over a period of weeks, or up to six months after long-term treatment.

Pregnancy and lactation

There is uncertainty about the safety of SSRIs during pregnancy. Toxicity in animal models has been reported with fluvoxamine, citalopram and sertraline and epidemiological studies have raised the possibility of cardiovascular defects after first trimester exposure to fluoxetine and paroxetine.

### Table 1. Doses for depression and basic costs of SSRIs

<table>
<thead>
<tr>
<th>SSRI</th>
<th>Dose range* (mg/day)</th>
<th>Basic cost per 28 days (£)</th>
<th>Elimination half-life (hr)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>citalopram</td>
<td>20–40</td>
<td>1.10–1.28</td>
<td>about 1.5 days</td>
<td>adjust dose in increments of 20mg/day every 3–4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(active metabolites not stated)</td>
<td></td>
</tr>
<tr>
<td>escitalopram</td>
<td>10–20</td>
<td>14.91–25.20</td>
<td>30</td>
<td>response in 2–4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(active metabolites ‘significantly longer’)</td>
<td></td>
</tr>
<tr>
<td>fluoxetine</td>
<td>20–60</td>
<td>1.02–3.05</td>
<td>4–6 days</td>
<td>adjust initial dose after 3–4 weeks if necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(active metabolite 4–16 days)</td>
<td></td>
</tr>
<tr>
<td>fluvoxamine</td>
<td>50–300</td>
<td>7.89–47.32</td>
<td>17–22</td>
<td>adjust initial dose after 3–4 weeks if necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(no active metabolites)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>usual maintenance dose 100mg/day</td>
</tr>
<tr>
<td>paroxetine</td>
<td>20</td>
<td>1.76</td>
<td>about 24 hours</td>
<td>adjust initial dose after 3–4 weeks if necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(no active metabolites)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no evidence of greater efficacy at doses &gt;20mg/day</td>
</tr>
<tr>
<td>sertraline</td>
<td>50–200</td>
<td>1.75–4.30</td>
<td>22–36</td>
<td>adjust initial dose after one week if necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(active metabolite 62–104)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>usual maintenance dose 50mg/day</td>
</tr>
</tbody>
</table>

*adult <65 years with depression; * based on prices from MIMS online

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Use during late pregnancy may be associated with neonatal pulmonary hypertension and with serotoninergic or withdrawal symptoms in the neonate. The SSRIs have been shown to impair sperm quality in animal models; any such effects reported in humans has been reversible.

The SSRIs occur in breast milk, albeit at low levels, and their use is generally not recommended during breastfeeding. Paroxetine is an exception, because levels are very low and have not been shown to affect the infant.

**Adverse effects**

Though the SSRIs are considered better tolerated than other antidepressants they are nonetheless associated with a wide range of adverse effects including gastrointestinal symptoms (which are dose-related and common), hypersensitivity reactions, CNS and autonomic effects, movement disorders, bleeding disorders and sexual dysfunction. The appearance of rash, which may be associated with vasculitis, may precede the onset of serious systemic effects.

**Declaration of interests**

Steve Chaplin has none to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics

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**Place in therapy**

**Rajeev Krishnadas**

The antidepressant properties of iproniazid (an antituberculous drug with MAOI) and imipramine (tricyclic antidepressant, TCA) were accidentally discovered in the 1950s. However, it was not until the late 1960s that researchers unravelled the effects of these medications on the brain.

The catecholamine theory of depression by Schildkraut in 1965, proposed that depressive states were due to a decrease in synaptic monoamine neurotransmitters, particularly serotonin. Serotonin, a neurotransmitter derived from tryptophan, plays a role in sleep, appetite, sexual behaviour, and cognitive and emotional function. Serotonergic abnormalities have since been implicated in a number of psychiatric conditions, including depression and anxiety disorders.

Unlike iproniazid and imipramine, the new class of antidepressants, SSRIs, were first discovered in the 1970s through ‘rational drug discovery’. This is a process by which biologically active compounds are designed to act on a target of interest, in this case, the serotonin transporter (SERT). SSRIs predominantly inhibit SERT, a protein on the neuronal membrane that actively transports serotonin from the synaptic cleft back into the neuron. Inhibition of SERT is therefore thought to increase synaptic serotonin availability. How exactly this leads to the remission of depressive symptoms is, however, unknown.

Prozac (fluoxetine) is often considered to be the prototype SSRI. However, the first SSRI to be marketed was zimelidine, which was withdrawn due to rare case reports of Guillain-Barre syndrome. Recent studies, including large meta-analyses, conclude that later SSRIs (fluoxetine, fluvoxamine, sertraline, citalopram, paroxetine and escitalopram) are at least as effective as other available medications for depression, with a favourable risk/benefit ratio.

When pharmacotherapy is indicated, SSRIs are indeed the first-choice medications for the treatment of mood disorders, OCD and anxiety disorders. There is robust evidence to support the use of SSRIs in moderate to severe depression, and most guidelines, including NICE’s, recommend their use. There is some evidence to say that differences exist between commonly prescribed antidepressants in terms of efficacy. However, the choice of any particular medication should depend on patient preference and acceptability, previous response, presence of co-morbid conditions and medications.

**References**


**Declaration of interests**

Dr Rajeev Krishnadas has none to declare.

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