Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) selectively inhibit the reuptake of serotonin (5-hydroxytryptamine, 5-HT) in central nervous system (CNS) synapses, thus increasing the intra-synaptic concentration of serotonin.

Depression and serotonin

It has long been postulated that a deficiency in CNS serotonergic activity is the cause of, or a predisposing factor for, depression\[1\]. However, the evidence for this association is largely circumstantial and it certainly does not represent an adequate and full model for depression, probably due to there being multiple aetiological factors\[2\].

National Institute for Health and Care Excellence guidance recommends SSRI use in adults with\[3\]:

1. Mid-to-moderate depression where low-intensity psychosocial intervention has not helped.
2. Patients with fewer than five of the symptoms required to make a diagnosis of depression (termed subthreshold depression).
3. Moderate-to-severe depression with concomitant high-intensity psychosocial interventions.

Selective serotonin reuptake inhibitors versus other antidepressants

SSRIs appear to be similar in efficacy to the older tricyclic antidepressants (TCAs) but have fewer antimuscarinic side-effects and are less cardiotoxic in overdosage. Although SSRIs are, on the whole, better tolerated than older antidepressants, the difference is not significant enough to justify always choosing SSRIs as first-line agents to treat depression.

A meta-analysis of primary care trials of SSRIs and TCAs demonstrates similar efficacy and tolerability for both, which is superior to placebo\[4\]. A Cochrane review has similar findings and concludes that there are no clinically significant differences in effectiveness between SSRIs and TCAs and that treatment decisions should be based on considerations of relative patient acceptability, toxicity and cost\[4\]. An analysis of antidepressant drug adherence shows that any differences in tolerability between SSRIs and TCAs are relatively subtle and difficult to extrapolate into improved acceptance of SSRIs by real patients in the real world\[5\]. Where there is a significant risk of overdose, medical comorbidity which precludes antimuscarinic activity, or diabetes, SSRIs are usually preferred as first-line agents over TCAs.

St John's wort (SJW) has also been compared to SSRIs. Szegedi and colleagues reported that SJW use was associated with greater depressive symptom reduction and fewer adverse effects compared with SSRIs (paroxetine)\[6\]. However, a meta-analysis of SJW failed to find a substantial benefit over other forms of therapies\[7\]. It may be that SJW is safe and effective in the short-term relief of depression. SJW may be more useful in milder depression\[7, 8\]. NICE guidance does not recommend its use, given the uncertainties in efficacy and the potential adverse effects and drug interactions with other medications\[6\].

Currently available selective serotonin reuptake inhibitors

- Citalopram\[9\]
- Escitalopram\[10\]
- Fluoxetine (long half-life)\[11\]
- Fluvoxamine\[12\]
- Paroxetine\[13\]
- Sertraline\[14\]

Refer to each individual drug's Summary of Product Characteristics (SPC) for details.

Indications

- Depression - all SSRIs are licensed for this indication; paroxetine is licensed only for the treatment of major depression.
- Panic disorder - citalopram, escitalopram, paroxetine, sertraline.
- Social anxiety disorder/social phobia - escitalopram, paroxetine.
- Bulimia nervosa - fluoxetine.
- Obsessive-compulsive disorder - fluoxetine, escitalopram, fluvoxamine, paroxetine, sertraline (the latter under specialist supervision in children) .
- Post-traumatic stress disorder - paroxetine, sertraline (the latter in females only).
- Generalised anxiety disorder - paroxetine, escitalopram.
- Premenstrual syndrome (unlicensed)\[15, 16\].

There have been a number of trials assessing the role of SSRIs as add-on therapy to improve the negative symptoms of schizophrenia. Unfortunately, a meta-analysis failed to find any difference with SSRIs\[17\].
Contra-indications

Use in children and adolescents

The Committee on Safety of Medicines (CSM) advises that balance of risks and benefits for the treatment of depressive illness in individuals aged <18 years is unfavourable for the SSRIs citalopram, escitalopram, paroxetine and sertraline. They may be used by specialists, with close supervision for suicidal behaviour, self-harm or hostility. Fluoxetine has shown some benefit but there may be increased risk of self-harm and suicidal thoughts in individuals. Careful observation and monitoring are advised.

A meta-analysis of a number of trials of SSRIs in children suggests that the benefits of SSRIs appear to outweigh any suicidal risks in a number of conditions including depression and anxiety disorders. Furthermore, the use of SSRIs in children is associated with a number of problems of which increased activity is prominent.

Mania

SSRIs should be discontinued or avoided in patients displaying active manic symptoms.

Cautions

- History of mania.
- Epilepsy - there is the need to weigh up the risks and benefits; avoid if poorly controlled and discontinue if there is deterioration; seek specialist advice if necessary.
- Cardiac disease - however, SSRIs (such as sertraline) are probably the safest antidepressants in cardiac disease.
- Acute angle-closure glaucoma.
- Diabetes mellitus (monitor glycaemic control after initiation).
- Proton pump inhibitors - concomitant use with drugs that cause bleeding, gastrointestinal (GI) bleeding, or where there is history of GI bleeding.
- Hepatic/renal impairment.
- Pregnancy and breast-feeding: seek specialist advice - eg, the National Teratology Information Service (neonatal withdrawal syndrome, particularly with paroxetine).
- Young adults (possible increased suicide risk).
- Suicidal ideation.

Important interactions

- With monoamine-oxidase inhibitors (MAOIs)/moclobemide: serious toxicity risk. If changing from an SSRI, an MAOI or moclobemide should not be started until: five weeks after stopping fluoxetine; two weeks after stopping sertraline; one week after other SSRIs. Also, more than five weeks should elapse if on high doses or there is chronic use of fluoxetine. If changing from an MAOI, do not start SSRIs until two weeks after stopping an MAOI (but after stopping moclobemide, SSRIs can be started the following day, as moclobemide has a short duration of action).
- There is a range of interactions with a number of drugs, particularly with psychiatric medications, including other antidepressants (including St John’s wort (SJW)).
- The risk of serotonin syndrome is increased by interactions with other drugs and care should be taken to monitor for its symptoms when starting new therapies in those on SSRIs. It is worth checking for known interactions of the individual SSRI with other drugs when starting new treatments.
- SSRIs inhibit platelet function and thus interact with other antiplatelet agents - eg, aspirin, clopidogrel, glycoprotein IIb/IIIa inhibitors. This interaction appears to be beneficial in acute coronary syndromes but the risk of bleeding is increased.

Problems

- Minor sedation and antimuscarinic side-effects may occur but are usually less frequent and troublesome than with TCAs.
- GI side-effects such as nausea, vomiting, dyspepsia and constipation are quite common. Anorexia or increased appetite with weight gain may occur.
- Hypersensitivity reactions with rash may be encountered and discontinuation should be considered, as it may herald a vasculitis.
- Urticaria, angio-oedema, anaphylaxis, arthralgia, myalgia and photosensitivity may occur as idiosyncratic reactions. A range of minor CNS symptoms such as headache, insomnia, tremor and dizziness may occur.
- Hallucinations, drowsiness and convulsions have been reported (see the note on epilepsy under ‘Cautions’, above). Sexual dysfunction, including ejaculatory delay and anorgasmia may occur.
- Hyponatraemia may occur in the elderly with SSRIs and, less commonly, with other antidepressants. It is thought to be due to the syndrome of inappropriate antidiuretic hormone (ADH) secretion. CSM advises considering the diagnosis in all elderly patients on antidepressants who develop drowsiness, confusion or convulsions.
- Other side-effects include sweating, galactorrhoea, urinary retention, movement disorders and dyskinesias and cutaneous bleeding (purpura and ecchymoses).
- Increased risk of suicidal ideation is postulated but as yet unproven.
- Serotonin syndrome - this can occur with overdose or concurrent MAOI use. It includes altered mental state, autonomic dysfunction, and neuromuscular abnormalities.
- There may also be an increased tendency of apathy in elderly individuals treated with SSRIs, despite improvement of depression. Similarly, some data suggest an increase in fracture risk in patients over the age of 50 years on SSRIs.
Initiation and discontinuation

- Before starting SSRIs ensure that patients are aware that they may take a few weeks to work, that they must stop if they develop a rash and that they must obtain help if agitation/suicidal feelings occur.
- Patients should be reviewed 1-2 weeks after starting treatment.
- A trial of at least 4-8 weeks (six weeks in older patients) should be given before deciding to discontinue/change an agent.
- If there is partial response, allow another two weeks to decide if effective or not.
- There is little evidence to support the use of dose escalation in patients who do not respond to standard doses [54].
- After remission of symptoms, continue for at least 4-6 months (12 months in the older patient).
- Maintenance treatment may be needed in those with recurrent depression.

'Withdrawal' symptoms

These may occur after stopping SSRIs. GI symptoms, 'chills', insomnia, hypomania, anxiety and restlessness may occur. Aim to reduce the dose gradually over about four weeks or so to try to avoid/ameliorate this. In patients who have taken the drug long-term, they may need six months or so to withdraw gradually.

Monitoring

As there is a potential risk of increased suicidal ideation in those taking SSRIs, it is a good idea to ask explicitly about these symptoms and to document them before initiating these agents, and when reviewing a patient on SSRIs.

Further reading & references

1. Maes Mand Meultzer H; The Serotonin Hypothesis of Major Depression (2000). Website of American College of Neuropsychopharmacology
3. Depression in adults: recognition and management; NICE Clinical Guideline (April 2016)
5. Antidepressant Drug Adherence; Bandelier
7. Williams JW Jr, Holsinger T; St John's for depression, words and all. BMJ. 2005 May 14;330(7500):E350
10. Escitalopram 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets information leaflet; Medicines and Healthcare products Regulatory Agency (Mhra), April 2016
13. Summary of Product Characteristics (SPC) Paroxetine 10 mg Film-coated Tablet; Astra UK Ltd., electronic Medicines Compendium, February 2016
15. No authors listed; SSRIs for premenstrual dysphoric disorder. Drug Ther Bull. 2002 Sep;40(9):70-2.
19. Selective serotonin reuptake inhibitors and serotonin and noradrenaline reuptake inhibitors; Medicines and Healthcare products Regulatory Agency (Mhra) (archived content)
22. The Maudsley Prescribing Guidelines
25. UK Teratology Information Service; Regional Drug and Therapeutics Centre (RDTC)