# Review of Selective Serotonin Reuptake Inhibitors

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## Abstract

Selective serotonin reuptake inhibitors (SSRIs) are amongst the most widely prescribed class of antidepressants worldwide. Their extensive use is due to their better safety and effectiveness profile when compared to other classes of antidepressants. Several differences in pharmacology of the various SSRIs may affect the treatment choice in individual patients. This article summarises the role of SSRIs in the management of psychiatric and other disorders.

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## Introduction

Selective serotonin reuptake inhibitors (SSRIs) are amongst the most prescribed antidepressants globally because of their effectiveness in treating many psychiatric disorders.[1,2] Medicines in this class are used for the treatment of depression, anxiety, and certain behavioural disorders such as obsessive compulsive disorder, panic disorder and bulimia nervosa.[3,4] SSRIs are considered to be safer and more tolerable alternatives to older antidepressant generations such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).[2,5] They are also considered to be safer and generally more cost-effective when compared to some newer antidepressant classes such as noradrenergic and specific serotonergic antidepressants (NaSSAs), norepinephrine reuptake inhibitors (NRIs), reversible inhibitors of monoamine oxidase A (RIMAs), serotonin–norepinephrine reuptake inhibitors (SNRIs), serotonin modulators and stimulators (SMSs), serotonin antagonists and reuptake inhibitors (SARIs), tetracyclic antidepressants (TeCAs).[6,7] Fluoxetine was discovered in 1972 and later other SSRIs, namely sertraline, paroxetine, fluvoxamine, citalopram and escitalopram (which is the S-enantiomer of citalopram) became available on the market.[2,8]

## Mechanism of action

SSRIs act by inhibiting the action of the serotonin reuptake transporter, leading to an influx of serotonin (5-hydroxytryptamine or 5-HT) at the neurotransmitter junction.[9] Medicines in the SSRI class predominantly exert their effect on the serotonin pathway and show relatively less affinity for dopamine ($D_2$), norepinephrine (NE), acetylcholine (Ach) and histamine receptors in comparison to other anti-depressant classes.[10] The SSRIs vary considerably in their chemical structure, which results in pharmacological differences among medicines in this class and may affect various aspects of treatment, such as dosing, administration, side-effect profile as well as discontinuation.[10,12] For example, sertraline has relatively more potency for dopamine receptors when compared to other SSRIs and patients may present with extra-pyramidal side-effects.[11,12]

The full therapeutic effect of SSRIs occurs gradually and may take two to six weeks before it is optimal.[11] While serotonin reuptake inhibition occurs soon after an SSRI is started, the delay in achieving the full clinical response may be explained by a compensatory synthesis of enzymes that aim to increase metabolism of the elevated serotonin, also coupled with down-regulation of serotonin receptors.[12] The mechanism of action of the SSRIs is illustrated in Figure 1.[13]

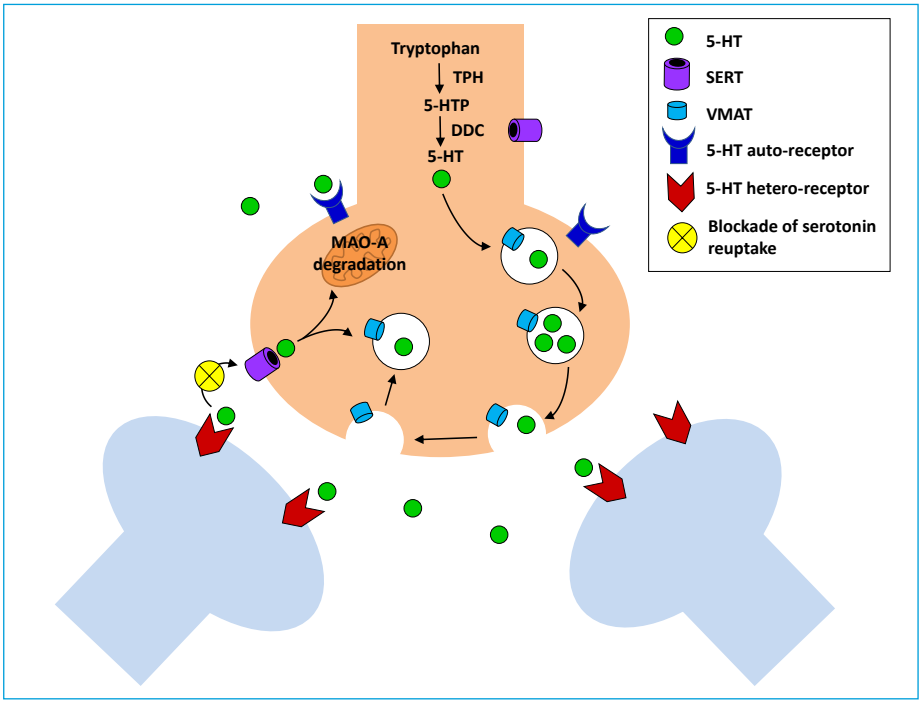
## Pharmacokinetics

SSRIs are rapidly metabolised by the liver and absorption is not affected by food.[14] Co-administration with food would thus have an additional benefit in preventing the gastro-intestinal side effects associated with SSRI use.[14] The half-life of SSRIs varies across the different drug classes. Fluoxetine has the longest half-life (72-96 hours) and its steady state is reached after 2-3 weeks of treatment.[10,14] Table I shows the respective half-lives of the different drugs within the pharmacological class of SSRIs.[10,14,15]

## Indications

### *Approved indications*

SSRIs are commonly used to treat major depression, anxiety disorder, panic disorder, obsessive-compulsive disorder and posttraumatic stress disorder in both children and adults.[11,16]




VMAT, Vesicular mono-amine transporter; 5-HT, 5-hydroxytryptamine (serotonin)

**Figure 1. Mechanism of action of SSRIs[13]**

Fluoxetine is furthermore used in the treatment of bulimia nervosa, and escitalopram is also approved for use in the management of social anxiety disorder.[1,17]

## *Off-label use of SSRIs*

SSRIs are also used off-label to treat impulse control disorders, premenstrual dysphoric disorder, premature ejaculation, migraine prophylaxis, fibromyalgia, eating disorders and chronic pain management.[1,11,18] They are often prescribed for the treatment of depression in cancer patients and for women suffering from post-partum depression.[3,19] The paroxetine salts (mesylate and HCl) have proven to be safe and reasonably effective treatments for vasomotor symptoms associated with menopause resulting in reduced severity and frequency of hot flushes, especially for patients who prefer non-hormonal therapy.[9] Study results from several clinical trials have confirmed the safety and tolerability of SSRIs in post-stroke patients as well as their efficacy in enhancing stroke recovery.[10]

### *Antitumour effects*

The SSRIs have been shown to be oncolytic *in vitro* and *in vivo* and have reduced the risk to some types of cancers.[3] Paroxetine is assumed to cause cell death through apoptosis on human osteosarcoma cells.[20] Fluoxetine demonstrated inhibition of prostate cancer cell proliferation, and exposure to sertraline and paroxetine proved to reduce malignant T-cell viability.[3,20] Studies have also shown that sertraline has cytotoxic effects in multidrug-resistant human colon carcinoma, human T leukaemia cells, human breast cancer cells and hepatocellular carcinoma.[3,20] Sertraline has the strongest antitumour effects followed by paroxetine, fluvoxamine, and escitalopram in order of decreasing strength.[3,20]

**Table I.** Currently available SSRIs in South Africa[10,14,15]

| Drug name | Examples of trade names available in SA | Dosage | Mean half-life (hours) |
|---|---|---|---|
| **Citalopram hydrobromide** | Adco-Talomil®, Arrow Citalopram®, Austell-Citalopram®, Bio Citalopram®, Cilate®, Cilift®, Ciloram®, Cipramil®, Depramil®, Recita® | 20 mg once daily; maximum dose: 60 mg daily | Medium (30 hours) |
| **Escitalopram oxalate** | Accord Escitalopram®, Aspen Escitalopram®, Cipralex®, Citraz®, Dolin®, Escitalopram Winthrop®, Lexamil®, Marprem®, Mylan Escitalopram®, Zitolex®, Zytomil® | 10 mg once daily; maximum dose: 20 mg daily | Medium (30 hours) |
| **Fluoxetine hydrochloride** | Deprozan®, Lilly-Fluoxetine®, Lorien®, Nuzak®, Prohexal 20®, Prozac®, Ranflocs® | 20 mg once daily; maximum dose: 60 mg daily | Long (96 hours) |
| **Fluvoxamine maleate** | Faverin®, Fluoxetine Actor 20®, Luvox® | 100 mg once daily; maximum dose: 300 mg daily; Doses > 150 mg should be given in 2–3 divided doses | Short (15 hours) |
| **Paroxetine hydrochloride** | Adco-Paroxetine®, Aropax®, Deparoc®, Lenio®, Paroxetine Unicorn 20®, Paxil®, Serrapress®, Texine®, Xet 20® | 20 mg once daily; maximum dose: 50 mg daily (gradual 10 mg increments) *Controlled release formulation:* 25 mg once daily; maximum dose: 62.5 mg daily (gradual increments of 12.5 mg) | Short (21 hours) |
| **Sertraline hydrochloride** | Austell-Sertraline®, Dyna-Sertraline®, Serdep®, Serlife, Sertra®, Sertraline-Winthrop®, Zolid®, Zoloft®, Zylin® | 50 mg once daily; maximum dose: 200 mg daily | Short (26 hours) |

***Cardio-protective effects***

Previous research indicated that SSRIs are cardio-protective through various mechanisms.[21,22] One of the protective roles of the new generation of SSRIs is related to their effects on inhibiting platelet aggregation as well as improving serotonin-related platelet abnormalities, thereby reducing cardiovascular mortality and morbidity especially with citalopram.[21,22] Another beneficial effect of some SSRIs, such as sertraline, is its anti-inflammatory effect as well as improving endothelial function.[21]

***Management of irritable bowel syndrome symptoms***

SSRIs may be considered therapeutic options for irritable bowel syndrome because of their potential to exert analgesic effects both peripherally and centrally.[2,23] However, the evidence regarding the effectiveness of SSRIs in providing symptomatic relief in irritable bowel syndrome is inconsistent and there is a need for further investigation.[2,23]

***Adjunct therapy in Parkinson's disease***

Enhancing central serotonin transmission with SSRIs might provide an adjunctive treatment for motor impulsivity in Parkinson's disease.[24] Citalopram increases the extracellular levels of serotonin in the prefrontal cortex four-fold, but not the levels of noradrenaline or dopamine. Subsequently behavioural impulsivity is improved in terms of action restraint and cancellation in patients with relatively more severe disease.[24]

## Drug interactions

Combination therapy of SSRIs with other therapeutic agents is common in the management of psychiatric conditions. SSRIs are often prescribed together with tricyclic antidepressants (TCAs) in patients with mood disorders and are known to increase the plasma concentration of TCAs following co-administration.[11,25] This is due to SSRI inhibition of the cytochrome P450 enzymes (CYP2D6) responsible for the metabolism of TCAs, leading to elevated serum concentrations of TCAs and possible toxicity.[25] The possibility of SSRI drug interactions is the highest with fluoxetine, paroxetine and fluvoxamine, and the lowest with escitalopram, citalopram and sertraline.[25,26] Fluoxetine and paroxetine specifically, are known to cause a five-fold increase in serum TCA concentration upon co-administration. In addition, fluoxetine causes an elevation of lithium levels warranting the need for monitoring lithium levels during treatment.[25] Studies have also shown serotonin toxicity associated with concurrent use of SSRIs and MAOIs, such as linezolid.[26] A similar effect is experienced with concurrent use of SSRIs and the anticonvulsants, carbamazepine and phenytoin. SSRIs increase the serum concentrations of the latter two drugs, potentiating their effects and increasing the risk of toxicity.[11] Fluvoxamine causes a four-fold increase in the TCA imipramine upon co-administration.[11,14]

Compared to the other SSRIs, citalopram, escitalopram and sertraline have a lesser potential to cause drug interactions, as they are weaker inhibitors of the cytochrome P450 enzymes.[27] These drugs are thus the treatment of choice in instances where patients are on several treatment options, such as when managing depression in patients on highly active antiretroviral treatment or in the elderly with deteriorating renal and liver function.[14] Important pharmacokinetic and pharmacodynamic interactions are summarised in Table II.[25,28]

### Serotonergic syndrome

Serotonergic syndrome results from the drug interaction which occurs when SSRIs are used concurrently with other serotonergic agents (serotonin-releasing drugs, serotonin precursors, serotonin agonists, drugs causing serotonin release, serotonin reuptake inhibitors, and monoamine oxidase inhibitors).[29,30] The signs and symptoms of serotonin syndrome are outlined in Table III.[31]

***Management of serotonin syndrome***

The following strategies are recommended in the management of serotonin syndrome:

- *Discontinuation* of the serotonergic agents should be done immediately.
- *Supportive care* is aimed at normalisation of vital signs in nature and also involves symptomatic treatment of clinical manifestations.[29,30] This includes monitoring pulse, temperature, blood pressure, urine output and ensuring the patient is adequately hydrated.[25]
- *Benzodiazepines* are used to manage the clonus, tremors and agitation associated with the syndrome.[29]
- *Serotonin antagonists* are administered to manage the hyperthermia and reduce symptoms. Examples include olanzapine 10 mg, which may be given sublingually and chlopromazine (50–100 mg) intramuscularly. Cyproheptadine is the therapy of choice for serotonin syndrome and a dose of 8–16 mg is administered over a 24-hour period with a maximum dose of 32 mg.[25] Hyperthermia may also be managed by induced paralysis by use of non-depolarising agents.[25]
- *Beta blockers* such as esmolol are used to manage the tachycardia associated with serotonin syndrome.[25,29]
- *Direct-acting sympathomimetic amines* such as norepinephrine, phenylephrine and epinephrine are used to manage hypotension.[29]

## Safety aspects

### Use in children

The safety of SSRIs for the treatment of depression in children and adolescents has been a subject of debate, especially with the suspected increased risk of suicidal ideation/suicidal behaviour in children and adolescents treated with SSRIs.[32] For severe depression, fluoxetine may be used as trials have shown that the benefits outweigh the risks while it remains unclear for other SSRIs.[14,33] Sertraline and citalopram may be considered as second-line treatment if fluoxetine is ineffective or not well tolerated.[33] Initiation of treatment requires a comprehensive approach that includes supportive, problem-focused psychotherapeutic

**Table II.** Summary of the major pharmacokinetic and pharmacodynamic interactions that involve SSRI drugs[25,28]

| Drug | Effect on drug metabolising enzymes | Examples of drug-drug interactions | Pharmacodynamic interactions (All SSRIs) |
|---|---|---|---|
| **Fluvoxamine** | Potent inhibitor of CYP 1A2, 2C19 | Leads to increased levels of the following, which may result in toxicity (avoid concomitant use):<br>Agomelatine<br>Benzodiazepines<br>Caffeine<br>Clozapine<br>Duloxetine<br>Haloperidol<br>Melatonin<br>Olanzapine<br>Proton pump inhibitors<br>Phenytoin<br>Quetiapine<br>Theophylline<br>Tricyclic antidepressants<br>Warfarin | Potential serotonin syndrome when combined with the following:<br>Monoamine oxidase inhibitors e.g. linezolid, moclobemide, phenelzine, tranylcypromine<br>Serotonin-releasing agents e.g. amphetamine , imipramine, tramadol, St John's wort, SNRIs<br>Other agents e.g. lithium, buspirone<br><br>Increased risk of bleeding with NSAIDs, warfarin and other anticoagulants, antiplatelet agents<br><br>Other interactions:<br>Antipsychotics: Sexual side-effects<br>Acetylcholinesterase inhibitors: Gastrointestinal side-effects<br>Thiazide diuretics: Hyponatraemia<br>Alcohol, benzodiazepines, antihistamines: Increased effect on central nervous system<br>Neuromuscular blockers e.g. pancuronium, suxamethonium: SSRIs reduce plasma cholinesterase activity resulting in prolonged neuromuscular blocking action |
| **Fluoxetine**<br>**Paroxetine** | Potent inhibitor of CYP 2D6 | Atomoxetine<br>Beta blockers (e.g. carvedilol, metoprolol)<br>Clozapine<br>Flecainide<br>Phenothiazine neuroleptics<br>Tamoxifen<br>Warfarin<br>Risperidone<br>Tricyclic antidepressants | |
| **Sertraline** | Potent inhibitor of CYP 2D6 (at doses > 200 mg/day) | | |
| **Citalopram**<br>**Escitalopram** | None | Contraindicated with other medicines that can prolong QT interval | |

**Table III.** Signs and symptoms of serotonin syndrome classified according to severity[31]

| Severity | Autonomic signs | Neurological signs | Mental status | Other |
|---|---|---|---|---|
| **Mild** | Afebrile or low grade fever (< 38.5 °C)<br>Tachycardia<br>Mydriasis<br>Diaphoresis or shivering | Intermittent tremor<br>Akathisia<br>Myoclonus<br>Mild hyperreflexia | Restlessness<br>Anxiety | |
| **Moderate** | Increased tachycardia<br>Fever (up to 41 °C)<br>Diarrhoea with hyperactive sounds<br>Diaphoresis with normal skin colour | Hyperreflexia<br>Inducible clonus<br>Ocular clonus (slow continuous lateral movements)<br>Myoclonus | Easily startled<br>Increased confusion<br>Agitation and hypervigilance | Rhabdomyolysis<br>Metabolic acidosis<br>Renal failure<br>Disseminated intravascular coagulopathy (secondary to hyperthermia) |
| **Severe** | Temperature often > 40 °C (Secondary to increased tone) | Increased muscle tone (lower limb > upper)<br>Spontaneous clonus<br>Substantial myoclonus or hyperreflexia | Delirium<br>Coma | Rhabdomyolysis<br>Metabolic acidosis<br>Renal failure<br>Disseminated intravascular coagulopathy (secondary to hyperthermia) |

interventions, assessment and monitoring of suicide risk, patient counselling about these disorders and treatment options.[14,33]

### *Sexual dysfunction*

SSRIs are associated with significant sexual side-effects (occuring in 50–70% of patients) including decreased libido, anorgasmia, lack of vaginal lubrication, genital anaesthesia and erectile dysfunction.[16,22] SSRI-associated sexual dysfunction may be resolved in various ways which include dose adjustment, switching to a different antidepressant, augmentation with another antidepressant such as bupropion or combining SSRIs with treatment for sexual dysfunction, such as sildenafil and sublingual testosterone.[16,22] A clinical study found that the incidence of sexual side-effects was highest with paroxetine, followed by fluvoxamine, sertraline, and fluoxetine.[34]

Although the use of SSRIs has several benefits, there are also safety aspects that need to be considered as they often lead to early discontinuation of these medicines.[17] The adverse effects that are associated with the use of SSRIs are summarised in Table IV.[2,17,21,22,35-43]

### *Discontinuation syndrome*

Discontinuation syndrome occurs on abrupt withdrawal of SSRIs, and is experienced by at least a third of patients who have been on long-term SSRI therapy (longer than four weeks).[37,44] The onset of symptoms is usually within three days of stopping treatment and usually resolves spontaneously within two weeks; however, the syndrome can persist for up to six weeks after drug withdrawal. SSRI withdrawal symptoms occur when the drug's pharmacological effects diminish after dose decrease or discontinuation.[34]

The symptoms of discontinuation syndrome are more prominent in the elderly and can include lethargy, dizziness, light-headedness, headache, nausea, insomnia, vivid dreams, paraesthesia, numbness, 'electric-shock'-like sensations, irritability and mood disorders.[45] Table V represents the characteristic symptoms of serotonin-specific and nonspecific discontinuation syndrome.[34]

Discontinuation syndrome can be mistaken for a relapse of the underlying psychiatric condition and can often be misdiagnosed by the clinician.[37,38,44] The discontinuation syndrome is common, particularly with more-potent and shorter-acting SSRIs, such as

**Table IV.** Summary of adverse effects associated with SSRI use[2,17,21,22,35-43]

| System involved | Adverse effects | SSRI drugs mostly implicated |
|---|---|---|
| Common | Headache | Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline |
| | Sweating | |
| | Rash | |
| | Gastrointestinal – nausea, vomiting | |
| | Sexual dysfunction – low libido, erectile dysfunction, delayed ejaculation, anorgasmia | |
| | Fatigue | |
| | Increased risk of bleeding | |
| | QT interval prolongation | |
| Sexual disorders | Low libido, erectile dysfunction, delayed ejaculation, anorgasmia | |
| Gastrointestinal disorders | Diarrhoea, nausea, vomiting, abdominal pain, constipation, dyspepsia | |
| Ophthalmic disorders | Visual disturbances, mydriasis, glaucoma | |
| Psychiatric disorders | Suicidal ideation, insomnia, hallucination, paranoia, nightmares, depression, anxiety | |
| Breast disorders | Galactorrhoea, gynecomastia | Fluvoxamine, sertraline |
| Metabolism and nutrition disorders | Anorexia, decreased appetite | Citalopram, fluoxetine, fluvoxamine, paroxetine, |
| | Weight gain, increased appetite | Escitalopram, fluoxetine, sertraline |
| Renal and urinary disorders | Urinary retention, urinary incontinence, nocturia | Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline |
| Musculoskeletal and connective tissue disorders | Arthralgia, osteoarthritis, back pain, bone fractures | Citalopram, fluoxetine, paroxetine, sertraline |
| Risk during pregnancy and breastfeeding | Heart, musculoskeletal defects, craniosynostosis, post-partum haemorrhage, persistent pulmonary hypertension of the new born | Fluoxetine, fluvoxamine, paroxetine |
| Skin and subcutaneous tissue disorders | Photosensitivity, purpura, facial oedema, hyperpigmentation of skin and nails, skin reactions | Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline |
| Vascular disorders | Hot flushes, hypertension, abnormal bleeding | Paroxetine, sertraline |
| Nervous system disorders | Somnolence, tremor, convulsion, extrapyramidal effects, serotonin syndrome | Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline |
| Other | Hyponatraemia, palpitations, tachycardia | Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline |
| | Infections e.g. pharyngitis | Sertraline |
| | Hypothyroidism | Sertraline |
| | Akathisia | Citalopram, escitalopram, fluoxetine, fluvoxamine |
| | Alopecia | Escitalopram, sertraline |
| | Dry mouth | Paroxetine, sertraline |
| | Seizures | Citalopram, fluoxetine, paroxetine, sertraline |

**Table V.** SSRI withdrawal symptoms: specific serotonin-related symptoms and nonspecific symptoms[34]

| System involved | | Symptoms |
|---|---|---|
| Autonomic | General | Flu-like symptoms[1],vertigo, flushing[1], chills[1], dizziness[1], light headedness, sweating |
| | Visual | Visual changes, blurred vision |
| | Cardiovascular | Tachycardia[1] |
| | Gastrointestinal | Diarrhoea[1], loose stools, abdominal pain[1], nausea, vomiting, anorexia |
| | Sensory | Paresthesias[1], electric shock sensation[1], brain zap[1], rushing noise in head, tinnitus, altered taste, pruritus |
| | Neuromuscular | Myoclonus, restlessness, muscle rigidity, myalgia, neuralgias, jerkiness, ataxia, facial numbness, tremor |
| Mental | Cognition | Confusion[1], amnesia[1], disorientation[1], decreased concentration |
| | Affective | Anxiety, agitation, tension, anxiety, irritation, anger, tearfulness |
| | Psychotic | Visual and auditory hallucinations |
| Other | Sleep | Insomnia, hypersomnia, vivid dreams, nightmares |
| | Sexual | Premature ejaculation[1], genital hypersensitivity[1] |

[1] Specific serotonin related symptoms

paroxetine, and can generally be prevented by tapering off the drug over a period of four weeks.[44]

## Patient counselling

The goals of treatment (restoration of psychosocial functioning and remission of symptoms) should be discussed with the patient in accordance with the principles of pharmaceutical care.[5,45] The onset of effect of SSRIs is slow, and pharmacists should explain to their patients that it usually takes at least two weeks for the medication to exert a full antidepressant activity.[11] SSRIs have the potential to cause drug-drug interactions and undesirable side-effects which may result in poor adherence. The pharmacist must therefore explain these to the patient and educate the patient that many of the side-effects that occur initially in treatment, often diminish over time.[23,26,29]

In addition, it is noteworthy to mention to the patient the possible need for long-term (sometimes indefinite) SSRI therapy, even after their mood has improved, to prevent recurrence of the depression.[29]

A supportive relationship between the pharmacist and clinician, and between the pharmacist and the patient, can help improve treatment outcomes.[46]

## Conclusions

SSRIs have emerged as a major therapeutic advance in the management of psychiatric disorders due to their relatively safe- and cost-effective profile. SSRIs have fewer antimuscuranic effects than the older tricyclics and they are less cardio-toxic in overdosage. Fluoxetine is currently the most prescribed antidepressant worldwide. The choice of SSRI should be guided by a diligent clinical assessment of the patient's symptoms, co-morbid medical conditions and concomitant medication, as well as any contraindications to the treatment and an analysis of therapeutic benefits, cost, adverse effects and potential drug interactions. Sufficient patient counselling should be carried out to ensure adherence to the SSRI in order to achieve the goals of treatment. Pharmacists are in an ideal position to improve adherence to treatment by educating patients and clinicians regarding the characteristics of depression and the treatment with SSRIs, and by establishing a supportive relationship with patients being treated with antidepressants.

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