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Problems associated with long-term treatment with selective serotonin reuptake inhibitors

C Moret *NeuroBiz Consulting & Communication, Castres, France.*
M Isaac *South London & Maudsley NHS Trust/Institute of Psychiatry, London, UK.*
M Briley *NeuroBiz Consulting & Communication, Castres, France.*

Abstract

Although the selective serotonin reuptake inhibitors (SSRIs), which are now widely used as a first-line treatment for depression and many other psychiatric conditions, are generally well tolerated, they are not devoid of side effects. Most short-term treatment-related side effects of SSRIs are transient and disappear after a few days or weeks. However, following long-term treatment with the SSRIs, some serious adverse events may occur. Some of them can be difficult to recognise because they can resemble residual symptoms of depression. The most serious can be life threatening. They all have a negative influence on the patient's quality of life and are frequently a prime reason for a lack of long-term compliance with the associated increased risk of recurrence of a depressive episode. This article is an overview of the more common adverse events, which are seen with non-acute treatment with the SSRIs.

Key words

adverse events; compliance; long-term; selective serotonin reuptake inhibitors

Introduction

The discovery of monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) in the 1950s revolutionised the treatment of depression. Although these compounds can bring profound benefit and relief, they are associated with considerable side effects and even life-threatening toxicity (Gumnick and Nemeroff, 2000; Pacher, *et al*., 2001; Martinez and Marangell, 2004; Pacher and Kecskemeti, 2004). The introduction in the mid-1980s of more selective and better-tolerated drugs, the selective serotonin reuptake inhibitors (SSRIs), has enabled many patients to benefit from effective antidepressant therapy without uncomfortable, distressing and often dangerous adverse effects.

SSRIs are now widely used as a first-line treatment for depression in part because of their relatively benign adverse effects and safety in overdose (Vaswani, *et al*., 2003). However, their efficacy in depression is no greater than the earlier drugs and their onset of action no more rapid. SSRIs are also the treatment of choice for many other psychiatric conditions, including dysthymia, bipolar depression, panic disorder, obsessive-compulsive disorder, eating disorders, social phobia and premenstrual dysphoric disorder, again because of their efficacy, good side-effect profile, tolerability and safety in overdose, as well as patient compliance (Masand and Gupta, 1999). Although the SSRIs are better tolerated than their earlier counterparts, they are not devoid of side effects (Mourilhe and Stokes, 1998).

The therapeutic mechanism of action of SSRIs involves alteration in the 5-hydroxytryptamine, serotonin (5-HT) system (Richelson, 1996). The plethora of biological substrates, receptors and pathways for 5-HT mediates not only the therapeutic actions of SSRIs but also their side effects. SSRIs are devoid of receptor interactions, and their only apparent pharmacological activity is the inhibition of the reuptake of serotonin. Most of the side effects appear to result from an over-stimulation of various serotonin receptors in both the brain and the periphery (Lieberman, 2003). For example, the most common side effects associated with SSRIs such as nausea and headache, nervousness, insomnia and sexual dysfunction (Kelsey, 2001) are related to the stimulation of 5-HT_2 and 5-HT_3 receptors. Many of the side effects of SSRIs are transient and subside over time and can be minimised by having patients take the drug with meals and starting treatment with low doses followed

Corresponding author: Chantal Moret, 27 Impasse des Greses, Castres 81100, France. Email: chantal.moret@neurobiz.com

by a slow titration to recommended doses (Kelsey, 2001). However, with the passage of time, certain problems have emerged in relation to long-term treatment with the SSRIs.

We review the side effects associated with long-term treatment with SSRIs in this article. In an attempt to be exhaustive, in addition to the common and well-documented effects, we also discuss adverse effects that have only been reported in only a few cases or which are based on evidence, which now is flimsy. To enable the reader to readily appreciate the relative importance of the different effects, Table 1 gives a semi-quantitative estimate of the seriousness, the frequency and the quality of the evidence for each adverse event discussed.

Suicidality

Cases of SSRI-induced suicidality (suicide attempts and suicidal ideation) have been reported in adults (Teicher, *et al*., 1990; Rothschild and Locke, 1991; Hawthorne and Lacey, 1992). The risk of suicidality has been shown to be modestly increased in adolescents and children participating in randomised, placebo-controlled trials (Hammad, *et al*., 2006). It should be noted, however, that in spite of a certain risk of suicidality with SSRIs (and probably with all antidepressants), a recent study showed that continued antidepressant treatment is associated with overall reduced risk of suicide (Sondergard, *et al*., 2007). In addition, it seems important to distinguish between youngsters and the adults/elderly.

Paediatric and adolescent patients

Recent attention has focused on the possible risks of antidepressant treatment in children and adolescents. The US Food and Drug Administration (FDA) reviewed 24 placebo-controlled trials of antidepressants in paediatric and adolescent patients with depression and found that they cause a twofold increased risk for suicidal behaviour/ideation. Thus, in 2004, the FDA warned the public about the risks of these drugs in children and adolescents (under 18 years) but did not prohibit their use. In 2005, FDA asked manufacturers of SSRIs to include a black box warning statement in product labelling recommending monitoring in young patients for the occurrence of suicidality. Following the FDA warnings, families and clinicians have become increasingly reluctant to use antidepressants in children and adolescents, and the number of prescriptions has fallen dramatically with a disconcerting parallel increase in adolescent suicide (Lineberry, *et al*., 2007).

A meta-analysis in patients younger than 19 years with major depressive disorder showed that the benefits of second-generation antidepressants (SSRIs, nefazodone, venlafaxine and mirtazapine) were significantly greater than the risks of suicidal ideation and suicide attempts, which supports the careful, well-monitored use of these agents (Bridge, *et al*., 2007).

In May 2007, the FDA proposed that the existing black box suicidality warning be extended to young adults aged 18–24. The new proposed warning emphasises, however, that depression itself may lead to suicide and that antidepressant medication benefits most patients. The FDA advises that patients of all ages who are started on antidepressants should be monitored for worsening depressive symptoms, especially suicidal thoughts or behaviours or unusual changes in behaviour.

Table 1 Hierarchy of importance of adverse events following long-term treatment with the SSRIs

	Seriousness	Frequency	Evidence
Suicidality	+++	+	+
Risks during pregnancy	+++	++	+++
Hyponatremia	+++	++	+++
Sexual dysfunction	++	+++	+++
Sleep disturbance	++	++	+++
Risk of fracture and osteoporosis	++	+	++
Bleeding	++	+	+
Extrapyramidal symptoms	++	+	+
Cardiovascular side effects	++	+	+
Discontinuation effects	++	+++	+++
Apathy, amotivation and frontal lobe syndrome	+	+	++
Weight gain	+	+	+

The adverse events are ranked semi-quantitatively (+, ++, +++) according to their seriousness, frequency, quality and weight of the evidence.

Adult patients

A study in adult patients in the Veterans Administration Health Care System found that suicide attempt rates were lower among subjects who were treated with SSRIs than among those who were not treated (Gibbons, *et al*., 2007). This effect was significant in all adult age groups (18–25, 26–45, 46–65, >65) when SSRIs were compared with no antidepressant. Suicide attempt rates were also higher before treatment with SSRIs than after the start of treatment, and this effect was observed in all adult age groups and was significant in all but the 18–25 group (Gibbons, *et al*., 2007). These data suggest that SSRI treatment does not place patients at greater risk of suicide but in fact has a protective effect.

Despite the frequent use of antidepressants in elderly patients (Mamdani, *et al*., 2000; Sambamoorthi, *et al*., 2003), only two studies have addressed the risk of suicidality in this population. One study found a substantial increase in the relative risk of suicide following the initiation of SSRI treatment in the patients 66 years of age and older (Juurlink, *et al*., 2006), whereas the other (Barak, *et al*., 2006) study has shown that in a population of elderly depressed patients (mean age 76.5 years), those treated with SSRIs had a reduced risk of attempting suicide.

Risks during pregnancy

Up to 20% of pregnant women suffer from depression (Patkar, *et al*., 2004; Ryan, *et al*., 2005), and pharmacotherapy for depression is often necessary during pregnancy (Ryan, *et al*., 2005). In a study of 201 women with a history of major depressive disorder before pregnancy, 68% of those who discontinued treatment relapsed during pregnancy compared with only 26% of those who continued treatment (Cohen, *et al*., 2006), indicating the importance of treating depressed pregnant women. Moreover, depressive symptoms are common during pregnancy, and the symptoms may occur more frequently during pregnancy than in the postpartum period (Suri, *et al*., 2007). However, in a prospective study involving 90 pregnant women, these authors have shown that depression was not associated with lower gestational age at birth and increased risk of preterm birth (Suri, *et al*., 2007).

The question remains as to whether infants of women taking antidepressants are at risk, and, if so, whether the risks are due to the medication or to the psychiatric condition. SSRIs freely cross the placental barrier and are, thus, transferred to foetus, as well as to the newborn, during lactation (Lattimore, *et al*., 2005; Austin, 2006). Therefore, both the foetus and the newborn can suffer from the adverse effects of the SSRIs, including long-term neurodevelopmental disturbances. It has been shown that infants exposed to SSRIs during pregnancy had a significant increase in preterm delivery risk (Davis, *et al*., 2007). These authors have also found that full-term infants exposed to SSRIs during the third trimester had an increased risk for respiratory distress syndrome, endocrine and metabolic disturbances, hypoglycemia, temperature regulation disorders and convulsions.

There is an increased risk for neonatal adaptation problems in offspring exposed to SSRIs in late (third trimester) pregnancy, which may cause irritability, constant crying, eating and sleeping difficulties and even seizures in newborns (Laine, *et al*., 2003). It has been suggested that the symptoms may be related to central nervous system serotonergic over stimulation.

The main effects of SSRIs during pregnancy are the following.

Teratogenicity

In general, SSRIs are not major teratogenic compounds. However, some recent studies have shown that the use of SSRIs, particularly paroxetine, early in pregnancy is related to a moderately increased risk of congenital malformations in offspring (Wogelius, *et al*., 2006; Donnelly and Paton, 2007). Increased risk of having an infant with major congenital malformations (adjusted odds ratio = 2.23) or major cardiac malformations (adjusted odds ratio = 3.07) was found in women exposed to >25 mg/day of paroxetine during the first trimester of pregnancy (Berard, *et al*., 2007). A meta-analysis (Bar-Oz, *et al*., 2007) has shown that first trimester paroxetine exposure was associated with an increase in the risk for cardiac malformation (odds ratio = 1.72). A more recent study has found adjusted odds ratio for all congenital malformations associated with first trimester exposure to paroxetine was 1.89, and adjusted odds ratio for cardiovascular malformations associated with first trimester exposure to paroxetine was 1.46 (Cole, *et al*., 2007). However, paroxetine exposure during the third trimester of pregnancy was not linked with an increased risk for cardiovascular anomalies, according to another study (Davis, *et al*., 2007).

Infants of women who received SSRIs underwent approximately twice as many echocardiograms in the first year of life compared with children of women who used nothing (Bar-Oz, *et al*., 2007). Two recent studies (Alwan, *et al*., 2007; Louik, *et al*., 2007), however, did not find any significant increased risks of defects associated with SSRI use overall. Specific SSRIs, notably paroxetine and sertraline, may confer increased risks for some specific defects (Louik, *et al*., 2007). These defects are rare, however, and the absolute risks are small.

Persistent pulmonary hypertension

When taken during late (after the 20th week of gestation) pregnancy, SSRIs can be associated with the development of persistent pulmonary hypertension in the newborn, according to the results of a recent case-control study (Chambers, *et al*., 2006). This study needs replication, however, before any conclusions can be drawn.

Neonatal withdrawal syndrome

A database analysis has found that SSRIs given during pregnancy may lead to withdrawal symptoms in the neonate characterised by convulsions, irritability, abnormal crying and tremor (Sanz, *et al*., 2005). A review by Thormahlen (2006) has concluded that SSRIs are associated with neonatal withdrawal symptoms such as respiratory distress, irritability, lethargy and tremors. Paroxetine is more commonly associated with neonatal withdrawal than other SSRIs. In a cohort study, 30% of infants exposed to SSRIs had poor neonatal adaptation compared with 9% of drug-free controls ($P = 0.018$) (Oberlander, *et al*., 2004).

In 2006, the American College of Obstetricians and Gynaecologists (ACOG, 2006) has recommended against the use of SSRIs during pregnancy unless treatment is absolutely required and no other options exist. The ACOG proposes that clinicians and patients should decide on an individual basis whether the benefits of SSRI therapy outweigh the associated risks.

Hyponatremia

Hyponatremia (serum sodium concentrations below 130 mEq/L) can lead to disturbing symptoms (Table 2), which can cause serious morbidity and even death (Guay, 2000). Hyponatremia is associated with SSRI use, with an incidence that varies from

Table 2 Symptoms related to hyponatremia

Na^+ (mEq/L)	Symptoms
135–145	None (normal values)
120–130	Nausea and malaise
	Headache
	Lethargy
	Muscle cramps
	Disorientation
	Restlessness
<120	Seizures
	Coma
	Respiratory arrest
	Death

0.5% to 32% (Jacob and Spinler, 2006). The condition develops within the first few weeks of treatment and resolves within 2 weeks of therapy discontinuation. SSRI-induced hyponatremia is probably secondary to development of a syndrome of inappropriate secretion of antidiuretic hormone (Romero, *et al*., 2007; Rottmann, 2007). Risk factors for developing SSRI-induced hyponatremia are advanced age, female gender and the concomitant use of diuretics. This potentially life-threatening adverse event should be taken seriously particularly in the fragile population of elderly who often are polymedicated and take diuretics.

Sexual dysfunction

Sexual dysfunction is common among both men and women with major depressive disorder. A study showed that of the 134 patients with major depression surveyed, 40% of men and 50% of women reported decreased sexual interest (Kennedy, *et al*., 1999), whereas 40–50% of the sample also reported reduced levels of arousal. Sexual dysfunction is also a common side effect of SSRIs (Balon, 2006). The assessment of SSRI-induced sexual dysfunction is, thus, complicated by the fact that such effects may result from the depressed state. It is clear, however, that SSRIs may negatively influence any or all phases of the sexual cycle with decreased or absent libido, impairment of arousal and erectile dysfunction but delayed ejaculation and absent or delayed orgasm are their most common effects (Rosen, *et al*., 1999). A European survey (Williams, *et al*., 2006) estimated the prevalence of SSRI-induced sexual dysfunction to be 26.6% in a French sample and 39.2% in a British sample. Patients reported that experiencing these sexual impairments negatively affected their quality of life, self-esteem, mood and relationships with sexual partners.

If ignored, sexual dysfunction can maintain the depression, compromise treatment outcome and lead to non-compliance. This may be a particular problem for patients on maintenance therapy because treatment interruption may trigger recurrence of depression (Werneke, *et al*., 2006; Cohen, *et al*., 2007). Consequently, patients should be monitored early in the treatment with SSRIs for adverse sexual effects.

Sleep disturbance

SSRIs interfere with sleep architecture. Fluoxetine, paroxetine and sertraline delay Rapid eye movement (REM) sleep onset, whereas fluoxetine and paroxetine increase awakenings and reduce REM sleep, slow-wave sleep, total sleep time and sleep efficiency. On the contrary, sertraline tends to reduce nocturnal wakening (Ferguson, 2001). In a naturalistic setting, drowsiness was reported by 17% of patients receiving SSRIs (Hu, *et al*., 2004). The acute adverse effects of SSRIs on sleep persist with long-term treatment (Ferguson, 2001; Silvestri, *et al*., 2001). SSRI use by older women, including those with no depressive symptoms, is associated with sleep disturbance, including poor sleep efficiency, long sleep latency and sleep fragmentation, manifested by multiple long-wake episodes (Ensrud, *et al*., 2006).

Risk of fracture and osteoporosis

SSRI use in adults over 50 years is associated with increased risk of incident clinical fragility fracture, increased odds of falling and lower bone mineral density at the hip (Richards, *et al*., 2007). Another study in men over 65 has also reported significantly lower bone mineral density in SSRI users but not in those taking other antidepressants (Haney, *et al*., 2007). In addition, the use of SSRIs but not TCAs was found to be associated with an increased rate of bone loss at the hip in a cohort of 2722 elderly women (mean age, 78.5 years; Diem, *et al*., 2007). Because depression and bone fragility are both common in the elderly people, it is highly recommended to avoid the SSRI therapy in this age group. Osteoblasts and osteoclasts possess both 5-HT receptors and 5-HT transporters, which probably explains the action of SSRIs in osteoporosis and skeletal fractures (Lerner, 2005).

Bleeding

Release of serotonin from platelets facilitates platelet aggregation. Platelets do not synthesise serotonin and are dependent on the reuptake process for their serotonin content. SSRIs, by inhibiting the reuptake of serotonin into the platelet, cause a decrease in platelet serotonin, leading to a decrease in serotonin release, resulting in reduced platelet aggregation and prolonged bleeding (Dalton, *et al*., 2003). The few epidemiology studies that have investigated the association between SSRIs and upper gastrointestinal tract bleeding provide only weak evidence to support a link (Yuan, *et al*., 2006). In general, the risk of bleeding with SSRI treatment is low (Serebruany, 2006; Reeves, *et al*., 2007). However, the risk of bleeding is increased with concomitant use of aspirin or non-steroidal

anti-inflammatory drugs (NSAIDs; Yuan, *et al*., 2006; Turner, *et al*., 2007). Two studies found that the risk for an upper gastrointestinal bleed from the concurrent use of NSAIDs or low-dose aspirin with a SSRI exceeded the additive risk of the agents alone (Mort, *et al*., 2006). In addition, more recently a meta-analysis has shown markedly increased risk of gastrointestinal bleeding with concomitant SSRIs and NSAIDs (Loke, *et al*., 2007). The odds ratio for upper gastrointestinal haemorrhage (UGIH) was 2.36 for SSRIs alone, 3.16 for NSAIDs alone and 6.33 for the combination of SSRIs and NSAIDs. The estimated number-needed-to-harm was 318 patients per year with a SSRI and 82 patients per year with concomitant SSRI and NSAID use. The number-needed-to-harm was even lower for patients with other risk factors for gastrointestinal bleeding. From postmarketing reports to regulatory agencies, the median time to occurrence of UGIH was 25 weeks of SSRI treatment, with 38% of the reported cases occurring in patients younger than 60 years (Loke, *et al*., 2007). A multicentre retrospective analysis (Wessinger, *et al*., 2006) concluded that it is highly recommended to avoid the combination of SSRIs with any medication that increase bleeding risk.

Extrapyramidal symptoms

Extrapyramidal symptoms (EPS) are rare adverse drug reactions to SSRIs. The risk of EPS appears to increase with advanced age (>65 years) and with the presence of the A1 allele of D2 dopamine receptor gene Taq1A polymorphism (Hedenmalm, *et al*., 2006a). The mechanism involved in SSRI-induced extrapyramidal symptoms has been suggested to be the inhibitory influence of serotonin on dopaminergic neurotransmission (Arya, 1994). This same mechanism is thought to be involved in other rare dopaminergic adverse events seen with SSRIs namely hyperprolactinemia, galactorrhea, mammary hypertrophy and gynaecomastia (Damsa, *et al*., 2004).

Cardiovascular side effects

Cases of arrhythmias, prolonged QTc interval on electrocardiogram (Isbister, *et al*., 2004; Odar-Cederlöf, *et al*., 2006) and orthostatic hypotension (Pacher and Ungvari, 2001) have been reported with SSRIs in patients with no previous history of cardiovascular disorders suggesting possible exceptions to the cardiovascular safety initially reported for these compounds. Experimentally, in different mammalian animal and human cardiovascular preparations, SSRIs have been shown to elicit strong cardiovascular depressant effects by inhibiting cardiac and vascular Na^+, Ca^{2+} and K^+ channels, suggesting possible mechanisms of the clinical reports (see the review of Pacher and Kecskemeti, 2004). Although relatively rare, the existence of clinically important cardiac and vascular effects shows the need for vigilance especially when prescribing SSRIs to patients with cardiovascular disorders.

Discontinuation effects

When SSRIs are discontinued, adverse effects such as nausea, irritability, anxiety and muscular aches can occur (Himei and Okamura, 2006). These effects can be minimised by gradually tapering the dose when discontinuing an SSRI (Martinez and Marangell, 2004). The discontinuation syndrome is most commonly associated with the use of paroxetine and is more likely to occur in patients who experienced adverse reactions in the early phase of treatment (Himei and Okamura, 2006). Persistent sexual side effects after SSRI discontinuation have been observed (Csoka and Shipko, 2006).

Apathy, amotivation and frontal lobe syndrome

Rare cases of apathy, lack of motivation and frontal lobe syndrome have been reported in adults, adolescents and children treated with SSRIs (Hoehn-Saric, *et al*., 1990, 1991; George and Trimble, 1992; Garland and Baerg, 2001). A recent case control study in elderly depressed patients also showed that apathy occurred more frequently in those receiving SSRIs than non-SSRI antidepressants (Wongpakaran, *et al*., 2007). A comparison of SSRIs and selective noradrenaline reuptake inhibitors in depression (Dubini, *et al*., 1997) concluded that although both classes were similarly active on most depressive symptoms, serotonergic drugs produce less improvement in motivation than the noradrenergic agents. This is consistent with a more widespread negative effect on motivation by SSRIs.

Weight gain

When used for six months or less, SSRIs are not likely to cause weight gain, and opinions vary as to whether they cause weight gain when used for 1 year or longer (Deshmukh and Franco, 2003). Paroxetine may be more likely than other SSRIs to cause weight gain during both short-term and long-term treatments (Pae and Patkar, 2007). However, this adverse event induced by the SSRIs is less of a problem than that caused by other recent antidepressants such as mirtazapine (Laimer, *et al*., 2006) and many older antidepressants (tricyclics and monoamine oxidase inhibitors; Cassano and Fava, 2004).

Other effects

Cases of alopecia associated with SSRIs have been reported, notably with sertraline administered for 1 year at 50 mg per day (Hedenmalm, *et al*., 2006b). Hair loss improved after a dose reduction to 25 mg per day (Hedenmalm, *et al*., 2006b). However, this adverse event is rare and appears to be more common in women. Although SSRIs do not increase road accident risk in depressed patients (Barbone, *et al*., 1998), a

controlled study assessing actual driving performance has found that depressed patients receiving long-term treatment with SSRI antidepressants showed impaired driving performance, without deficits in memory, psychomotor and attention functions (Wingen, *et al*., 2006). The impairment observed following the acute administration of the SSRIs persisted with time for up to a year.

Conclusions

SSRIs are considered as one of the first-line drugs not only in the treatment of depression but also in many other psychiatric disorders (see the reviews of Masand and Gupta, 1999; Vaswani, *et al*., 2003). The wide use of SSRIs may explain why so many adverse events have been detected. Currently, it is rare to have a week without the publication of an article mentioning sexual dysfunction, suicidality, pregnancy problems or other undesirable effects induced by the SSRIs. Many early-onset side effects of the SSRIs, such as nausea, diarrhoea, headache and agitation, disappear within 2–3 weeks. Long-term treatment of depression and other psychiatric conditions is necessary, however, to consolidate the improvement obtained during the acute phase of the treatment. Long-term side effects are an important factor for patient compliance and quality of life. Adverse events that persist as long as the patient takes the medication such as many of those described in this article represent a conundrum. Many of the long-term adverse effects are not as well described as those in the drug package insert, which are based principally on short-term studies. In addition, many of the long-term problems such as sexual dysfunction, weight changes and sleep disturbance, which are the most troubling adverse events according to Ferguson (2001), can be confused with manifestations of depression making it difficult to distinguish them from residual depressive symptoms (Wingen, *et al*., 2006). Furthermore, some adverse events are insidious and give no reason to suspect their existence until it is sometimes too late. As long as serum sodium concentrations do not fall below a certain threshold, hyponatremia, for example, is not life threatening and its symptoms are common to many situations. Below a certain threshold, however, it can be fatal.

Therefore, it is advised that whenever a long-term SSRI treatment is undertaken, patients of all ages should be monitored carefully at initiation and during early and continuous phases of the therapy.

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