

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

by

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Although the selective serotonin reuptake inhibitors (SSRIs) are now used as a first-line treatment for depression, 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 adverse events may occur. They are often difficult to recognise since they often resemble residual symptoms of the depression. They have a clear negative influence on the patient's quality of life and are one of the main reasons for a lack of long-term compliance with the associated increased risk of recurrence of a depressive episode. This article is an overview of some of the more common long-term adverse events seen with SSRIs.

1. 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 from suffering they are associated with considerable side effects and even 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 used as a first-line treatment for depression, in part because of their relatively benign adverse effect profile and safety in overdose, especially compared with the older TCAs and MAOIs. However, their efficacy in depression is no greater and their onset of action is no more rapid than that of the MAOIs or TCAs. In addition, they are not completely devoid of side effects (Mourilhe and Stokes, 1998). Sexual dysfunction, weight gain and sleep disturbance are the most troubling adverse events seen during long-term SSRI therapy (Ferguson, 2001). SSRIs are devoid of receptor interactions and their associated side effects which characterise MAOIs and TCAs (Richelson, 1996), and their only apparent pharmacological activity is the inhibition of the reuptake of serotonin. Most of side effects result from an over-stimulation of various serotonin receptors in both the brain and the periphery (Lieberman, 2003). 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-HT₂ and 5-HT₃ receptors.

Many of the side effects of SSRIs are transient and subside over time, and can be minimized by having patients take the drug with meals and starting treatment with low doses followed by a slow titration to recommended doses (Kelsey, 2001).

Overall, compared to the old generations of antidepressants, the SSRIs present a therapeutic option that is attractive to the majority of primary care physicians, psychiatrists and patients. However, with the passage of time certain problems are emerging in relation to long term treatment with the SSRIs.

2. 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 of 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⁺, Ca²⁺ and K⁺ channels, providing possible mechanistic explanations of the clinical reports (see the review of Pacher and Kecskemeti, 2004). Although rare, the existence of clinically important cardiac and vascular effects shows the need for vigilance especially when prescribing SSRIs to patients with cardiovascular disorders.

3. Suicidality

Cases of SSRI-induced suicidality (suicide attempts and suicidal ideation) have been reported both in adults (Teicher et al., 1990; Rothschild and Locke 1991; Hawthorne and Lacey 1992) and in adolescents and children. It is worth noting, however, that in spite of a certain risk of suicidality with SSRIs (and probably with all antidepressants) a recent study demonstrated that continued antidepressant treatment is associated with overall reduced risk of suicide (Sondergard et al., 2007).

- 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 2-fold (4% v 2%) 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 prescriptions numbers have reduced 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) was 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 makers of all antidepressant medications extend the existing black box suicidality warning to young adults aged 18 to 24. The new proposed warning emphasizes, however, that depression itself may lead to suicide and that antidepressant medications 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.

For more details on these findings and decisions, [see Controversy section.](#)

- Elderly patients

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 older patients (Juurlink et al., 2006), while the other (Barak et al., 2006) has shown that elderly depressed patients treated with SSRIs may be at reduced risk of attempting suicide.

4. Sexual dysfunction

Sexual dysfunction is common among both men and women with major depressive disorder. A study revealed that of 134 patients with major depression surveyed, 40% of men and 50% of women reported decreased sexual interest (Kennedy et al., 1999), while 40% to 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% of a French sample and 39.2% of 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 since 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.

5. 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. The question remains as to whether infants of women taking antidepressants have worse birth outcomes and, if so, whether the risks are due to the medication or to the psychiatric condition. SSRIs cross freely 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. 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 were 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 OR = 2.23), or major cardiac malformations (adjusted OR = 3.07) was found in women exposed to > 25 mg/day of paroxetine during the first trimester of pregnancy (Berard et al., 2007). Another recent study (Louik et al., 2007) did not find any significantly increased risks of defects associated with SSRI use overall. Specific SSRIs, notably paroxetine and sertraline; may confer increased risks for some specific defects. 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).

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) 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.

6. Hyponatremia

Hyponatremia (serum sodium concentrations below 130 mEq/l) can lead to disturbing symptoms (Table 1) which can cause serious morbidity and even death (Guay, 2000).

Table 1. Symptoms related to hyponatremia

Na⁺ (mEq/l)	Symptoms
120 - 130	Nausea and malaise Headache Lethargy Muscle cramps Disorientation Restlessness
< 120	Seizures Coma Respiratory arrest

Hyponatremia is associated with SSRI use, with an incidence which varies from 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.

7. Bleeding

Release of serotonin from platelets facilitates platelet aggregation. Platelets do not synthesize 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). A multicentre retrospective analysis (Wessinger et al., 2006) concluded that it is highly recommendable to avoid the combination of SSRIs with any medication that increase bleeding risk.

8. Risk of fracture and osteoporosis

SSRI use in older 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). Since depression and bone fragility are both common in the elderly, it is highly recommendable 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).

9. Extrapyrarnidal symptoms

Extrapyrarnidal symptoms (EPS) are rare adverse drug reactions to SSRIs. The risk of EPS seems 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).

10. 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, while 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.

11. Weight gain

When used for 6 months or less, SSRIs are not likely to cause weight gain and opinions vary as to whether they cause weight gain when used for one year or longer (Deshmukh and Franco, 2003). Paroxetine may be more likely than other SSRIs to cause weight gain during both short-term or long-term treatment (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).

12. Sleep disturbance

SSRIs interfere with sleep architecture. Fluoxetine, paroxetine and sertraline delay REM sleep onset, while fluoxetine and paroxetine increase awakenings and reduce REM sleep, slow-wave sleep, total sleep time and sleep efficiency. In contrast sertraline tends to reduce nocturnal waking (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).

13. Other effects

Cases of alopecia associated with SSRIs have been reported, notably with sertraline administered for one 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.

14. Discontinuation effects

When SSRIs are discontinued, adverse effects such as nausea, irritability, anxiety, and muscular aches can also occur (Himei and Okamura, 2006). These effects can be minimized 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).

15. Conclusion

Depression is a highly prevalent, chronic and recurrent disorder. Long-term treatment of depression consolidates the improvement obtained during the acute phase of the treatment and prevents relapses and recurrences of the disorder. Many early-onset side effects of the SSRIs such as nausea, diarrhoea, headache and agitation, disappear within 2-3 weeks. Long-term side effects may, however, be more important in terms of patient compliance and quality of life. Adverse events that persist as long as the patient takes the medication such as those described here represent a knottier problem. Unfortunately many of them are not as well described as those in the drug package insert, which are based on short-term studies. In addition many of the long-term adverse effects such as sexual dysfunction, weight changes and sleep disorders can be confused with depressive symptoms making it difficult to distinguish them from residual depressive symptoms (Wingen et al., 2006).

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