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Tolerability and safety of fluvoxamine and other antidepressants

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SUMMARY

Selective serotonin [5-hydroxytryptamine (5-HT)] reuptake inhibitors (SSRIs) and the 5-HT noradrenaline reuptake inhibitor, venlafaxine, are mainstays in treatment for depression. The highly specific actions of SSRIs of enhancing serotonergic neurotransmission appears to explain their benefit, while lack of direct actions on other neurotransmitter systems is responsible for their superior safety profile compared with tricyclic antidepressants. Although SSRIs (and venlafaxine) have similar adverse effects, certain differences are emerging. Fluvoxamine may have fewer effects on sexual dysfunction and sleep pattern. SSRIs have a cardiovascular safety profile superior to that of tricyclic antidepressants for patients with cardiovascular disease; fluvoxamine is safe in patients with cardiovascular disease and in the elderly. A discontinuation syndrome may develop upon abrupt SSRI cessation. SSRIs are more tolerable than tricyclic antidepressants in overdose, and there is no conclusive evidence to suggest that they are associated with an increased risk of suicide. Although the literature suggests that there are no clinically significant differences in efficacy amongst SSRIs, treatment decisions need to be based on considerations such as patient acceptability, response history and toxicity.

Keywords: Antidepressants; selective serotonin reuptake inhibitors; fluvoxamine; tolerability; safety; review

INTRODUCTION

Over the years, there have been considerable advances in the development of new antidepressants with the emergence of the selective serotonin [5-hydroxytryptamine (5-HT)] reuptake inhibitors (SSRIs) and 5-HT noradrenaline reuptake inhibitors (SNRIs). Since their introduction, it has become apparent that these drugs have certain advantages over the older tricyclic antidepressants and monoamine oxidase inhibitors, notably in the area of safety and tolerability. Most clinicians now consider the SSRIs and some of the other new antidepressants first-line treatment for depression and anxiety disorders. However, the issue of safety and tolerability, and indeed efficacy, becomes more complex when comparing members of the newer generations of antidepressants. Not only are SSRIs chemically different from the tricyclic, tetracyclic and other antidepressant agents, considerable structural differences also exist between the various SSRIs. For example, fluvoxamine is the only monocyclic SSRI and belongs to the 2-aminoethyl oxime ethers of aralkylketones. Therefore, some differential pharmacology between the drugs in the same class may be expected. The aim of this review, which was based on a Medline literature search, is to provide a comprehensive comparative overview of the main clinical features of some antidepressants based on pharmacology, pharmacokinetics, tolerability and safety.

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PHARMACOLOGIC AND PHARMACOKINETIC ASPECTS

Receptor Binding

Most of the effects of antidepressants, whether therapeutic or adverse, can be directly related to their pharmacology. Although the ultimate mechanism of action of antidepressants remains uncertain, it is reasonable to assume that the effects on monoamine systems in the brain are central to their therapeutic effects. SSRIs attain this effect by blocking the 5-HT transporters (5-HTTs) in the brain. Although this is the primary pharmacological effect of all SSRIs, their spectrum of activity is not confined to the blockade of 5-HTT. Venlafaxine, for instance, is one of the most potent antidepressants at blocking the dopamine transporter, and paroxetine, although the most potent blocker of 5-HTT, also has appreciable affinity for the noradrenaline transporter (NAT) (1). In general, SSRIs are weaker than older antidepressants (especially the tricyclic antidepressants) at blocking receptors

for neurotransmitter, but sertraline shows some potency at the α_1-adrenoreceptor, paroxetine has anticholinergic properties similar to imipramine, and fluoxetine has significant affinity for the 5-HT_{2C} receptor (2–6).

In comparison with the other SSRIs, paroxetine has the highest affinity for the muscarinic receptor (Figure 1) (1), which at higher dosages, or at low dosages in slow metabolisers, may lead to anticholinergic side effects such as dry mouth, constipation, dizziness, tachycardia, blurred vision, urinary retention and fatigue (7). Anticholinergic side effects also include memory impairment (7,8), confusion (7), problems with concentration (7) and sexual dysfunction, but these side effects are less likely to occur at normal dosages of paroxetine (9–12). Compared with other antidepressants, paroxetine also has an affinity for binding at the NAT (Figure 2) (1).

Of all the SSRIs, citalopram has the highest affinity at histamine receptors (Figure 3). This property, which may cause somnolence (13), sedation (13,14), sexual dysfunction (10), weight gain (15,16), memory impairment (17), attention deficit (17) and psychomotor alterations (18,19), has no or only minor clinical significance for citalopram at normal dosages.

Fluvoxamine has virtually no affinity for any of the above receptors, but preclinical evidence suggested that fluvoxamine has a high affinity for the σ_1-receptor, which is believed to play a role in psychosis and aggression. As shown in Figure 4, of all the SSRIs, fluvoxamine has the highest affinity at the σ_1-receptor in rat brain, followed by sertraline, fluoxetine and citalopram. Paroxetine has the lowest affinity for this binding site (20). All SSRIs are more selective for the σ_1-receptor than for the σ_2-receptor. Although the clinical significance of binding to this receptor remains uncertain, it might account for the superior efficacy of fluvoxamine in psychotic depression (21,22).

Half-Life and Active Metabolites

The half-lives of fluvoxamine, paroxetine, sertraline and citalopram are all approximately 1 day. The half-life of fluoxetine is approximately 2 days after a single dose and 6 days after multiple dosing (23). The half-life of venlafaxine is relatively short (about 4 h), and hence this drug requires twice daily (b.i.d.) or three times daily dosing (24); the extended-release formulation (venlafaxine XR) permits once-daily dosing.

Fluoxetine has a pharmacological active metabolite, norfluoxetine, which has a half-life of 7–15 days (23–25). Sertraline also has an active metabolite (26), citalopram has three active metabolites (27), and escitalopram has two (28). Of the seven metabolites identified from venlafaxine, at least three of them are pharmacologically active (18).

A long half-life of the parent compound or the presence of active metabolites may cause accumulation, which is associated with an increased risk of late-emergent side effects, may be cardiotoxic (especially in case of overdose) and may have clinically unexpected consequences (29).

The significant longer half-lives of fluoxetine and its metabolite, norfluoxetine, are associated with a significantly slower onset of action in comparison with other SSRIs (29). A double-blind study comparing SSRIs in patients with depression have shown

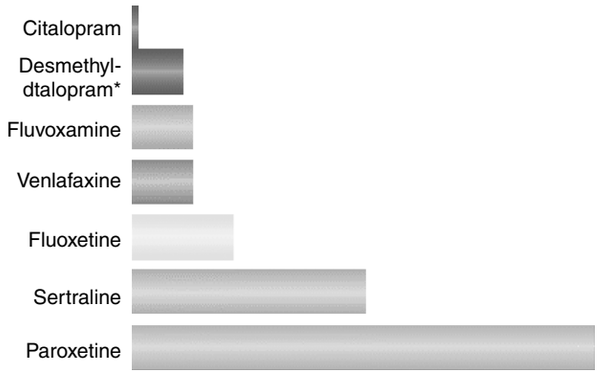

Figure 2 Relative potency of the antidepressants for binding at the noradrenaline transporter. Potency of antidepressants at noradrenaline transporter based on IC_{50} values: citalopram, 6100; desmethylcitalopram, 740; fluvoxamine, 620; venlafaxine, 620; fluoxetine, 370; sertraline, 160; paroxetine, 81 (1). *Active member of citalopram

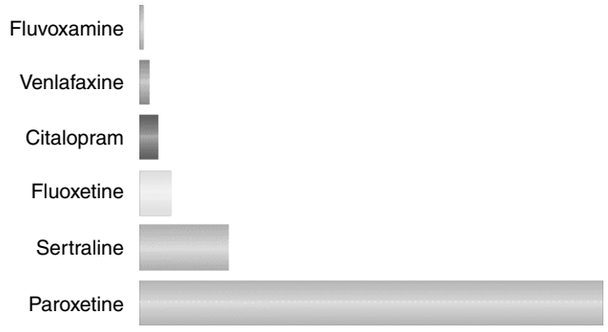

Figure 1 Relative potency of the antidepressants for binding at muscarinic receptors. Potency of antidepressants for binding at muscarinic receptors based on IC_{50} values: fluvoxamine, 34,000; venlafaxine, 11,000; citalopram, 5600; fluoxetine, 3100; sertraline, 1100; paroxetine, 210 (1)

Figure 3 Relative potency of the antidepressants for binding histaminergic (H1) receptors. Potency of antidepressants for binding H1 receptors based on K_i values: fluvoxamine (1), 29,250; paroxetine (1), 23,770; venlafaxine (5), 11,000; sertraline (1), 6578; fluoxetine (1), 1548; citalopram (1), 283 (15)

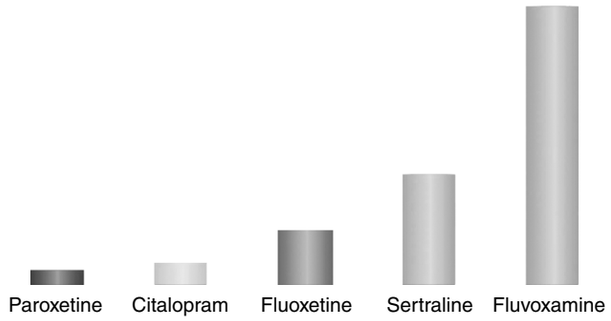

Figure 4 Relative affinity for σ_1-receptors. Affinities of selective serotonin reuptake inhibitors for the subtypes of σ-receptors (K_i ratio σ_1/σ_2) (20)

that fluoxetine has a significantly slower onset of therapeutic action compared with fluvoxamine (30). In fact, a slower onset of action with fluoxetine compared with the other SSRIs has been reported in a recent meta-analysis of 20 comparative studies (31). Moreover, the gradual accumulation of norfluoxetine may produce a high ratio of norfluoxetine : fluoxetine plasma concentration, which is associated with a poor clinical response (32,33). This elevated norfluoxetine : fluoxetine ratio may also explain the loss of therapeutic efficacy sometimes observed in long-term treatment with fluoxetine (34).

With the possible exception of citalopram, SSRIs are relatively safe in cases of overdose (35–37). Citalopram's active metabolite, didesmethylcitalopram, has played an important role in several cases of cardiotoxicity (29), because it may cause a QT prolongation (35,37,38). After discontinuation, residual amounts of fluoxetine and norfluoxetine in the plasma may increase the potential toxicity of subsequent TCA overdose due to pharmacokinetic drug–drug interactions (39).

It is worth noting that the metabolites of sertraline (desmethylsertraline), fluoxetine (norfluoxetine) and paroxetine all inhibit cytochrome P (CYP)450 isoenzymes, notably CYP 2D6 (23). Although CYP 2D6 makes up only about 2–5% of the total CYP in the human liver, it is a major enzyme catalysing the oxidation of more than 30 drugs (40).

Protein Binding

The plasma protein binding of the SSRIs ranges from about 50% up to 99%. Fluvoxamine and citalopram have the lowest plasma protein binding of all SSRIs, of 77% and 50%, respectively (23). Venlafaxine has the lowest protein binding of all modern antidepressants with a binding of 27% (24). Although this issue is considered of minimal clinical significance, there are reports of important adverse events related to protein-binding displacement interactions (41).

CYP450 2D6 Drug Metabolising Enzymes

The interactions related to CYP liver enzymes may have no effect, lead to intoxication or improve the therapeutic response of a given agent. The different pharmacokinetic profiles of the antidepressants, especially their potential for drug–drug interactions, should always be considered especially when multiple drugs are prescribed (42).

The CYP 2D6 subenzyme metabolises numerous drugs, including many typical and atypical antipsychotics (e.g. risperidone), antiarrhythmics (e.g. flecainide), tricyclic antidepressants (e.g. imipramine and amitryptiline), antihypertensive drugs (e.g. some β-blockers) and codeine (43–45). Interindividual variation in the gene that encodes CYP 2D6 plays an important role in the variable drug treatment responses (44). About 5–10% of all Caucasians lack a functional CYP 2D6 enzyme and are phenotypically poor metabolisers (44). Conversely, about 5% are ultra-rapid metabolisers, resulting in rapid biotransformation of antidepressants. In fact, CYP 2D6 polymorphisms may contribute to development of adverse effects or may be a reason for the poor efficacy of antidepressant treatment (46).

Paroxetine and fluoxetine (and norfluoxetine) are very potent inhibitors of CYP 2D6 (42,47–49). Of all SSRIs, fluvoxamine has the lowest potential for drug interactions involving this enzyme (43).

CYP 2D6 may play a minor in the metabolism of citalopram, but one of its main metabolites, *N*-desmethylcitalopram, is further extensively metabolised by CYP 2D6 to didesmethylcitalopram (45,50). Indeed, in a recent publication, pharmacokinetic interactions were found for citalopram due to CYP 2D6 (50). The interactions with CYP 2D6 may be clinically significant not only for citalopram but also for escitalopram (51).

CYP 2D6 is the major enzyme involved in the metabolism of venlafaxine (52). Although venlafaxine is considered by some investigators to be a weak inhibitor of CYP 2D6 (43), CYP 2D6 plays an important role in the formation of *O*-desmethylvenlafaxine that is one of venlafaxine's major metabolites (53). Decreased CYP 2D6 activity has been associated with cardiovascular toxicity observed during treatment with venlafaxine (54).

Fluvoxamine inhibits CYP 1A2, CYP 2C19 and CYP 3A3/4 (55–57). Fluoxetine substantially inhibits CYP 2D6, CYP 3A3/4, CYP 2C9 and CYP 2C19 (55,56,58); its active metabolite, norfluoxetine, inhibits CYP 3A3/4, CYP 2C19 and CYP 2B6 (59).

As the effect of the SSRIs on hepatic CYP450 enzymes differ markedly and may be clinically important, selection of the antidepressant should be appropriate for the patient (59).

TOLERABILITY

Gastrointestinal Adverse Events

The most common adverse event reported during treatment with SSRIs is nausea, which tends to disappear after some

days of treatment (60). The overall incidence of nausea is similar for all SSRIs (61), occurring quite frequently as a consequence of increased availability of 5-HT in the gastrointestinal tract and also probably in central nervous system. Stimulation of 5-HT_3 receptors plays a pivotal role in the development of this side effect, as antagonists for this receptor are capable of reducing the effect (62). Nausea is also among the most common adverse reactions for venlafaxine (63,64).

Recently, sertraline has been shown to cause statistically significantly more diarrhoea than other SSRIs ($p < 0.05$) (65).

Sexual Dysfunction

Depressed male patients are almost twice as likely to present with erectile dysfunction compared with non-depressed men (66). Furthermore, patients treated with an SSRI may present with sexual dysfunction as an unwanted side effect of therapy. Paroxetine, sertraline and citalopram are reported to cause delayed ejaculation. A double-blind, randomised comparative study in 60 patients with premature ejaculation showed that placebo and fluvoxamine had no effect on the ejaculation time after 6 weeks of treatment, while paroxetine, fluoxetine and sertraline all significantly ($p < 0.05$) increased ejaculation latency; the greatest effect was seen with paroxetine (67).

The SSRIs are reported to cause sexual dysfunction in the following descending order of frequency: paroxetine, fluoxetine, citalopram, sertraline and fluvoxamine (66). This is confirmed in part in a direct double-blind comparison between fluvoxamine and sertraline in which the incidence of abnormal ejaculation and decreased libido was significantly ($p < 0.05$) higher with sertraline than with fluvoxamine (68). In addition, in several studies in which patients were specifically interviewed with a sexual dysfunction questionnaire, orgasm/ejaculation delay and impotence were reported significantly more frequently with paroxetine than with other SSRIs (69,70).

The SNRI, venlafaxine, has been associated with impotence, abnormal ejaculation and orgasm, especially at higher doses, and it is reported to have an incidence of sexual side effects at least as high as that seen with paroxetine and sertraline (71).

Sexual side effects should be taken into consideration before prescribing a drug treatment for depression, because sexual dysfunction may play an important role in compliance with treatment and can act as an additional stress factor for the patient (72).

Central Nervous System Impairment

In contrast to the tricyclic antidepressants, SSRIs at normal clinical doses have little effect on cognitive psychomotor functioning. However, sertraline, paroxetine and fluoxetine have all shown some alerting effects and excitation (73,74) that may be detrimental in elderly patients. Indeed, fluoxetine has been reported to be associated with an increased incidence of nervousness and insomnia compared with the tricyclic antidepressants (75,76). Paroxetine has also been shown to impair cognition and vigilance, which may also be particularly problematic in elderly patients (77).

Drug-induced behaviour arousal features in activation, over motivation, pathological anxiety, compromised sexual function and cognitive impairment (78). In contrast to sertraline, paroxetine and fluoxetine, fluvoxamine has been shown to have little or no effect on behavioural arousal (78). Indeed, fluvoxamine has no effect on psychomotor speed, cognitive processing or arousal (73). Similarly, fluvoxamine showed no potentiation of alcohol-related cognitive impairment (79). As fluvoxamine (50 mg and 100 mg) was found not to impair psychomotor performance or cognitive ability in any relevant tests, including choice reaction time, tracking, critical flicker fusion threshold and memory scanning, it may be of value for use in outpatients who wish to carry out the tasks of everyday life.

In a double-blind study comparing dothiepin and venlafaxine in elderly patients, venlafaxine 37.5 mg administered b.i.d. did not have any negative effect on cognitive function and psychomotor performance (80). However, venlafaxine 75 mg/day is not considered to be the usual effective venlafaxine dose for the treatment of major depression.

Sleep Quality

Evidence suggests that fluvoxamine has beneficial effects on sleep in depressed patients. A recent double-blind study comparing fluvoxamine and fluoxetine showed that depressed patients treated with fluvoxamine improved their sleep quality both significantly more and more rapidly than patients on fluoxetine (81). Another direct comparative study involving fluvoxamine and paroxetine (72) showed that paroxetine caused a greater disruption of sleep patterns than fluvoxamine, and the paroxetine-induced sleep disruption persisted into the withdrawal phase (82).

The beneficial effects of fluvoxamine on sleep quality have also been reported in patients with post-traumatic stress disorder (PTSD). Fluvoxamine was effective in reducing all three symptom clusters of PTSD (intrusion, avoidance and hyperardusal), including nightmares and insomnia (83). In addition, patients suffering from other anxiety disorders, such as obsessive-compulsive disorder and panic disorder, have been found to experience a significant reduction of insomnia when treated with fluvoxamine (84). It has been suggested that the beneficial effects of fluvoxamine on sleep may be related to its inhibitory effect on melatonin degradation; this effect has not been observed with other SSRIs (85,86).

In a double-blind placebo-controlled study, venlafaxine was found to decrease sleep continuity, markedly increase the time

to rapid eye movement (REM) sleep and decrease the duration of total REM sleep (87). Other more recent publications confirm that venlafaxine worsens sleep quality (88–90).

Bodyweight

Changes in bodyweight are associated with a low acceptance of treatment and an increased risk of non-compliance during long-term treatment by patients (91). Typically, SSRIs mediate a reduction in food intake, particularly in the initial phase of therapy. However, weight is frequently regained after 6 months of treatment and can be followed by additional weight gain during long-term treatment (92).

Paroxetine, fluoxetine, citalopram and sertraline have been shown to significantly increase bodyweight after 6–12 months of administration (93). Weight gain could be related to carbohydrate craving, as reported for citalopram (94). However, an alteration in metabolic rate may be responsible for the weight changes (95). In this regard, fluvoxamine was reported to promote an increase in resting metabolic rate, resulting in less weight gain (95). Of the SSRIs, paroxetine may be responsible for the highest amounts of weight gain (92,93). However, follow-up over 2 years of patients receiving open-label clomipramine, citalopram, fluoxetine, fluvoxamine, paroxetine or sertraline showed that clomipramine was associated with the highest weight increase and fluoxetine and sertraline with the lowest (96).

Weight changes observed with SSRIs appear to involve the interaction of 5-HT with multiple mechanisms, with the extent of weight gain being dependent on small, yet pharmacological important differences in this class of antidepressants (97). Venlafaxine, such as fluoxetine, at least in short term, reduces food intake (98,99).

SAFETY

Safety in Special Populations

Patients with cardiovascular impairment. The SSRIs are more suitable than the tricyclic antidepressants for the treatment of patients with cardiovascular and cerebrovascular diseases (both of which are associated with a high incidence of depression) due to their superior cardiovascular safety profile. Evidence for the safety of fluoxetine, sertraline and paroxetine has been inferred from cardiac effects in healthy volunteers, while sertraline has also been used safely in patients with recent myocardial infarctions or unstable angina (100). A review of the citalopram database found that the majority of patients with abnormal ECGs had pre-existing cardiac disease or were receiving medication likely to affect the QTc interval (101). Fluvoxamine has been widely studied in patients with cardiovascular impairment, and evidence suggests it has no effect on cardiovascular function in physically healthy patients and is safe in patients with cardiovascular disease (102–107).

In contrast, venlafaxine causes increases in heart rate and blood pressure in some patients (108). In a sample of 3744 depressed patients treated with venlafaxine, a dose-dependent elevation of supine diastolic blood pressure was reported that was statistically and clinically significant, especially in doses above 300 mg/day (108). An overall tendency to mildly raised blood pressure may be apparent in 10% of individuals on venlafaxine, regardless of the daily dose (109). Hypertensive crises have also been reported for venlafaxine (110). Regular blood pressure monitoring is advised in patients receiving venlafaxine while discontinuation is recommended in patients with a sustained elevation. Indeed, preliminary evidence suggests that venlafaxine may be an effective treatment in patients with severe orthostatic hypotension (111).

Elderly patients. The good safety profile of the SSRIs in comparison with the tricyclic antidepressants is particularly important when treating elderly patients. Differences in the safety and tolerability profile between the SSRIs suggest that some may be more suitable than others for the treatment of elderly patients. Fluoxetine, for example, is associated with nervousness (112–114) and insomnia (114), which suggests that it should be employed with caution in frail, elderly patients. It should also be noted that although considerable interindividual variation exists, higher plasma levels of paroxetine have been observed in elderly patients along with its reduced elimination.

The clearance of citalopram has also been observed to generally decrease with increasing age (115); a dose reduction or close monitoring is therefore advised for the elderly patient taking citalopram.

The excellent safety profile of fluvoxamine in the elderly, without the need of dose adjustments, was confirmed in an analysis of data from 4843 patients (mainly depressed) aged 65–97 years enrolled in world-wide post-marketing studies conducted over periods of up to 1 year (116). Findings from a study in 137 elderly patients aged between 75 and 97 years (mean 81 years), who also had a high incidence of concomitant illnesses and requirement for other medications, have also confirmed the excellent safety of fluvoxamine (117).

Treatment-emergent hypertension may occur in a small percentage of older patients taking venlafaxine in doses above 150 mg/day (118), and thus careful monitoring of these patients is advisable.

Discontinuation Symptoms

Discontinuation symptoms upon abrupt withdrawal have been reported for all SSRIs (119), although it is now evident

that they are considerably more common with paroxetine than with the other SSRIs. An evaluation of the UK post-marketing surveillance database of adverse reactions revealed more reports of discontinuation symptoms with paroxetine (0.3 reports per 1000 prescriptions) than sertraline (0.03) or fluvoxamine (0.03), and the least with fluoxetine (0.002) (120).

In a double-blind, placebo-controlled study specifically designed to assess the effects of interruption of fluoxetine, sertraline or paroxetine treatment, placebo substitution for paroxetine was associated with an increase in the number and severity of adverse events following the second missed dose and increases in functional impairment at 5 days (121). Effects were considerably less marked with the other SSRIs. Similar findings were reported in another double-blind, placebo-controlled trial in which treatment with paroxetine, fluoxetine, sertraline or citalopram was suddenly interrupted for 4–7 days (122). Interruption of paroxetine was associated with significantly more cognitive problems and poorer quality of sleep.

Neonatal withdrawal syndrome has also been reported after *in utero* exposure to paroxetine (123), while high rates of neonatal complications in women exposed to paroxetine during the third trimester of pregnancy have been possibly attributed to the withdrawal syndrome (124).

Of the top 20 medicines in UK with reports of symptoms of withdrawal entered on to the British ADROIT database (125), paroxetine was at the top of the list with 1281 reports. Venlafaxine occupied the second position with 272 reports, while fluoxetine, sertraline and citalopram were fourth, fifth and sixth, respectively. Fluvoxamine was placed 19th (Table 1). It appears that a long drug half-life delays the onset of discontinuation symptoms rather than preventing them. A review of the literature found that the mean length of time for the appearance of discontinuation symptoms was 6.4 days with fluoxetine compared with 2–4 days for sertraline, fluvoxamine and paroxetine (126).

Table 1 Antidepressants associated with reports of suspected withdrawal reactions on the UK Adverse Drug Reactions On-line Information Tracking

Drug substance	*Number of UK reports of withdrawal reactions*
Paroxetine	1281
Venlafaxine	272
Fluoxetine	91
Sertraline	81
Citalopram	49
Bupropion	18
Clomipramine	18
Amitriptyline	15
Fluovoxamine	13
Mirtazapine	13

From: Medicines Control Agency UK 2002 ADROIT database – from the top 20 medicines associated with reports of suspected withdrawal reactions.

Suicide Risk

There is controversy about the possibility that SSRI antidepressants might induce suicidality in some patients; the role of antidepressants in suicide prevention has therefore become a major public health question. In a review of randomised controlled trials, meta-analyses of clinical trials and epidemiological studies, an excess of suicidal acts on active treatments compared with placebo made it difficult to sustain the hypothesis that SSRIs do not cause problems in some individuals (127). A more recent systematic review of randomised controlled trials, which included 87,650 patients, also found a significant increase in the odds of suicide attempts for patients receiving SSRIs compared with placebo (128).

Other studies have failed to support either an overall difference in suicide risk between antidepressant- and placebo-treated depressed individuals or a difference between SSRIs and either other types of antidepressants or placebo. Similar suicide rates were seen among those randomly assigned to an SSRI, a standard comparison antidepressant, or placebo in a review of 48,277 depressed patients participating in the Food and Drug Administration (FDA) reports of controlled clinical trials for modern FDA-approved antidepressants (129). Neither was there evidence that the risk of suicide or non-fatal self-harm in adults prescribed SSRIs was higher than in those prescribed tricyclic antidepressants in a UK study of 146,095 individuals with a first prescription of an antidepressant for depression; there was some weak evidence of an increased risk of non-fatal self-harm for current SSRI use among those aged 18 or younger, although none committed suicide (130). Epidemiological studies also have not supported the hypothesis that SSRIs may have a suicide-emergent effect. Over a period of 9 years (1992–2000), treatment of depressed individuals with SSRIs was not associated with an increased risk of suicide in adults, children or adolescents in Sweden (131).

However, there may be an association between the fall in suicide rate and greater use of non-tricyclic antidepressants. This is suggested by data from US where, from 1985 to 1999, there was a decline by 13% in suicide rate and an increase of over fourfold in antidepressant prescription rates, with the increase mostly due to SSRIs (132). Data from all US individuals who committed suicide between 1996 and 1998 showed that prescriptions for SSRIs and other new-generation non-SSRI antidepressants were associated with lower suicide rates and that higher suicide rates in rural areas were associated with fewer antidepressant prescriptions (133). This, along with evidence to suggest that most of those who commit suicide and who have major depressive disorder at the time of death are either untreated or receiving subtherapeutic

doses of antidepressants (134), implies that improved treatment delivery of antidepressants may potentially reduce suicide rates.

Safety in Overdose

The SSRIs are considerably safer than tricyclic antidepressants if taken in overdose. However, citalopram may be a possible exception to the overall good safety profile of the SSRIs in overdose.

In a review of 393 cases admitted to hospital for antidepressant overdose (no co-medication) from 1987 to 2003, 5-HT syndrome was relatively common (14% of cases). Despite this, all the SSRI were demonstrated to be relatively safe in overdose and only citalopram was significantly associated with QTc prolongation. The overall incidence of seizures was 1.9% and coma was 2.4% (35). In contrast, in a retrospective review of 225 patients, citalopram was associated with a significantly longer QT interval on ECG recording, but mean QTc durations were not significantly different between all drugs studied. Only venlafaxine and citalopram caused seizures and were associated with admission to intensive care units (38). In another study in 538 patients hospitalised due to antidepressant overdose, SSRIs were shown to be less likely to cause coma, to require admission to an intensive care unit and prolong the QRS, but were more likely to cause 5-HT toxicity than venlafaxine. Venlafaxine was comparable with the tricyclics in terms of the risk of seizures and suicide (126).

CONCLUSION

The SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine and citalopram), and also the SNRI venlafaxine, have become a mainstay and first-line treatment for depression. The highly specific actions of the SSRIs involving enhancement of predominantly serotonergic neurotransmission explain their beneficial effects in depressed patients and patients with anxiety disorders, while the lack of direct actions on other neurotransmitter systems is responsible for their superior safety profile as compared with that of tricyclic antidepressants.

As a class, the SSRIs possess the following mild to moderate adverse effects that do not require dose reductions or discontinuation: erectile and ejaculatory dysfunction, decreased libido, jitteriness, sweating, tachycardia, tremors, anorexia, anxiety, diarrhoea, headache, insomnia and nausea. Although a comparison of the adverse effects of SSRIs (and venlafaxine) reveals little distinction among the agents, certain differences are emerging. For example, the impact of SSRIs on sexual function is perhaps the most deleterious side effect from the point of view of the patient's quality of life. In contrast to several other SSRIs and also venlafaxine, evidence suggests that fluvoxamine has beneficial effects on sleep in depressed patients and a lower impact on bodyweight. In terms of cardiotoxicity, it is established that the SSRIs are more suitable than the tricyclic antidepressants for the treatment of patients with cardiovascular disease due to a superior cardiovascular safety profile. Fluvoxamine has been widely studied in this regard, and evidence suggests it has no effect on cardiovascular function in physically healthy patients and is safe in patients with cardiovascular disease. Fluvoxamine also has an excellent safety profile in frail elderly patients. A discontinuation syndrome (involving disequilibrium, nausea, vomiting, fatigue, sleep disturbances, lethargy, irritability and agitation) may develop upon abrupt cessation of an SSRI. This syndrome is more common with the SSRIs with shorter half-lives and inactive metabolites. Finally, the SSRIs are considerably more tolerable than tricyclic antidepressants in overdose, and there is no conclusive evidence to suggest that they are associated with an increased risk of suicide.

This review therefore suggests that while clinically significant differences in efficacy amongst SSRIs do not exist, treatment decisions need to be based on considerations such as patient acceptability, patient history of prior response, toxicity and cost. It is noteworthy in this respect that fluvoxamine has a comparatively good profile in terms of adverse events. It has a particularly low impact on sexual function (this may therefore reduce patient non-compliance) and an excellent safety profile in the elderly.

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