Fluvoxamine in the treatment of anxiety disorders

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Abstract: Fluvoxamine is a selective-serotonin reuptake inhibitor (SSRI) that has proved effective in large double-blind, randomized, controlled trials involving patients with social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), and panic disorder. Improvements have also been demonstrated in patients with post-traumatic stress disorder, as well as those with a range of obsessive-compulsive spectrum disorders including binge eating disorder, bulimia nervosa, pathological gambling, and body dysmorphic disorder. Several well controlled studies have confirmed the efficacy of fluvoxamine in children and adolescents with OCD, SAD, and other anxiety disorders, and it was the first SSRI to be registered for the treatment of OCD in children. Fluvoxamine is well tolerated. In common with other SSRIs, the most frequently reported adverse event is nausea. Fluvoxamine does not cause sedation or cognitive impairment and is associated with a low risk of sexual dysfunction, suicidality, and withdrawal reactions. It is safe in overdose and has no significant effect on body weight or cardiovascular parameters.

Keywords: fluvoxamine, anxiety disorders, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder

Introduction

Fluvoxamine was the first of the selective serotonin reuptake inhibitors (SSRIs) that remains in clinical use. Although originally developed as an antidepressant (Wilde et al 1993) (an indication for which it is licensed in many countries, with the exception of the United States), its most widespread application is in the treatment of anxiety disorders, particularly obsessive-compulsive disorder (OCD). It was the first drug licensed for use in adults, and subsequently for children as well, in OCD in the United States. In recent years, there have been a number of studies of fluvoxamine in other anxiety disorders, particularly in social anxiety disorder (SAD) and its eastern equivalent taijin kyofusho (fluvoxamine was the first SSRI to be licensed in Japan).

There have been few recent reviews of fluvoxamine, and the majority of the older reviews focus largely on its use in depression. Whilst fluvoxamine is undoubtedly effective in depression, it is in the context of anxiety disorders that the drug is most frequently encountered and where there is a lack of critical overviews of its utility. This review examines the evidence for efficacy of fluvoxamine in OCD, SAD, obsessive compulsive spectrum disorders, panic disorder, and post-traumatic stress disorder (PTSD). Apart from the SSRIs, treatment options in these disorders have major tolerability disadvantages, with benzodiazepines, tricyclic antidepressants, and neuroleptics being the mainstay of treatment until the advent of the SSRIs. Fluvoxamine has probably been better evaluated in a wider range of anxiety disorders than any of the other SSRIs, and the publication of recent data in this area warrants further review.

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Pharmacology

Fluvoxamine is a SSRI antidepressant. It potently inhibits the reuptake of serotonin but has little effect on dopamine and norepinephrine uptake systems. In addition, apart from binding to σ_1 receptors, it has a low affinity for neurotransmitter receptors (Leonard 1992; Hyttel 1993). The affinity of fluvoxamine for σ_1 receptors, which may be involved in psychosis and aggression, is greater than that seen with the other SSRIs (Narita et al 1996).

The anxiolytic activity of fluvoxamine has been demonstrated in a number of animal models including the ultrasonic rat pup vocalization test, anticipatory anxiety in mice, and schedule-induced polydipsia in rats (Njung'e and Handley 1991; Olivier et al 1993; Woods et al 1993).

Pharmacokinetics

The key pharmacokinetic properties of fluvoxamine are summarized in Table 1. It is efficiently absorbed after oral administration and its bioavailability is not affected by food. Thereafter it undergoes widespread distribution, although it has lower plasma protein binding than all other SSRIs with the exception of citalopram. Extensive metabolism occurs in the liver, with less than 4% of the dose being excreted unchanged. None of the resulting metabolites have psychotropic activity (Overmars et al 1983). Fluvoxamine has an elimination half-life of approximately 15 hours after a single dose, which increases by 30%–50% after multiple dosing, thus making it suitable for once-daily dosing. Excretion is via the urine. There is minimal excretion of fluvoxamine in breast milk (Piontek et al 2001).

The pharmacokinetic profile of fluvoxamine is unchanged in patients with renal impairment (van Harten 1995), but slower elimination in patients with hepatic

Table 1 Pharmacokinetic properties of fluvoxamine

Oral absorption	$\geq 94\%$
C_{max}	31–87 mg/L
T_{max}	2–8 hours
Time to reach steady-state	≈ 10 days
Absolute bioavailability	$\approx 50\%$
AUC	927 μg/L⁻hour
V_d	25 L/kg
Plasma protein binding	$\approx 77\%$
$t_{1/2\beta}$	15 hours after a single dose
Route of metabolism	Hepatic oxidation
Route of excretion	Urine

Data adapted from van Harten (1995).
Abbreviations: C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; AUC, area under the plasma concentration-time curve; V_d, volume of distribution; $t_{1/2\beta}$, terminal elimination half-life.

impairment may necessitate an initial dose reduction (van Harten et al 1993). Age has little impact (de Vries et al 1992), although slow titration is advised in elderly patients and the recommended maximum dose for children is 200 mg/day.

In contrast to a number of other SSRIs, fluvoxamine is only a weak inhibitor of cytochrome P450 (CYP) 2D6 and is therefore unlikely to result in interactions when used in combination with drugs that are metabolized by this isoenzyme, eg, many antipsychotics (DeVane 1998). Fluvoxamine is, however, a potent inhibitor of CYP1A2 and a moderate inhibitor or CYP3A4 and CYP2C19, and may prolong the elimination of agents metabolized by these isoenzymes, eg, warfarin, theophylline, and some benzodiazepines (DeVane 1998). There are no interactions between fluvoxamine and alcohol (van Harten et al 1992), lithium (Milijkovic et al 1997), or digoxin (Ochs et al 1989).

Clinical studies
Social anxiety disorder

SAD is the most common of the anxiety disorders, after specific phobia, with a lifetime prevalence of at least 10% (Kessler et al 1994; Weiller et al 1996). It is characterized by a fear of embarrassment in social or performance situations, and occurs in either the generalized form, which is associated with a fear of many situations including, for example, speaking, eating, writing in front of others, or socializing in a group; or the nongeneralized form, where the fear occurs in just one or two situations. The symptoms can be severe, particularly in the generalized form, and lead to significant impairment in education, work, social, and family situations. Because onset is usually before or during adolescence, patients can suffer for many years, and a high risk of comorbidity with other psychiatric disorders contributes to further disability.

A number of randomized, double-blind, placebo-controlled studies have confirmed the efficacy of fluvoxamine in improving the symptoms of SAD, as well as reducing the disruption it causes in everyday life (Table 2) (van Vliet et al 1994; Stein et al 1999, 2003; Davidson et al 2004; Westenberg et al 2004). Good evidence also exists for the efficacy of paroxetine and sertraline (MacQueen et al 2001; Wagstaff et al 2002), although fluoxetine showed no significant difference from placebo in the only reported double-blind study (Kobak et al 2002).

Fluvoxamine was the first SSRI to be evaluated in a randomized, controlled trial for the treatment of SAD (van Vliet et al 1994); the results from this small study showed a

Table 2 Summary of randomized, double-blind, placebo controlled trials with fluvoxamine in social anxiety disorder

| Study | N | Duration | Regimens | Percentage change in score from baseline at end of study | | | Response rate |
				LSAS	CGI severity score	SDS	
van Vliet et al 1994	28	12 weeks	FLV 150 mg/day	–46% (anxiety)[***] –37% (avoidance)			46%[a]
			Placebo	–14% (anxiety) –20% (avoidance)			7%
Stein et al 1999	86	12 weeks	FLV 50–300 mg/day	–28%[**]		–35% (work) –25% (social) –28% (family)	43%[b*]
			Placebo	–9%		+8% (work) 0% (social) +22% (family)	23%
Stein et al 2003	109	24 weeks	FLV CR 100–300 mg/day	–60%	–52%[**]	–68%[*]	80%[b]
			Placebo	–51%	–40%	–54%	74%
Davidson et al 2004	279	12 weeks	FLV CR 100–300 mg/day	–30%[**]	–22%[***]	–34%[*]	34%[b***]
			Placebo	–15%	–11%	–20%	17%
Westenberg et al 2004	294	12 weeks	FLV CR 100–300 mg/day	–37%[*]	–31%[*]	–41%[*]	48%[b]
			Placebo	–28%	–21%	–32%	44%

Abbreviations: FLV, fluvoxamine; CR, controlled-release; LSAS, Liebowitz Social Anxiety Scale; SDS, Sheehan Disability Scale; CGI, Clinical Global Impression severity score.
[a] Based on LSAS.
[b] Based on CGI improvement.
*p < 0.05 vs placebo; **p < 0.01 vs placebo; ***p < 0.001 vs placebo.

significantly greater improvement with fluvoxamine than with placebo on the Liebowitz Social Anxiety Scale (LSAS), Hamilton Anxiety Scale, and the 90-item Symptom Checklist. In a larger study involving 86 patients who had been suffering from SAD for an average of around 25 years, fluvoxamine was significantly superior to placebo on the LSAS, Brief Social Phobia Scale, Social Phobia Inventory, and the Clinical Global Impression (CGI) response rate (Stein et al 1999). Two subsequent studies, each involving more than 250 patients diagnosed specifically with the generalized form of SAD, confirmed that the controlled release formulation of fluvoxamine (100–300 mg/day) was significantly more effective than placebo on the LSAS, CGI severity scale, and the Sheehan Disability Scale (SDS) (Davidson et al 2004; Westenberg et al 2004). Interestingly, fluvoxamine has also shown some efficacy in patients with taijin kyofusho, a disorder thought to be a form of SAD unique to Eastern cultures that is centred on a fear of embarrassing or offending other people (Matsunaga et al 2001).

Because SAD is a chronic disorder, maintenance treatment may be necessary. A 24-week, double-blind extension study, conducted in 109 patients who had experienced at least minimal improvement after 12 initial weeks of treatment with fluvoxamine CR (100–300 mg/day) or placebo (Westenberg et al 2004), showed that patients treated with fluvoxamine continued to show greater improvement than those given placebo, although the magnitude of change was smaller in the extension than in the acute phase (Stein et al 2003).

Fluvoxamine is also effective in children and adolescents with SAD and other anxiety disorders and was the first SSRI to be approved by the Food and Drug Administration for use in children. In a randomized, double-blind study in 128 children and adolescents aged 6–17 years (>70% aged ≤12 years) with SAD, separation anxiety disorder, or generalized anxiety disorder, fluvoxamine (up to 300 mg/day) was significantly more effective than placebo from week 3 onwards on the Pediatric Anxiety Rating Scale (Figure 1) (Research Unit on Pediatric Psychopharmacology Anxiety Study Group 2001). By the end of the 8-week study, the mean score was <10 in the fluvoxamine group, indicating no more than mild anxiety, whilst it remained high in the placebo group. The response rate (CGI improvement score of <4) was 76% with fluvoxamine and 29% with placebo (p<0.001). A 6-month open-label extension of this study

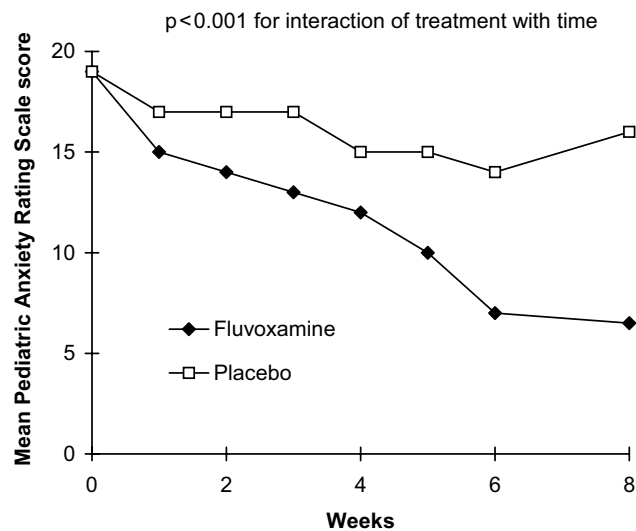p<0.001 for interaction of treatment with time

Figure 1 Mean Pediatric Anxiety Rating Scale score in children and adolescents with SAD (separation anxiety disorder) or generalized anxiety disorder treated with fluvoxamine or placebo. Source: Research Unit on Pediatric Psychopharmacology Anxiety Study Group. 2001. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *N Engl J Med*, 344:1279–85. Copyright © 2001. Reproduced with permission from Massachusetts Medical Society.

showed that anxiety symptoms remained low in 94% of patients who initially responded to fluvoxamine (Walkup et al 2002). Amongst the 48 initial placebo nonresponders, 56% had a clinically significant improvement in anxiety when switched to fluvoxamine; 71% of the 14 initial

fluvoxamine nonresponders also showed a significant improvement when switched to fluoxetine.

Obsessive-compulsive disorder

OCD is characterized by recurrent or persistent obsessions (thoughts) and compulsions (behaviors) that cause marked distress and significantly interfere with everyday functioning. It has a lifetime prevalence of 2%–5% (Karno et al 1988) and a high degree of comorbidity.

The efficacy of fluvoxamine in the management of OCD has been confirmed in a number of randomized, double-blind, controlled studies, and it was the first SSRI to be registered for this indication. Placebo-controlled studies conducted over 6–12 weeks have consistently shown a significantly better response to fluvoxamine (100–300 mg/day) than to placebo as assessed by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), National Institute of Mental Health Obsessive-Compulsive (NIMH-OC) scale, and the CGI scales (Perse et al 1987; Goodman et al 1989, 1996; Jenike et al 1990; Greist et al 1995; Hollander et al 2003). There is evidence from two placebo-controlled studies to indicate that fluvoxamine significantly augments the efficacy of behavior therapy (Cottraux et al 1993; Hohagen et al 1998).

The majority of double-blind, active treatment-controlled studies have been conducted with the tricyclic antidepressant

Table 3 Summary of randomized, double-blind, active controlled trials with fluvoxamine in obsessive-compulsive disorder

| Study | N | Duration | Regimens | Percentage change in score from baseline at end of study | | | |
				Y-BOCS	NIMH-OC	CGI severity score	Response rate
Versus CMI							
Freeman et al 1994	64	10 weeks	FLV 150–250 mg/day	–68%	–73%		59%[a]
			CMI 150–250 mg/day	–69%	–73%		53%
Koran et al 1996	73	10 weeks	FLV 100–300 mg/kg	–30%			56%[b]
			CMI 100–250 mg/kg	–30%			54%
Milanfranchi et al 1997	25	9 weeks	FLV 300 mg/kg	–38%			85%[a]
			CMI 300 mg/kg	–40%			83%
Mundo et al 2000	128	10 weeks	FLV 150–300 mg/kg	–46%	–40%	–32%	60%[a,b]
			CMI 150–300 mg/kg	–50%	–40%	–33%	67%
Mundo et al 2001	217	10 weeks	FLV 150–300 mg/day	–46%	–40%	–32%	62%[b]
			CMI 150–300 mg/kg	–47%	–39%	–33%	65%
Versus DMI							
Goodman et al 1990	40	8 weeks	FLV 100–300 mg/kg	–29%[*]			52%[a*]
			DMI 100–300 mg/kg	–1%			11%

Abbreviations: FLV, fluvoxamine; CMI, clomipramine; DMI, desipramine; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; NIMH-OC, National Institute of Mental Health Obsessive-Compulsive scale; CGI, Clinical Global Impression severity score.
[a] Based on CGI improvement.
[b] Based on Y-BOCS.
*p ≤ 0.05 vs comparator.

clomipramine, a serotonin reuptake inhibitor (Table 3) (Freeman et al 1994; Koran et al 1996; Milanfranchi et al 1997; Mundo et al 2000, 2001). These studies all showed that fluvoxamine and clomipramine are equally effective for the treatment of OCD, although fluvoxamine was generally better tolerated. One study compared the effects of fluvoxamine with the tricyclic antidepressant desipramine which, in contrast to clomipramine, is a noradrenaline reuptake inhibitor (Table 3) (Goodman et al 1990). The response rate and the percentage reduction in the Y-BOCS score at the end of the study were both significantly greater with fluvoxamine than with desipramine ($p \leq 0.05$).

Long-term maintenance treatment with fluvoxamine appears to reduce the risk of relapse, and there is some indication that lower dosages may be effective, although only small studies have been conducted to date (Ravizza et al 1996; Mundo et al 1997).

As with other anxiety disorders, fluvoxamine has proved effective in children and adolescents with OCD. A 10-week, double-blind, placebo-controlled study in 120 children and adolescents (approximately 50% were aged 8–12 years and 50% aged 13–17 years) showed that fluvoxamine (50–200 mg/day) was significantly superior to placebo on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) from week 1 onwards ($p < 0.05$) (Figure 2) (Riddle et al 2001). Such an early response is not generally observed in studies in adult patients. Statistically significant differences between fluvoxamine and placebo were also seen on the NIMH-OC and CGI scales and a response ($\geq 25\%$ reduction in CY-BOCS total score) was achieved in 42% of fluvoxamine patients and 26% of placebo patients. In a 1-year open extension phase involving 98 patients, continuation of fluvoxamine (200 mg/day) resulted in further small beneficial effects, whilst patients switched from placebo to fluvoxamine experienced a marked improvement in CY-BOCS score (Walkup et al 1999).

Obsessive-compulsive spectrum disorders

Obsessive-compulsive spectrum disorders consist of a group of conditions, each of which has distinct diagnostic criteria, which share certain features with OCD (eg, demographics, symptoms, neurobiology, and effective treatments) (Hollander and Wong 1995). Fluvoxamine has proved effective in a number of these disorders and is probably one of the most widely studied SSRIs in this area, although many
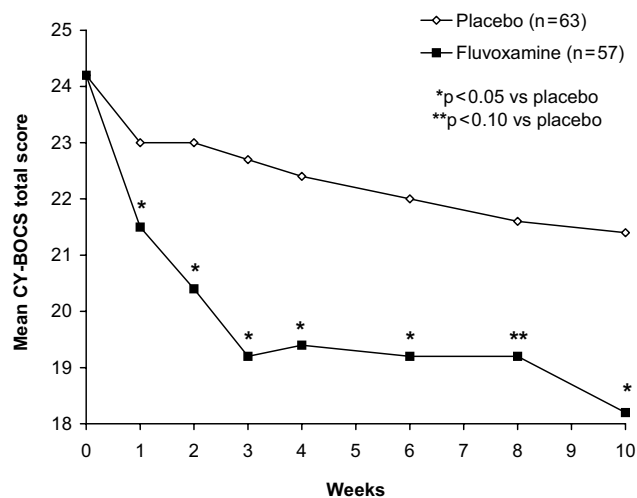

Figure 2 Mean CY-BOCS total score in children and adolescents with OCD treated with fluvoxamine or placebo. Source: Riddle MA, Reeve EA, Yaryura-Tobias J, et al. 2001. Fluvoxamine for children and adolescents with obsessive-compulsive disorder: a randomized, controlled, multicenter trial. *J Am Acad Child Adolesc Psychiatry*, 40:222–9. Reproduced with permission from Lippincott Williams & Wilkins.

of the studies had an open design and involved only small numbers of patients. Randomized, double-blind, controlled studies have, however, been conducted in patients with binge eating disorder, bulimia nervosa, pathological gambling, compulsive buying, and autism.

Binge eating disorder
Binge eating is one of the common eating disorders and is characterized by recurrent episodes of uncontrolled over-eating. Unlike patients with bulimia nervosa, no measures are taken to avoid weight gain. In a randomized, double-blind study in 83 patients, fluvoxamine (50–300 mg/day) was significantly ($p < 0.05$) more effective than placebo after 9 weeks in terms of rates of reduction in CGI severity score, body mass index, and the frequency of binges, and rate of increase in CGI improvement score and level of response (Hudson et al 1998). The addition of fluvoxamine (300 mg/day), but not fluoxetine (60 mg/day), has also been reported to enhance the efficacy of cognitive behavioral therapy in a 6-month randomized study involving 108 patients (Ricca et al 2001).

Bulimia nervosa
Patients with bulimia nervosa also experience compulsive eating binges, but their fear of loss of control and consequent weight gain leads them to use measures such as vomiting and taking laxatives. Fluvoxamine (100–300 mg/day) proved significantly ($p < 0.05$) more effective than placebo in preventing relapse in a 12-week, randomized, double-blind

study in 72 patients who had already been successfully treated with psychotherapy (Fichter et al 1996, 1997). An earlier open study in 20 patients showed that fluvoxamine (50–150 mg/day) significantly (p < 0.05) reduced various aspects of bulimic behavior (Ayuso-Gutierrez et al 1994).

Pathological gambling

Pathological gambling is a chronic and progressive condition that results in significant impairment in everyday living and a high rate of suicide attempts. Following promising findings with fluvoxamine (100–300 mg/day) in a single-blind crossover study, in which a response was achieved in 7 out of the 10 patients (Hollander et al 1998), a small (n = 10) randomized, double-blind crossover study was conducted by the same group (Hollander et al 2000). Fluvoxamine (100–250 mg/day) treatment for 8 weeks resulted in a significantly greater improvement in overall gambling severity on the Pathological Gambling-CGI scale compared with placebo (41% vs 17%; p < 0.005). Gambling urge and behavior were also significantly improved with fluvoxamine treatment.

Compulsive buying

A response (as assessed by the shopping version of the Y-BOCS) to fluvoxamine (up to 300 mg/day) was reported in 9 out of 10 patients enrolled in a 9-week open study; patients were less preoccupied with shopping and reported spending less money (Black et al 1997). A subsequent 9-week, randomized, double-blind study in 23 patients reported a significantly (p < 0.05) greater improvement with fluvoxamine (up to 300 mg/day) than with placebo on the Maudsley Obsessive-compulsive Inventory (Black et al 2000). However, there were no other statistically significant differences between the two treatment groups.

Autism

The efficacy of fluvoxamine (50–300 mg/day) in autistic adults was demonstrated in a 12-week, randomized, double-blind study involving 30 patients (McDougle et al 1996). Significant (p < 0.05) benefits over placebo were seen in repetitive thoughts and behaviors, maladaptive behavior, and aggression and aspects of social relatedness, notably language use. A response was seen in 53% of fluvoxamine-treated patients compared with none in the placebo group (p < 0.01). Autistic children have also shown a response to fluvoxamine in an open study (Yokoyama et al 2002) and a double-blind, crossover study (Fukuda et al 2001). The latter involved 18 children and showed significant (p < 0.05)

improvements in a number of behaviors including eye contact and language use.

Body dysmorphic disorder

Although no double-blind studies have been reported to date, there are considerable data from noncomparative trials to indicate that fluvoxamine is beneficial in patients with body dysmorphic disorder (Hollander et al 1994; Perugi et al 1996; Phillips et al 1998, 2001). Scales used to assess the efficacy of fluvoxamine include the Y-BOCS modified for body dysmorphic behavior, the Brown Assessment of Beliefs Scale, and the CGI. Psychogenic skin excoriation, which is commonly seen in patients with body dysmorphic disorder, has also been shown to respond to fluvoxamine (Arnold et al 1999; O'Sullivan et al 1999).

Other disorders

Other disorders in which fluvoxamine has shown beneficial effects include pervasive developmental disorders (Martin et al 2003), trichotillomania (Stanley et al 1997), and hypochondriasis (Fallon et al 2003).

Panic disorder

Patients with panic disorder suffer from recurrent panic attacks characterized by a range of somatic and cognitive symptoms including sweating, trembling, shortness of breath, palpitations, and fear of dying or losing control. It has a lifetime prevalence of around 3% (Kessler et al 1994), and patients often suffer from comorbid agoraphobia or depression.

Randomized, double-blind, placebo- and active-controlled studies have shown that fluvoxamine is effective in patients with panic disorder (with or without agora-phobia), reducing both the number of panic attacks and the level of anxiety. Three short-term, placebo-controlled studies (one large-scale [n = 179 Asnis et al 2001] and two smaller scale [n = 36 Hoehn-Saric et al 1993; and n = 46 Sandmann et al 1998]) showed that fluvoxamine (up to 300 mg/day) was significantly (p < 0.05) more effective than placebo in reducing the number of panic attacks. In two studies (Hoehn-Saric et al 1993; Asnis et al 2001), the frequency of full panic attacks per week was reduced by 74%–100% with fluvoxamine and 33%–66% with placebo (p < 0.05) at the end of treatment, whilst the third study (Sandmann et al 1998) showed a significant difference only in the frequency of limited symptom attacks (53% vs 31%; p < 0.05). Anxiety, as assessed by the Clinical Anxiety Scale (CAS), was also reduced to a significantly greater extent by fluvoxamine.

Four small, short-term studies have compared fluvoxamine with other active pharmacotherapeutic treatments. In two of these studies, fluvoxamine (up to 150 mg/day) was significantly (p < 0.05) more effective than ritanserin and maprotiline, although neither are indicated for the treatment of panic disorder (den Boer and Westenberg 1988, 1990). Fluvoxamine (up to 300 mg/day) proved significantly (p < 0.01) more effective than imipramine (up to 300 mg/day) in reducing the total number of panic attacks in a placebo-controlled study involving 54 patients with severe panic disorder (Bakish et al 1996). Anxiety was improved to a similar extent in both groups. A lower dose of fluvoxamine (150 mg/day) did not differ significantly from brofaromine (150 mg/day) in reducing the frequency of panic attacks, anxiety, and avoidance behavior in a somewhat smaller study of 30 patients (van Vliet et al 1995).

Four randomized, placebo-controlled studies have assessed the effects of fluvoxamine in comparison with, or in combination with, various behavioral treatments. Fluvoxamine (up to 300 mg/day) proved more effective than cognitive therapy in 55 patients with moderate to severe panic disorder (Black et al 1993). After 8 weeks, the percentage of patients free of panic attacks was 73% in the fluvoxamine group compared with 48% and 25% in the cognitive therapy and placebo groups, respectively. The final CAS score was significantly lower with fluvoxamine than with cognitive therapy or placebo (p < 0.05). In a somewhat larger (n = 149) 12-week study, a lower dose of fluvoxamine (up to 150 mg/day) did not show any significant benefits over cognitive therapy, although an additive effect was observed when the two treatments were used together (Sharp et al 1996). Fluvoxamine (up to 150 mg/day) also enhanced the effects of exposure therapy in a 12-week study in 76 patients (de Beurs et al 1995). A 2-year follow-up showed that the beneficial effects of fluvoxamine plus exposure therapy were maintained and that these patients tended to require less aftercare than those not treated with fluvoxamine (de Beurs et al 1999).

Post-traumatic stress disorder

Patients with post-traumatic stress disorder (PTSD) re-experience previous extreme trauma (eg, rape or combat) in the form of persistent dreams and flashbacks and suffer from hyperarousal and numbing symptoms. Only a minority of patients who survive trauma go on to develop PTSD, thus suggesting that it is not just a normal reaction.

Fluvoxamine has shown efficacy in both civilians and war veterans with PTSD, although only small open, noncomparative studies have been conducted to date. Four studies involved veterans from either World War II (de Boer et al 1992) or the Vietnam War (Marmar et al 1996; Neylan et al 2001; Escalona et al 2002) treated with fluvoxamine (100–300 mg/day) for between 10 and 14 weeks. Improvements were seen in intrusion, avoidance, and hyperarousal symptoms in all four studies, together with a reduction in anxiety. In one study that focused particularly on sleep disturbance, fluvoxamine improved all domains of subjective sleep quality, the greatest effect being seen for reduction of dreams linked to the traumatic experience (Neylan et al 2001). Sleep maintenance insomnia and troubled sleep also showed a large treatment response. A substantial improvement in sleep quality was also noted in the study involving World War II veterans (de Boer et al 1992).

Two studies have assessed fluvoxamine in civilians with PTSD. In a 4-week study in 14 patients who had experienced a variety of traumatic events (mainly traumatic bereavement and childhood sexual trauma), fluvoxamine (50–300 mg/day) significantly (p < 0.05) improved the symptoms of PTSD on a range of efficacy scales, the mean reduction from baseline ranging from 35% to 48% (Davidson et al 1998). Autonomic reactivity (heart rate, blood pressure) to trauma scripts fell significantly (p < 0.05) following 10 weeks of fluvoxamine treatment (100–300 mg/day) in 16 PTSD patients (Tucker et al 2000). Significant improvements were also seen in PTSD symptom clusters and depression.

Tolerability and patient acceptability

Fluvoxamine is generally well tolerated and has proved safe in all age groups from children (Research Unit on Pediatric Psychopharmacology Anxiety Study Group 2001; Riddle et al 2001) to the elderly (Wagner et al 1996; Jaquenoud and Kat 1997) and in patients with mild cardiovascular disease or epilepsy (Harmant et al 1990; Präger et al 1991). In common with other SSRIs, nausea is the most frequent adverse event. A review of 66 postmarketing studies conducted worldwide in 34 587 patients (mainly suffering from depression) treated with fluvoxamine (50–300 mg/day; modal dose 100 mg/day) for between 4 to 52 weeks showed that nausea occurred in 15.7% of patients; all other adverse events had an incidence of < 10% (Table 4). Prescription-event monitoring of fluvoxamine in 10 401 patients also showed nausea to be the only event seen in > 10% of patients (Edwards et al 1994). A very low level of suicidality was reported in these studies (Edwards et al 1994; Wagner et al

Table 4 Incidence of adverse events (≥ 2%) with fluvoxamine in postmarketing studies (n = 34 587)

Adverse event	Incidence (%)
Nausea	15.7
Somnolence	6.4
Asthenia	5.1
Headache	4.8
Dry mouth	4.8
Insomnia	4.0
Dizziness	3.7
Abdominal pain	3.5
Vomiting	3.5
Dyspepsia	3.2
Constipation	3.2
Nervousness	3.2
Tremor	2.8
Diarrhea	2.4
Anorexia	2.2

Adapted from Wagner et al (1994).

1994) and this was confirmed in global postmarketing surveillance data obtained over 17 years in an estimated 28 million patients exposed to fluvoxamine (Buchberger and Wagner 2002). Switch to mania, serotonin syndrome, and convulsions are rarely reported and, although some patients may experience withdrawal symptoms, they are generally mild and resolve spontaneously. Fluvoxamine is relatively safe in overdose, an important consideration in patients with psychiatric disorders. In a review of 221 cases of overdose (≤ 9 g), the acute toxicity that could be attributed to fluvoxamine alone was rarely severe and cardiotoxicity was rare (Garnier et al 1993).

Fluvoxamine does not significantly change body weight (Harris and Ashford 1991) and has few cardiovascular or anticholinergic effects (Präger et al 1991; Flett et al 1992; Wagner et al 1994; Hochberg et al 1995). Studies have shown negligible sedation or impairment in cognitive or psychomotor function (Saletu et al 1983; Hindmarch 1995). A meta-analysis of 73 double-blind, crossover, placebo- or verum-controlled studies assessing the effects of drugs used in the treatment of SAD on objective parameters of cognitive and psychomotor performance in healthy volunteers showed that only fluvoxamine and bupropion were entirely free of impairment in any test (Hindmarch and Trick in press). A total of 1949 individual psychometric tests were evaluated, of which 428 (22%) showed impairment after drug administration. Fluvoxamine does not appear to disrupt sleep (Silvestri et al 2001) and has indeed shown beneficial effects on sleep in patients with PTSD (Neylan et al 2001).
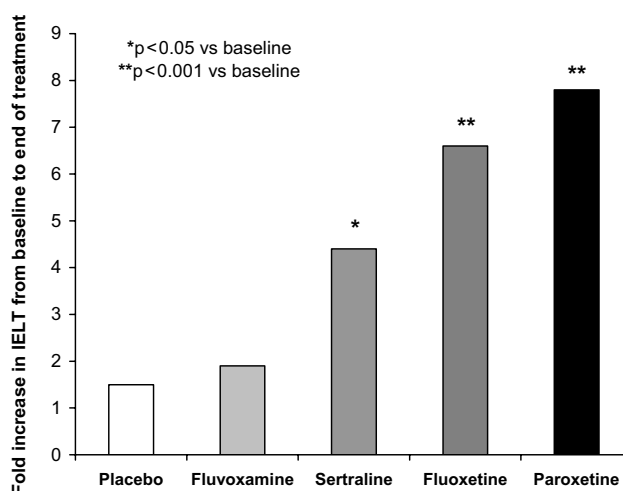

Figure 3 Increase in intravaginal ejaculation latency time (IELT) after 6 weeks in patients with premature ejaculation. Data adapted from Waldinger et al (1998).

In contrast to many antidepressants, fluvoxamine has a low incidence of sexual dysfunction. Prescription event monitoring and postmarketing studies rarely report sexual problems. However, in studies designed to specifically assess sexual side effects, fluvoxamine appears to have less effect than the other SSRIs on sexual function (Nemeroff et al 1995; Montejo et al 1996, 1997). A 6-week, double-blind study in healthy men with premature ejaculation showed that placebo and fluvoxamine had no effect on ejaculation time whilst paroxetine, fluoxetine, and sertraline all significantly increased ejaculation latency, the greatest effect being seen with paroxetine (Figure 3) (Waldinger et al 1998).

Conclusions

Anxiety disorders are extremely common, highly disabling, and associated with considerable comorbidity with depression, substance abuse disorders, and other serious psychiatric illnesses. This category of illness therefore represents an important area of medical need. The well known disadvantages of the benzodiazepines, tricyclic antidepressants, and neuroleptics have resulted in the SSRIs, with their relatively benign adverse event profile, becoming first-line treatment for many anxiety disorders. Among the SSRIs, fluvoxamine has been particularly well studied and was the first to be approved in OCD. Importantly, fluvoxamine has also been fully studied in children and adolescents, since some anxiety disorders (OCD and SAD in particular) have their onset in childhood.

The efficacy of fluvoxamine has been demonstrated by double-blind, randomized, controlled studies in OCD, SAD, and panic disorder. It lacks the common treatment-limiting

anticholinergic and cognitive side effects and cardiotoxicity of the tricyclic antidepressants (heretofore clomipramine was the mainstay of OCD treatment), and the cognitive impairment and dependence susceptibility of the benzodiazepines that are used in a variety of other anxiety disorders. It is also safe in overdose and is associated with a low incidence of suicidality. Compared with the other SSRIs, fluvoxamine has a generally similar tolerability profile, dominated by usually mild and self-limiting gastrointestinal complaints, but appears to cause less sexual side effects and less cognitive disturbance. Unlike paroxetine, it does not induce a significant withdrawal syndrome. Fluvoxamine can therefore be considered a first-line treatment for adults and children with a range of anxiety disorders.

As well as clinical trials, the safety and tolerability of fluvoxamine has been established in extensive, published postmarketing studies, prescription event monitoring, and specific studies in patients with concomitant medical problems such as cardiovascular disease and multi-medicated elderly patients. The safety and tolerability of fluvoxamine in real-world use has thus been widely studied. Whilst the efficacy of fluvoxamine in a variety of anxiety disorders is well established from randomized, clinical studies, there is a relative lack of published large naturalistic efficacy studies. However, there is now considerable clinical experience with fluvoxamine and no reason to believe that the efficacy of fluvoxamine under routine clinical conditions would differ in any significant way from that observed in clinical studies.

Overall, fluvoxamine is an important first-line therapy in the treatment of OCD, SAD, and panic disorder. Its tolerability profile is better than traditional treatments and may offer some advantages over other SSRIs.

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