

Extended-release fluvoxamine for social anxiety disorder and OCD

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New formulation allows once-daily dosing and might improve tolerability, reduce side effects

Fluvoxamine extended-release formulation was FDA-approved to treat generalized social anxiety disorder (GSAD) and obsessive-compulsive disorder (OCD) because it demonstrated efficacy in reducing anxiety symptoms of these disorders in 3 clinical trials. The new formulation may benefit patients unable to tolerate the existing immediate-release form.

Clinical implications

Like other selective serotonin reuptake inhibitors (SSRIs), fluvoxamine alleviates symptoms of GSAD and OCD. The extended-release formulation allows the medication to be administered once daily (*Table 1*) and, according to the manufacturer, may reduce side effects and improve tolerability.

Many clinicians have prescribed immediate-release fluvoxamine once daily, and the efficacy and tolerability of the immediate- and extended-release formulations have not been compared in head-to-head trials. In addition, no studies have examined the efficacy of extended-release fluvoxamine in treating other psychiatric conditions.

How it works

Decreased serotonin levels are associated with GSAD and OCD. Fluvoxamine's therapeutic effect is thought to be mediated through its specific serotonin reuptake inhibition in the CNS.¹

The drug acts primarily on serotonin 2C receptors, with no reported significant af-

Table 1

Extended-release fluvoxamine: Fast facts

Brand name: Luvox CR

Class: Selective serotonin reuptake inhibitor

Indication: Generalized social anxiety disorder and obsessive-compulsive disorder

Approval date: February 29, 2008

Availability date: March 2008

Manufacturer: Jazz Pharmaceuticals

Dosing forms: 100 mg and 150 mg extended-release capsules

Recommended dose: Starting dose: 100 mg/d. Titrate in 50-mg/week increments until maximum therapeutic benefit is achieved. Maximum recommended dose: 300 mg/d

finity for histaminergic, adrenergic, muscarinic, or dopaminergic receptors.¹ Fluvoxamine's 1-sigma receptor antagonism is unique among SSRIs, and researchers have suggested that this may make fluvoxamine more effective than other SSRIs in treating anxious or delusional depression.²

The extended-release formulation uses a spheroidal oral drug absorption system, a proprietary technology that limits peak-to-trough variance for 24 hours.¹ The manufacturer postulates that decreased plasma concentration variability will improve fluvoxamine's tolerability.¹

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Table 2

Fluvoxamine extended-release: What the evidence says

Study	Measures used	Results
Generalized social anxiety disorder		
Westenberg et al (2004) ³	LSAS, CGI-S, CGI-I, SDS, PGI	Fluvoxamine was significantly more effective than placebo in decreasing LSAS total score (primary measure) starting at week 4 and in improving SDS, CGI-S, and CGI-I (secondary measures)
Stein et al (2003) ⁴	LSAS, CGI-S, CGI-I, SDS, PGI	Severity of illness on the CGI-S scale and disability on the SDS were significantly lower in the fluvoxamine group than in the placebo group; fluvoxamine-treated subjects had a numerically greater decrease in LSAS total scores than subjects treated with placebo
Davidson et al (2004) ⁵	LSAS, CGI-G, SDS, CGI-S, PGI	Fluvoxamine produced statistically and clinically significant improvements in symptoms starting at week 4 on the LSAS and CGI-I and at week 6 on the SDS, CGI-S, and PGI
Obsessive-compulsive disorder		
Hollander et al (2003) ⁶	YBOCS, CGI-S, CGI-I	Fluvoxamine was significantly more effective than placebo in decreasing YBOCS total score beginning at week 2 and in improving CGI-S and CGI-I scores
<small>LSAS: Liebowitz Social Anxiety Scale; SDS: Sheehan Disability Scale; CGI-S: Clinical Global Impression-Severity of illness; CGI-I: Clinical Global Impression-Improvement; PGI: Patient Global Impression of Improvement; YBOCS: Yale-Brown Obsessive Compulsive Scale</small>		

Clinical Point

Extended-release fluvoxamine's lower maximum plasma concentration might reduce the risk of adverse effects

Pharmacokinetics

In a single-dose crossover study of 28 healthy subjects, the mean maximum concentration of drug (C_{max}) for extended-release fluvoxamine was 38% lower than that of the immediate-release formulation, which may reduce the risk of adverse effects.¹ Its relative bioavailability was 84%, and mean plasma half-life was 16.3 hours in male and female volunteers.¹

Fluvoxamine is extensively metabolized in the liver, primarily through oxidative demethylation and deamination.¹ Nine metabolites constitute 85% of the urinary excretion product; the main metabolite is fluvoxamine acid.¹ Approximately 2% of fluvoxamine is excreted unchanged in urine. Administering extended-release fluvoxamine capsules with food does not appear to affect the drug's absorption.¹

Fluvoxamine is a potent inhibitor of the cytochrome P450 (CYP) 1A2 isoenzyme and also is believed to significantly inhibit CYP3A4, CYP2C9, CYP3A4, and CYP2C19. It is a relatively weak inhibitor of CYP2D6.¹

Efficacy

The FDA based its approval of extended-release fluvoxamine on data from 3 clinical trials with positive outcomes: 2 for GSAD and 1 for OCD (*Table 2*).^{1,3-6}

GSAD trials. In the first GSAD study—a randomized, double-blind, placebo-controlled, multicenter trial of 300 subjects with GSAD—participants were randomly assigned to receive extended-release fluvoxamine or placebo for 12 weeks.³ The extended-release fluvoxamine group started at 100 mg administered at night, with dosages titrated at 50 mg/week based on efficacy and tolerability to a maximum of 300 mg/d.¹ Subjects in the extended-release fluvoxamine group demonstrated a statistically significant change in Liebowitz Social Anxiety Scale (LSAS) scores from baseline compared with those receiving placebo ($P=0.02$). Researchers observed similar results in secondary measures.

In an extension of this study, 112 subjects who demonstrated at least minimal improvement from extended-release flu-

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Table 3

Extended-release fluvoxamine: Adverse events*

Study	Adverse events
Both GSAD and OCD studies	Abnormal ejaculation, anorexia, anorgasmia, asthenia, diarrhea, nausea, somnolence, sweating, tremor
GSAD studies only	Dyspepsia, dizziness, insomnia, yawning
OCD study only	Accidental injury, anxiety, decreased libido, myalgia, pharyngitis, emesis

* Includes events with an incidence ≥5% and at least twice that of placebo
 GSAD: generalized social anxiety disorder; OCD: obsessive-compulsive disorder
 Source: References 3-6

voxamine by week 12 continued the same dosing regimen for an additional 12 weeks. Investigators found the drug’s beneficial effects persisted to 24 weeks, although the magnitude of the effect decreased.⁴

A separate study using the same dosing regimen enrolled 279 adult patients in a 12-week, multicenter, randomized, placebo-controlled trial.⁵ The fluvoxamine-treated group showed statistically and clinically significant improvement:

- by week 4 on the LSAS and the Clinical Global Impression-Improvement (CGI-I) scale
- by week 6 on the Sheehan Disability Scale, Clinical Global Impression-Severity scale (CGI-S) and Patient Global Impression of Improvement (PGI) scale.⁵

OCD trial. Hollander et al⁶ conducted a 12-week, double-blind, placebo-controlled, flexible-dose, parallel multicenter trial of 253 adult patients with OCD.⁶ Compared with those receiving placebo, subjects treated with extended-release fluvoxamine, 100 to 300 mg/d, showed a statistically significant decrease in score on the Yale-Brown Obsessive Compulsive Scale (P=0.001).⁶ Analysis of the CGI-S and CGI-I also revealed statistically significant improvement compared with placebo. The effect appeared to begin at week 2.

As did the GSAD studies, this study compared extended-release fluvoxamine with placebo and not with the immediate-release formulation. Although no additional studies have examined the efficacy of extended-release fluvoxamine in

treating OCD and the drug has not been evaluated in pediatric patients, the manufacturer notes that the immediate-release formulation has been evaluated in 2 studies with adult OCD patients and 1 pediatric OCD study, all of which had positive results.¹

Tolerability

In the 3 published trials of extended-release fluvoxamine, adverse event rates were similar and consistent with earlier studies of the immediate-release formulation.¹ The manufacturer considered adverse events likely to be drug-related if they had an incidence ≥5% and at least twice that of placebo (*Table 3*).^{1,3-6}

Adverse events caused 26% of patients in the GSAD studies and 19% in the OCD trial to discontinue treatment. No deaths, life-threatening adverse events, or suicide attempts were reported.³⁻⁶ No statistically significant differences in weight gain or loss, vital signs, laboratory findings, or ECG changes were found between patients treated with extended-release fluvoxamine and those receiving placebo.¹

Contraindications

Immediate- and extended-release fluvoxamine have the same active ingredient and therefore the same contraindications. Coadministration of alosetron, pimozide, thioridazine, or tizanidine, is contraindicated, as is using monoamine oxidase (MAO) inhibitors with extended-release fluvoxamine or within 14 days of discontinuing

Clinical Point
 Coadministration of alosetron, pimozide, thioridazine, or tizanidine is contraindicated

Clinical Point

Extended-release fluvoxamine must be administered only once daily, regardless of dosage

fluvoxamine treatment. Extended-release fluvoxamine has the same warnings that all SSRIs share regarding clinical worsening and suicide risk, administration to bipolar patients, neuroleptic malignant syndrome, serotonin syndrome, and possible increases in coagulation.^{1,2}

The FDA classifies extended-release fluvoxamine as pregnancy category C.¹ The drug is not contraindicated for lactating mothers, but because fluvoxamine is secreted in breast milk discuss with breast-feeding patients the benefits and risks of continuing fluvoxamine therapy.¹ Infants exposed to immediate-release fluvoxamine in late pregnancy have developed serious adverse reactions, including respiratory distress, cyanosis, apnea, and seizures.¹

Dosing

The recommended starting dose of extended-release fluvoxamine is 100 mg once daily, with or without food.¹ The dose can be titrated in 50-mg/week increments as tolerated to achieve maximum therapeutic benefit, to the maximum recommended dose of 300 mg/d. Unlike immediate-release fluvoxamine, which is occasionally split into twice-daily doses, extended-

Related Resource

• Luvox CR prescribing information. www.jazzpharmaceuticals.com/content/news/documents/LUVOX_CR.pdf.

Drug Brand Names

Alosetron • Lotronex	Pimozide • Orap
Fluvoxamine • Luvox	Thioridazine • Mellaril
Fluvoxamine extended-release • Luvox CR	Tizanidine • Zanaflex

Disclosures

Dr. Kuzma reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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release fluvoxamine must be administered only once daily, even at high doses.^{1,2}

References

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Bottom Line

In clinical trials, fluvoxamine extended-release significantly improved symptoms of generalized social anxiety disorder and obsessive-compulsive disorder compared with placebo. Decreased variability of the extended-release formulation's plasma concentration might reduce side effects and improve tolerability compared with the immediate-release form. Both fluvoxamine formulations carry the same contraindications and warnings.