Fluvoxamine: A Review of the Controlled Trials in Depression

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Fluvoxamine, a serotonin selective reuptake inhibitor, has been available as an antiobsessional agent in the United States since 1995. However, it has been utilized as an effective antidepressant for many years in various European countries. The controlled trials of fluvoxamine in the pharmacotherapy of depression are reviewed. The drug compares well with a variety of other antidepressants. It appears safe and well tolerated in daily doses of 50 to 300 mg. The most common adverse events are gastrointestinal complaints, particularly nausea. Initiating pharmacotherapy at lower doses and increasing over the period of 1 to 2 weeks minimizes this discomfort.

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Serotonin may be the most phylogenetically ancient of the known central neurotransmitters. It was independently isolated and identified by Page and Erspamer in 1949.[1] Although serotonin appears to be concentrated in the brain stem raphe nuclei, its neuronal projections are quite extensive and innervate diverse structures including the limbic system, basal ganglia, and cerebral cortex. As a result, the serotonergic neurotransmitter system is recognized as the largest chemical network contained within mammalian brain tissue.[2] Increasingly, investigators have discovered that serotonin regulates many basic psychobiological functions including food consumption, sexual activity, sleep, aggression, cognitive processes, and mood.[1,2] Indeed, serotonin plays a pivotal role in the pharmacotherapy of depression, anxiety disorders, eating disorders, schizophrenia, insomnia, and migraine headaches.

Fluvoxamine is a serotonin selective reuptake inhibitor (SSRI) and chemically a member of the 2-aminoethyloximethers of the aralkyl ketones.[3,4] It is a potent and selective inhibitor of the reuptake of serotonin into the presynaptic neuron, while having minimal affinity for muscarinic, histaminergic, and α-adrenergic receptors.[4,5] In addition, it does not possess any monoamine oxidase inhibiting properties.[3,6] Fluvoxamine has a metabolic half-life of ≈ 15 hours,[7] and no major active metabolites are formed as a result of biotransformation.[7,8] As a result of its neurotransmitter specificity, fluvoxamine is safer and better tolerated than the older tricyclic antidepressants (TCAs). For instance, fluvoxamine has no significant adverse cardiac effects aside from a slight and clinically insignificant reduction in heart rate.[9]

Fluvoxamine became available in the United States for the treatment of obsessive-compulsive disorder in December 1994; however, the drug has been utilized for the treatment of depression in several European countries since 1983. The purpose of this paper is to review the safety and efficacy of fluvoxamine in the pharmacotherapy of depression. Data were derived from a computerized search of the Medline data base to identify English language, double-blind, placebo- and/or drug-controlled studies of fluvoxamine in depression.

CONTROLLED DEPRESSION DATA

A total of 31 double-blind, randomized clinical trials that tested the efficacy of fluvoxamine in depression were reviewed. Fluvoxamine has been compared with imipramine and placebo,[10–17] imipramine alone,[18–22] clomipramine,[23–27] amitriptyline,[28,29] dothiepin,[30,31] desipramine alone,[32] desipramine and placebo,[33] mianserin,[34,35] moclobemide,[36] placebo,[37] maprotiline,[38] flupenthixol,[39] and sertraline.[40] These efficacy data are grouped together and summarized in Tables 1–6; however, a few comments are appropriate about the studies in general before discussing the individual data sets.

First, fluvoxamine has been tested in multiple European countries and the United States. Fourteen of these 31 trials involve multiple sites to evaluate the compound, while the remaining 17 studies appeared to be conducted at a single center.

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Table 1. Fluvoxamine Versus Imipramine and Placebo in Depression*

Study	Diagnosis	Design	Randomized	Mean Dose	Depression Assessments	Results
Amin et al, 1984[10]	Feighner criteria HAM-D (17 item) ≥ 15	Inpatients/outpatients 4–6 wk treatment	F = 161 I = 153 P = 150	F = 155 mg I = 156 mg	HAM-D CGI	F = I > P
Dominguez et al, 1985[11]	DSM-III HAM-D (17 item) ≥ 15	Outpatients 4 wk treatment	F = 35 I = 35 P = 31	…	HAM-D CGI	F = I > P
Feighner et al, 1989[12]	DSM-III	Inpatients 6 wk treatment	F = 31 I = 36 P = 19	F = 145 mg I = 159 mg	HAM-D CGI BPRS	F > I = P
Itil et al, 1983[13]	RDC HAM-D (17 item) ≥ 15	Outpatients 4 wk treatment	F = 22 I = 25 P = 22	F = 101 mg I = 127 mg	HAM-D CGI	F = I > P
Lapierre et al, 1987[14]	DSM-III HAM-D (17-item) ≥ 15	Inpatients 6 wk treatment	F = 22 I = 21 P = 20	F = 180 mg I = 172 mg	HAM-D CGI	F = I > P
Lydiard et al, 1989[15]	DSM-III HAM-D (17 item) ≥ 22	Outpatients 6 wk treatment	F = 18 I = 18 P = 18	F = 240 mg I = 180 mg	HAM-D CGI MADRS	F = I = P
March et al, 1990[16]	DSM-III HAM-D (17 item) ≥ 22	Outpatients 6 wk treatment	F = 18 I = 18 P = 18	…	HAM-D CGI MADRS	F = I > P
Norton et al, 1984[17]	RDC HAM-D (17 item) ≥ 15	Outpatients 4 wk treatment	F = 33 I = 30 P = 25	F = 132 mg I = 153 mg	HAM-D CGI BPRS	F = I = P

*Abbreviations: DSM-III = Diagnostic and Statistical Manual of Mental Disorders, Third Edition; RDC = Research Diagnostic Criteria; F = fluvoxamine; I = imipramine; P = placebo; HAM-D = Hamilton Rating Scale for Depression; CGI = Clinical Global Impressions scale; BPRS = Brief Psychiatric Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale.

Second, diagnostic criteria for depression varied among studies, with all but 3 trials employing DSM-III, DSM-III-R, Feighner, or Research Diagnostic Criteria. Two trials did not specify how the diagnosis of depression was made,[21,39] and in a third, the diagnosis of vital depression was considered to be comparable to endogenous depression.[26] Only the Nathan et al.[32] study utilized a structured interview to diagnose depression. In addition, all but 1 study[12] required a minimum threshold of depression severity before drug randomization, with most trials using the Hamilton Rating Scale for Depression (HAM-D) as the benchmark. The rating instrument, the number of items utilized from it, and the cutoff criteria required for drug randomization are listed in Tables 1–6.

Third, patient populations enrolled in these studies were also variable. Overall, the majority of patients treated with fluvoxamine were women (> 60%) and were typically in their mid-to-late thirties or forties. Two studies enrolled female subjects exclusively.[26,37] Two other trials enrolled geriatric patients only.[31,35] In two additional trials, all but a total of five subjects met criteria not only for depression but also for the melancholia subtype.[12,14]

Fourth, the requirement of a washout period and its duration prior to instituting active medication was variable. Twenty of the 31 trials mandated a single-blind placebo washout prior to drug randomization, but the length of washout varied from 3 days (N = 4) to 2 weeks (N = 2). Fifty percent of these 20 studies mandated a one-week, single-blind placebo washout. The remaining 11 studies either did not describe a washout period (N = 2) or did not specify if placebo was utilized (N = 9). After washout, the majority of trials permitted flexible or fixed flexible dosing of study medications, with only 4 trials mandating fixed doses of study compounds. Mean doses of study drugs when available are noted.

Lastly, there was variation in the way in which efficacy data were reported. The majority of studies utilized the HAM-D and the Clinical Global Impressions (CGI) scales as the main determinants of antidepressant efficacy. Twenty data sets gave sufficient details to determine the mean baseline and endpoint rating scale scores, while 6 trials graphed the results, and neither occurred in the remaining 5 trials. In the next section the results of the individual trials are discussed. As much as possible, the trials have been grouped together to facilitate interstudy comparison among identical or similar comparator agents versus fluvoxamine.

Fluvoxamine Compared With Imipramine and Placebo

Eight trials determined the efficacy of fluvoxamine compared with both imipramine and placebo.[10–17] As noted in Table 1, five of these studies recruited outpatients and two utilized inpatient populations exclusively. The Amin et al.[10] study recruited from both groups of subjects. Trial length ranged from 4 to 6 weeks of active medication or placebo. In sum, 340 patients were randomly assigned to

Table 2. Fluvoxamine Versus Imipramine in Depression*

Study	Diagnosis	Design	Randomized	Mean Dose	Depression Assessments	Results
Amore et al, 1989[18]	DSM-III HAM-D (21 item) ≥ 21	Inpatients 4 wk treatment	F = 15 I = 15	…	HAM-D CGI	F = I
Bramanti et al, 1988[19]	DSM-III/Feighner HAM-D (21 item) ≥ 18	Outpatients 4 wk treatment	F = 30 I = 30	…	HAM-D CGI	F = I
Gonella et al, 1990[20]	DSM-III HAM-D (21 item) ≥ 25	Outpatients 4 wk treatment	F = 10 I = 10	F = 140 mg I = 130 mg	HAM-D CGI	F = I
Guelfi et al, 1983[21]	Unspecified HAM-D (26 item) ≥ 25	Inpatients 4 wk treatment	F = 77 I = 81	F = 221 mg I = 112 mg	HAM-D CGI	F = I
Guy et al, 1984[22]	RDC HAM-D (17 item) ≥ 15	Inpatients 4–6 wk treatment	F = 17 I = 19	…	HAM-D CGI BPRS	F = I

*Abbreviations: DSM-III = Diagnostic and Statistical Manual of Mental Disorders, Third Edition; RDC = Research Diagnostic Criteria; F = fluvoxamine; I = imipramine; HAM-D = Hamilton Rating Scale for Depression; CGI = Clinical Global Impressions scale; BPRS = Brief Psychiatric Rating Scale.

Table 3. Fluvoxamine Versus Clomipramine in Depression*

Study	Diagnosis	Design	Randomized	Mean Dose	Depression Assessments	Results
DeWilde and Doogan, 1982[23]	Feighner criteria HAM-D (17 item) ≥ 17	Inpatients 4 wk treatment	F = 15 C = 15	F = 259 mg C = 231 mg	HAM-D CGI	F = C
DeWilde et al, 1983[24]	Feighner criteria HAM-D (17 item) ≥ 16	Inpatients/outpatients 4–6 wk treatment	F = 37 C = 36	F = 259/300 mg[a] C = 231/144 mg[a]	HAM-D CGI	F = C
Dick and Ferrero, 1983[25]	Feighner criteria HAM-D (17 item) ≥ 16	Inpatients 4 wk treatment	F = 17 C = 15	F = 131 mg C = 133 mg	HAM-D CGI	F = C
Klok et al, 1981[26]	Unspecified HAM-D (17 item) = 16–29	Female inpatients 4 wk treatment	F = 18 C = 18	…	HAM-D CGI	F = C
Ottevanger, 1995[27]	Feighner criteria HAM-D (17 item) ≥ 17	Inpatients 4 wk treatment	F = 20 C = 20	F = 204 mg C = 106 mg	HAM-D CGI	F = C

*Abbreviations: F = fluvoxamine; C = clomipramine; HAM-D = Hamilton Rating Scale for Depression; CGI = Clinical Global Impressions scale.
[a]Mean dose for three times daily/once daily dose patients.

fluvoxamine, 336 to imipramine, and 303 to placebo. The mean dose of fluvoxamine ranged from 101 to 240 mg/day compared with 127 to 180 mg/day of imipramine. Five of the eight trials found fluvoxamine and imipramine both equally efficacious and better than placebo. Two others found fluvoxamine equivalent to both imipramine and placebo, while only the Feighner et al.[12] study reported fluvoxamine as superior to both active and inactive controls. Percentage change on rating scales (HAM-D) was reported for six studies.[10,11,13–15,17] Over the span of 4 weeks, the improvement in depression scores as a result of fluvoxamine ranged from 37.4% to 51.9%. Improvement with imipramine was similar, with HAM-D scores decreasing from 41.8% to 53.6%. Placebo fared less well, with symptomatic improvement of 18.7% to 41.7%. In general, the three trials reporting 6-week data[10,14,15] found approximately 10% greater improvement in response rates for both fluvoxamine and imipramine subjects, while individuals taking placebo did not experience further gains.

Fluvoxamine Compared With Imipramine

Five trials compared the efficacy of fluvoxamine with that of imipramine without placebo controls.[18–22] The typical subject was an inpatient (> 70%) who took active medication for 4 weeks. In sum, 149 subjects ingested fluvoxamine (140–222 mg/day), and 155 took imipramine (112–130 mg/day). All five trials found fluvoxamine equivalent to imipramine in the short-term treatment of depression, but only three listed baseline and endpoint HAM-D scores.[19–21] Improvement between the two drugs was similar, with the fluvoxamine HAM-D scores falling 36.4% to 67% compared with the imipramine decline of 30.5% to 62.5%.

Fluvoxamine Compared With Clomipramine

Table 3 summarizes the controlled trials comparing fluvoxamine with the antiobsessional antidepressant clomipramine.[23–27] These five trials are the most consistently similar studies of the fluvoxamine data base in terms of methodology, with four employing Feighner criteria for diagnosis, all recruiting from inpatient samples, all with similar numbers of subjects enrolled, and all utilizing the HAM-D and CGI rating scales. A total of 107 subjects were randomly assigned to fluvoxamine and 104 to clomipramine. The mean dose of fluvoxamine generally exceeded 200 mg/day, while the clomipramine dose ranged from 106 to 231 mg/day. All five trials reported fluvoxamine as being equivalent to clomipramine in antidepres-

Table 4. Fluvoxamine Versus Miscellaneous Tricyclics in Depression*

Study	Diagnosis	Design	Randomized	Mean Dose	Depression Assessments	Results
Harris et al, 1991[28]	DSM-III HAM-D (17 item) ≥ 17	Outpatients 6 wk treatment	F = 35 AMI = 34	F = 115 mg AMI = 99 mg	HAM-D CGI	F = AMI
Remick et al, 1994[29]	DSM-III HAM-D (17 item) ≥ 20	Outpatients 7 wk treatment	F = 16 AMI = 17	F = 175 mg AMI = 135 mg	HAM-D CGI Raskin Covi	F = AMI
Mullin et al, 1988[30]	DSM-III HAM-D (17 item) ≥ 17	Outpatients 6 wk treatment	F = 37 DOT = 36	…	HAM-D CGI	F = DOT
Rahman et al, 1991[31]	DSM-III MADRS ≥ 30	Inpatients > 65 y 6 wk treatment	F = 26 DOT = 26	F = 157 mg DOT = 159 mg	MADRS CGI	F = DOT
Nathan et al, 1990[32]	DSM-III, RDC HAM-D (17 item) ≥ 15	Inpatients 4 wk treatment	F = 17 DES = 20	F = 203 mg DES = 206 mg	HAM-D Raskin	F = DES
Roth et al, 1990[33]	DSM-III HAM-D (17 item) ≥ 22	Outpatients 6 wk treatment	F = 27 DES = 24 P = 29	F = 218 mg DES = 224 mg	HAM-D CGI MADRS	F = DES = P

*Abbreviations: DSM-III = Diagnostic and Statistical Manual of Mental Disorders, Third Edition; RDC = Research Diagnostic Criteria; F = fluvoxamine; AMI = amitriptyline; DOT = dothiepin; DES = desipramine; P = placebo; HAM-D = Hamilton Rating Scale for Depression; CGI = Clinical Global Impressions scale; MADRS = Montgomery-Asberg Depression Rating Scale; Raskin = Raskin Depression Scale; Covi = Covi Anxiety Scale.

Table 5. Fluvoxamine Versus Mianserin in Depression*

Study	Diagnosis	Design	Randomized	Mean Dose	Depression Assessments	Results
Perez and Ashford, 1990[34]	DSM-III MADRS ≥ 30	Outpatients 6 wk treatment	F = 30 M = 33	F = 176 mg M = 100 mg	MADRS CGI	F = M
Phanjoo et al, 1991[35]	DSM-III MADRS ≥ 30	Inpatients/outpatients ≥ 65 y 6 wk treatment	F = 25 M = 25	F = 170 mg M = 60 mg	MADRS CGI	F = M

*Abbreviations: DSM-III = Diagnostic and Statistical Manual of Mental Disorders, Third Edition; F = fluvoxamine; M = mianserin; CGI = Clinical Global Impressions scale; MADRS = Montgomery-Asberg Depression Rating Scale.

sant efficacy. In subjects treated for 4 weeks, fluvoxamine produced a decline in HAM-D scores of 54.1% to 72.9%, compared with a 59.1% to 66.3% decline for clomipramine. The three studies reporting CGI scores found similar results.[23,24,26] The group of outpatients treated by DeWilde et al.[24] for 6 weeks reported a decline in HAM-D scores of 72% for fluvoxamine and 78% for clomipramine. Interestingly, three investigators measured plasma levels of both fluvoxamine and clomipramine.[23,24,26] None of the three groups found any relationship between plasma levels of either drug and the efficacy of antidepressant treatment.

Fluvoxamine Compared With Miscellaneous Tricyclics

Six studies compared several other TCAs with fluvoxamine (Table 4). Two used amitriptyline,[28,29] two dothiepin,[30,31] and two desipramine.[32,33] The Roth et al.[33] study also employed the inactive control placebo. Here, all 158 subjects receiving fluvoxamine and 186 randomly assigned to a TCA or placebo met DSM-III criteria for depression. Outpatients made up more than 70% of study participants. Only one study was shorter than 6 weeks, and all but one used the HAM-D as the principal outcome measure. In sum, fluvoxamine was found to be equivalent to amitriptyline, desipramine, and dothiepin. Four of the six studies detailed mean baseline and endpoint HAM-D scores.[28,30,32,33] Fluvoxamine produced a decline of 39.2% to 60.9% compared with the 28.9% to 59.9% decline of the TCA, while placebo induced a modest reduction of 29%. Nathan et al.[32] also measured plasma levels of both fluvoxamine and desipramine. They reported a direct linear relationship between plasma fluvoxamine levels and clinical response, but a nonlinear relationship between plasma desipramine levels and clinical response. Further, their data suggest that a fluvoxamine level of ≥ 160 to 220 ng/mL will increase the likelihood of a positive response.

Fluvoxamine Compared With Mianserin

Table 5 lists the two comparison trials of the tetracyclic antidepressant mianserin with fluvoxamine. Although two different patient samples were recruited, in both studies patients met DSM-III criteria for depression and had a minimum score of 30 on the Montgomery-Asberg Depression Rating Scale (MADRS). Both groups were treated for 6 weeks and with similar mean doses of medications. Fifty-five patients were randomly assigned to fluvoxamine, while 58 received mianserin. In both studies, fluvoxamine was found equivalent to mianserin. The Perez and Ashford[34] study reported overall reductions in depressive symptoms of 65.5% for fluvoxamine compared with 60.8% for mianserin as determined by the MADRS.

Table 6. Fluvoxamine Versus Miscellaneous Agents in Depression*

Study	Diagnosis	Design	Randomized	Drug/Mean Dose	Depression Assessments	Results
Bougerol et al, 1992[36]	DSM-III HAM-D (17 item) ≥ 17	Inpatients/outpatients 4–6 wk treatment	F = 64 MOC = 67	F = 121 mg MOC = 336 mg	HAM-D CGI	F = MOC
Conti et al, 1988[37]	DSM-III HAM-D (17 item) ≥ 16	Inpatient females 4 wk treatment	F = 23 P = 22	F = 273 mg	HAM-D CGI BPRS	F > P
deJonghe et al, 1991[38]	DSM-III HAM-D (17 item) ≥ 12	Outpatients 6 wk treatment	F = 24 MAP = 24	F = 210 mg MAP = 118 mg	HAM-D CGI	F = MAP
Hamilton et al, 1989[39]	Unspecified HAM-D (17 item) ≥ 15	Outpatients 4 wk treatment	F = 36 FPX = 36	…	HAM-D CGI	F < FPX
Nemeroff et al, 1995[40]	DSM-III-R …	Outpatients 7 wk treatment	F = 49 S = 48	… Raskin Covi	HAM-D CGI	F = S

*Abbreviations: DSM-III = Diagnostic and Statistical Manual of Mental Disorders, Third Edition; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised; F = fluvoxamine; MOC = moclobemide; P = placebo; MAP = maprotiline; FPX = flupenthixol; S = sertraline; HAM-D = Hamilton Rating Scale for Depression; CGI = Clinical Global Impressions scale; BPRS = Brief Psychiatric Rating Scale; Raskin = Raskin Depression Scale; Covi = Covi Anxiety Scale.

Table 7. Adverse Effects: Fluvoxamine Versus Imipramine and Placebo*

Study	Mean Dose	Side Effect Assessment(s)	Adverse Effects	Dropouts Due to Adverse Effects
Amin et al, 1984[10]	F = 155 mg I = 156 mg	Self-report	F = nausea, vomiting I = ACH[a]	…
Dominguez et al, 1985[11]	…	DOTES TWIS	F = nausea, insomnia,[b] somnolence I = dry mouth,[a] ACH	F = 10 I = 8 P = 2
Feighner et al, 1989[12]	F = 145 mg I = 159 mg	Self-report	F = nausea, agitation I = ACH, syncope	F = 7 I = 13 P = 1
Itil et al, 1983[13]	F = 101 mg I = 127 mg	DOTES	F = dry mouth, somnolence, insomnia, nausea I = ACH,[a] insomnia	F = 9 I = 7 P = 1
Lapierre et al, 1987[14]	F = 180 mg I = 172 mg	DOTES TWIS	F = nausea, vomiting, constipation I = dry mouth,[a] syncope,[a] dizziness[a]	F = 1 I = 1
Lydiard et al, 1989[15]	F = 240 mg I = 180 mg	Self-report	F = diarrhea, dry mouth, headache, nausea I = constipation, dry mouth, sweating, dizziness	F = 1 I = 2 P = 1
March et al, 1990[16]	…	Self-report	F = nausea, headache, insomnia, fatigue I = dry mouth, headache, fatigue, constipation, tachycardia[a]	F = 4 I = 3 P = 2
Norton et al, 1984[17]	F = 132 mg I = 153 mg	DOTES TWIS	F = anorexia, nausea, vomiting, diarrhea I = ACH, orthostatic hypotension[a]	F = 2 I = 0 P = 0

*Abbreviations: F = fluvoxamine; I = imipramine; P = placebo; ACH = anticholinergic side effects (i.e., dry mouth, blurred vision, sweating, constipation); DOTES = Dosage Record and Treatment Emergent Symptom Scale; TWIS = Treatment Emergent Symptoms Write-In Scale.
[a]Adverse effect(s) occurred significantly more often with imipramine than fluvoxamine.
[b]Adverse effect occurred significantly more often with fluvoxamine than imipramine.

Fluvoxamine Compared With Miscellaneous Antidepressants

Table 6 outlines the results of the comparative trials of fluvoxamine with the reversible monoamine oxidase inhibitor moclobemide,[36] placebo,[37] the tetracyclic antidepressant maprotiline,[38] the antipsychotic flupenthixol,[39] and with the SSRI sertraline.[40] A mixture of both inpatients and outpatients was recruited, and Conti et al.[37] enrolled inpatient female subjects exclusively. Study length ranged from 4 to 7 weeks, and the HAM-D was the principal outcome measure. A total of 195 subjects received fluvoxamine, 175 were randomly assigned to the comparative agent, and 22 received placebo. Overall, fluvoxamine was found equivalent to moclobemide, maprotiline, and sertraline and superior to placebo. Fluvoxamine was found significantly less effective than flupenthixol on both the HAM-D and CGI scales. This was the only study of 31 total trials that found fluvoxamine inferior to a comparative

Table 8. Adverse Effects: Fluvoxamine Versus Imipramine in Depression*

Study	Mean Dose	Side Effect Assessment(s)	Adverse Effects	Dropouts Due to Adverse Effects
Amore et al, 1989[18]	…	DOTES TWIS	F = insomnia, weight gain, anorexia I = ACH, hypotension	F = 0 I = 2
Bramanti et al, 1988[19]	…	DOTES TWIS	F = excitation, insomnia, dry mouth, constipation I = excitation, insomnia, dry mouth, constipation	F = 0 I = 1
Gonella et al, 1990[20]	F = 140 mg I = 130 mg	DOTES	F = constipation, nausea, vomiting, anorexia I = ACH, hypotension	F = 0 I = 0
Guelfi et al, 1983[21]	F = 221 mg I = 112 mg	Self-report	F = dry mouth, nausea, somnolence, tremor I = ACH, tremor	F = 2 I = 5
Guy et al, 1984[22]	…	DOTES	F = tachycardia, weight loss, headache I = ACH, tremor	F = 1 I = 3

*Abbreviations: F = fluvoxamine; I = imipramine; DOTES = Dosage Record and Treatment Emergent Symptom Scale; TWIS = Treatment Emergent Symptoms Write-In Scale; ACH = anticholinergic side effects (i.e., dry mouth, blurred vision, sweating, constipation).

Table 9. Adverse Effects: Fluvoxamine Versus Clomipramine in Depression*

Study	Mean Dose	Side Effect Assessment(s)	Adverse Effects	Dropouts Due to Adverse Effects
DeWilde and Doogan, 1982[23]	F = 259 mg C = 231 mg	Self-report	F = dry mouth, tremor, sweating, insomnia C = ACH, headache, tremor	F = 0 C = 0
DeWilde et al, 1983[24]	F = 259 mg/300 mg[a] C = 231 mg/144 mg[a]	Self-report	F = tremor C = ACH, tremor, hypotension	F = 0 C = 0
Dick and Ferrero, 1983[25]	F = 131 mg C = 133 mg	Self-report	F = asthenia, constipation, dry mouth C = asthenia, ACH	F = 1 C = 1
Klok et al, 1981[26]	…	23-item checklist	F = agitation, nausea, anxiety C = ACH, anxiety, agitation	F = 2 C = 2
Ottevanger, 1995[27]	F = 204 mg C = 106 mg	Self-report	F = nausea, gastric pain, somnolence C = ACH, gastric pain	F = 2 C = 1

*Abbreviations: F = fluvoxamine; C = clomipramine; ACH = anticholinergic side effects (i.e., dry mouth, blurred vision, sweating, constipation).
[a]Mean dose for three times daily/once daily dose patients.

agent. It was conducted in general practice outpatients with mild to moderate depression. Research design and possibly conservative dosing of fluvoxamine may explain these results.

SAFETY AND TOLERABILITY OF FLUVOXAMINE IN DEPRESSION

Tables 7–11 summarize the safety and tolerability data of fluvoxamine versus comparator agents and placebo. A number of the studies failed to report how adverse effects were elicited from patients. In these cases, it was assumed to be by self-report. Fortunately, 14 of the 31 trials utilized a structured method in assessing adverse events. The majority employed the Dosage Record and Treatment Emergent Symptom Scale (DOTES) and the Treatment Emergent Symptoms Write-In Scale (TWIS), while several employed symptom checklists, and one a semi-structured interview. In only one study[40] was the self-report Sexual Symptoms Distress Index utilized. The most common reported fluvoxamine adverse events are listed in the tables along with those side effects commonly reported with the comparator agent. Dropouts due to adverse effects, also a measure of patient tolerability of an antidepressant, are also listed.

Overall, fluvoxamine was consistently associated with inducing a variety of gastrointestinal adverse effects. Nausea, vomiting, and/or a general sense of gastrointestinal distress were the most frequently voiced complaints. Indeed, gastrointestinal complaints are the most common adverse events experienced by patients taking any of the four SSRIs currently available in the United States.[41] As recently reviewed by DeVane,[41] nausea was shown to be the most common adverse effect associated with fluvoxamine use initially; however, with continued use over several weeks, nausea was no more common with fluvoxamine than with the other three SSRIs. Nausea also appears to be dose-related, and lower starting doses may minimize this complaint.

Concerning the comparative agents, TCAs (particularly ones having strong muscarinic effect) were associated with the typical anticholinergic adverse effects such as dry mouth, blurred vision, dizziness, sweating, and constipation. Indeed, a number of the TCA comparative trials found anticholinergic side effects significantly more frequently among their subjects than among those individuals

Table 10. Adverse Effects: Fluvoxamine Versus Miscellaneous Tricyclics*

Study	Mean Dose	Side Effect Assessment(s)	Adverse Effects	Dropouts Due to Adverse Effects
Harris et al, 1991[28]	F = 115 mg AMI = 99 mg	Self-report	F = nausea, vomiting, headaches AMI = ACH,[a] nausea, somnolence	F = 5 AMI = 6
Remick et al, 1994[29]	F = 175 mg AMI = 135 mg	Adverse Events Form	F = insomnia, dry mouth, nausea AMI = ACH, fatigue	F = 3 AMI = 5
Mullin et al, 1988[30]	…	Self-report	F = nausea, vomiting, somnolence DOT = ACH,[a] dyspepsia	F = 9 DOT = 6
Rahman et al, 1991[31]	F = 157 mg DOT = 159 mg	Self-report	F = nausea, dizziness, headache, somnolence DOT = nausea, dizziness, dry mouth, asthenia	F = 2 DOT = 2
Nathan et al, 1990[32]	F = 203 mg DES = 206 mg	Self-report	F = nausea, vomiting DES = dry mouth,[a] nausea, vomiting	F = 0 DES = 2
Roth et al, 1990[33]	F = 218 mg DES = 224 mg	Nondirected interview	F = somnolence, fatigue, nausea DES = dry mouth,[a] insomnia, nausea	F > 3 DES > 6 P > 1

*Abbreviations: F = fluvoxamine; AMI = amitriptyline; DOT = dothiepin; DES = desipramine; P = placebo; ACH = anticholinergic side effects (i.e., dry mouth, blurred vision, sweating, constipation).
[a]Adverse effect(s) occurred significantly more often with tricyclic than fluvoxamine.

Table 11. Adverse Effects: Fluvoxamine Versus Miscellaneous Agents in Depression*

Study	Mean Dose	Side Effect Assessment(s)	Adverse Effects	Dropouts Due to Adverse Effects
Conti et al, 1988[37]	F = 273 mg	DOTES TWIS	F = nausea, vomiting, sleepiness P = dry mouth, constipation, syncope	F = 1 P = 1
Hamilton et al, 1989[39]	…	Self-report	F = gastrointestinal complaints FPX = headache, gastrointestinal complaints	F = 4 FPX = 0
Perez and Ashford, 1990[34]	F = 176 mg M = 100 mg	Self-report	F = nausea,[a] insomnia, dizziness, headache M = somnolence, insomnia	F = 6 M = 5
Phanjoo et al, 1991[35]	F = 170 mg M = 60 mg	Self-report	F = agitation, dizziness, ataxia, tension M = agitation, dizziness, somnolence, headache	F = 7 M = 4
deJonghe et al, 1991[38]	F = 210 mg MAP = 118 mg	Adverse Events Inventory	F = nausea MAP = constipation, dry mouth	F = 1 MAP = 1
Bougerol et al, 1992[36]	F = 121 mg MOC = 336 mg	Self-report	F = gastrointestinal complaints, insomnia MOC = insomnia, nausea	F = 9 MOC = 6
Nemeroff et al, 1995[40]	…	Self-report Sexual Symptoms Distress Index	F = ejaculatory abnormality 5%, libido decrease 6% S = ejaculatory abnormality 22%, libido decrease 19%	…

*Abbreviations: F = fluvoxamine; MOC = moclobemide; P = placebo; MAP = maprotiline; FPX = flupenthixol; M = mianserin; S = sertraline; DOTES = Dosage Record and Treatment Emergent Symptom Scale; TWIS = Treatment Emergent Symptom Write-In Scale.
[a]Adverse effect occurred significantly more often with fluvoxamine than mianserin.

receiving fluvoxamine. In general, fluvoxamine appeared to be better tolerated than the comparator agents, with equivalent or lower dropout rates due to adverse events.

Sexual dysfunction induced by the SSRIs is an increasingly acknowledged problem among clinicians. In the only head-to-head trial of fluvoxamine with another SSRI, fluvoxamine was shown to cause significantly fewer sexual dysfunctions than sertraline based on the Sexual Symptoms Distress Index. Indeed, sertraline produced more than three times the rate of ejaculatory abnormality and decreased libido compared with fluvoxamine.

Three of the four studies that determined plasma antidepressant levels also sought to demonstrate a relationship between plasma levels and adverse effects.[23,24,26] In all three cases, no significant relationship existed between plasma fluvoxamine or plasma clomipramine levels and adverse events. Thus, fluvoxamine is commonly associated with gastrointestinal complaints, particularly early on in treatment studies. Nausea appears the most common adverse event, which tends to diminish over the first couple of weeks of treatment and appears to be dose-related. In general, fluvoxamine appears to be well-tolerated with a relatively conservative number of dropouts due to adverse events.

SUMMARY

Although new to physicians in the United States, fluvoxamine is actually the oldest of the SSRIs utilized by clinicians worldwide. In fact, Saletu et al.[42] published the

first clinical experience with fluvoxamine in depressed patients in 1976. Since that initial report, 31 double-blind, placebo- and/or comparator drug-controlled studies evaluating the safety and efficacy of fluvoxamine in depression have been published worldwide. Fluvoxamine has been shown to be at least as good as, or superior to, placebo and the other antidepressants with which it has been compared. The drug appears to be safe and well-tolerated by patients in a range from 50 to 300 mg/day. The most common adverse effects are gastrointestinal, with nausea leading the list. Since this adverse effect appears transient and dose-related, initiating pharmacotherapy with lower doses and increasing over 1 to 2 weeks is likely to minimize gastrointestinal complaints. Because of its neurotransmitter specificity, fluvoxamine is considerably safer than many of the currently available antidepressants, including TCAs, monoamine oxidase inhibitors, and the second-generation heterocyclic drugs. Fluvoxamine also has an important advantage by having a broad spectrum of pharmacotherapeutic efficacy. Not only is it an effective antidepressant, but it has already demonstrated efficacy in obsessive-compulsive disorder, panic disorder, and social phobia (see Goodman et al., Ninan, and Tancer and Wade in this issue). It is likely that additional therapeutic indications will be forthcoming for this SSRI.

Drug names: amitriptyline (Elavil and others), clomipramine (Anafranil), desipramine (Norpramin and others), fluvoxamine (Luvox), imipramine (Tofranil and others), maprotiline (Ludiomil), sertraline (Zoloft).

REFERENCES

1. Whitaker-Azmitia PM. The Neuropharmacology of Serotonin: Current Concepts. Kalamazoo, Mich: Upjohn Company; 1992
2. Grimsley SR, Jann MW. Paroxetine, sertraline, and fluvoxamine: new selective serotonin reuptake inhibitors. Clinical Pharmacy 1992;11:930–957
3. Claassen V, Davies JE, Hertting G, et al. Fluvoxamine, a specific 5-hydroxytryptamine uptake inhibitor. Br J Pharmacol 1977;60:505–516
4. Fuller RW, Wong DT. Serotonin reuptake blockers in vitro and in vivo. J Clin Psychopharm 1987;7:36S–43S
5. Richelson E. Pharmacology of antidepressants: characteristics of the ideal drug. Mayo Clin Proc 1994;69:1069–1081
6. Lapierre YD, Rastogi RB, Singhal RL. Fluvoxamine influences serotonergic system in the brain: neurochemical evidence. Neuropsychobiology 1983;10:213–216
7. DeVane CL. Pharmacokinetics of the newer antidepressants: clinical relevance. Am J Med 1994;97(suppl 6A):13S–23S
8. Caccia S, Garattini S. Pharmacokinetic and pharmacodynamic significance of antidepressant drug metabolites. Pharmacol Res 1992;26:317–329
9. Roos JC. Cardiac effects of antidepressant drugs: a comparison of the tricyclic antidepressants and fluvoxamine. Br J Pharmacol 1983;15:439S–445S
10. Amin MM, Ananth JV, Coleman BS, et al. Fluvoxamine: antidepressant effects confirmed in a placebo-controlled international study. Clin Neuropharmacol 1984;7(suppl 1):580–581
11. Dominguez RA, Goldstein BJ, Jacobson AF, et al. A double-blind placebo-controlled study of fluvoxamine and imipramine in depression. J Clin Psychiatry 1985;46:84–87
12. Feighner JP, Boyer WF, Meredith CH, et al. A placebo-controlled inpatient comparison of fluvoxamine maleate and imipramine in major depression. Int Clin Psychopharmacol 1989;4:239–244
13. Itil TM, Shrivastava RK, Mukherjee S, et al. A double-blind placebo-controlled study of fluvoxamine and imipramine in outpatients with primary depression. Br J Clin Pharmacol 1983;15:433S–438S
14. Lapierre YD, Browne M, Horn E, et al. Treatment of major affective disorder with fluvoxamine. J Clin Psychiatry 1987;48:65–68
15. Lydiard RB, Laird LK, Morton WA, et al. Fluvoxamine, imipramine, and placebo in the treatment of depressed outpatients: effects on depression. Psychopharmacol Bull 1989;25:68–70
16. March JS, Kobak KA, Jefferson JW, et al. A double-blind, placebo-controlled trial of fluvoxamine versus imipramine in outpatients with major depression. J Clin Psychiatry 1990;51:200–202
17. Norton KRW, Sireling LI, Bhat AV, et al. A double-blind comparison of fluvoxamine, imipramine, and placebo in depressed patients. J Affect Disord 1984;7:297–308
18. Amore M, Bellini M, Berardi D, et al. Double-blind comparison of fluvoxamine and imipramine in depressed patients. Current Therapeutic Research 1989;46:815–820
19. Bramanti P, Ricci RM, Roncari R, et al. An Italian multicenter experience with fluvoxamine, a new antidepressant drug, versus imipramine. Current Therapeutic Research 1988;43:718–724
20. Gonella G, Baignoli G, Ecari U. Fluvoxamine and imipramine in the treatment of depressive patients: a double-blind controlled study. Curr Med Res Opin 1990;12:177–184
21. Guelfi JD, Dreyfus JF, Pichot P. A double-blind controlled clinical trial comparing fluvoxamine with imipramine. Br J Clin Pharmacol 1983;15:411S–417S
22. Guy G, Wilson WH, Ban TA, et al. A double-blind clinical trial of fluvoxamine and imipramine in patients with primary depression. Psychopharmacol Bull 1984;20:73–78
23. DeWilde JEM, Doogan DP. Fluvoxamine and chlorimipramine in endogenous depression. J Affect Disord 1982;4:249–259
24. DeWilde JE, Mertens C, Wakelin JS. Clinical trials of fluvoxamine vs chlorimipramine with single and three times daily dosing. Br J Clin Pharmacol 1983;15:427S–431S
25. Dick P, Ferrero E. Double-blind comparative study of the clinical efficacy of fluvoxamine and chlorimipramine. Br J Clin Pharmacol 1983;15:419S–425S
26. Klok CJ, Brouwer GJ, VanPraag HM, et al. Fluvoxamine and clomipramine in depressed patients. Acta Psychiatr Scand 1981;64:1–11
27. Ottevanger EA. Fluvoxamine and clomipramine in depressed hospitalized patients: results from a randomized, double-blind study. L'Encéphale 1995;21:317–321
28. Harris B, Szulecka TK, Anstee JA. Fluvoxamine versus amitriptyline in depressed hospital out-patients: a multicentre double-blind comparative trial. British Journal Clinical Research 1991;2:89–99
29. Remick RA, Reesal R, Oakander M, et al. Comparison of fluvoxamine and amitriptyline in depressed outpatients. Current Therapeutic Research 1994;55:243–250
30. Mullin JM, Pandita-Gunawardena VR, Whitehead AM. A double-blind comparison of fluvoxamine and dothiepin in the treatment of major affective disorder. Br J Clin Pract 1988;42:51–55
31. Rahman MK, Akhtar MJ, Sharma RR, et al. A double-blind, randomized comparison of fluvoxamine with dothiepin in the treatment of depression in elderly patients. Br J Clin Pract 1991;45:255–258
32. Nathan RS, Perel JM, Pollock BG, et al. The role of neuropharmacologic selectivity in antidepressant action: fluvoxamine versus desipramine. J Clin Psychiatry 1990;51:367–372
33. Roth D, Mattes J, Sheehan KH, et al. A double-blind comparison of fluvoxamine, desipramine, and placebo in outpatients with depression. Prog Neuropsychopharmacol Biol Psychiatry 1990;14:929–939
34. Perez A, Ashford JJ. A double-blind, randomized comparison of fluvoxamine with mianserin in depressive illness. Curr Med Res Opin 1990;12:234–241
35. Phanjoo AL, Wonnacott S, Hodgson A. Double-blind comparative multicentre study of fluvoxamine and mianserin in the treatment of major depressive episode in elderly people. Acta Psychiatr Scand 1991;83:476–479
36. Bougerol T, Uchida C, Gachoud JP, et al. Efficacy and tolerability of moclobemide compared to fluvoxamine in depressive disorder (DSM-III). Psychopharmacology (Berl) 1992;106:S102–S108
37. Conti L, Dell'Osso L, Re F, et al. Fluvoxamine maleate: double-blind clinical trial vs placebo in hospitalized depressed patients. Current Therapeutic Research 1988;43:468–480
38. deJonghe F, Swinkels J, Tuynman-Qua H. Randomized double-blind study of fluvoxamine and maprotiline in treatment of depression. Pharmacopsychiatry 1991;24:21–27
39. Hamilton BA, Jones PG, Hoda AN, et al. Flupenthixol and fluvoxamine in mild to moderate depression: a comparison in general practice. Pharmatherapeutica 1989;5:292–297

40. Nemeroff CB, Ninan PT, Ballenger JC, et al. Safety and tolerance of fluvoxamine versus sertraline in depressed outpatients. In: New Research Program and Abstracts of the 148th Annual Meeting of the American Psychiatric Association; May 20–25, 1995; Miami, Fla. Abstract NR 455:177
41. DeVane CL. Comparative safety and tolerability of selective serotonin reuptake inhibitors. Human Psychopharmacology 1995;10:S185–S193
42. Saletu B, Schjerve M, Grunberger J, et al. Fluvoxamine: a new serotonin reuptake inhibitor: first clinical and psychometric experience in depressed patients. Journal of Neural Transmission 1976;41:17–36