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Once-Weekly Fluoxetine

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Contents

Abstract

▲ The relatively long half-life of the selective serotonin reuptake inhibitor fluoxetine has allowed the development of a delayed-release (enteric-coated) formulation containing 90mg fluoxetine per capsule for once-weekly oral administration.

▲ The cumulative relapse rate in patients switched to once-weekly fluoxetine 90mg for 25 weeks (after responding to 13 weeks of fluoxetine 20 mg/day) was similar to that in patients continuing to receive fluoxetine 20 mg/day and significantly lower than seen in patients switched to placebo.

▲ The efficacy of the once-weekly formulation was also similar to that of the daily formulation in other assessment parameters (modified 17-item Hamilton Rating Scale for Depression, Clinical Global Impressions – Severity of Illness Scale).

▲ Patient compliance (measured using an electronically monitored tablet bottle) was maintained at 87.5% in evaluable patients receiving once-weekly fluoxetine 90mg for 12 weeks from a baseline of 85.4% after responding to 4 weeks of fluoxetine 20 mg/day; in contrast, compliance declined significantly (from 87.3% at baseline to 79.4%; $p < 0.001$) in patients continuing to receive 20 mg/day for 12 weeks.

▲ Once-weekly fluoxetine is well tolerated, with a tolerability profile similar to that of the immediate-release formulation.

Features and properties of once-weekly fluoxetine	
Indications	
Continuation treatment of major depressive disorder	
Mechanism of action	
Both fluoxetine and its metabolite norfluoxetine are selective serotonin reuptake inhibitors	Enhance serotonergic neurotransmission
Dosage and administration (from clinical trials)	
Dose	90mg
Route of administration	Oral
Frequency of administration	Once weekly, begun 7 days after the last dose of immediate-release fluoxetine
Pharmacokinetic profile	
Flux in steady-state plasma concentrations	Fluoxetine: 6.8-fold increase with 90 mg/week *vs* 20 mg/day Norfluoxetine: 2.4-fold increase with 90 mg/week *vs* 20 mg/day
Metabolism	Norfluoxetine formed by demethylation via cytochrome P450 enzymes during first-pass through liver
Excretion	Mainly from kidney after metabolism. Elimination half-lives of fluoxetine and norfluoxetine are 2-7 days and 4-16 days, respectively, with once-daily formulation
Adverse effects	
Most frequent	Nervousness, headache, asthenia, diarrhoea

In many patients, depression can become recurrent or chronic, with associated long-term social and functional impairment.[1] Prevention of this development, through adequate treatment of the initial episode and appropriate prophylactic therapy for a sufficient period of time (usually at least 4 to 6 months), is thus recommended.[2] Patients with depression who feel well on daily antidepressant medication may, however, be reluctant to continue taking the medication for sufficiently long. Reasons for stopping medication include adverse effects and fear of stigmatization,[3] and finding continued daily medication bothersome. While the efficacy of the immediate-release formulation of the selective serotonin reuptake inhibitor (SSRI) fluoxetine 20 to 80 mg/day is well established in both the short- and long-term treatment of depressive disorders,[4-10] the attractions of improving patient compliance where possible are obvious.

The relatively long elimination half-life of fluoxetine has allowed the development of a once-weekly oral formulation. The aim is to improve compliance in patients already responding to the immediate- release formulation, for the prevention of relapse or recurrence of symptoms with long-term administration. While early trials indicated potential for once-weekly administration of fluoxetine 60 mg/ week,[11] this review summarises the efficacy and tolerability of the once-weekly formulation containing fluoxetine 90 mg/capsule in the form of pellets with an enteric coating to delay the release of the drug.[12]

1. Pharmacodynamic Profile

Data on the specific pharmacodynamics of extended-release fluoxetine for once-weekly administration have not yet been published. An overview of previously published pharmacodynamic data on immediate-release fluoxetine is given below.

- Fluoxetine and its major metabolite norfluoxetine are both potent and selective inhibitors of neuronal reuptake of serotonin (presumed to be the basis of the antidepressant actions of fluoxetine), and have little effect on norepinephrine (noradrenaline) reuptake.[8]
- Fluoxetine is a racemic mixture and the *R*- and *S*-enantiomers, present in equal proportions, appear to have equal effects on serotonin reuptake.[12]
- Fluoxetine is less selective in its effects on serotonin reuptake than some other SSRIs such as citalopram and paroxetine.[8]
- Unlike tricyclic antidepressants, fluoxetine has little affinity for muscarinic, histaminergic and α_1-adrenergic receptors, thought to be responsible for anticholinergic, sedative and cardiovascular adverse effects.[8]
- Fluoxetine is associated with reductions in food intake and increased resting energy expenditure, which may result in weight loss.[8]
- In contrast with the tricyclic antidepressants, fluoxetine has no significant adverse clinical effects on cognitive and psychomotor abilities.[8]

2. Pharmacokinetic Profile

Absorption and Distribution

- The kinetics of fluoxetine are nonlinear (disproportionately increased plasma concentrations with increased doses).[13]
- At steady state, the mean peak plasma concentrations (C_{max}) of fluoxetine and norfluoxetine decreased by 19% and 30%, respectively, with the change from 20 mg/day to 90mg once weekly (see figure 1) in a randomised nonblind study in 19 study participants (not stated whether they were healthy volunteers or patients).[13] The mean minimum plasma concentrations of fluoxetine and norfluoxetine decreased by 76 and 47%, respectively, with the change in formulation.[13]
- Fluctuations between peak and trough concentrations of fluoxetine and norfluoxetine at steady state were 24 and 17%, respectively, with 20 mg/

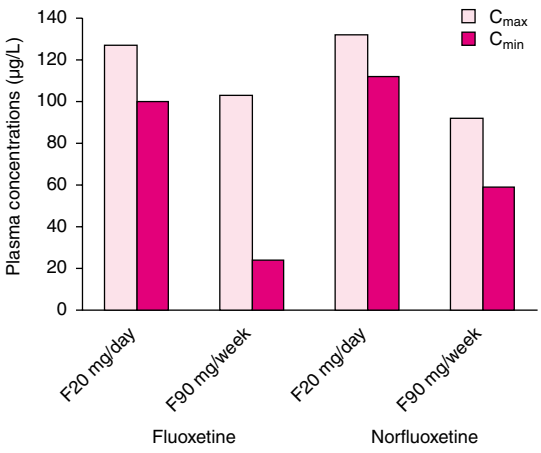

Fig. 1. Flux in steady-state plasma concentrations with once-weekly fluoxetine (F). Mean maximum (C_{max}) and minimum (C_{min}) plasma fluoxetine and norfluoxetine concentrations at steady state after fluoxetine 20mg given once daily and 90mg given once weekly to 19 study participants.[13]

day and 164% (6.8-fold increase over those with 20 mg/day) and 43% (2.5-fold increase), respectively, with 90 mg/week.[13]

• The pellets containing fluoxetine in the once-weekly formulation are designed to extend the time before dissolution so as to reach a segment of the gastrointestinal tract where the pH is >5.5.[12] Thus, although the 90mg enteric-coated formulation is bioequivalent (equivalent rate and extent of absorption) to a 90mg dose of immediate-release fluoxetine,[13] the time to C_{max} (t_{max}) for the extended-release formulation is 1 to 2 hours longer than that for the immediate-release formulation (which is 6 to 8 hours).[12]

• In patients changing from a dosage of 20 mg/day to 90 mg/week, the area under the plasma concentration-time curve during a dosage interval at steady state decreased by 54% for fluoxetine and by 38% for norfluoxetine.[13]

• The timing of the transition from once-daily to once-weekly administration may be important. After transition to the once-weekly formulation on the next day after the last daily dose, peak concentrations were 1.7-fold higher than those seen with the daily dosage; however, when the first weekly dose was given one week after the last daily dose, peak concentrations were similar (after an initial drop before the dose).[12]

• Coadministration of the immediate-release formulation with food increases t_{max} by 3 to 5 hours without altering the extent of absorption or C_{max}.[8] Similarly, t_{max} for the enteric-coated pellet formulation is increased by 1 to 2 hours when it is given with food.[13] However, because the onset of absorption is not critical when fluoxetine is administered once weekly, the extended-release formulation can be given either with or without food.[12]

• Steady-state plasma concentrations are reached after 3 to 4 weeks of immediate-release fluoxetine administration.[4,13]

• Fluoxetine is highly bound to human serum proteins.[12]

Metabolism and Elimination

• Fluoxetine undergoes extensive first-pass metabolism in the liver; the primary metabolite, norfluoxetine, is formed by demethylation via cytochrome P450 (CYP) enzymes, primarily CYP2D6.[8,12]

• After metabolism, the main route of elimination is excretion by the kidney.[4]

• The elimination half-life ($t_{½β}$) of the immediate-release formulation after multiple doses is 2 to 7 days for fluoxetine and 4 to 16 days for norfluoxetine.[8,12]

• The *S*-enantiomer of fluoxetine is eliminated more slowly than the *R*-enantiomer.[12]

• Liver impairment prolongs the $t_{½β}$ of immediate-release fluoxetine, but renal impairment appears not to alter the pharmacokinetic profile of fluoxetine.[4,12]

3. Therapeutic Efficacy

The efficacy of once-weekly oral enteric-coated fluoxetine 90mg in the maintenance treatment of depression has been investigated in one fully published randomised, double-blind, placebo-controlled, multicentre trial[3] and a noncomparative study available as data on file from Eli Lilly and Company.[14]

Randomised Double-Blind Trial

- The randomised, double-blind, placebo-controlled, multicentre trial[3] involved 501 responders from 932 adult outpatients with nonpsychotic major depression and a current episode duration of ≥4 weeks and at least moderate severity who had received 13 weeks' nonblind treatment with immediate-release fluoxetine 20 mg/day in the US. The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and the Structured Clinical Interview for DSM-IV, patient version, (SCID-P) [i.e. modified 17-item Hamilton Rating Scale for Depression (HDRS-17) score ≥18; Clinical Global Impressions-Severity of Illness scale (CGI-S) score ≥4] were used for initial assessment. Response in the nonblind phase was defined as no major depressive disorder (DSM-IV), an HDRS-17 score ≤9 and a CGI-S score ≤2 on two consecutive visits. Patients with any history of a psychotic disorder or a recent history of a bipolar, substance abuse or anxiety disorder were excluded.

- The randomised patients received fluoxetine 90 mg/week (n = 190), fluoxetine 20 mg/day (n = 189) or placebo (n = 122) for 25 weeks. The primary efficacy assessment was the incidence of relapse, which was defined as meeting the criteria for major depressive episode (SCID-P) without the duration restriction, and an increase in CGI-S score of ≥2 versus the pre-randomisation score. Secondary assessments included the HDRS-17 and HDRS-28 subscales and the CGI-S. Efficacy was assessed using the last observation carried forward. Hypnotics were not allowed during the double-blind phase.

- Log-rank analysis indicated that relapse was statistically significantly less likely to occur in either group receiving fluoxetine than in placebo recipients (90mg once weekly, $p = 0.007$; 20mg once daily, $p < 0.001$). The cumulative 25-week relapse rate was 37% in patients receiving 90 mg/week, 26% in those receiving 20 mg/day and 50% in the placebo group. More patients relapsed in the once-weekly fluoxetine group than in those receiving daily fluoxetine, but the difference was not statistically significant.[3]

- Changes from baseline in most secondary efficacy endpoints also indicated statistically significant differences between fluoxetine and placebo recipients. For fluoxetine 90 mg/week, fluoxetine 20 mg/day and placebo recipients, mean changes in score from baseline (p-value *vs* placebo) were as follows: CGI-S 1.0 ($p = 0.01$), 0.9 ($p = 0.001$), 1.4; HDRS-17 6.6 ($p < 0.05$), 6.4 ($p < 0.05$), 8.6; HDRS-28 core (items 1, 2, 3, 7, 8) 3.1 ($p < 0.05$), 2.7 ($p < 0.01$), 4.1; HDRS-28 subscale 5 (items 1, 2, 3, 7, 8, 14, 15, 16, 17) 3.6 ($p < 0.05$), 3.3 ($p < 0.01$), 4.8; anxiety subscale 1.8 ($p < 0.05$), 1.7 ($p < 0.01$), 2.4; retardation subscale 2.7 (not significant), 2.3 ($p < 0.01$), 3.4; depressed mood 1.1 ($p < 0.05$), 0.8 ($p < 0.001$), 1.4. There were no significant differences between the fluoxetine groups in any of these parameters. Changes in sleep parameters from the HDRS-28 subscale were similar for all groups.[3]

- Treatment was continued for significantly longer in patients receiving fluoxetine 90 mg/week (105.4 days, $p = 0.009$) or 20 mg/day (109.0 days, $p = 0.003$) than in placebo recipients (86.2 days).[3]

- Patients with high baseline anxiety (an HDRS anxiety/somatisation factor score >7; about one-third of the original cohort) were investigated in a subanalysis of this trial, reported as an abstract.[15] Relapse rates (values not reported) for patients re-

ceiving fluoxetine 90mg once weekly (n = 52) or 20mg once daily (n = 57) were significantly lower (p = 0.006 and p = 0.004, respectively) than those for the placebo group (n = 30), with no significant difference between the fluoxetine groups.[15]

Noncomparative Trial

• In a multicentre, noncomparative study, patients with nonpsychotic major depressive disorder (DSM-IV) responsive to (HDRS-17 score ≤10, CGI-S score ≤2) citalopram 20 to 40 mg/day (n = 83), paroxetine 20 mg/day (n = 77) or sertraline 50 to 100 mg/day (n = 86) over a period of 6 to 52 weeks were switched to once-weekly fluoxetine 90mg for 12 weeks.[14] Patients were excluded if previously unresponsive to fluoxetine or if they had a history of psychotic disorder, bipolar disorder or substance abuse.

• Relapse (HDRS-17 score ≥18, CGI-S score increased from baseline by ≥2 for two consecutive visits) occurred in one, two and one patients previously receiving citalopram, paroxetine and sertraline, respectively (total 1.6%).[14] Once-weekly fluoxetine 90mg was considered by investigators to lack efficacy in a further nine, three and seven patients, respectively (cumulative total for relapse/lack of efficacy 9.3%). There were no significant differences in efficacy among patients from the three previous therapy groups according to HDRS-17 and CGI-S scores, and these scores did not increase significantly from baseline during therapy with fluoxetine.[14]

• Quality of life, measured using the 36-item short form health survey, improved significantly in all three groups in areas of general mental health, role limitations due to emotional problems and vitality. There were no statistically significant negative changes in quality of life on switching to once-weekly fluoxetine.[14]

4. Patient Compliance

Compliance to fluoxetine 90mg once weekly (n = 56) was compared with that to fluoxetine 20 mg/day (n = 53) over a period of 12 weeks in a randomised, nonblind, multicentre, intent-to-treat trial performed in the United Kingdom.[16] Patients with a nonpsychotic major depressive episode (DSM-IV) responsive to fluoxetine 20 mg/day (Montgomery-Åsberg Depression Rating Scale score ≤12 and CGI-S score ≤2) who had had at least one other medically treated episode previously were enrolled into the initial 4-week nonblind period during which they received fluoxetine 20 mg/day to establish baseline compliance, before randomisation.

Compliance was assessed using an electronic drug exposure monitor in the container cap which measured the time and date of opening and closing the cap. All patients received oral instructions on when and how often to take the medication and on the importance of taking it as prescribed. Patients randomised to once-weekly fluoxetine also received written instructions on when and how often to take the capsules, and stickers to remind themselves.

The primary endpoint was the percentage of compliant doses, calculated as the number of adherent doses divided by the number of prescribed doses multiplied by 100. An adherent dose was taken within 25% of the dosage interval, i.e. 1 day ± 6 hours after the previous dose for once-daily fluoxetine recipients, and 7 days ± 42 hours after the previous dose for once-weekly fluoxetine recipients.

• Six patients receiving fluoxetine 90 mg/week discontinued treatment for lack of efficacy (not defined) and one discontinued because of relapse (not defined), versus two recipients of fluoxetine 20 mg/day discontinuing for lack of efficacy (no statistically significant difference between groups).[16]

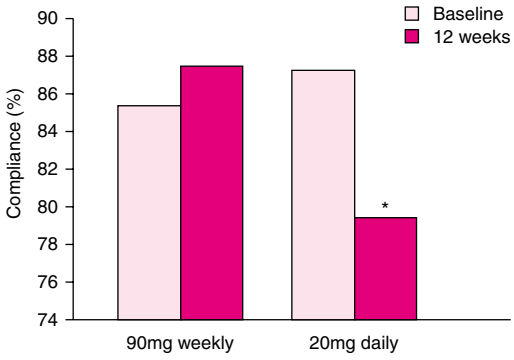

Fig. 2. Compliance with once-weekly fluoxetine in patients with depression. Evaluable patients with a nonpsychotic major depressive episode responsive to fluoxetine 20 mg/day received fluoxetine 90mg once weekly (n = 55) or fluoxetine 20mg daily (n = 53) for 12 weeks in a randomised nonblind multicentre study.[16] Compliance was measured as the percentage of doses taken within 25% of the dosage interval, using an electronic drug exposure unit.
* $p < 0.001$ *vs* baseline.

• Baseline compliance for all 109 randomised patients was 86.3%. Mean compliance over 12 weeks was 85.9% for patients receiving fluoxetine 90 mg/week and 79.4% for those receiving fluoxetine 20 mg/day (a trend in favour of once-weekly treatment) in the intent-to-treat analysis.[16]

• An assessment of change in compliance before and after randomisation for 108 evaluable patients (see figure 2) indicated that, during the 12-week treatment period, compliance increased slightly in patients receiving once-weekly treatment (n = 55) from 85.4% at baseline to 87.5%. In patients continuing to receive 20 mg/day (n = 53), compliance decreased significantly from 87.3% at baseline to 79.4% ($p < 0.001$ *vs* baseline).[16]

5. Tolerability

• The tolerability profile of the once-weekly fluoxetine formulation is similar to that of the immediate-release formulation.[3]

• Treatment-emergent adverse events, recorded after nonprobing inquiry during the double-blind trial outlined in section 3,[3] occurred in 73.9% of randomised patients. The most frequent events were nervousness, headache, asthenia and diarrhoea in the 90mg once-weekly group; headache, rhinitis, somnolence and asthenia in the 20 mg/day group; and nervousness, headache and somnolence in the placebo group (see figure 3).

• Treatment was discontinued because of adverse events in 4.2, 2.1 and 1.6% of the fluoxetine 90 mg/week, fluoxetine 20 mg/day and placebo groups, respectively (no significant differences).[3]

• The incidence of abnormal thinking (8.4 *vs* 1.6%; $p = 0.004$) and nervousness (13.7 *vs* 6.3%; $p = 0.025$) was significantly higher among recipients of once-weekly fluoxetine 90mg than among those receiving daily fluoxetine 20mg, peaking during the first 4 weeks of treatment and declining thereafter. There were no significant differences in the incidences of these parameters between fluoxetine 90 mg/week and placebo recipients, however.[3]

• Diarrhoea was reported significantly more often by recipients of fluoxetine 90 mg/week than by placebo recipients ($p = 0.042$). There was no significant difference in this parameter between the fluoxetine 20 mg/day and placebo groups or between the two fluoxetine groups.[3]

• In addition to the spontaneously reported adverse events, supplemental data were solicited using the Association for Methodology of Documentation in Psychiatry – Module 5 questionnaire. These data indicated that the incidence of gastric discomfort was significantly lower in the fluoxetine 90 mg/week group (6.3%) than in those receiving 20 mg/day (15.3%; $p = 0.005$), and was similar to that in the placebo group (10.7%).[3]

• There were no significant differences among the groups receiving once-weekly or daily fluoxetine or placebo in vital signs or laboratory parameters in the randomised double-blind trial.[3]

• Sexual dysfunction was investigated in a prospective assessment, reported as an abstract,[17] of

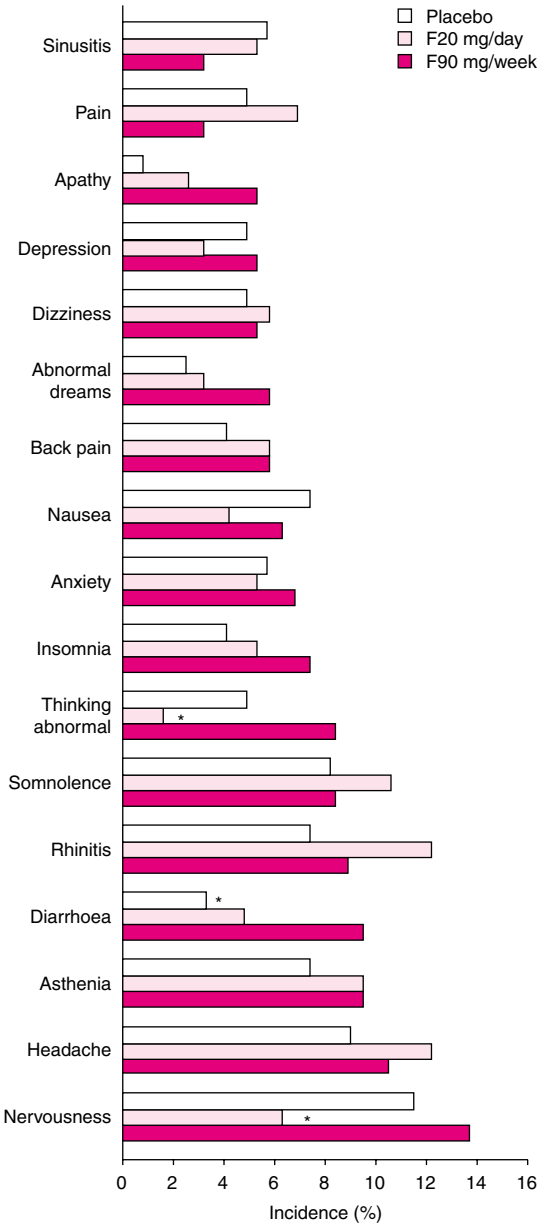

Fig. 3. Treatment-emergent adverse events with once-weekly oral administration of extended-release fluoxetine (F) 90mg. Incidence of adverse events spontaneously reported by patients with depression responding to immediate-release fluoxetine 20 mg/day during continuation treatment with extended-release fluoxetine 90 mg/week (n = 190), immediate-release fluoxetine 20 mg/day (n = 189) or placebo (n = 122) for 25 weeks. * $p < 0.05$ *vs* 90 mg/week.[3]

patients in the double-blind trial outlined in section 3.[3] 51.6% of women and 40.6% of men reported improvement of overall sexual function during 13 weeks of nonblind fluoxetine 20 mg/day while 13.4 and 17.4%, respectively, reported worsening during this period.[17] There were no statistically significant differences in change in sexual function among recipients of fluoxetine 20 mg/day, fluoxetine 90 mg/week or placebo during the 25-week continuation phase.[17] Worsening sexual function was strongly associated with worsening depression.

- Monoamine oxidase inhibitors or thioridazine should not be administered in combination with or within 5 weeks of discontinuation of fluoxetine.[12]

6. Once-Weekly Fluoxetine: Current Status

Once-weekly fluoxetine 90mg has been approved for use in several countries worldwide, including the US, for the continuation treatment phase of major depressive disorder in adult patients. It is indicated for the prevention of relapse or recurrence of symptoms in patients whose depressive symptoms have stabilised with once-daily medication.[18]

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