# Once weekly fluoxetine, tolerability and safety according to use patterns in the psychiatric clinical practice

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***Fluoxetina semanal. Tolerabilidad y seguridad según patrones de uso en la práctica clínica***

**Summary**

Introduction. *Treatment with selective serotonin reuptake inhibitors (SSRI) has become generalized in all the medical setting although its efficacy and good tolerability may be affected by long term non-compliance. Once weekly fluoxetine could improve compliance due to the comfort of its use. The objective is to evaluate the safety, tolerability and efficacy of once weekly fluoxetine (90 mg) in a sample of out-patients, following naturalistic criteria in the usual clinical practice.*

Method. *A total of 46 patients (age: 41.89 ± 1.85) who received once weekly fluoxetine for at least 3 months (mean time: 135.24 days) were analyzed retrospectively. Clinical Global Impression of Severity (CGI-S) at the onset and end of the period evaluated, presence of adverse events, drop-out index and impression of patient's satisfaction with the treatment and use pattern were used.*

Results. *The mean of the final CGI-S was 2.09, compared with the onset 3.09 (p < 0.02), indicating significant improvement in the efficacy with once weekly fluoxetine. The most frequent adverse effects were: anxiety (10.87 %), headache (8.69 %) and restlessness (8.69 %) related with once weekly fluoxetine. Compliance was very high at the onset (99 %) and at the end (96 %). Ten patients dropped-out of the treatment (27.74 %), 6 due to appearance of undesirable effects (anxiety, headache and insomnia), three due to voluntary wish and only one due to lack of efficacy. The CGI of satisfaction of clinical global efficacy on the final visit was 1.43 (satisfied-very satisfied) and the CGI of satisfaction for the treatment pattern was 1.17 (very satisfied).*

Conclusion. *Change to once weekly fluoxetine generally improves satisfaction of treatment efficacy and its use pattern, although some patients return to the initial regime after adverse effects appear.*

***Key words:*** *Once weekly fluoxetine. Depression. Tolerability. Safety. Antidepressant. Use pattern.*

**Resumen**

Introducción. *El tratamiento con inhibidores selectivos de la recaptación de serotonina (ISRS) se ha gneralizado a todo el ámbito médico, si bien su eficacia y buena tolerabilidad pueden verse comprometidas por el incumplimiento a largo plazo. La fluoxetina semanal podría mejorar el cumplimento debido a su comodidad de uso. El objetivo es evaluar la seguridad, tolerabilidad y eficiencia de la fluoxetina semanal (90 mg) en una muestra de pacientes ambulatorios siguiendo criterios naturalísticos en la práctica clínica habitual.*

Método. *Se analizaron retrospectivamente 46 pacientes (edad: 41,89 ± 1,85) que recibieron fluoxetina semanal al menos durante 3 meses (tiempo medio: 135,24 días). Se utilizó la Escala de Impresión Clínica Global de Severidad (ICG-S) al inicio y al final del período evaluado, la presencia de acontecimientos adversos, el índice de abandonos y la impresión de satisfacción del paciente con el tratamiento y con el patrón de uso.*

Resultados. *La media de la ICG-S final fue de 2,09 comparada con la inicial 3,09 (p < 0,02), indicando mejoría significativa en la eficacia con fluoxetina semanal. Los efectos adversos más frecuentes fueron: ansiedad (10,87 %), cefalea (8,69 %) e inquietud (8,69 %) relacionados con fluoxetina semanal. El cumplimiento fue muy alto al inicio (99 %) y al final (96 %). Diez pacientes abandonaron el tratamiento (27,74 %), 6 por aparición de efectos indeseables (ansiedad, cefalea e insomnio), tres por deseo voluntario y sólo uno por falta de eficacia. La ICG de satisfacción por la eficacia clínica global en visita final fue de 1,43 (satisfecho-muy satisfecho) y la ICG de satisfacción por el patrón de tratamiento fue de 1,17 (muy satisfecho).*

Conclusión. *El cambio a fluoxetina semanal por lo general mejora la satisfacción de la eficacia del tratamiento y del patrón de uso del mismo, si bien algunos pacientes regresan a la pauta inicial tras la aparición de efectos adversos.*

***Palabras clave:*** *Fluoxetina semanal. Depresión. Tolerabilidad. Seguridad. Antidepresivos. Patrón de uso.*

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## INTRODUCTION

Compliance problems and lack of adherence to antidepressive treatment are common in the depressive disorders population. The evidence that maintenance of

antidepressive treatment during 6 months reduces relapse risk by at least 50% is presently accepted[1]. In spite of this, multiple naturalistic studies show that the average antidepressive treatment duration is inferior to this time and that the drop-out rates are high, especially in the primary care setting[2]. Different descriptive epidemiological studies verify that approximately one third of the patients do not complete their treatment[3] and drop-out rates of 28% during the first month and 44% in the first three months are calculated[4].

Among the causes that explain this antidepressive treatment drop-out are: *a)* adverse effects associated to treatment; *b)* difficulty to maintain the dosage administration schedule as clinical improvement occurs, especially in the longer term maintenance treatments, and *c)*, subjective sensation of taking too much medication. Thus, the need to develop new antidepressive formulas that make it possible to reduce these disadvantages and improve patient satisfaction with the drug and dose pattern is suggested.

Considering the relative prolonged high life of fluoxetine, an extended release formulation has been developed (fluoxetine, 90 mg per capsule) that allows for the administration of antidepressive treatment in a single weekly dose. Its greater administration comfort may constitute a useful factor to assure better long term compliance and adherence to antidepressive treatment, which would place once weekly fluoxetine as a feasible and advantageous alternative in maintenance treatment for depression.

Different studies have demonstrated similar antidepressive efficacy in patients under treatment with daily fluoxetine and once weekly fluoxetine[5,6]. Some of them also seem to demonstrate a better profile in treatment compliance, associated, in the beginning, to greater administration comfort in a once weekly dose and in the psychological perception by the patient of less treatment load[6,7]. However, it is very important that the efficacy and comfort of administration are associated to a good safety and tolerability profile of the drug that contributes to treatment compliance and adherence. As the use of once weekly fluoxetine increases, data begin to appear that answer the questions on the safety and tolerability of this new formulation.

Up to now, the limited safety and tolerability data have come from clinical trials, there being no data published in the common clinical practice. Schmidt et al.[8] performed a double blind, randomized and placebo controlled study to determine safety and efficacy of the enteric coated formulation of 90 mg fluoxetine in patients diagnosed of Major Depressive Disorder, according to the DSM-IV criteria. They established three groups: one treatment group with 90 mg once weekly fluoxetine, one treatment group with 20 mg fluoxetine, daily administration and a placebo group. Comparison of efficacy between them demonstrated a significantly lower relapse percentage in the two groups treated with fluoxetine, no significant differences being found between the latter two. Safety was measured by the incidence of adverse events, drop-outs for this reason and changes in vital signs and laboratory clinical data. Fluoxetine 90 mg in week administration was generally well tolerated by the patients. In this study, no significant differences were found in regards to safety and tolerability between the once weekly and daily administration of fluoxetine 20 mg.

Miner et al.[9] carried out an open label study in out-patients diagnosed of major depressive disorder without psychotic symptoms, according to DSM-IV criteria, who had received previous treatment with citalopram (20-40 mg/day), paroxetine (20 mg/day) or sertraline (50-100 mg/day) with positive response to it, who were changed to once weekly fluoxetine 90 mg. Most of the patients (94.5%) found the once weekly dosage more satisfactory than the daily one in regards to use pattern. A total of 82% of the patients found that the once weekly regime better adjusted to heir life study than the daily dosage.

Besides the indication in treatment of depression, fluoxetine is used in other indications, such as bulimia nervosa or obsessive-compulsive disorder (OCD), besides other still unapproved uses, however with some signs of efficacy as personality disorders and impulsivity spectrum[10,11]. Satisfaction, and consequently, better degree of compliance in this diseases are also extremely important, as is tolerability and safety of the doses that the clinician uses in them.

## STUDY OBJECTIVES

This retrospective pilot study aims to provide a first approach on the practical clinical use of once weekly fluoxetine in out-patient psychiatric visits. The main objective of the study is to determine tolerability and safety of once weekly fluoxetine in the common clinical practice.

As secondary objectives, the assessment of once weekly fluoxetine effectiveness, assessment of subject compliance grade and the patient's satisfaction grade with the once weekly fluoxetine formulation were established.

## MATERIAL AND METHOD

### Study design

An observational, multicenter, naturalistic and retrospective study was performed in patients who had initiated treatment with once weekly fluoxetine regardless of the diagnosis assigned. Given the practical and retrospective character of the study, it was considered to be better to include patients independently of the diagnosis for which fluoxetine had been prescribed.

Data collection was performed retrospectively from the existing data in the clinical records, from the time the patient had initiated treatment with once weekly fluoxetine. Those patients for whom there was at least one clinical evaluation in a visit after the change to once weekly fluoxetine were included, as long as they had taken the treatment for at least 3 months.

### Patient population

A total of 46 patients over 18 years of age who had received treatment with once weekly fluoxetine for at least 3 months prior to the data collection and who had changed from a previous antidepressive treatment to once weekly fluoxetine, including the change from daily fluoxetine, were selected.

Neither the diagnostic criteria determined nor the disorder seriousness constituted exclusion criteria. Only those patients who suffered uncontrolled chronic or serious physical diseases that could affect the subsequent data analysis on drug tolerability were excluded.

### Evaluation

Based on the clinical records of each patients, the following data were retrospectively collected: *a)* sociodemographic data; *b)* diagnosis and seriousness according to the seven item Clinical Global Impression of Severity Scale (CGI-S); *c)* antidepressive medication received by the patient in previous months (up to 1 year) to the change to once weekly fluoxetine; *d)* treatment dose pattern with once weekly fluoxetine, and *e)* effectiveness, tolerability and safety data of once weekly fluoxetine.

The main measurement variable of efficiency used has been the score on the CGI-S scale. The safety variables used have been report of adverse effects, intensity and frequency of appearance and the complementary medical test results performed during the treatment with once weekly fluoxetine that could be related with the treatment use.

In relationship with the compliance and adherence variables, the compliance grade in each visit (in % over the total of treatment weeks in each visit) and the number of drop-outs, in relationship with its associated cause were evaluated.

In regards to the satisfaction variables, the subjective grade of satisfaction of the patient regarding treatment and the administration regime was measured, according to the following score scale in both items: 1: very satisfied; 2: satisfied; 3: unsatisfied, y 4: very unsatisfied.

### Statistical analysis

The main objective of the study is the analysis of tolerability and safety of once weekly fluoxetine in the common clinical practice. To do so, a descriptive analysis was carried out of the type, intensity and frequency of appearance of treatment associated adverse events and of the results of the laboratory tests or abnormal tests derived from the patient's usual follow-up.

The analysis of efficiency and compliance was performed with the descriptive analysis of the mean and the Wilcoxon sign-rank test for inferential analysis.

The rate of drop-outs associated to its cause was also analyzed by descriptive analysis of frequencies. The possible existence of relationship between the appearance of adverse effects and treatment drop-out was evaluated with contingence tables and the Chi squared test. For estimation of risk of drop-out associated to the appearance or not of adverse effects, the Mantel-Haenszel odds ratio of common advantages was used.

For the evaluation of the satisfaction grade, a descriptive analysis of the patient's satisfaction mean regarding the perceived treatment efficacy and the administration by frequencies analysis were carried out. It was also analyzed if there was a relationship between the patient's satisfaction regarding perceived treatment efficacy and satisfaction regarding administration regime by contingence tables and Kendall's and Spearman's symmetric correlation analysis as well as the possible relationship between satisfaction grade and treatment drop-out with the Mann Whitney test.

Finally, a descriptive analysis of the remaining variables collected was carried out: sociodemographic variables, diagnosis, mean treatment time, once weekly fluoxetine dose pattern and concomitant medication.

## RESULTS

### Patients

A total of 46 patients were included in the study. The mean age was 41.89 ± 1.85 years, 26% men and 74% women (table 1). Although the age range is short, the information coincides with other populations in which the group of young women under treatment with fluoxetine as most frequent use pattern predominated.

Based on the ICD-10 diagnostic criteria, the most frequent diagnostic entity was recurrent depressive disorder (F33: 37 %), followed by depressive episode (F32: 34.8 %), persistent mood disorders: cyclothimia/dysthymia (F34: 10.9 %), eating behavior disorder (F50: 6.5 %), anxiety disorder, panic disorder, generalized anxiety disorder and mixed anxiety and depressive disorder (F41:4.3 %; F42: 4.3 %, and F31: 2.2 %, respectively).

**TABLE 1. Demographic characteristics of the sample**

| *Demographic variable* | *n* | *%* |
|---|---|---|
| Patients | 46 | — |
| Gender | | |
| Men | 12 | 26.1 |
| Women | 34 | 73.9 |
| | *Mean* | *SD* |
| Age | | |
| Total population | 41.89 | 1.85 |
| Men | 42.92 | 3.29 |
| Women | 41.53 | 2.25 |

SD: standard deviation.

## Treatment pattern

The mean days of treatment per patient in the period analyzed were 135.24 days (SD: 15.88). The dose pattern on the initial visit was fluoxetine 90 mg/week (1 capsule weekly) in 37 patients (80.4%), 180 mg/week in eight patients (17.4%) and 270 mg/week in one patient (2.2%). The dose pattern on the final visit was fluoxetine 90 mg/week in 35 patients (76.1%), 180 mg/week in seven patients (15.2%) and 270 mg/week in four patients (8.7%) (fig. 1).

In regards to other treatments, the number of patients with concomitant medication at some time of the treatment was 31, eigth of whom underwent reduction of this concomitant medication during the treatment period. It was increased in two and the rest (20) continued the same.

## Efficiency analysis

In relationship with the seriousness of the disorder, the mean of the CGI-S in the initial visit was 3.09 (SD: 0.173) and in the final visit 2.09 (SD: 0.137; $p = 0.02$), indicating significant improvement produced during the study associated to once weekly fluoxetine in the global sample.

## Safety and tolerability

### *Adverse events*

Thirteen patients (28.3%) reported at least one adverse effect during all the visits. The adverse effects reported, in descending order of presentation frequency were: anxiety (10.87 %), headache (8.69 %), restlessness (8.69 %), insomnia (6.52%), dyspepsia (4.35%), nausea (4.35%), regurgitation (2.17%), diarrhea (2.17%), bloating (2.17%) and increased sweating (2.17 %) (table 3). No serious event was reported during the treatment. No significant newly appearing abnormality of vital signs appeared. No complementary medical tests were required in any of the patients after treatment onset with once weekly fluoxetine 90 mg. The adverse effects mentioned are of new appearance, not having been reported with the treatments prior to the once weekly fluoxetine.

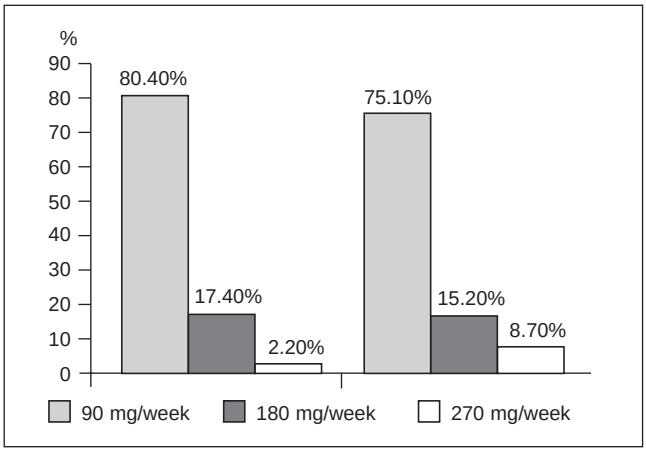


**Figure 1.** Once weekly fluoxetine dose pattern in initial and final visits.

**TABLE 2. Distribution by diagnosis**

| | *n* | % |
|---|---|---|
| Diagnosis by ICD-10 (n, %) | | |
| F.33 | 17 | 37.0 |
| F.32 | 16 | 34.8 |
| F.34 | 5 | 10.9 |
| F.50 | 3 | 6.5 |
| F.41 | 2 | 4.3 |
| F.42 | 2 | 4.3 |
| F.31 | 1 | 2.2 |

## Compliance and adherence

### *Compliance*

Compliance on the first visit was 99.24% and on the final one 96.09%. The analysis of the compliance tendency during treatment with Wilcoxon sign rank test indicates that there are no significant differences in the compliance variable between the initial and final visit, the high adherence values to the initial treatment being maintained.

Discontinuation of treatment

Ten of the 46 patients (27.74%) dropped out of the treatment with once weekly fluoxetine, two men and eigth women. Six of them did so due to appearance of undesirable effects (13.04 %), three due to voluntary desire of the patient (6.52) and one due to lack of efficacy (2.17%).

The appearance of adverse effects constituted the most frequent reason for treatment drop-out with once

**TABLE 3. Adverse effects. Presentation frequency**

| | *n* | % |
|---|---|---|
| Anxiety | 5 | 10.87 |
| Headache | 4 | 8.69 |
| Restlessness | 4 | 8.69 |
| Insomnia | 3 | 6.52 |
| Dyspepsia | 2 | 4.35 |
| Nausea | 2 | 4.35 |
| Regurgitation | 1 | 2.17 |
| Diarrhea | 1 | 2.17 |
| Bloating | 1 | 2.17 |
| Increase in sweating | 1 | 2.17 |

weekly fluoxetine. The most reported adverse effect in the group of 10 patients who dropped out of the treatment was anxiety/restlessness (seven cases), headache (two), dyspepsia (two), insomnia (two) and headache and bloating in one case. Regurgitation and increase in sweating were not reported by any of the individuals who abandoned the treatment.

The relationship between treatment drop-out and appearance of adverse effects by Pearson's chi squared test shows statistically significant results ($p = 0.012$), verifying the existence of this relationship between the appearance of undesirable effects and the termination of treatment with once weekly fluoxetine. Analysis by contingence tables between the variables appearance of adverse effects/treatment drop-out show that the drop-out rate was 456.15 % in the population who presented any adverse effect, while it was 12.12 % in those who did not present them.

The estimation of the risk of drop-out when adverse events occur is 6.214 times greater than when these effects do not occur, according to the Mantel-Haenszel odds ratio of common advantages (p = 0.018). All the patients who abandoned once weekly fluoxetine returned to the daily fluoxetine regime without undergoing subsequent clinical deteriorations and the adverse effects reported disappeared.

**TABLE 4. Summary of statistical analysis results**

| | | | |
|---|---|---|---|
| **CGI-S** | | | |
| Initial visit (mean ± SD) | 3.09 ± 0.173 | | |
| Final visit (mean ± SD) | 2.09 ± 0.137 | | |
| Significance (p) | p = 0.02 | | |
| **Compliance** | | | |
| Initial visit (%) | 99.24 | | |
| Final visit (%) | 96.09 | | |
| Wilcoxon rank test | p = 0.175 | | |
| **Satisfaction**[1] | | | |
| Satisfaction due to improvement (mean ± SD) | 1.43 ± 0.81 | | |
| Satisfaction on dose pattern (mean ± SD) | 1.17 ± 0.44 | | |
| *Treatment drop-out* | *N* | *%* | p |
| Total | 10 | 27.74 | |
| Cause | | | |
| Adverse effects[2] | 6 | 13.04 | 0.012 |
| Voluntary desire | 3 | 6.52 | |
| Lack of efficacy | 1 | 2.17 | |

[1] Satisfaction scale in both items: 1) very satisfied; 2) satisfied; 3) unsatisfied; 4) very unsatisfied. [2] Relationship between treatment drop-out and appearance of side effects.

### Analysis of patient satisfaction

*Satisfaction due to improvement*

Mean satisfaction due to subjective improvement in the final visit was 1.43 (SD: 0.81), which places it in the average between satisfied and very satisfied. It was observed that the sum of satisfied and very satisfied patients in the first visit accounted for 93.5 %, and, in the same group in the final visit, it accounted for 89.1 %. Thus, it could be stated that satisfaction due to improvement was maintained during all the treatment process.

### Satisfaction about treatment pattern

Regarding satisfaction about treatment pattern, the mean in the final visit was 1.17 (SD: 0.44), which places it very close to the value (1) that corresponds to very satisfied. The sum of satisfied and very satisfied patients in the final visit is 97.8 %, which places us in a very high level of satisfaction for the treatment pattern, slightly superior to that of satisfaction for subjective improvement.

A summary of the results can be seen in table 4.

## DISCUSSION

This study aims to supply information in the usual clinical practice on the use of once weekly fluoxetine 90 mg with special interest on tolerability and safety data. The adverse effects observed, both in type as well as frequency of appearance, show us similar results to those collected in the studies published on fluoxetine 20 mg, daily administration, and in the few studies available on once weekly fluoxetine 90 mg[8,9,13]. No more gastrointestinal adverse effects have been observed, indicating that in spite of the greater dosing per dose, there was no significant increase of gastrointestinal malaise regarding daily fluoxetine. No serious adverse effects have been observed and the results of the vital signs and laboratory tests also do not provide any information that establishes doubts on the treatment safety. These results support the safety of the middle term once weekly fluoxetine treatment in the different uses for those whom it is prescribed for in the out-patient psychiatric visit.

However, in our study, the drop-out rate in relationship with the appearance of adverse effects is somewhat greater to that observed in the Schmidt et al. study[8] in the once weekly fluoxetine group (13.04 % vs 4.2 %). This could be related with the lower sample population of our study (n = 46), although it still means a low percentage of discontinuation in relationship with the total study population. In general, it seems to corroborate the hypothesis of treatment safety and good tolerance with once weekly fluoxetine. However, it is observed that most of the drop-outs occurred in those patients presenting the greatest rate of adverse effects, which coincides with the Sleath et al.[14] results on maintenance treatment with antidepressants.

Considering that all the patients who drop out of treatment due to intolerance returned to the daily fluo-

xetine regime without clinically worsening and with disappearance of adverse effects, the proposal of the once weekly regime cannot be considered to affect compliance since, in the worst case, reinitiating the previous regime solves the undesirable symptoms.

The drop-out rate due to lack of efficacy is similar to that of the Schmidt et al.[8] study (2.17% vs 1.6%). It is interesting that, in our case, no drop-out occurred due to relapse versus 35.8% of that study, in spite of the greater mean treatment duration (135.24 days vs 105.4 days). Perhaps the fact that our study's patients were clinically stabilized before changing to once weekly fluoxetine could at least partially explain this fact. This could be related with the good efficiency profile of once weekly fluoxetine demonstrated in this study, in the different clinical entities for which it was prescribed since the CGI-Severity mean in the initial visit was 3.09 and significantly improved in the final visit (2.09; $p = 0.02$). On the one hand, the long term treatment maintenance and patient satisfaction about the new use pattern on the other hand could have undoubtedly contributed to the improvement of the efficiency observed.

In any case, the global drop-out rate during treatment (4 and a half months long) was 27.7% significantly less than the 44% found by Masand[4] or the 73% according to Rajinder in the antidepressant maintenance treatment with SSRI at three months.

Analysis of compliance shows an elevated rate maintained during the time analyzed, which never decreases below 95%. We could relate this variable with the results obtained both in satisfaction due to subjective improvement of the patient as well as satisfaction with the use pattern that are maintained in a mean satisfaction index superior to 90% in the first case and 95% in the second. The fact that one of the indexes frequently associated to greater antidepressive treatment adherence is satisfaction due to treatment efficacy in relationship with the improvement observed is corroborated[16,17].

On the other hand, the high satisfaction index related with the dose pattern presented is interesting. The patients positively evaluate the dosage regime of a single weekly dose in a significant way, which may be closely related with the high degree of compliance observed.

## CONCLUSION

Once weekly fluoxetine is generally well tolerated, although 28% have new adverse effects that could be related with the 90 mg dose in a single dose. One patient group (13%) returned to the previous regime due to adverse effects (anxiety, headache and insomnia) that were poorly tolerated. Its use is not associated with safety pattern abnormalities.

Its administration regime in a single weekly dose was assessed very positively by the patients, who showed an elevated satisfaction index in relationship to the dosage regime. This may have implications with a better treatment adherence, which, in turn, makes it possible to infer a better long term prognosis, collaborating in the maintenance of the remission and in the reduction of the relapse rates.

Its efficacy, safety and tolerability profile added to the positive perception of this new formulation by the patients, in relationship with its comfort of use, convert once weekly fluoxetine in a viable and advantageous alternative in all those indications for which conventional fluoxetine has demonstrated its efficacy.

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