Patient Compliance With Enteric-Coated Weekly Fluoxetine During Continuation Treatment of Major Depressive Disorder

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Background: A once-weekly enteric-coated formulation of fluoxetine represents a new, effective option for the long-term treatment of clinically diagnosed depression. This study assessed compliance with the new once-weekly fluoxetine as compared with once-daily fluoxetine treatment. ***Method:*** Adult patients from the United Kingdom who had responded to fluoxetine treatment for a current episode of depression (DSM-IV criteria) were monitored for compliance with daily and weekly dose administration of fluoxetine. The study consisted of 2 study phases. Study phase I was a baseline assessment of 20 mg of fluoxetine daily dosing for 4 weeks (N = 117). The second phase of the study consisted of randomly assigning patients to either once-weekly (90 mg/wk) or once-daily (20 mg/day) fluoxetine for 3 months (weekly, N = 56; daily, N = 53). Compliance with the dosing regimen was measured using an electronic Drug Exposure Monitor (eDEM, AARDEX Ltd., Zug, Switzerland). ***Results:*** For those patients randomly assigned to weekly fluoxetine, compliance was 85.4% during study period I while on treatment with daily fluoxetine and then 87.5% while on treatment with weekly fluoxetine. This difference was not significant. For once-daily dosing, however, compliance declined from 87.3% during period I to 79.4% during period II ($p < .001$). After adjusting for compliance during study period I, weekly compliance during study period II was 87.8% and daily compliance was 79.0%, a statistically significant difference ($p = .006$). ***Conclusion:*** Compliance with once-weekly fluoxetine was better than that with once-daily fluoxetine. Compliance decreased over time when patients remained on daily dosing; however, when patients switched from daily dosing to weekly dosing, compliance did not decrease. The results of this study allay concerns about inferior compliance with a once-weekly regimen compared with the conventional once-daily regimen. *(J Clin Psychiatry 2001;62[suppl 22]:43–47)*

Depression is a serious illness that often requires long-term treatment.[1] Many depressed patients remain undertreated[2–7] in spite of the public health burden presented by depression and the availability of medications with well-demonstrated efficacy. Nonadherence with the recommended dosing regimen is one factor contributing to undertreatment, including both missed doses and early discontinuation of medication. Decreasing adherence over time is another concern. Furthermore, continuous treatment requiring daily doses of antidepressant medications may be associated with uncertainty about continued benefit, fear of the stigma of mental illness, and objectionable side effects. The availability of an effective agent that could be taken once weekly might alleviate some of these concerns. However, little is known about the ability of patients to adhere to a weekly dosing regimen compared with adherence to a daily dosing regimen.

Electronic medication event monitoring[8–13] has greatly enhanced the measurement of patient compliance with prescribed dosing regimens. This method provides reliable and precise information on the temporal patterns of dosing and is currently regarded as the gold standard of compliance measurement.[11–13] For that reason, compliance was assessed in this study using electronic medication event monitoring. The objective of the study was to determine whether the level of compliance of patients with a weekly dosing regimen (90 mg weekly) was different than compliance with the standard regimen of 20 mg fluoxetine once daily. A separate study[14] confirmed the safety and efficacy of this new weekly formulation.

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METHOD

Subjects were adult patients in the United Kingdom who had responded to 6 to 16 weeks of daily 20-mg fluoxetine treatment for a current nonpsychotic major depressive episode (DSM-IV criteria). Response was defined as a Montgomery-Asberg Depression Rating Scale (MADRS)[15] score ≤ 12 and a Clinical Global Impressions-Severity of Illness (CGI-S)[16] score ≤ 2. Patients also must have been treated with an antidepressant for symptoms of depression on at least 1 other occasion and have given their signed informed consent prior to entering the study. Other entry criteria were previously described.[17] In study period I, patients were continued on treatment with open-label fluoxetine, 20 mg, taken once daily for 4 weeks. In study period II, patients were randomly assigned to remain on treatment with open-label daily fluoxetine, 20 mg, or to switch to open-label weekly fluoxetine for 12 weeks.

The eDEM (electronic Drug Exposure Monitor) medication event monitoring system (AARDEX Ltd., Zug, Switzerland) was used to measure compliance with the prescribed drug regimen. This system consists of a standard medication container fitted with a special closure that records the time and date of each opening and closing of the closure through integrated microcircuitry. Patients randomly assigned to once-weekly fluoxetine received the eDEM monitor in paper packaging containing text on the importance of long-term treatment, space to write in the intended dates of dosing, and stickers to use as an optional reminder. Patients randomly assigned to once-daily fluoxetine received the eDEM monitor without the paper packaging materials. Additional instructions to the patients were previously reported.[17] Two eDEM monitors were dispensed to each patient: 1 each for study period I and study period II. Data from the 2 eDEM monitors were downloaded to a Windows-based software package, Compliance Software System (version 2.1, AARDEX Ltd., Zug, Switzerland) to merge the data and transform individual dosing histories to a summary compliance variable.

The primary endpoint in this study was compliance with the prescribed dosing regimen, defined for the purposes of this study as the percentage of prescribed doses taken within predefined timing limits during the study period. Doses were considered adherent if taken within the prescribed interdose interval ± 25%. Thus, for the once-daily regimen, a dose was classified as adherent if taken 1 day ± 6 hours after the previous dose, and for the once-weekly regimen, if taken 7 days (168 hours) ± 42 hours after the previous dose. All adherent doses were summed and divided by the total number of doses prescribed to provide 1 summary compliance statistic per patient. Compliance calculation details, statistical analyses, and other measures (MADRS, CGI-S, and Quality of Life in Depression Scale[18] scores) were previously reported.[17]

Table 1. Fluoxetine Treatment Discontinuations During Study Period II[a]

Reason for Discontinuation	90 mg Weekly (N = 56) N (%)	20 mg Daily (N = 53) N (%)
Lack of efficacy	6 (10.7)	2 (3.8)
Relapse	1 (1.8)	0 (0.0)
Adverse events	1 (1.8)	1 (1.9)

[a]Data from Claxton et al.[17] Analyses revealed no statistically significant differences between treatment groups in reasons for discontinuation.

RESULTS

Of the 117 patients who entered study period I, 109 were randomly assigned to the 3-month open-label continuation phase at visit 2 (study period II): 56 patients were randomly assigned to 90 mg of fluoxetine once weekly and 53 patients were randomly assigned to 20 mg of fluoxetine once daily. There were no statistically significant differences between the treatment groups in age, gender, ethnic origin, or baseline disease characteristics. The mean ± SD age of the patients was 46 ± 14 years, 83% of the patients were female, and all the patients were white. Reasons for discontinuation are shown in Table 1. There were no statistically significant differences between treatment groups for any reason for study discontinuation.

Mean baseline compliance, as measured by the electronic monitoring system, was 83% for all patients enrolled in study period I and 86% for all patients who were randomly assigned to continuation treatment in study period II, with median compliance being 92% (range, 0%–100%) for both periods. The data are sharply skewed toward higher compliance, and compliance was virtually identical between all enrolled patients and those who went on to random assignment.

For those patients randomly assigned to weekly fluoxetine, compliance was 85.4% during study period I while on daily treatment with fluoxetine and 87.5% while on weekly treatment with fluoxetine, a difference that was not significant. For once-daily dosing, however, compliance declined from 87.3% during period I to 79.4% during period II ($p < .001$). Table 2 displays the results of the analysis of covariance model of compliance during study period II adjusted for compliance during study period I. The initial model included (1) compliance during study period I, (2) treatment, (3) investigator, and (4) treatment-by-investigator interaction terms as fixed effects. A reduced model (compliance during study period I and treatment) was constructed in a backward stepwise fashion, since the investigator and interaction terms were not statistically significant, and is reported in Table 2. After adjusting for compliance during study period I, compliance with weekly dosing during study period II was 87.8% and compliance with daily dosing was 79.0%, a statistically significant difference ($p = .006$). As in study period I, the

Table 2. Analysis of Covariance of Compliance With Baseline Compliance as a Covariate[a]

Treatment	N	Study Period I (baseline) Mean (%)	Study Period I (baseline) SD (%)	Study Period II (endpoint) Mean (%)	Study Period II (endpoint) SD (%)	Least Squares (%)	p Value
90 mg weekly	55	85.37	22.09	87.47	18.13	87.79	
20 mg daily	53	87.25	12.89	79.42	16.01	79.02	0.006

[a]Reprinted, with permission, from Claxton et al.[17] Ns represent numbers of patients for whom there were baseline compliance data. Analyses of covariance with treatment as the independent term and baseline compliance as the covariate; p value is for the test of equality of 90 mg once weekly vs. 20 mg once daily after adjusting for baseline compliance. Compliance reported as percentage of doses taken.

average compliance during study period II is again skewed toward higher compliance, with notable differences between the daily and weekly treatment groups. The weekly dosing regimen results in a much larger percentage of patients with compliance greater than 90% relative to the once-daily patients (64% vs. 30%, respectively).

Figure 1 shows the change in compliance between study period I and II of individual patients in the once-daily dosing group (Figure 1A) and the once-weekly dosing group (Figure 1B). Of the 53 patients in the daily dosing group, 43 (81.1%) had a decrease in compliance, which appears to be equal in patients with high, medium, and low compliance during study period I. In the once-weekly group, only 17 (30.4%) of the 56 patients had a decrease in compliance. Unlike the once-daily patients, it appears that the once-weekly patients who had very high compliance during study period I had a decrease in compliance during study period II, while those who had low compliance in study period I mostly increased in compliance during study period II.

DISCUSSION

A change from the conventional once-daily regimen of fluoxetine in continuation therapy for major depressive disorder to a once-weekly regimen raises the question of the impact of the once-weekly regimen on compliance. The answer to this question is only as valid as the methods used to measure compliance. The measurement of patient compliance underwent a fundamental revolution with the introduction of electronic medication event monitoring in the late 1980s.[8,12,13,19–21] Prior to electronic monitoring, all methods for measuring compliance relied on the patient's recall and full cooperation with the intent of the study, thus affording patients the easy ability to censor evidence for delayed or omitted doses. It is now evident from studies using either electronic monitoring or low-dose chemical markers that returned tablet counts, diaries, interviews, and self-report grossly exaggerate the level of patient compliance.[8,12,13,19–21] With electronic monitoring, it is now possible to study patient compliance with reliable methods that reveal dose timing hour by hour, day by day, and week by week, as well as information on the aggregate intake of drug. Electronic monitoring allows one to define patient compliance as the extent to which the patient's dosing history conforms to the prescribed drug regimen,[22] a definition that is inherently quantitative and thus amenable to analysis. In other words, patient compliance is defined as the outcome of the comparison of 2 time series: the prescribed regimen and the actual dosing history.

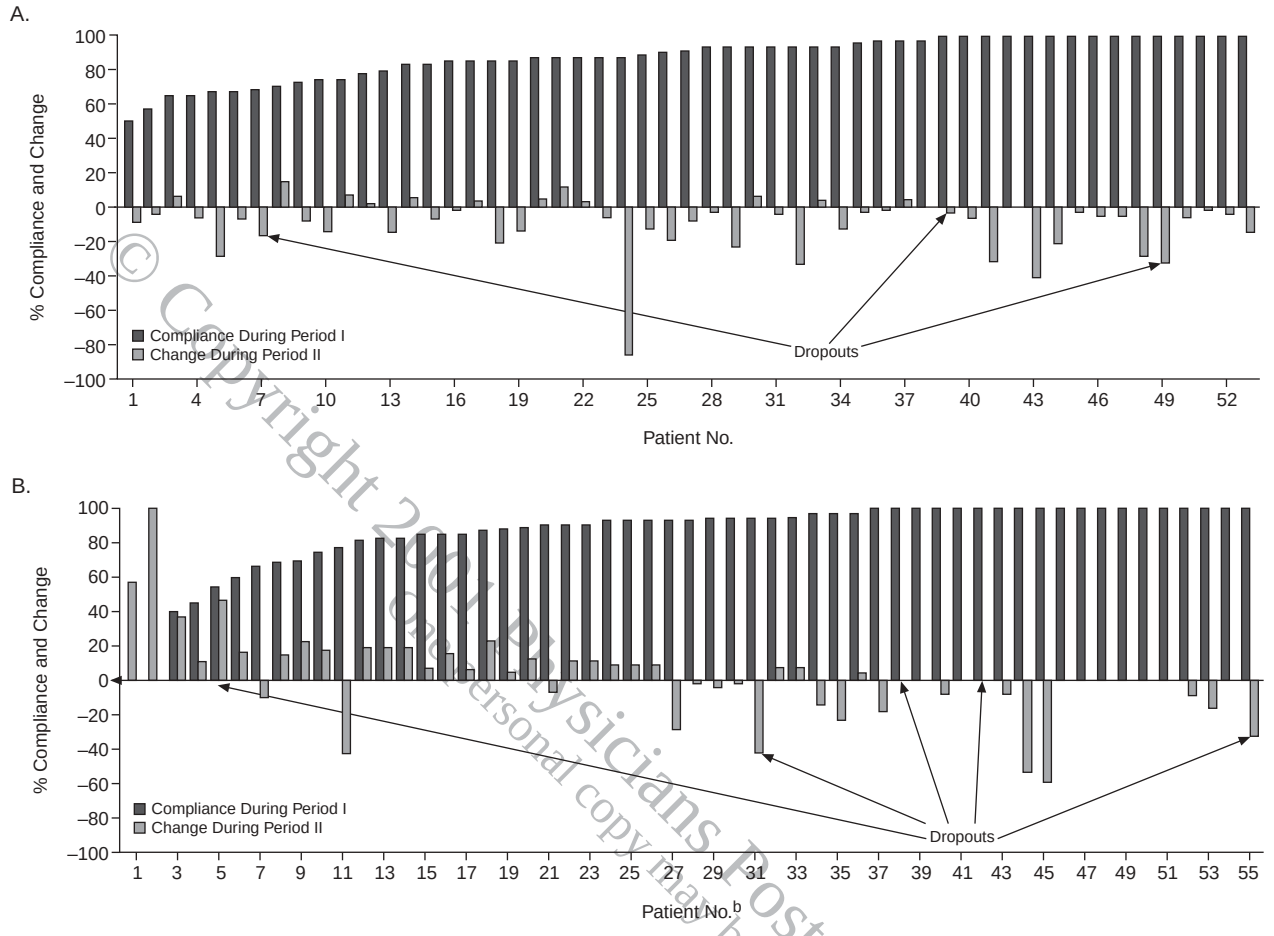
This study documents patient compliance with the use of electronic medication event monitors (eDEMs) with weekly dosed fluoxetine and as such provides valuable insights into the extent of noncompliance and the differences in compliance between conventional daily dosing and the new weekly formulation. In this study, compliance to a once-weekly regimen of fluoxetine was better than compliance to a once-daily regimen. Indeed, the overall pattern of compliance was skewed further toward higher compliance for the weekly dosing regimen, resulting in a much larger percentage of once-weekly patients with compliance of greater than 90% relative to the once-daily patients.

In accordance with observations from other studies of compliance over time, compliance significantly declined over time in those patients randomly assigned to continue fluoxetine, 20 mg once daily. Interestingly, this decline was arrested in patients randomly assigned to switch to enteric-coated fluoxetine, 90 mg once weekly. Patients on treatment with once-weekly fluoxetine did not experience a decrease in compliance, but rather maintained their high level of compliance throughout study period II.

To maintain full recovery and prevent relapse, at least 4 to 9 months of maintenance treatment is recommended following successful antidepressant therapy.[23] Weekly dosing with fluoxetine may prove to be a valuable addition to the therapeutic arsenal of antidepressive treatment because it seems to arrest the decline of adherence over time, as seen with once-daily dosing.

A limitation of this study is that neither the clinicians nor the researchers were blinded with respect to treatment regimen. The nature of the question being asked in this study did not permit blinding of treatment. In addition, one of the goals of the study was to test compliance in a design that included features intended for implementation in clinical practice, such as a reminder type of packaging for the weekly dosing. Blinding to treatment was not done, to generate reasonable estimates of "real-life" outcomes. However, the absence of blinding permits investigator and subject bias regarding weekly treatment that could have influenced the outcome of this trial. For example, patients assigned to weekly treatment may have experienced a renewed level of attention or commitment to treatment as a response to the change in dosing schedule.[24–26] At the same time, educational and reminder packaging materials were provided to those patients assigned to the weekly treatment, so the ultimate effect on compliance in the weekly dosing

Figure 1. Change in Compliance With Fluoxetine Treatment Between Study Period I and Study Period II Compared With Compliance During Study Period I for (A) Once-Daily and (B) Once-Weekly Dosing[a]



[a]Compliance reported as percentage of doses taken.
[b]Figure 1B represents patients for whom there were baseline compliance data.

group could have been due to a combination of both the change in dosing interval and the special packaging materials. Indeed, while single-focus intervention programs have generally had little impact on compliance, multiple-focus programs have been able to improve compliance.[27–29] Here, the unique dosing regimen along with the accompanying packaging with educational materials and reminders for weekly dosing in essence provided a multiple-focus approach. If the ultimate goal is to improve patient compliance with long-term treatment, then such a combination of behavioral and educational interventions may in fact be essential to achieve compliance rates at least as high as those my colleagues and I observed. At the same time, while these design features may have contributed to higher compliance to the weekly regimen, it is also possible that random assignment may have reduced the potential compliance in the weekly arm. Compliance with antidepressant treatment has been reported to be significantly higher among patients who actively choose their dosing regimen.[30]

In summary, patients assigned to take the enteric-coated 90-mg fluoxetine formulation once weekly were highly compliant with the dosing regimen during the long-term treatment of their depression. This study suggests that patients will not be more likely to forget once-weekly doses compared with once-daily doses. A once-weekly regimen could be a valued option for many patients, in that weekly dosing may be more convenient and less of an intrusion in daily activities.

Drug name: fluoxetine (Prozac).

REFERENCES

1. Kupfer DJ. Long-term treatment of depression. J Clin Psychiatry 1991;52: 28–34
2. Katon W, von Korff M, Lin E, et al. Adequacy and duration of antidepressant treatment in primary care. Med Care 1992;30:67–76
3. Donoghue JM, Tylee A. The treatment of depression: prescribing patterns of antidepressants in primary care in the UK. Br J Psychiatry 1996;168: 164–168

4. MacDonald TM, Reid IC, McMahon AD. Patients receive an inadequate dose of antidepressants for an inadequate period [letter]. BMJ 1997;315:56
5. Simon GE, VonKorff M, Heiligenstein JH, et al. Initial antidepressant choice in primary care: effectiveness and cost of fluoxetine vs tricyclic antidepressants. JAMA 1996;275:1897–1902
6. Simon GE. Can depression be managed appropriately in primary care? J Clin Psychiatry 1998;59(suppl 2):3–8
7. Hirschfeld RM, Keller MB, Panico S, et al. The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression. JAMA 1997;277:333–340
8. Cramer JA, Mattson RH, Prevey ML, et al. How often is medication taken as prescribed? a novel assessment technique. JAMA 1989;261:3273–3277
9. Kruse W, Weber E. Dynamics of drug regimen compliance: its assessment by microprocessor-based monitoring. Eur J Clin Pharmacol 1990;38: 561–565
10. Weintraub M. Compliance in the elderly. Clin Geriatr Med 1990;6: 445–452
11. Cramer J, Vachon L, Desforges C, et al. Dose frequency and dose interval compliance with multiple antiepileptic medications during a controlled clinical trial. Epilepsia 1995;36:1111–1117
12. Kastrissios H, Blaschke TF. Medication compliance as a feature in drug development. Annu Rev Pharmacol Toxicol 1997;37:451–475
13. Urquhart J. The electronic medication event monitor: lessons for pharmacotherapy. Clin Pharmacokinet 1997;32:345–356
14. Schmidt ME, Fava M, Robinson JM, et al. The efficacy and safety of a new enteric-coated formulation of fluoxetine given once weekly during the continuation treatment of major depressive disorder. J Clin Psychiatry 2000; 61:851–857
15. Montgomery SA, Asberg MC. A new depression rating scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
16. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
17. Claxton A, de Klerk E, Parry M, et al. Patient compliance to a new enteric-coated weekly formulation of fluoxetine during continuation treatment of major depressive disorder. J Clin Psychiatry 2000;61:928–932
18. Hunt SM, McKenna SP. The QLDS: a scale for the measurement of quality of life in depression. Health Policy 1992;22:307–319
19. Cramer JA. Microelectronic systems for monitoring and enhancing patient compliance with medication regimens. Drugs 1995;49:321–327
20. Urquhart J, de Klerk E. Contending paradigms for the interpretation of data on patient compliance with therapeutic drug regimens. Stat Med 1998;17: 251–267
21. Urquhart J, Chevalley C. Impact of unrecognized dosing errors on the cost and effectiveness of pharmaceuticals. Drug Information J 1988;22: 363–378
22. Urquhart J. Patient compliance with prescribed drug regimens: overview of the past 30 years of research. In: Nimmo WS, Tucker GT, eds. Clinical Measurement in Drug Evaluation. New York, NY: John Wiley & Sons Ltd; 1995:213–227
23. Clinical Practice Guideline Number 5: Depression in Primary Care, vol 2. Treatment of Major Depression. Rockville, Md: US Dept Health Human Services, Agency for Health Care Policy and Research; 1993. AHCPR publication 93-0550
24. Kruse W, Eggert Kruse W, Rampmaier J, et al. Dosage frequency and drug-compliance behaviour: a comparative study on compliance with a medication to be taken twice or four times daily. Eur J Clin Pharmacol 1991;41: 589–592
25. Kruse W, Rampmaier J, Ullrich G, et al. Patterns of drug compliance with medications to be taken once and twice daily assessed by continuous electronic monitoring in primary care. Int J Clin Pharmacol Ther 1994;32: 452–457
26. Kruse W, Nikolaus T, Rampmaier J, et al. Actual versus prescribed timing of lovastatin doses assessed by electronic compliance monitoring. Eur J Clin Pharmacol 1993;45:211–215
27. Sclar DA, Tartaglione TA, Fine MJ. Overview of issues related to medical compliance with implications for the outpatient management of infectious diseases. Infect Agents Dis 1994;3:266–273
28. Tashkin DP. Multiple dose regimens: impact on compliance. Chest 1995; 107:176S–182S
29. Roter DL, Hall JA, Merisca R, et al. Effectiveness of interventions to improve patient compliance: a meta-analysis. Med Care 1998;36:1138–1161
30. Myers ED, Branthwaite A. Out-patient compliance with antidepressant medication. Br J Psychiatry 1992;160:83–86