# Patient Compliance to a New Enteric-Coated Weekly Formulation of Fluoxetine During Continuation Treatment of Major Depressive Disorder

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***Background:*** A new formulation of enteric-coated fluoxetine given once weekly could be a useful option for the long-term treatment of depression, but compliance to once-weekly fluoxetine treatment has not been assessed.

***Method:*** Patients were adults from the United Kingdom who had responded to fluoxetine treatment for a current episode of depression (DSM-IV criteria). In the baseline assessment phase, all patients (N = 117) were continued on 20 mg of open-label fluoxetine once daily for 4 weeks. In the follow-up phase, patients (N = 109) were randomly assigned to once-weekly or once-daily fluoxetine for 3 months. Patient compliance was monitored by electronic devices during both phases of the study.

***Results:*** Compliance to once-weekly fluoxetine treatment was higher than compliance to once-daily fluoxetine (85.9% vs. 79.4%, respectively).

***Conclusion:*** Once-weekly fluoxetine treatment allows for new flexibility for both the clinician and the patient, and this study alleviates the concern that patients will forget weekly doses.

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Depression is a serious illness that often requires long-term treatment.[1] In spite of the public health burden presented by depression and the availability of medications with well-demonstrated efficacy, many depressed patients remain undertreated.[2–7] One factor contributing to undertreatment is nonadherence to the recommended treatment regimen, including both missed doses and early discontinuation of medication. Because continuous treatment requiring daily doses of antidepressant medications may be associated with objectionable side effects, uncertainty about continued benefit, and fear of the stigma of mental illness, reduced dosing frequency may provide a unique strategy for improving compliance with long-term treatment.

The measurement of patient compliance with prescribed dosing regimens has been greatly enhanced by the method of electronic medication event monitoring.[8–13] Traditional compliance measurement methods such as pill counts, patient self-report, and questionnaires afford patients the ability to easily self-censor evidence for missed doses and to overestimate drug intake.[13–16] In contrast, electronically monitored dosing histories provide reliable and precise information on the temporal patterns of dosing and are currently regarded as the gold standard of compliance measurement.[11–13]

Compliance in the present study was assessed using an electronically monitored pill bottle that recorded each opening and closing of the cap. The objective of the study was to determine if compliance with a new dosing regimen of enteric-coated fluoxetine, 90 mg once weekly, was different than compliance with the standard regimen of a 20-mg dose of fluoxetine once daily for up to 3 months of continuation therapy. Although the once-weekly formulation may be safe and efficacious,[17] it is also imperative that patients are able to adhere to such a dosing schedule.

## METHOD

The study was a multicenter, open-label, randomized, controlled clinical trial conducted at 18 primary care centers in the United Kingdom. The study consisted of 2 phases: study period I, a 4-week period in which all patients received 20 mg of open-label fluoxetine once daily to provide a baseline compliance estimate, and study period II, a 12-week period during which patients were randomly assigned to continue treatment with either 20 mg of fluoxetine once daily or 90 mg of enteric-coated fluoxetine once weekly.

Patients were eligible for enrollment if they were being currently treated with 20 mg of fluoxetine once daily for a nonpsychotic major depressive episode (DSM-IV crite-

ria). The diagnosis was assessed by a review of the patient's clinical history prior to beginning the current antidepressant treatment. The dose could have been titrated from some other initial dose, but the patient must have been successfully tolerating 20 mg once daily for at least 2 weeks prior to enrollment. Patients should have received at least 6 weeks, but no more than 16 weeks, of treatment with fluoxetine, and, in the judgment of the investigator and the patient, the patient must have responded to treatment. As an indicator of clinical benefit, the Montgomery-Asberg Depression Rating Scale (MADRS) score had to be ≤ 12 and Clinical Global Impressions-Severity of Illness scale (CGI-S) score had to be ≤ 2. Lastly, patients must have been treated with an antidepressant for symptoms of depression on at least 1 other occasion. All patients signed informed consent before entering the study. The study protocol was approved by 3 Medical Ethical Committees covering the 18 study centers.

Compliance with the prescribed drug regimen was measured using the eDEM system (electronic Drug Exposure Monitor, AARDEX Ltd., Sion, Switzerland). This system consists of a normal pill bottle fitted with a special cap capable of recording time and date of each opening and closing of the cap through integrated microcircuitry. Patients randomly assigned to once-weekly fluoxetine received the eDEM system 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 an optional reminder system. Those patients randomly assigned to once-daily fluoxetine received the bottle and eDEM cap without the paper packaging materials. To balance the guidance on compliance given during the trial, investigators were provided with a set of oral instructions to be given to all patients at the second visit of the trial, when they were randomly assigned to continue on daily dosing or switch to weekly dosing. The instructions were as follows: "You will be taking Prozac on a [daily/weekly] basis for the rest of the study. So that we will know how well you are staying on schedule please tell me the [hour (for daily)/hour and day of the week (for weekly)] that you will be taking your capsule." All patients were instructed by the investigator on the importance of taking each capsule as prescribed and were aware of the monitoring nature of the cap. However, the cap itself provided no reminder to the patients as to when to take their medication. During the study, 2 eDEM caps were dispensed for each patient: 1 for study period I and 1 for study period II. The data from the 2 eDEM caps were downloaded to a Windows-based software package, Compliance Software System (version 2.1, AARDEX Ltd., Sion, Switzerland), to merge the data and transform individual dosing histories into compliance summary variables.

Visits to the clinic were conducted at approximately monthly intervals. The primary endpoint in this study was compliance with the prescribed dosing regimen. The endpoint was calculated by coding each dose as adherent or nonadherent (0/1) on the basis of whether the dose was taken within the prescribed interdose interval ± 25%. Thus, for patients randomly assigned to 20 mg of fluoxetine once daily, an adherent dose was taken 1 day ± 6 hours after the previous dose. For patients randomly assigned to 90 mg of fluoxetine once weekly, an adherent dose was taken 7 days (168 hours) ± 42 hours after the previous dose. Percentage of compliant doses was calculated for each patient as the number of adherent doses divided by the number of prescribed doses multiplied by 100. The percentages of compliant doses were averaged to yield the overall compliance for each randomly assigned group. At the first and last visits, the physician completed the MADRS and CGI-S, and the patient completed the Quality of Life in Depression Scale (QLDS)[18] and a patient satisfaction survey (PSS).

Statistical analyses were based on the intention-to-treat principle. In case of early discontinuation, the last-observation-carried-forward (LOCF) principle was used. The primary test of differences in compliance between the 20 mg of fluoxetine once-daily and 90 mg of fluoxetine once-weekly groups was an analysis of covariance (ANCOVA) with baseline compliance during study period I, treatment, investigator, and treatment-by-investigator interaction terms as fixed effects. All analyses were performed using SPSS 8.0 for Windows.

## RESULTS

A total of 117 patients entered the 4-week, open-label baseline assessment phase of compliance to 20 mg of fluoxetine once daily (study period I). Eight patients (6.8%) discontinued during study period I. Five of these patients discontinued because of protocol violations: 1 patient became pregnant by visit 1, 2 patients did not meet MADRS and CGI-S entry criteria, 1 patient was not dispensed an eDEM monitor with study period I medication, and 1 patient took an excluded medication. One patient was discontinued by the principal investigator because of a hospitalization unrelated to the study that would have interfered with the patient's ability to be in control of time of drug intake, 1 patient discontinued for unknown personal reasons, and 1 patient discontinued owing to an adverse event.

Of the 109 patients who completed study period I, all were randomly assigned to the 12-week 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 to 20 mg of fluoxetine once daily. No statistically significant differences were found between the treatment groups in age, gender, ethnic origin, or baseline disease characteristics (Table 1). Within the weekly dosing group, 8 patients discontinued before the last visit: 6 because of lack of efficacy, 1 because of relapse, and 1 because of an adverse event (somnolence). Within the daily

**Table 1. Summary of Patient Characteristics[a]**

| Variable | Study Period I 20 mg Daily (N = 117) | Study Period II 90 mg Weekly (N = 56) | Study Period II 20 mg Daily (N = 53) |
|---|---|---|---|
| Age, y, mean ± SD | 46 ± 13 | 46 ± 14 | 46 ± 11 |
| Female, N (%) | 97 (83) | 46 (82) | 43 (81) |
| White, N (%) | 117 (100) | 56 (100) | 53 (100) |
| CGI-S score, mean ± SD | 1.75 ± 0.56 | 1.71 ± 0.46 | 1.68 ± 0.47 |
| MADRS score, mean ± SD | 8.79 ± 4.12 | 8.32 ± 3.19 | 8.42 ± 3.15 |

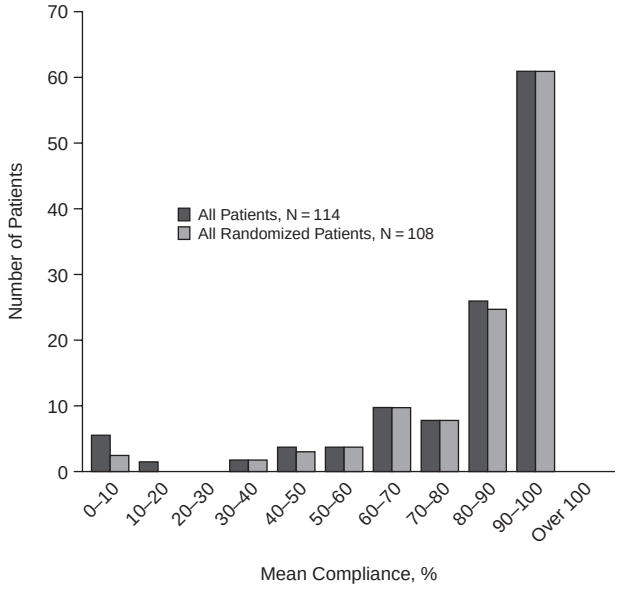
[a]Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, MADRS = Montgomery-Asberg Depression Rating Scale.

**Table 2. Rate of Compliance to Fluoxetine, 20 mg Daily, During Study Period I (%)[a]**

| Summary Statistics | All Patients (N = 114) | All Randomized Patients (N = 108) |
|---|---|---|
| Mean ± SD | 83.15 ± 23.29 | 86.29 ± 18.11 |
| Minimum | 0 | 0 |
| First quartile | 78.28 | 81.76 |
| Median | 91.84 | 92.31 |
| Third quartile | 100 | 100 |
| Maximum | 100 | 100 |

[a]Compliance reported as percentage of doses taken.

**Figure 1. Mean Compliance to Fluoxetine, 20 mg Daily[a]**



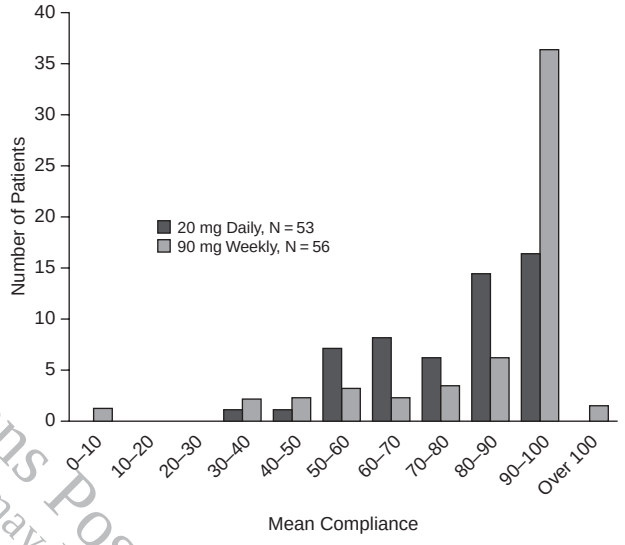

[a]Compliance reported as percentage of doses taken. The percentage of compliant doses for an individual patient in either treatment group may exceed 100% if the patient took several doses at the earlier end of the adherence window. This pattern of early, but still adherent dosing, if maintained over the course of the study, would result in more adherent doses than the number of prescribed doses (eg, 90 mg once weekly ingested every 6 days over 12 weeks would result in 14 adherent doses out of 12 prescribed doses, resulting in a compliance rate of 117%).

**Table 3. Rate of Compliance (%) by Treatment Group, Randomized Patients Only (Study Period II)[a]**

| Summary Statistics | 90 mg Weekly (N = 56) | 20 mg Daily (N = 53) |
|---|---|---|
| Mean ± SD | 85.91 ± 21.43 | 79.42 ± 16.01 |
| Minimum | 0 | 38.46 |
| First quartile | 81.82 | 68.02 |
| Median | 81.76 | 83.13 |
| Third quartile | 100 | 94.91 |
| Maximum | 109.09 | 100 |

[a]See footnote to Figure 1.

**Figure 2. Mean Compliance by Treatment Group, Randomized Patients Only[a]**




[a]See footnote to Figure 1.

dosing group, 3 patients discontinued before the last visit: 2 because of lack of efficacy and 1 because of an adverse event (decreased libido). The difference in number of discontinuations between the treatment groups for lack of efficacy was not statistically significant (p = .165).

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 (Table 2). The histogram of compliance data (Figure 1) shows that the data are sharply skewed toward higher compliance. Compliance with the regimen of 20 mg of fluoxetine once daily during study period I was virtually identical between all enrolled patients and those who went on to randomization.

Table 3 summarizes the average compliance to 90 mg of fluoxetine once-weekly (85.9%) and 20 mg of fluoxetine once-daily (79.4%) regimens during study period II. Although the histogram (Figure 2) is again skewed toward higher compliance, there are notable differences between the daily and the weekly treatment groups. In gen-

**Table 4. Comparison of Mean ± SD Compliance (%) Within Treatment Groups Before and After Randomization[a]**

| Randomized Group Assignment | Study Period I (20 mg Daily) | Study Period II (90 mg Weekly or 20 mg Daily) | p Value[b] |
|---|---|---|---|
| 90 mg weekly[c] | 85.37 ± 22.09 | 87.47 ± 18.13 | .541 |
| 20 mg daily[d] | 87.25 ± 12.89 | 79.42 ± 16.01 | < .001 |

[a]Compliance reported as percentage of doses taken.
[b]Paired t test.
[c]N = 55.
[d]N = 53.

**Table 5. Analysis of Covariance of Compliance (%) With Baseline Compliance as a Covariate[a]**

| | Baseline | | Endpoint | | Least Squares | | |
|---|---|---|---|---|---|---|---|
| Treatment | Mean | SD | Mean | SD | Mean | SE | p Value |
| 90 mg weekly[b] | 85.37 | 22.09 | 87.47 | 18.13 | 87.79 | 2.16 | |
| 20 mg daily[c] | 87.25 | 12.89 | 79.42 | 16.01 | 79.02 | 2.20 | .006 |

[a]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.
[b]N = 55.
[c]N = 53.

eral, compliance with the 90 mg of fluoxetine once-weekly regimen was skewed further toward higher compliance than was the 20 mg of fluoxetine once-daily regimen. This analysis was repeated, shortening the weekly window to ± 24 hours, resulting in a compliance rate for the once-weekly group of 80.0% ± 22.0%. From this analysis, it is clear that only a small number of weekly doses were coded as adherent because they occurred in the outside edges of the a priori ± 42-hour window for weekly adherence.

Comparison of mean compliance within treatment groups before and after randomization (Table 4) shows that in patients randomly assigned to 20 mg of fluoxetine once daily, compliance declined significantly after randomization (87.3% in study period I vs. 79.4% in study period II; $p < .001$). In contrast, in patients randomly assigned to 90 mg of fluoxetine once weekly, compliance remained essentially unchanged from baseline values (85.4% in study period I vs. 87.5% in study period II; $p = .541$).

Table 5 displays the results of the ANCOVA 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. Since the investigator and interaction terms were not statistically significant, a reduced model (compliance during study period I and treatment) was constructed in a backward stepwise fashion and is reported in Table 5. After adjusting for compliance during study period I, weekly compliance was 87.8% and daily compliance was 79.0%, a statistically significant difference ($p = .006$).

## DISCUSSION

Patient compliance with the dosing regimen of any medication is relevant to both efficacy and safety. Compliance is a patient behavior that plays a permissive role in the ultimate success or failure of any treatment, for it is a necessary (although not, of course, sufficient) condition for therapeutic success. Substantial underconsumption of an effective drug, through missed doses or early discontinuation, can lead to reduced clinical effectiveness, whereas substantial overconsumption can be expected to exaggerate dose-dependent side effects and safety problems. Because compliance is a dynamic, complex construct, involving not only the quantity of doses taken or not taken but also the timing of doses taken, the goal of any drug treatment is to achieve correspondence between the patient's real-life drug intake and the recommended dosing regimen.

To maintain full recovery and prevent relapse, at least 4 to 9 months of maintenance treatment is recommended following successful antidepressant therapy.[19] Because weekly dosing offers more flexibility in the dosing schedule during maintenance treatment for depression, it may prove to be a more convenient alternative for some patients. However, weekly dosing is a relatively uncommon dosing regimen, and a natural concern of the prescribing physician is the patient's ability to comply with a weekly regimen. Only a few other medications (e.g., alendronate, methotrexate, some medications for malaria prophylaxis) can be dosed in this way. Although it has been widely shown that once-daily dosing improves compliance over more frequent regimens,[11,20–24] very little is known about the impact of less-frequent-than-daily dosing on compliance. In this study, compliance to a once-weekly regimen of fluoxetine was no worse 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 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 20 mg of fluoxetine once daily. Interestingly, this decline was arrested in patients randomly assigned to switch to 90 mg of enteric-coated fluoxetine once weekly. Patients on the once-weekly regimen did not experience a decrease in compliance, but rather maintained their high level of compliance throughout study period II.

A limitation of this study is that subject and investigator variables normally controlled by randomization and double-blinded treatment were limited to control by random assignment. The nature of the question being asked

in this study did not permit blinding of treatment. In addition, one of our goals was to test compliance in a design that included features intended for implementation in clinical practice, such as the reminder packaging for the weekly dosing. This format was created 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, which constituted a major behavioral intervention. 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 group could have been due to a combination of both the change in dosing interval and packaging materials. Indeed, while single-focus intervention programs have generally had little impact on compliance, multiple-focus programs have been able to improve compliance.[25] 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 we 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.[26]

## CONCLUSION

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 new formulation of fluoxetine and reminder packaging for weekly dosing could allow the clinician greater flexibility in the continuation treatment of depression. This study suggests that patients will not be more likely to forget doses prescribed to be taken weekly than those to be taken daily. More importantly, 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. Enteric-coated fluoxetine, 90 mg once weekly, would provide such an alternative for long-term treatment of depression.

*Drug names:* alendronate (Fosamax), fluoxetine (Prozac), methotrexate (Rheumatrex and others).



## REFERENCES


1. Kupfer DJ. Long-term treatment of depression. J Clin Psychiatry 1991;52 (5, suppl):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, comment]. 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. Pullar T, Kumar S, Tindall H, et al. Time to stop counting the tablets? Clin Pharmacol Ther 1989;46:163–168
15. 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; 1995:213–227
16. Pocock SJ, Abdalla M. The hope and the hazards of using compliance data in randomized controlled trials. Stat Med 1998;17:303–317
17. 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
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. 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 93-0551
20. 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
21. 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
22. 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
23. 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
24. Tashkin DP. Multiple dose regimens: impact on compliance. Chest 1995; 107:176S–182S
25. Roter DL, Hall JA, Merisca R, et al. Effectiveness of interventions to improve patient compliance: a meta-analysis. Med Care 1998;36:1138–1161
26. Myers ED, Branthwaite A. Out-patient compliance with antidepressant medication. Br J Psychiatry 1992;160:83–86