Improving Antidepressant Adherence

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Frequently, patients suffering from depressive disorders discontinue antidepressant treatment due to the unpleasant side effects of these medications, particularly in the first month of therapy. Good tolerability (particularly in the early stages of treatment), patient education, and the quality of the relationship between physicians and patients are all common determining factors of patient adherence. Controlled-release antidepressant agents have the potential to improve tolerability early in the course of therapy, one of the most likely periods of dropout from treatment. Side effects for controlled-release formulations are often more favorable because controlled-release formulations exhibit lower peak plasma drug concentrations when compared with immediate-release formulations. Venlafaxine extended-release (XR), bupropion sustained-release (SR), and paroxetine controlled-release (CR) are 3 commonly utilized controlled-release antidepressants that have demonstrated improvement over their immediate-release predecessors in reducing certain adverse effects.

(J Clin Psychiatry 2003;64[suppl 18]:25–30)

Nearly one third of patients abruptly discontinue antidepressant treatment within the first month,[1] and data indicate that as many as 44% of patients discontinue treatment within the first 3 months.[2–4] Although reasons for the cessation of antidepressants have not been extensively studied in controlled, randomly assigned, clinical trials, one of the most frequently reported barriers to patient adherence with this medication class and others is clearly unpleasant side effects.[5–8] Poor tolerability, particularly in the early stages of treatment, is associated with a high incidence of patient dropouts.[4]

Controlled-release formulations of antidepressant agents have the potential to improve tolerability by reducing adverse effects early in the course of therapy—a critical period of dramatic dropout. By lowering the peak plasma drug concentrations inherent to the immediate-release formulations, side effects for controlled-release formulations can frequently be reduced to more acceptable levels. Venlafaxine extended-release (XR), bupropion sustained-release (SR), and paroxetine controlled-release (CR) are 3 commonly utilized antidepressant formulations that have demonstrated effectiveness in reducing some of the adverse effects associated with antidepressant treatment.

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This article is derived from the teleconference "Treating Depression: New Choices for a Chronic Problem," which was held July 1, 2002, and was supported by an unrestricted educational grant from GlaxoSmithKline.

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PATIENT ADHERENCE

The degree to which a patient follows a treatment regimen has been described in a variety of ways. The term *compliance* has traditionally referred to "the extent to which the patient adheres behaviorally to the treatment regimen and is most usually used to refer to the extent to which the patient takes the medications as prescribed."[9(p1)] However, clinical pharmacologists often define *compliance* as the consistency with which a patient's body processes a consistent level of medication, revealing a distinction between behavioral noncompliance and biological noncompliance. Because of this confusion, Frank et al.[9] suggested that the term *adherence* rather than *compliance* be used to describe the extent to which a patient takes medications as prescribed. Using the term *adherence* instead of *compliance* may also remind physicians to form a therapeutic alliance with the patient, through educational techniques aimed at increasing behavioral compliance. Patient education is of particular importance because studies have indicated that physicians may be able to enhance the adherence of patients to antidepressant treatments by offering detailed information to patients about their treatment regimens.[4,10] Poor adherence to antidepressant medications accounts for a surprisingly large proportion of treatment failures, and barriers to patient adherence include insufficient knowledge in the nature of depression, how treatments can be expected to work, what side effects of medications may occur, and what alternative treatments may be available that are associated with fewer adverse events.

Prevalence of Nonadherence

Nonadherence with antidepressant medication is common. Lingam and Scott[11] reviewed data published between

1976 and 2001 that examined the prevalence of psychotropic medication nonadherence in affective disorders and reported that estimates of medication nonadherence for these disorders ranged from 10% to 60%, with a median of 40%. They further stated that the trend of nonadherence had not changed significantly in recent years.

In 1992, Katon et al.[12] analyzed data on the duration of antidepressant therapy for a sample of health maintenance organization enrollees. They found that only 20% of those patients who had been given prescriptions for first-generation tricyclic antidepressants (imipramine, doxepin, and amitriptyline), and only 34% of patients who had been given prescriptions for antidepressants then considered to be newer (desipramine, trazodone, fluoxetine, and nortriptyline) had filled 4 or more prescriptions before the end of the recommended 6 months of therapy. They concluded that a substantial proportion of patients with depression discontinue antidepressant treatment prematurely.

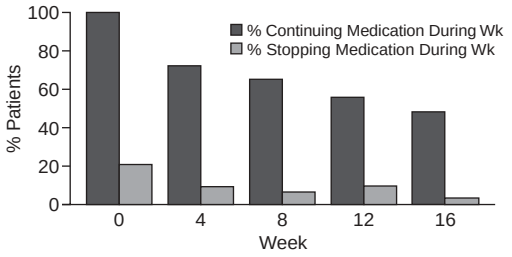
Maidment et al.[13] attempted to assess adherence to antidepressant medication in primary care patients aged 65 years or older. Utilizing a number of questionnaires that measured antidepressant medication adherence, researchers surveyed 67 patients who were being prescribed antidepressants in a rural general practice. They found that only 45 of the participants reported always being adherent to their antidepressant regimen, while 9 reported never being adherent. The remaining 13 participants were adherent to varying degrees that ranged from rarely to sometimes. Nonadherence to antidepressant medication was clearly a substantial problem for these patients, and researchers emphasized the likelihood that their study overestimated adherence rates because the outcome was determined using self-reporting questionnaires.

Predictors of Nonadherence

The strength of the relationship between physician and patient, demographic characteristics, severity of psychopathology, side effects, patient education, antidepressant choice, and patient personality are all factors that have been hypothesized to be predictors of antidepressant medication adherence.[14] Increasingly, however, data indicate that a lack of patient education, unpleasant adverse effects of antidepressant medications, and poor quality of the relationships between physicians and patients are primary determining factors in patient adherence.[4–7]

For example, Lin et al.[4] interviewed 155 patients 1 and 4 months after beginning antidepressant treatment to identify what educational messages, side effects, and features of the physician-patient relationship influenced adherence to antidepressant therapy. Remarkably, 28% of patients discontinued antidepressant treatment during the first month, and 44% had discontinued the prescribed antidepressant by the end of the third month of therapy (Figure 1). Prior to antidepressant administration, some patients in the study had received the following 5 educational messages: (1) take the medication daily, (2) antidepressants must be taken for 2 to 4 weeks for a noticeable effect, (3) continue to take the medicine even if feeling better, (4) do not stop taking the antidepressant without checking with the physician, and (5) specific instructions regarding what to do to resolve questions regarding antidepressants. Those patients who had received educational messages were more likely to comply during the first month of treatment (Table 1), and discussions about prior experience and scheduling pleasant activities increased the likelihood of early adherence. Side effects, when they occurred at severe levels, were associated with nonadherence. For example, of the 13.3% of patients who reported severe daytime sleepiness, 50% discontinued therapy before 31 days compared with 26.9% of patients who did not report severe daytime sleepiness. In the second and third months of treatment, severe side effects highly associated with nonadherence were fatigue, blurred vision, trouble falling asleep, anxiety or jumpiness, change in appetite, and weight gain. When asked why they had discontinued taking antidepressant medication, approximately 62% of the early terminators and 66% of late terminators cited problematic side effects.

Figure 1. Rates of Compliance With Antidepressant Treatment[a]



[a]Data Lin et al.[4]

Bull et al.[15] assessed the major predictors of selective serotonin reuptake inhibitor (SSRI) noncompliance in another study that attempted to identify factors compelling patients to prematurely discontinue antidepressant treatment by interviewing 672 patients 3 and 6 months after they initiated SSRI therapy for a new or recurrent episode of depression. Researchers found that, in the first 3 months of treatment, 43% (N = 289), and in the second 3 months, 27% (N = 181) of patients either discontinued or switched their SSRI because of an adverse event. Adverse events were the most commonly reported catalysts for early discontinuation or switching in the first 3 months. For these patients, drowsiness/fatigue occurring in 10.2%, anxiety in 6.2%, headache in 5.8%, and nausea in 5.3% were the most frequently reported reasons. Overall, most adverse effects appeared to improve from the first 3 months to the second 3 months. The risk of discontinuation was significantly less for patients who remembered being told to

Table 1. Early Adherence Among Patients Receiving Versus Not Receiving Significant Items of Patient Education and Behavioral Discussion[a]

Topic Discussed by MD	Patient Receiving Discussion %	(N)	Percent Adherent: Receiving Education	Percent Adherent: Not Receiving Education	p Value
Take medication daily	79.6	(121)	75.2	54.8	.026
What to do if questions	62.0	(93)	76.3	57.9	.017
MD inquired about prior use of medicine	60.7	(85)	75.3	56.4	.019
Medicine takes 2 to 4 weeks for noticeable effect	49.6	(56)	83.9	59.7	.004
Don't stop medication without checking with MD	46.1	(65)	83.1	56.6	.001
Pleasant activities	39.5	(60)	81.7	60.9	.007
Continue medicine even if better	38.5	(57)	79.0	63.7	.050

[a]Reprinted with permission from Lin et al.[4]

take the antidepressant medication for at least 6 months compared with those who did not ($p < .001$). The acute phase of treatment is an obvious critical period when dropout rates are high; however, ensuring that patients are informed about how long to take the antidepressant medication can decrease rates of nonadherence considerably.

CONTROLLED-RELEASE ANTIDEPRESSANT TREATMENTS

Although tremendous advances have been made in the treatment of depression, there is still considerable room for improvement. One of the areas in which antidepressant treatments need to be substantially improved is in tolerability. Poor tolerability, particularly early in the course of therapy, can result in a higher incidence of dropouts, and nonadherence is an impediment toward people attaining lasting remission—the ultimate goal of depression therapy.[4,15]

Although most antidepressants have similar response rates, controlled-release formulations may be viable alternatives for those patients with tolerability problems that are commonly associated with immediate-release antidepressant formulations. Agents such as venlafaxine XR and bupropion SR are slowly released over time to decrease dosage requirements and increase safety. Controlled-release paroxetine (paroxetine CR) combines slow release with an enteric coating to decrease nausea and improve overall tolerability. The reduction in side effects for patients taking a controlled-release antidepressant formulation may improve adherence and therefore the likelihood of achieving a favorable treatment outcome.

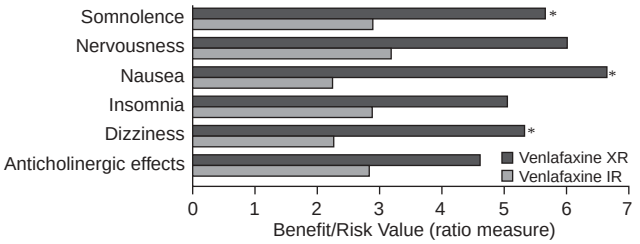
Venlafaxine

Venlafaxine is classified as a dual reuptake inhibitor antidepressant blocking the presynaptic reuptake of both serotonin and norepinephrine. Venlafaxine was initially introduced in an immediate-release (venlafaxine IR) form; however, for many patients venlafaxine IR proved to have a relatively unfavorable side effect profile—in particular, a high rate of nausea and, in higher doses, a tendency to increase blood pressure.[16] The propensity for venlafaxine to induce considerable side effects led to the development of an extended-release form of venlafaxine (venlafaxine XR), which reduces the peak plasma concentrations that occur with the immediate-release preparation. Studies have suggested that owing to this reduction, venlafaxine XR has a less severe side effect profile than venlafaxine IR, particularly in the early stages of treatment.[17,18]

In one such study,[17] researchers evaluated the efficacy (benefit) and tolerability (risk) of venlafaxine XR compared with venlafaxine IR in a double-blind, placebo-controlled, benefit-risk analysis of 278 outpatients with major depression. Patients were randomly assigned to receive 37.5 mg of venlafaxine IR twice daily (N = 87), 75 mg of venlafaxine XR once daily (N = 92) plus placebo once daily, or placebo twice daily (N = 99). Efficacy was defined as a final on-therapy Clinical Global Impressions-Improvement score of 1 (very much improved) or 2 (much improved). Treatment-emergent study events were also measured and defined as any new adverse event or any adverse event that was apparent at baseline and increased in severity during treatment, and benefit-risk was assessed using linear and ratio measures for insomnia, nervousness, somnolence, dizziness, nausea, and a composite of anticholinergic events. Results indicated that venlafaxine XR was superior on benefit-risk analyses compared with venlafaxine IR (Figure 2), with significant differences for somnolence, nausea, and dizziness.

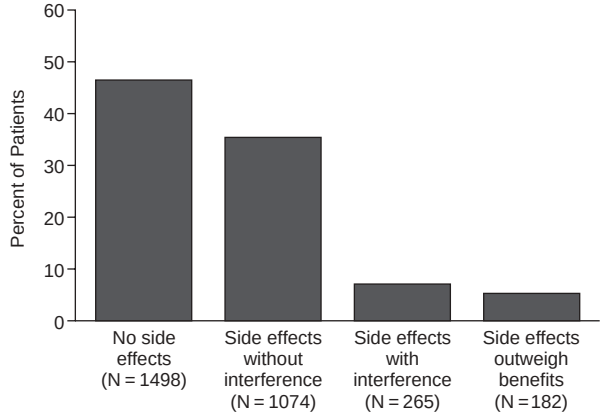
Another study[19] reviewed a number of randomized, double-blind, multicenter trials that examined the efficacy of venlafaxine XR compared with venlafaxine IR, fluoxetine, paroxetine, and placebo. Researchers reported that venlafaxine XR demonstrated efficacy in the treatment of major depression and that it was more effective than venlafaxine IR and at least as effective as paroxetine and fluoxetine. Additionally, findings indicated that venlafaxine XR was effective at reducing anxiety symptoms in patients with depression. The study reported that the incidence of adverse events in patients receiving venlafaxine XR was similar to the incidence of adverse events in patients receiving treatment with SSRIs.

Figure 2. Benefit-Risk Values With Venlafaxine XR and IR for Common Adverse Events[a]



[a]Reprinted with permission from Entsuah and Chitra.[17]
*p ≤ .05.

Figure 3. Tolerance of Bupropion SR[a]



[a]Reprinted with permission from Settle.[21] N = 3094 for entire study. Effects unknown for 75 patients.

Bupropion

For venlafaxine, the slow-release formulation provided an advantage by reducing the peak plasma levels associated with immediate-release preparations. This strategy was also utilized with bupropion when in 1996 a new sustained-release formulation (bupropion SR) was approved and marketed to physicians and their patients. Compared with the older bupropion IR formulation, bupropion SR has demonstrated similar efficacy, yet, fewer side effects: bupropion SR produces neither substantial sexual side effects[20] nor drug interactions[21] and decreases the risk of seizures that is a concern with high doses of bupropion IR.[22]

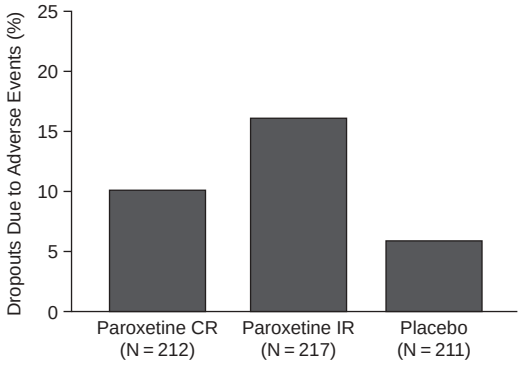
When dosages of bupropion IR exceed 450 mg/day, seizure risk increases considerably to an overall seizure incidence of 0.4%, or 4 per 1000.[22] Because seizure risk is strongly correlated with dosage and peak plasma levels, it was of interest to determine whether bupropion SR would in fact reduce seizure risk compared with bupropion IR. To test this hypothesis, a surveillance survey[21] of over 3000 patients was undertaken, and it was determined that 300 mg/day of bupropion SR or less was associated with a seizure rate of 0.06%, or fewer than 1 per 1000. The risk of seizures with bupropion SR is essentially not a significant concern in doses up to 400 mg/day; however, restricting dosages to a maximum of 400 to 450 mg/day would be prudent until more research is conducted. Moreover, bupropion SR was well tolerated—85% of patients had either no side effects, or side effects that did not interfere with their daily lives (Figure 3). Bupropion SR is generally well tolerated despite occasional side effects that in rare instances may include alopecia and sweating.[23] However, these idiosyncratic side effects are rarely serious.

Paroxetine

In an attempt to increase compliance, avoid compromising long-term efficacy, and reduce the premature termination of treatment by patients, a controlled-release form of paroxetine (paroxetine CR) was developed. This extended-release absorption formulation uses an enteric, film-coated tablet with a degradable polymeric matrix, which shifts absorption of the drug further down the gastrointestinal tract into the small intestine. With this formulation, absorption occurs over a 4- to 5-hour period, and releases about 80% of the paroxetine, which in turn necessitates an increase in the absolute dose that patients must ingest to account for half-life.

A few studies have evaluated the new paroxetine CR formulation in treating major depression.[24,25] Golden et al.[24] conducted a trial to examine the antidepressant efficacy and tolerability of paroxetine CR, in which patients were enrolled in 1 of 2 double-blind, randomized, flexible-dose, placebo-controlled, 12-week studies of identical design. Data from both studies were pooled. After a period of screening and a 1-week placebo washout, 212 patients were treated with 25 to 62.5 mg/day of paroxetine CR, 217 with 20 to 50 mg/day of paroxetine IR, and 211 with placebo. The majority of patients were women with a mean age of approximately 40 years and a mean Hamilton Rating Scale for Depression (HAM-D) score of about 23.4. Patients were evaluated at baseline and at weeks 1, 2, 3, 4, 6, 8, and 12. These trials revealed that paroxetine CR was as effective as paroxetine IR, and both were more effective than placebo over the 12-week period, as assessed by the reduction in 17-item HAM-D total scores in observed-case and last-observation-carried-forward (LOCF) analyses. A responder analysis was conducted in which response was defined as a ≥ 50% reduction in baseline HAM-D total score at endpoint, and remission rates were assessed by using the standard criterion of a HAM-D total score of ≤ 7. Response rates of observed-case analysis using the HAM-D among those patients who completed the study were 74% for paroxetine CR ($p \leq .05$ vs. placebo), 73% for paroxetine IR ($p \leq .05$ vs. placebo), and 61% for placebo. In the LOCF analysis, HAM-D response rates were 60% for paroxetine CR ($p \leq .05$ vs. placebo), 56% for paroxetine IR ($p \leq .11$ vs. placebo), and 48% for pla-

Figure 4. Overall Dropout Rates Due to Adverse Events for Paroxetine CR, Paroxetine IR, and Placebo[a]



[a]Reprinted with permission from Golden et al.[24] Paroxetine IR vs. placebo, p = .0008.
Abbreviations: CR = controlled-release, IR = immediate-release.

cebo. By endpoint, remission rates were 56% for paroxetine CR ($p < .05$ vs. placebo) compared with 53% for paroxetine IR and 44% for placebo. Additionally, there were a number of analyses of subfactors of the HAM-D, including depressed mood and psychological anxiety, which showed at least equal efficacy if not better efficacy for paroxetine CR than paroxetine IR or placebo.

Differences in tolerability between paroxetine CR, IR, and placebo were notable.[24] Paroxetine CR was well tolerated overall and was associated with lower rates of nausea than was paroxetine IR in the early weeks of treatment. Dropout rates due to adverse events were similar between placebo and paroxetine CR at 6% and 10%, respectively (Figure 4), while the dropout rate for paroxetine IR was considerably higher at 16%. There was no difference in baseline body weight (mean = 179 lb [81.2 kg]) in any of the groups at the beginning of the study, and there was essentially no difference in the pooled analysis in weight gain at endpoint. With regard to the patients' self-report on medication at endpoint, 44% of placebo-treated patients rated their treatment as good or very good compared with 52% of paroxetine IR patients and 67% of paroxetine CR patients. In this study, paroxetine CR appeared to have at least equal efficacy, if not slightly better efficacy, in terms of response and remission rates than paroxetine IR, and it appeared to be better tolerated, consistent with its pharmacokinetic profile.

Additional data[25] on the efficacy and tolerability of paroxetine CR include 3 randomized, double-blind, 10-week trials in panic disorder. The population comprised 889 patients with panic disorder treated with paroxetine CR, 12.5 to 75 mg/day (N = 444) or placebo (N = 445). At LOCF endpoint, 63% of patients from the pooled trials treated with paroxetine CR became panic-free for a 2-week interval compared with 53% of patients treated with placebo ($p < .005$). The proportion of Clinical Global Improvement responders at LOCF endpoint was significantly ($p < .01$) higher with paroxetine CR treatment (64%) than with placebo (46%), as well. Additionally, general anxiety and agoraphobic fear were significantly reduced in patients treated with paroxetine CR compared with placebo ($p < .001$). Paroxetine CR was well tolerated, and researchers concluded that the efficacy and tolerability of paroxetine CR in the treatment of panic disorder were well supported by the findings.

Other research comparing paroxetine CR with paroxetine IR includes a trial[26] of 323 elderly patients aged 60 to 88 years in which 12.5 to 50 mg/day of paroxetine CR, 10 to 40 mg/day of paroxetine IR, and placebo were compared. After 12 weeks, both paroxetine IR and paroxetine CR were superior to placebo; the placebo response rate using LOCF was approximately 25%, while the response rate for paroxetine IR was 42% and for CR, 43%. Further studies are ongoing that test the efficacy and tolerability of paroxetine CR in treating premenstrual dysphoric disorder, generalized anxiety disorder, seasonal affective disorder, and induced depression in patients with hepatitis C.

SUMMARY

Although all U.S. Food and Drug Administration–approved antidepressants are efficacious, patients discontinue treatment if the drug's side effects are intolerable. Fewer patients appear to discontinue therapy with controlled-release agents than with immediate-release formulations of antidepressants. Controlled-release formulations exhibit lower peak plasma drug levels compared to immediate-release formulations and generally reduce adverse effects during the critical early weeks of treatment. High rates of side effects associated with older immediate-release formulations have in recent years served as an impetus for the development of venlafaxine XR, bupropion SR, and paroxetine CR. Each controlled-release agent has demonstrated at least equivalent efficacy, and in some cases superior efficacy, perhaps due to enhanced likelihood of improved tolerability, particularly of higher doses compared with older immediate-release agents. The improved tolerability and associated improved adherence increase the likelihood of achieving favorable treatment outcomes for patients suffering from depressive disorders.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin and others), desipramine (Norpramin and others), doxepin (Sinequan and others), fluoxetine (Prozac and others), imipramine (Trofranil and others), nortriptyline (Aventyl and others), paroxetine (Paxil and others), trazodone (Desyrel and others), venlafaxine (Effexor).

Disclosure of off-label usage: It was determined that no investigational information about pharmaceutical agents has been presented that is outside U.S. Food and Drug Administration–approved labeling. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

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