Improving Adherence to Sertraline Treatment: The Effectiveness of a Patient Education Intervention

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Background: Previous attempts to improve antidepressant adherence have achieved mixed results. The current study evaluated the effectiveness of a patient education intervention designed to increase adherence to sertraline treatment.

Method: Data from a national pharmacy claims database were used to retrospectively match (along key demographic and clinical variables) consecutive patients prescribed sertraline (N = 1462) who received an educational intervention (Knowing More) between May 1, 2003, and April 30, 2004, with a control group of concurrent sertraline-treated patients who did not receive the intervention (N = 1462). The intervention consisted of 10 newsletters distributed over a 9-month period by mail and e-mail. The intervention and control groups were compared over a 7-month follow-up period on 3 adherence measures: time to discontinuation, days on therapy, and percentage of days on therapy.

Results: Cox regression analysis revealed that the time to discontinuation of sertraline (median = 100 days) was significantly greater ($p < .0001$) for the intervention group compared with the control group (median = 60 days). By the end of the follow-up period, 27% of patients remained on therapy with Knowing More versus 15% of those not enrolled in the compliance program. The mean number of days on therapy was 24.8 days (25.5%) longer for the intervention group compared with the control group (122.5 days for the intervention group versus 97.7 days for the control group). The percentage of days on therapy was 88.2% for the intervention group versus 77.7% for the control group among patients with at least 1 refill prescription ($p < .001$).

Conclusion: The educational compliance intervention, Knowing More, was associated with a significant increase in adherence to antidepressant treatment.

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An episode of major depressive disorder (MDD) will be experienced by nearly 1 in 5 individuals at some time in their lives.[1] Many patients who have an episode of MDD will experience a relapse or recurrence at some point.[2,3] The efficacy of antidepressant medications, including serotonin reuptake inhibitors (SRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclics, and monoamine oxidase inhibitors, in the treatment of MDD and other disorders has been established in numerous randomized clinical trials.[4–7] Maximum clinical improvement typically is observed after 2 to 6 months of treatment with antidepressant medications, and premature discontinuation of antidepressant therapy has been associated with increased risk of relapse of MDD.[8,9] Thus, current treatment guidelines recommend that antidepressant medication be continued for at least 4 to 5 months after symptom remission in order to prevent relapse, and longer (ongoing maintenance treatment) in patients with severe or recurrent MDD.[10]

Despite the need to continue antidepressant therapy to obtain a clinical response, treat residual symptoms to remission, and prevent relapse and recurrence, many patients discontinue treatment early. In clinical practice, discontinuation rates among those taking various antidepressants have been reported to be 28% during the first month[11] and 44% to 52% by 3 months.[11,12] While SSRIs have improved tolerability and lowered discontinuation rates compared with older antidepressants,[13,14] adherence remains a problem, with 28% of patients discontinuing treatment within 3 months.[15] Compounding the adherence problem is the fact that physicians are often unaware that patients have discontinued treatment. Available research suggests that only 30% of patients consult their physicians before discontinuing antidepressants,[16] and 25% of patients who discontinue treatment (as determined by pharmacy reports) continue to tell their physician that they are still taking their antidepressant medications.[17]

There are various reasons for discontinuing antidepressant therapy, most notably intolerable adverse events (e.g., nausea), lack of therapeutic response, and, conversely, improvement in depressive symptoms. Another factor implicated is lack of adequate communication between physicians and patients about side effects and the expected duration of treatment. A study[16] on this topic found that there are often differences between the instruc-

tions that physicians say were communicated to patients and what patients remember being told. In this study,[16] 72% of physicians reported that they typically instruct patients to continue their SSRI antidepressants for at least 6 months, but only 34% of patients reported that their physicians had asked them to continue taking antidepressants for this duration, and 56% stated they had received no instructions about duration of treatment. Those patients who reported that their physician had said they would be taking antidepressant medication for less than 6 months were 3 times more likely to discontinue treatment compared with patients who said they were told to continue therapy longer. Moreover, patients who discussed adverse effects with their physicians were less likely to discontinue their SSRIs than patients who did not discuss adverse events.[16] The authors suggest that instructions about possible adverse events and expected duration of therapy that are repeated throughout treatment might reduce premature discontinuations of SSRIs.[16]

Previous studies attempting to improve adherence to antidepressant medications have yielded mixed results. In general, those studies that focused on patient education about the nature and treatment of depression have largely failed to have an impact on adherence, while studies testing "collaborative care" models that place a mental health professional or psychiatrically trained nurse into a primary care setting to regularly review treatment-related issues with depressed patients have found more promising results,[18–20] as well as a nurse-telephonic intervention that improved outcomes for depressed patients treated in primary care settings.[21] However, existing studies of patient education approaches have suffered from a variety of methodological weaknesses, including short follow-up (in some cases only 2 weeks), very limited interventions, and small sample sizes.[18] Collaborative care models, while potentially useful, have substantial costs related to the additional personnel. Thus, further research is needed on the value of educational approaches that examine more intensive interventions and track patients over the duration of their medication use. Furthermore, because interventions to increase medication adherence in diverse areas of medicine typically have small effects,[22] it is important to have larger sample sizes to detect such effects.

The objective of the current study was to examine the effectiveness of an educational intervention designed to increase patient adherence to sertraline treatment in a primary care setting. Patients receiving the educational intervention were compared with a matched sample of sertraline-treated patients who did not receive the intervention. The intervention was designed to address weaknesses in previous approaches by having a greater intensity at the early phase of treatment, when risk for discontinuation is highest,[11] and by providing ongoing information over time (10 weeks) in order to continuously engage patients. A large sample size was available for analyses, and information on full treatment duration was obtained from pharmacy records, rather than relying on patient report.

METHOD

Source of Data

Data were analyzed using prescription data obtained from a company (Verispan) that compiles national retail pharmacy and medical claims data and constructs a Health Insurance Portability and Accountability Act (HIPAA)-compliant (no patient identifiers) database. Within this database, an intervention cohort was identified consisting of consecutive, sertraline-treated patients who were enrolled with Pfizer's patient program called Knowing More, an educational program for improving adherence for patients prescribed sertraline therapy. A control sample of patients who received sertraline but did not participate in the Knowing More program was also obtained from the database.

Patient Selection

Selected patients were men and women aged 18 to 65 years. For the intervention sample, patients were excluded if they had received any SSRI within 12 months prior to their first prescription for sertraline. This was done to identify patients new to SSRI antidepressant therapy. However, to be eligible, a patient needed to have pharmacy activity (any medication) during the first quarter of the period 12 months prior to enrollment in Knowing More and the last quarter of the period 7 months post enrollment to insure that only patients were selected whose pharmacy activity was continuously available in the database. All patients selected from the database were enrolled in the Knowing More program between May 1, 2003, and April 30, 2004.

When available (< 10% of patients), the presence/absence of a diagnosis of depression (e.g., ICD-9 codes 296.X, 311.X, and 300.X) was extracted from the database. The most recent relevant diagnosis code prior to enrollment in the Knowing More program was used. If the enrollee's first prescription preceded the enrollment date, the diagnosis closest to the prescription date was used.

The control group was created by matching sertraline-treated patients who did not receive the Knowing More program to those that did. Criteria for matching included age (in 10-year increments), gender, sertraline prescription counts, total antidepressant prescription counts, days supply of sertraline (in increments of 30), sertraline prescription dose (e.g., 50 mg), plan type (cash, Medicaid, private insurance), patient out-of-pocket cost for sertraline, and time (i.e., control patients' start date of sertraline therapy was matched within same day and/or month of enrollment of intervention patients in Knowing More program). Once matched on time (enrollment date), control

patients were also matched to intervention patients based on an initial prescription for sertraline occurring either 2 months before or 2 months after the enrollment date.

Adherence Measures

Three measures of adherence to sertraline were created: time to discontinuation, days on therapy, and percentage of days on therapy. The primary measure was time to discontinuation. A patient was determined to have discontinued if he or she did not refill a prescription within 15 days past his or her expected refill date, which was calculated as the previous prescription fill date plus days supply of drug provided. Length of therapy was defined as the total number of days supply of drug dispensed to a patient during the study period. The percentage of time on therapy was measured at 180 days and was defined as the number of days of sertraline supplied divided by the number of days between the first and last fill dates. The latter measure was calculated on the subset of patients having at least 1 refill.

Intervention

The Knowing More program was launched by Pfizer, Inc., in 2002 and was developed to address barriers to maintaining adherence to antidepressant therapy. Knowing More was developed with a panel of leading experts comprising psychiatrists and advocacy groups in the area of mental health. The program reinforces sertraline's effectiveness as a treatment, provides realistic expectations about clinical improvement and adverse events, emphasizes the importance of continued treatment, provides a source of ongoing support and reinforcement, and gives useful lifestyle tips and tools to enhance daily life. Though anyone was eligible to enroll in the program, the program was targeted primarily at those patients who had a duration of sertraline use of less than 3 months.

Patients were informed about the existence of the program and instructions for enrollment through several sources. These included various online advertisements, a description provided at the Zoloft.com Web site, "starter sample kits" given by physicians to patients beginning a new prescription of sertraline, and other documents available at physician offices, at pharmacies, and in print media. Through the starter sample kits, online advertisements, and pharmacy displays, patients were instructed to enroll in Knowing More through a variety of mechanisms including interactive voice recognition (IVR), a Web site, and business reply cards included with packages of professional samples of sertraline and available in physician offices.

The intervention, which is still available to sertraline users, consists of an initial greeting followed by a series of 10 patient communications (newsletters) over a period of 9 months. Because discontinuation is highest in the early stage of treatment, communications are more intensive during that stage. All communications come from Pfizer and are made by e-mail and mail for redundancy. The first contact (day 2 after enrollment) primarily educates the patient about depression ("you are not alone"). The message of the second contact (day 9) is that each patient is an individual and may respond differently to medications. The fact that it takes time to feel better with antidepressants is also emphasized in this communication. The third contact (day 14) discusses the importance of treating anxiety and depression in order to improve functioning ("you deserve a better life"). The primary message of the fourth contact (day 29) is "start living again." The fifth contact (day 49) stresses the importance of continuing to take sertraline so that additional improvement occurs. This communication also discusses the importance of an ongoing dialogue with the treating physician to review progress and side effects. Contact 6 (day 83) introduces the usefulness of staying on medication, even when symptoms have diminished, in order to prevent relapse. Patients are instructed to watch out for the signs of relapse and bring these to the attention of their doctors if such symptoms occur. A positive message about "seeking the good parts of life" is the central element of contact 7 (day 113). This positive message also continues with contact 8 (day 143) ("manage a healthy life"). The theme of contact 9 (day 173) is a review of the benefits and goals of treatment. Finally, contact 10 (day 263) discusses the goal of staying well throughout life, with general lifestyle advice. Success stories of patients with depression who recovered are described in several of the newsletters, and patients are consistently encouraged to talk to their loved ones, as well as to maintain communication with their doctor.

Analyses

Cox regression analysis compared Knowing More and control patients on time to discontinuation with age, gender, and whether enrollment in Knowing More was before or after sertraline therapy as covariates. Length of therapy and percentage of time on therapy were analyzed using t tests to compare the 2 groups (intervention vs. control).

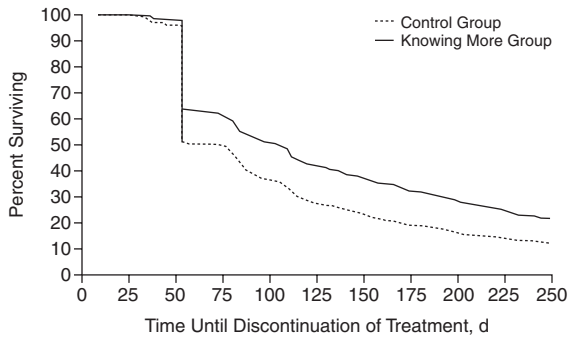
All analyses were 2-tailed, and statistical significance was declared at the .05 level.

RESULTS

Subject Disposition

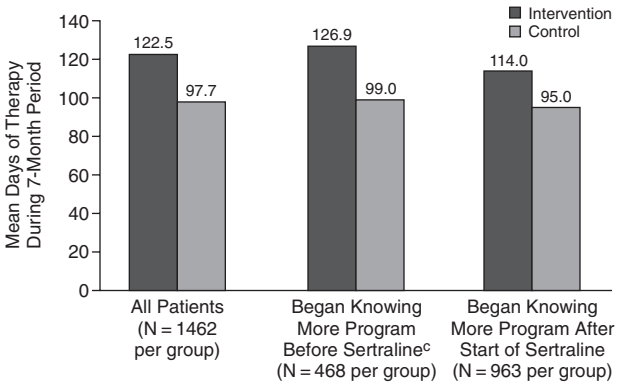
In the Verispan database of medical/pharmacy claims, there were 72,645 patients enrolled in the Knowing More program between May 1, 2003, and April 30, 2004. Of these, 23,039 were found to meet the eligibility criteria described above. After (1) limiting this eligible patient population to patients initiating a prescription for sertraline within 60 days before or after their date of enrollment and (2) removing patients who had received any SSRI

Figure 1. Survival Function[a] of Time to Treatment Discontinuation for Intervention and Control Groups on Sertraline Therapy[b]



[a]Adjusted for age, gender, and whether enrollment in Knowing More program was before or after sertraline therapy.
[b]Time until discontinuation of treatment includes days supplied for the last qualifying prescription.

Figure 2. Mean Length of Therapy (Days) for Intervention and Control Groups[a,b]



[a]Intervention group significantly ($p < .01$) greater than control in all comparisons.
[b]Total Ns for before and after analyses are less than for all patients because 31 patients who started the program on the same date as their initial sertraline prescription were excluded.
[c]Knowing More group that began intervention before sertraline treatment had significantly ($p < .01$) longer treatment durations compared with those that began Knowing More after start of sertraline.

within 12 months of their first prescription for sertraline, a final group of 1462 "new to therapy" sertraline patients was identified. Using the previously described matching criteria, a control group of 1462 patients receiving sertraline but not enrolled in Knowing More was identified from the database.

Of the patients enrolled in the Zoloft Knowing More program, most enrolled via either Zoloft.com or Knowing More Web sites or through literature provided with starter sample kits for sertraline (33% each). One-quarter of enrollees entered the program through more than 1 enrollment mechanism (i.e., signed on at the Web site and mailed in an enrollment form). Once enrolled in Knowing More, the majority of patients used the Web site as the vehicle for responding to the program (55%). IVR was used by 39% of patients to make responses.

Characteristics of Sample

The sample of patients receiving the Knowing More intervention (N = 1462) was 80% female and had a mean age of 42.7 years. The control sample was an identical number of patients (N = 1462) and, as a function of the success of the matching process, was also 80% female with a mean age of 42.7 years.

The starting daily dose of sertraline for those enrolled in Knowing More was an average of 61.1 mg. The control group had an average starting dose of 62.6 mg of sertraline.

Adherence to Sertraline Treatment

The Cox regression model examining time until discontinuation of sertraline treatment revealed a statistically significant difference (Wald $\chi^2 = 57,4$, $df = 1$, $p < .0001$) between the Knowing More and control groups (Figure 1). The median (unadjusted) times to discontinuation were 60 days (control) and 100 days (Knowing More). The unadjusted mean (SE) times to discontinuation were 100.4 (1.95) for the control group and 126.8 (2.2) for the Knowing More group.

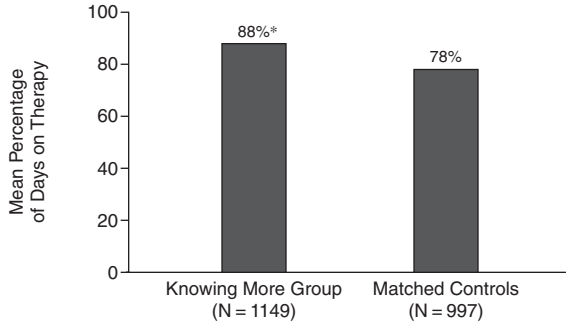
Length of Therapy

The mean number of days on therapy for those in the Knowing More program was 122.5 days, representing a 25% increase (24.8 days) compared with the control group (97.7 days). This difference was statistically significant ($p < .01$) (Figure 2). This effect was primarily apparent among those patients who began sertraline treatment after enrolling in Knowing More. The difference between intervention and control groups was an average of 27.9 days when considering only those patients who began treatment after enrollment. A difference of 19 days on average was apparent when the subsample who enrolled in Knowing More after treatment began was examined (Figure 2). The longer duration for those who enrolled in Knowing More before beginning sertraline (mean = 126.9 days) was significantly different from the mean duration (114.0 days, $p < .01$) of those enrollees who began sertraline treatment before the Knowing More program.

Percentage of Time on Therapy

Percentage of days on therapy was calculated in the subset of patients with at least 1 refill, which comprised 79% (N = 1149) of the Knowing More group and 68% (N = 997) of the control group. Patients enrolled in Knowing More had a significantly greater ($p < .001$)

Figure 3. Percentage of Days on Therapy Between the First and Last Prescription Fills[a]



[a]Only patients who remained on treatment for at least 180 days included.
*p < .001.

percentage of days on therapy than control patients among patients remaining on treatment for 180 days (Figure 3). The difference in mean percentage (88% vs. 78%) translates into 18 additional days on sertraline over the course of 180 days of treatment. Percentage of time on therapy was similar for those who enrolled in Knowing More before initiating sertraline (mean = 87%) compared with those who enrolled after initiating sertraline treatment (mean = 89%).

DISCUSSION

In this non-randomized, naturalistic comparison, patients receiving the Knowing More intervention, relative to matched controls, were found to have significantly greater adherence to sertraline treatment as measured by longer treatment duration and more consistent medication use while on treatment. The median time to discontinuation of sertraline was estimated by Cox proportional hazard methods as 100 days for patients participating in Knowing More, compared with 60 days for those not receiving Knowing More. At the 7-month follow-up, 27% of patients in Knowing More, compared with 15% of control patients, were still on treatment. At the 180-day follow-up period, on average, patients who enrolled in Knowing More had 18 more days of taking sertraline during their treatment period than did control patients.

In general, educational interventions designed to increase adherence with medications have yielded small effects when such effects are detectable at all.[22] In the case of antidepressant medications, reviews of previous research have indicated that there is little evidence that educational efforts, by themselves, can improve adherence.[18] However, the differences found in the current study between enrollees in the Knowing More program and matched controls suggest that such educational interventions can have an impact on SSRI adherence. While the absolute size of the difference between the intervention and control groups was modest, such differences may still have clinical usefulness. The clinical usefulness is evident when consideration is given to both persistence (staying on drug longer) and compliance (taking medication regularly throughout the treatment period). In particular, the educational intervention minimized the substantial drop-off in treatment rates occurring at the time of the first prescription refill, a critical juncture in treatment at which patients are at increased risk for early discontinuation.

It is also important to consider the modest, but significantly greater adherence found for Knowing More participants in the context of other available options for increasing adherence to antidepressants. Although "collaborative care" models have demonstrated some efficacy in increasing adherence, significant personnel costs (additional mental health specialist or trained nurse placed in the primary care setting) limit the practical application of such models. It is unclear who would pay for the additional costs of such "collaborative care" models. The costs of the Knowing More program were borne by Pfizer, Inc. Pharmaceutical companies are more likely to fund interventions that directly target consumers than to fund increased personnel costs in primary care settings. Thus, interventions like Knowing More that are designed and implemented by industry may be a more practical partial solution to the problem of antidepressant noncompliance than other approaches. Although industry support makes programs such as Knowing More less costly to public and private payers, only formal cost-effectiveness evaluation can provide information about the relative societal costs and benefits of different approaches to depression care.

The Knowing More intervention was designed to address some of the weaknesses with previous educational programs, and these enhancements may have been responsible for its success. Greater intensity of contact early in the treatment period may be especially important because of the high rate of discontinuation that occurs during this period.[8] Moreover, as suggested by Bull et al.,[16] it is likely to be important to continue to repeat instructions about possible adverse events and the expected duration of therapy treatment throughout the course of treatment. In fact, previous studies of educational interventions in medicine have suggested that mail reminders may be crucial for such programs to have an impact.[22] The Knowing More program had a more intensive, and more sustained, degree of contact than most other educational interventions designed to increase adherence to antidepressant therapy. Previous studies that failed to find an impact of educational interventions for increasing adherence either did not focus the intervention on 1 medication or class of antidepressants,[23] or had a brief intervention (about 3 hours of videotape education).[24]

Despite the success of the Knowing More program, much more work remains to be done. Only 27% of partici-

pants in the program remained on sertraline at the 7-month follow-up. Depressive disorders in primary care are often recurrent, and maintenance treatment of 1 year or more is recommended for these patients.[10,25] Thus, substantial further improvements in adherence will be needed to provide adequate pharmacotherapy to many individuals with depressive disorders in order to achieve remission and reduce relapse and recurrence. Lower relapse and recurrence rates are crucial to reducing the devastating effects of depression on social and occupational functioning.[26,27]

Limitations of the current study include the lack of random assignment and the lack of availability of other baseline, epidemiologic, and clinical variables such as diagnosis, depression severity, and treatment history that might be used to match groups or to control for statistically. Although comparisons suggest that the samples were well matched on available characteristics, patients already more motivated to remain on treatment may have been more likely to enroll in Knowing More. As a result, this study cannot establish a causal relationship between program participation and sertraline adherence. Randomized controlled trials are needed to confirm the benefits of such industry-directed patient adherence programs. Instead, present findings suggest that enrollment is a positive, prospective correlate of longer and more consistent antidepressant treatment.

CONCLUSION

A multi-communication, mail-based educational intervention program providing disease and treatment information to new-to-treatment sertraline patients that underscored the importance of patient adherence was associated with significantly greater persistence (longer time to treatment discontinuation), more days with drug on hand, and better compliance. These results suggest that mail-based educational programs, when administered to patients early in the course of therapy, may improve patient adherence.

Drug name: sertraline (Zoloft and others).

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