EDITORIAL

Switching Antidepressant Drug Therapy Helps Some Patients Some of the Time—What TORDIA, STAR*D, and Observational Research Have Taught Us About Treatment-Resistant Depression

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Based on results from clinical trials, including the recent Treatment of SSRI Resistant Depression in Adolescents (TORDIA) trial,[1] Khandker et al. introduce their study of antidepressant therapy class switching, published in this issue of *JMCP*, with the point that "between 30% and 50% of patients with major depression fail to respond to an initial course of antidepressant therapy" despite a wide range of antidepressant drug therapy options.[2] The high failure rate for antidepressant therapy in real-world settings is not surprising and poses an important challenge in treatment management. As Curtiss observed previously in *JMCP*, (a) antidepressant drug therapy alone is not much more effective than placebo, and the difference between antidepressant drug and placebo varies among clinical trials, with the effect of the active drug larger in patients with more severe depression, and (b) drug therapy is about as effective as psychotherapy, generally described as cognitive behavioral therapy (CBT).[3,4]

In a meta-analysis of data from 7 randomized controlled trials of the selective serotonin reuptake inhibitors (SSRIs), bupropion, or placebo, Thase et al. found that after 6-8 weeks of follow-up, 51% of outpatients with moderate to severe recurrent major depressive disorder (MDD) responded (i.e., demonstrated a ≥ 50% reduction in Hamilton Rating Scale for Depression [HAM-D] scores) to placebo as compared with 62%-63% for pharmacotherapy. Remission (i.e., a score of 7 or less on the first 17 HAM-D items) was experienced by 36% of the patients who received placebo and 47% who received pharmacotherapy.[5] Similarly, the meta-analysis by Walsh et al. of 75 controlled trials comparing placebo with antidepressant medication in the treatment of adults with MDD found that 30% of placebo-treated patients experienced a 50% or better HAM-D improvement. Although placebo response rates were variable, ranging from 13%-52%, placebo response exceeded 30% in more than one half of the studies.[6] Response rates to active medication, measured using the highest drug response rate in trials that tested more than 1 drug, were 50% overall, ranging from 32%-70%.

In the TADS (Treatment for Adolescents with Depression Study), results for active medication were more favorable; placebo was effective in about 35% of 439 patients aged 12-17 years with MDD, compared with about 43% response to CBT, 61% response to the SSRI fluoxetine, and 71% response to combined CBT and fluoxetine.[7] In the TADS study, the combination of CBT and fluoxetine (10 mg-40 mg per day) was superior to fluoxetine alone ($P = 0.02$) and to CBT alone ($P = 0.01$). However, in Emslie et al.'s study of 122 children and 97 adolescents with MDD, remission rates for patients treated with fluoxetine (65%) and placebo (53%) were similar ($P = 0.093$).[8]

After Initial Antidepressant Treatment Fails—Findings from Randomized Trials

Khandker et al.'s efforts to examine the extent and cost implications of a switch in antidepressant treatment in routine clinical practice would, at first glance, seem to be a logical follow-up to a recent surge of interest in treatment-resistant depression.[9] Appropriately, the report by Khandker et al. precipitates an important question: What can payers and patients expect from a switch from an SSRI to venlafaxine, or vice versa, in routine clinical practice? Randomized trial results published between 2006 and 2008 provide a partial answer.

The TORDIA trial examined the relative efficacy of 4 treatment strategies in adolescent patients with a primary diagnosis of MDD who had not responded to 2 months of initial treatment with an SSRI. In 334 patients aged 12-18 years, 12 weeks of CBT plus a switch to either an alternative SSRI (20 mg-40 mg per day of paroxetine, citalopram, or fluoxetine) or venlafaxine (150 mg-225 mg per day) elicited a higher response rate (54.8%; 95% confidence interval [CI] = 47%-62%) than did a medication switch alone (40.5%; 95% CI = 33%-48%).

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial studied 1,439 adult outpatients with non-psychotic MDD who had failed treatment with the SSRI citalopram, either because of non-response or intolerance to side effects.[10] Seven treatment options were studied in the first sequential treatment intervention: (a) a switch to either CBT, sustained-release buproprion, sertraline, or extended-release venlafaxine, or (b) augmentation of citalopram with either sustained-release buproprion, buspirone, or CBT. STAR*D employed an "equipoise-stratified" design, meaning that prior to randomization, patients were permitted to refuse treatment options that they considered unacceptable, with certain limits. For example, a patient could choose a drug switch only and refuse augmentation, or choose augmentation only and refuse a switch, but could not select the particular drug used. Choices with respect to CBT were similar; a patient could refuse to accept any further drug treatment and choose CBT only, or could refuse to accept any option that might involve CBT.

STAR*D was an effectiveness trial, the largest study to date of real-world patients (n = 4,041) who experienced a depressive episode as part of an MDD. In a breathtaking illustration of the

problems besetting efforts to marry the advantages of randomized designs with the reality of patient choice in clinical practice, all STAR*D patients were "strongly encouraged" to allow themselves to be randomized into any treatment arm, but only 21 patients (1%) did so. Notably, of 1,439 patients who failed initial treatment with citalopram and were eligible for randomization to a second treatment attempt, 583 (41%) accepted only a drug-switch option and an additional 430 (30%) accepted only drug augmentation. Only 44 patients (3%) requested CBT, and 71% refused any option that had the potential to include randomization to CBT.[10]

STAR*D results provided no evidence of superiority for any of the drug options. Among patients who permitted themselves to be assigned to a drug switch, rates of remission, as measured by HAM-D score of 7 or less, were not significantly different across the treatment groups: 21.3% for buproprion (n=239), 17.6% for sertraline (n=238), and 24.8% for venlafaxine (n=250).[10] Similarly, among patients who permitted the use of augmentation, remission rates were 29.7% for buproprion (n=279) and 30.1% for buspirone (n=286).[11] Considering all options, remission rates for the second-step treatments were a discouraging 25%, amounting to an overall response rate of about 50%-55% after 2 treatment attempts.[12]

What Can Payers and Patients Expect Following an Antidepressant Switch?

In an effort to determine the effects of antidepressant switching in routine clinical practice, Khandker et al. analyzed administrative claims for 48,950 patients who had at least 1 pharmacy claim for either an SSRI or venlafaxine (a selective norepinephrine reuptake inhibitor [SNRI]) in calendar year 2002 and at least 1 medical or hospital claim with a diagnosis code for depression (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 296.2x for MDD single episode, 296.3x for MDD recurrent episode, 300.4 for dysthymic disorder, and 311 for depressive disorder not elsewhere classified); less than 2% of patients included in the sample had at least 1 claim with a diagnosis of MDD (ICD-9-CM 296.2 or 296.3). The study's key outcome measure was switching across antidepressant class (i.e., from SSRI to venlafaxine or vice versa); patients switching from the initially prescribed SSRI to another SSRI drug were considered non-switchers. Of the 48,950 patients, 2,378 (4.9%) switched antidepressant therapy class within 1 year of the initial claim; 733 initial venlafaxine patients (13.8%) switched to an SSRI, and 1,645 initial SSRI patients (3.8%) switched to venlafaxine.

Key findings of Khandker et al.'s analysis addressed the relationship between antidepressant therapy class switching and costs for medical services and prescription drugs in the 12-month period following initiation of antidepressant drug therapy. First, patients who switched antidepressant drug therapy had higher 12-month follow-up all-cause and depression-related costs than did patients who did not switch therapy class. Second, mean monthly health care costs generally declined following the switch, with the exception that pharmacy costs increased for patients switching from an SSRI to venlafaxine.

Sequential Antidepressant Use Documented in Claims: A Switch for Major Depression, New Episode of Mild Depression, or What Exactly?

Khandker et al. posit that their finding of a decrease in average monthly cost from pre-switch to post-switch may represent improvement in patient outcomes, "consistent with results presented in the clinical literature showing improved response and remission rates for patients after they switch to an alternative antidepressant class." However, the perils inherent in observational research—particularly in translating complex clinical phenomena like "treatment resistance" into the relatively simple operational rules required for analyses of administrative claims data—are well known to those familiar with the research methods literature. Claims database researchers must inevitably make some trade-offs between external validity (the degree to which the study sample represents the population to which results will be applied) and internal validity (the degree to which the research actually assesses the phenomena that it purports to measure), and Khandker et al.'s work is no exception. A close look at Khandker et al.'s methodology reveals important questions about the degree to which their findings accurately represent outcomes for treatment-resistant patients.

Switch or new episode? First among these questions is whether the outcome measured by Khandker et al. was a drug switch or a new treatment episode. One would assume that a "switch" in antidepressants would occur within the same depression episode, with perhaps a gap in therapy of no more than 15-30 days. However, in defining a drug switch, Khandker et al. imposed no requirement on the length of time between depletion of the initially dispensed antidepressant and the first fill date for the new drug. The resulting gap in antidepressant treatment could have been as long as 360 days, and the mean gap in drug therapy was 60-61 days.

Treatment resistance, side effects, or something else? Even if all of the patients with sequential use of different antidepressant therapy classes represented true switches, there is reasonable doubt about how many of those switches were actually attributable to treatment resistance. Adverse effects have been implicated as an important factor prompting antidepressant treatment discontinuation or change.[13,14] In a telephone survey of 226 patients who either discontinued SSRI treatment (n=189) or switched to a different antidepressant (n=37) within 3 months of treatment initiation, 43% reported that their treatment change was due to at least 1 adverse effect, most prominently drowsiness or fatigue, with only 12% attributing the change to lack of symptomatic improvement.[15] In another telephone survey conducted with patients being treated with SSRIs and diagnosed with either MDD single episode (ICD-9-CM 296.2) or depressive disorder not elsewhere classified (ICD-9-CM 311), patients who reported

that they had discussed adverse events with their physician were much more likely to report switching antidepressants (odds ratio=5.60; 95% CI=2.31-13.60).[16] To maximize the possibility (albeit without guaranteeing) that switching was attributable to nonresponse, a reasonable approach would have been to apply a minimum length of initial antidepressant drug therapy prior to the switch, since it is unlikely that a practitioner would switch therapy for nonresponse after, for example, only 1 week of treatment. Unfortunately, Khandker et al. applied no minimum, and there were even a small number of patients (n=7) who received the initial and "switch" antidepressants on the same day.

Major depression or dysthymic disorder or some other condition? Identifying patients with "depression" using an administrative claims database is one of the trickiest tasks that a researcher will encounter. Diagnostic miscoding arising from concerns for patient insurability or reimbursement amount is reported to be routine in provider billing (and, therefore, in claims data[17]), and one half of primary care physicians in a 1994 survey reported that they had deliberately used a code other than major depression to bill for services provided to at least 1 patient with MDD during the previous 2 weeks.[18] "Superbills," the preprinted billing forms used by most physician offices, typically include only the top 20-30 diagnoses most commonly seen in the practice, encouraging the coding of some diagnoses more than others.[19] The superbill template promulgated by the American Academy of Family Physicians in 2006 includes only 1 code for depression—311—denoted on the form as "depression, not otherwise specified."[20]

Given all these factors suggesting that the depression diagnoses in medical claims data are imprecise and unreliable, Khandker et al.'s decision to include a broad spectrum of diagnoses in their search for patients with "MDD" is reasonable. Yet, one is left with questions about the clinical characteristics of the patients included in the study; more than 80% of patients in the sample carried a diagnosis of depression "not elsewhere classified" (ICD-9-CM 311). Perhaps more troubling, 22% of Khandker et al.'s study population carried a diagnosis of "dysthymic disorder" (ICD-9-CM 300.4), which is characterized by a "chronically depressed mood that occurs for most of the day more days than not for at least 2 years."[21] Sensitivity analyses using various diagnostic criteria would have been helpful, but were unfortunately not performed by Khandker et al.

What Do the Cost Analyses Really Mean?

Aside from the concerns about the validity of the definition of the patient categories used by Khandker et al., the drug cost data are not valid today. This study is based on data that are 6 years old, and the average SSRI drug-therapy cost, before patient cost share, is now less than $1 per day since all but escitalopram are available in generic form. Extended-release venlafaxine is also more expensive today than at the time of the Khandker et al. study. The real-world discounted price is now $4.00 per day for the 150 mg, 24-hour capsule of venlafaxine,[22] twice the median $2.00 per day reported by Khandker et al. for the post-switch patients who initially received an SSRI as their index medication. This is not a minor point since antidepressant drug therapy accounted for about two thirds of the total depression-related monthly medical cost after the switch.

Khandker et al. also attempt to make a point that switching antidepressant drug therapy may be a good thing because total monthly depression-related cost declines after the switch. However, the absolute costs and absolute cost differences between pre-switch and post-switch are small, and the cost variation within groups is large. For patients switching from an SSRI to venlafaxine, the median (mean [SD]) monthly depression-related total (medical plus pharmacy) costs were $52 ($158, [$916]) during the pre-switch period and $68 ($111 [$359]) after the switch. For patients switching from venlafaxine to an SSRI, pre-switch and post-switch median (mean [SD]) monthly depression-related total costs were $55 ($106 [$306]) and $44 ($64 [$146]), respectively. Also, despite the documented effectiveness of CBT in controlled trials, Khandker et al. unfortunately did not measure use of behavioral therapy services to help explain the (small) differences in resource utilization that they found.

However, the study by Khandker et al. does provide a first glimpse of the magnitude of cost and utilization differences between patients who receive only SSRIs or venlafaxine in 12 months ("no-switch") versus patients who receive at least 1 claim in both antidepressant drug classes in the same year ("switch"). It is not surprising that the "switch" patients had consistently higher 12-month depression-related medical and pharmacy costs, about 2 times higher for the patients initiated on an SSRI (mean $1,255 [median $684] for switch patients vs. $562 [$340] for no-switch patients), since presumably many of the no-switch patients either had a mild episode or experienced remission. For the patients who were initiated on venlafaxine, the higher cost of venlafaxine translates into higher 12-month median [mean] antidepressant costs for no-switch venlafaxine patients ($456 [$569]) compared with initial venlafaxine patients who switched to SSRI ($428 [$508], $P<0.001$), thereby narrowing the total 12-month depression-related medical and pharmacy cost difference between the switch and no-switch venlafaxine patients to a mean of $134 and a difference of $1 in median cost (medians of $527 and $528, respectively). In reviewing these cost outcome data, it is important to keep in mind that only about 5% of patients in the study by Khandker et al. switched to a second antidepressant drug class in the 12 months following the initial pharmacy claim for either an SSRI or venlafaxine.

Good Switch or Bad First Try? Switching Versus Pseudo-Resistance.

A recent commentary on STAR*D suggested that many patients who switch antidepressant treatments were never given an adequate trial with the initially dispensed drug.[12] Huynh and

McIntyre point out that up to one half of the patients in the STAR*D effectiveness trial who eventually experienced remission to index therapy did so after 6 weeks of therapy, and these authors draw our attention to the likelihood that a large proportion of the patients who were labeled as responders to augmentation/combination drug therapy may actually be late in responding to the index drug therapy.[12] That a large percentage of patients with depression receive suboptimal treatment, meaning antidepressant pharmacotherapy that does not meet guideline standards for dose and duration, has been well documented for about 25 years.[13,14,23,24]

The question of how to address treatment failure is more complex than simply focusing interventions on dose titration and duration of antidepressant drug therapy, because much of the problem is driven by patient nonadherence. A 1995 study conducted in a health maintenance organization (HMO) documented that 28% of patients prescribed antidepressants in primary care discontinued drug treatment during the first month.[13] A more recent study, conducted using chart review in another HMO, found that of 249 patients whose records indicated failure to meet Health Plan Employer Data Information Set (HEDIS) criteria for antidepressant treatment, 25% had told their doctor that they were taking their medication even though the pharmacy claims database indicated that they were not.[25]

Thus, even if the findings of Khandker et al. do accurately reflect the outcomes of an antidepressant class switch, they still do not address the question of the optimal course for payers interested in improving the quality of treatment of depression by better addressing the problem of initial treatment failure. Should payers encourage a switch in drug therapy, or should they focus on efforts to improve the course of the initial treatment, such as targeted collaborative management programs that have been successful in previous research?[26,27] Studies like Khandker et al.'s work that examine only the option of an antidepressant switch, although apparently consistent with the wishes of many patients, as expressed by their choices in the STAR*D trial, do not provide a complete picture of the managed care options available to payers and providers.

What Have TORDIA, STAR*D, and Observational Research Taught Us?

Despite its limitations, the work of Khandker et al. does inform us about the important nuances in performing research on antidepressant switch therapy and suggests alternate methods that might be used by others in future research. Although all of this data crunching may advance our knowledge of the cost outcomes associated with switching antidepressant drug therapy, Khandker et al. leave us without substantive discussion of the context for these cost outcomes. While Khandker et al. include a reference for TORDIA, the authors make no mention of the efficacy and safety outcomes for switch therapy with venlafaxine or SSRIs found by Brent et al. in the TORDIA clinical trial. For example, the TORDIA results appear to be consistent with Khandker et al.'s findings about the small changes in relative costs after the drug therapy switch, since 59% of the patients in TORDIA did not respond with significant improvement in depression when switched to a different drug therapy alone (without CBT).

While the TORDIA trial is directly relevant to the question about the value of switch therapy in achieving response to antidepressant drug therapy, direct comparison between TORDIA and the Khandker et al. study should be made cautiously. First, TORDIA's population differs from the population in the cost analysis performed on administrative claims data by Khandker et al. The TORDIA trial enrolled adolescents, while the cost analysis performed by Khandker excluded patients aged younger than 18 years. Second, as in most clinical trials, the exclusion criteria in the TORDIA trial were extensive, excluding, for example, patients with bipolar disorder, psychosis, and substance abuse or dependence. The cost analyses performed by Khandker et al. made none of these exclusions, perhaps explaining some of the apparent wide variation in severity of illness in the population, from mild depression to complicated medical-behavioral cases.

The large SDs in the annual and monthly costs in the analysis by Khandker et al. suggest that there is a wide range of disease severity, even among switchers. For example, mean (median) per-patient 12-month depression-related medical cost (excluding the cost of antidepressant drugs) was $583 ($59) for SSRI switchers with an SD of $3,339, nearly 6 times the mean cost, and a range of $0 to $88,403. For SSRI non-switchers, the 12-month depression-related medical costs ranged from $0 to $189,945. Similarly, the 12-month mean (median) depression-related medical cost for venlafaxine switchers was $355 ($42) with an SD ($1,397) nearly 4 times the mean cost. The 12-month depression-related medical cost ranges for venlafaxine switchers and non-switchers were, respectively, $0 to $16,787 and $0 to $29,326. Similar trends were observed in all-cause costs; for the entire sample, the range in minimum and maximum per-patient all-cause 12-month costs was $0 to $2,127,083.

It is, of course, impossible for the authors in the study reported by Khandker et al. to determine a cause-and-effect relationship between the costs outcomes for switch versus no-switch patients and between the SSRI versus venlafaxine subgroups. Additionally, there is convincing evidence to suggest that a large portion of treatment-resistant patients do not respond to the second (alternative) antidepressant. The STAR*D clinical trial showed that the response rate to the second (switch) antidepressant was less than 30%, depending on the depression inventory used, in adult patients unresponsive to initial SSRI therapy. Therefore, it is reasonable to assume that at least two thirds of the "switch" patients in the administrative claims analysis performed by Khandker et al. did not respond with improvement in their depression.

This point also highlights the questionable presumption that a medication switch can produce savings in total medical costs in a short course of therapy. Khandker et al. imposed no minimum length of therapy in calculating "post-switch" costs and report an extremely wide range of post-switch follow-up time days of therapy (for SSRI-to-venlafaxine switchers, mean=186, SD=104, median=195; for venlafaxine-to-SSRI switchers, mean=199, SD=102, median=203). In the limitations, the authors acknowledge that 10 patients had 0 post-switch days of drug therapy; for all patients with less than 30 days follow-up in either the pre-switch or post-switch time periods, Khandker et al. adopted the unusual strategy of assuming a minimum 30 days of follow-up and divided the cost figures by a denominator of 1 (i.e., 1 month).

The TORDIA and STAR*D results are also relevant to Khandker et al. because venlafaxine was not superior to an alternate SSRI as switch therapy, contrary to the hypothesis of the authors of the TORDIA results. It is also important to note that the TORDIA results are consistent with the STAR*D results that documented no advantage for any of the study medications. Right on point for the analysis by Khandker et al., the TORDIA trial found (a) no difference in the response rate between venlafaxine (48.2%; 95% CI=41%-56%) and an alternative SSRI (47.0%; 95% CI=40%-55%; $P=0.83$), and (b) more adverse events associated with venlafaxine compared with SSRIs, such as increased diastolic blood pressure and pulse, and more cases of skin problems (7.8% [n=13] vs. 1.8% [n=3]). A meta-analysis (2002) sponsored by the manufacturer of venlafaxine found venlafaxine slightly more effective than SSRIs, but not tricyclic antidepressants,[28] and a subsequent meta-analysis (2006) concluded that escitalopram (SSRI) was similar in efficacy to extended-release venlafaxine.[29]

In January 2007, the Agency for Healthcare Research and Quality (AHRQ) concluded from review of 2,099 citations and evaluation of 293 articles, from 2,099 citations and evaluation of 293 articles, that 38% of patients with depression do not respond to treatment for 6-12 weeks with second-generation antidepressants (e.g., SSRIs, bupropion, venlafaxine) and 54% do not achieve remission.[30] This AHRQ comparative effectiveness report also concluded that it was not possible to determine the factors that reliably predict individual patient response or non-response to second-generation antidepressant drug therapy. For treatment-resistant or recurrent depression, the AHRQ comparative effectiveness evaluation found only 1 good quality study (Rush et al., STAR*D) in concluding that there is no difference in effectiveness between SSRI (sertraline) and extended-release venlafaxine. However, the combination of safety and effectiveness results from TORDIA, STAR*D, and the AHRQ comparative effectiveness report deliver a preponderance of evidence that supports the choice of an SSRI over venlafaxine as a second-line antidepressant.

This exercise in putting some context around the administrative claims analysis performed by Khandker et al. reminds us of how much we still have to learn about the utility of administrative claims to inform us about cost outcomes associated with the interventions that we can only infer (imperfectly) from administrative claims. Particularly in the realm of inference from administrative claims for antidepressant drugs and at least 1 claim with a diagnosis code for a wide range of depressive conditions, the exercise is much like looking through a keyhole trying to ascertain the contents of a large room. Administrative claims analysis to answer questions about economic outcomes associated with switching antidepressant drugs needs considerable maturity, but perhaps Khandker et al. provide a useful step in attaining more informed analytical approaches for future research.

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