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## Gauging the Use of Second-Generation Antipsychotics: Medicaid Benefits Data Suggest Much Room for Improvement

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Antipsychotic medications such as chlorpromazine and thioridazine were commonly used in the first generation of psychopharmacology for treatment of depressive disorders, both alone—a practice that is now called monotherapy—and as adjuncts to or in combination with tricyclic antidepressants or monoamine oxidase inhibitors.<sup>1</sup> By the early 1990s, this practice had largely been limited to combined treatment of psychotic depression, primarily because of concerns about exposing patients with nonpsychotic mental disorders to the risk of tardive dyskinesia.<sup>2</sup> A number of newer options also were available for patients with more difficult to treat depressive disorders, including several newer generation antidepressants and the use of lithium salts and thyroid hormones as adjuncts to antidepressants.<sup>2</sup> Introduction of a second, newer generation of antipsychotic medications with tangibly lower risks of tardive dyskinesia led to a reevaluation of the role of these novel antipsychotic medications for patients with nonpsychotic depressive disorders, and, in the past decade, several of the so-called second-generation antipsychotics (SGAs) have received indications from the US Food and Drug Administration (FDA) for monotherapy of bipolar depression and adjunctive treatment of nonpsychotic major depressive disorder.<sup>3,4</sup> Nevertheless, it is widely appreciated that the potential for benefit derived from therapy with an SGA must be balanced against the risk associated with these medications, and there are ongoing concerns about whether or not the risk-benefit ratio of this strategy justifies such widespread use of SGAs for treatment of depressed patients with nonpsychotic mental disorders.<sup>5</sup> The report by Gerhard and colleagues<sup>6</sup> in this issue of the *Journal*, which taps into a large Medicaid database to examine the use of antipsychotic medications to treat depression in the United States during the first decade of the 21st century, is therefore of great interest. After briefly considering the clinical context of this work and interpretation of some of the key findings of Gerhard and colleagues, this commentary will consider some of the factors that influence clinicians' decisions to prescribe SGAs to patients with nonpsychotic depressive

disorders and suggest some strategies to preserve clinicians' flexibility while mitigating the costs and risks that are associated with this strategy.

### Clinical Context

For this analysis, the Medicaid database provides comprehensive information on the use of antipsychotic medications across most of the United States; it comprises nearly 1.6 million adults, aged 18–64 years, who were seeking treatment for a new episode of depression between 2001 and 2010. At the beginning of the decade, the American Psychiatric Association Practice Guideline<sup>7</sup> emphasized use of medications other than antipsychotics, including lithium, thyroid hormones, buspirone, and benzodiazepines, as adjuncts when antidepressants alone provided inadequate benefit. The first published report on the use of olanzapine-fluoxetine combination for treatment resistant depression (TRD) occurred early in the decade,<sup>8</sup> and the latter years of the decade were marked by FDA approval of aripiprazole (2007), quetiapine (2008), and olanzapine (2010)—specifically in combination with fluoxetine—for adjunctive therapy. By the end of the decade, coincident with publication of the third edition of the American Psychiatric Association Practice Guideline,<sup>4</sup> the SGAs were considered one of the best-established options for patients who obtained inadequate benefit from antidepressant monotherapy and were increasingly used for this indication.<sup>9</sup>

### Interpretation of Key Findings

Gerhard and colleagues<sup>6</sup> examined the Medicaid database (that, again, included nearly 1.6 million adults, aged 18–64 years, who were seeking treatment for a new episode of depression). About 1 in 7 of these individuals (nearly 225,000 patients, or 14% of those treated for depression) were prescribed an antipsychotic medication at some point during the first year after diagnosis. Prescription of an SGA accounted for almost all (97%) of the antipsychotic therapy provided to patients with depressive disorders. There were a number of correlates of antipsychotic use, and most could be considered markers for global illness severity or complexity (eg, disability status, psychiatric hospitalization, recent use of emergency services, the number of outpatient visits, comorbid substance abuse, diagnosis of major depressive disorder [MDD]). However, as African Americans and men of all ethnicities were also significantly more likely to receive an antipsychotic, it is clear that the decision to prescribe was made within a sociocultural context.

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About 40% of the time, the decision to prescribe an antipsychotic medication was linked to a clarification or revision of the diagnosis for which antipsychotic medication is indicated (ie, bipolar disorder, schizophrenia, or a psychotic/delusional form of MDD). Thus, in the remainder (constituting 8% of treated cases), an antipsychotic medication was prescribed for treatment of a person with a nonpsychotic depressive disorder. Almost one-half of this group (48%) received quetiapine, and about one-quarter (26%) were prescribed risperidone; olanzapine (22%), aripiprazole (16%), and ziprasidone (7%) were used to treat the remainder.

For the average patient, the decision to begin an antipsychotic medication was not hasty, as it occurred more than 3 months (mean = 99 days) after the initial diagnosis. However, time to prescription was quite variable, with a standard deviation of 106 days, which suggests that perhaps one-fourth of these prescriptions were initiated during the first month of therapy. Perhaps more surprisingly, the pattern of prescription suggested that, more often than not, antipsychotics were being prescribed relatively early in treatment algorithms and these medications were not, as is sometimes recommended, being held in reserve for treatment of patients with more refractory depressive episodes. Consistent with this, only about one-fourth (29%) of the patients met even the “thinnest” or least rigorous criteria for TRD, namely, nonresponse to 4 weeks of therapy with a minimum therapeutic dose of 1 first-line antidepressant. Moreover, pharmacy records suggested that nearly half (47%) of these patients were prescribed the antipsychotic as a monotherapy, ie, there was no ongoing or active prescription for an antidepressant.

One might be less concerned if most of the antipsychotic prescription was for low doses or short durations, intended to stabilize crises. However, Gerhard et al<sup>6</sup> found that, for the majority of the patients in this database, exposure to antipsychotic medications was not trivial in terms of both the dose and the duration of therapy. For example, the median durations of therapy ranged between 3 and 4 months for all of the antipsychotics studied. Moreover, significant minorities of patients received relatively high doses of these medications. For example, for the 3 SGAs with FDA indications for use in combination with antidepressants, 15% of those treated with quetiapine received doses above 300 mg/d, 17% of those treated with aripiprazole received doses above 15 mg/d, and 27% of those treated with olanzapine received doses above 12 mg/d.

The annual proportion of patients treated with antipsychotic medications was remarkably stable across the decade, never dropping below 8% and never reaching 10%. Such consistency across a decade suggests that clinicians' decisions to use antipsychotics to treat patients with nonpsychotic depressive episodes was well established at the start of the decade and was not a transient fad. Moreover, use of SGAs to treat nonpsychotic depression did not spike after publication of the first report on olanzapine-fluoxetine combination or the FDA approvals of aripiprazole or

quetiapine for this new indication, which suggests that the practice was not immediately influenced by press releases or marketing campaigns.

### Alternate Considerations

On the surface, one might simply conclude that a significant minority of the depressed people whose treatment is covered by Medicaid receive pharmacotherapy that deviates substantially from contemporary practice guidelines and that this may well denote “bad care.” Although dispiriting, this is not a shocking conclusion: one of the major driving forces behind the development and dissemination of practice guidelines is to improve the care that our patients receive.<sup>2,4</sup> If 1 in 12 of the treatment-seeking patients with nonpsychotic, nonbipolar depressive disorders actually received “bad care” via inappropriate prescription of an antipsychotic medication, the findings of Gerhard et al<sup>6</sup> clearly demonstrate that there is still much work to be done.

This conclusion must be tempered by an appreciation that a course of treatment that deviates from practice guidelines is not necessarily “bad” care. To more properly address this issue, one would need more knowledge about past treatment history and, most importantly, a detailed description of each patient's symptom presentation and comorbidities. For example, whereas monotherapy with quetiapine would be considered off-label in this US data set, it is “evidence-based” (ie, there are multiple positive controlled studies)<sup>10</sup> and is approved by regulatory authorities in several countries, including Australia. As quetiapine monotherapy also is now a well-established strategy for bipolar depression throughout most of the world,<sup>11</sup> it is virtually certain that some portion of these patients with so-called “unipolar” depression were judged by their treating physicians to have illnesses within a broader bipolar spectrum. Likewise, although persistent residual symptoms such as insomnia and anxiety constitute—at best—“gray area” indications for adjunctive SGA therapy, few psychiatrists would consider it “bad care” to prescribe a low dose of quetiapine or risperidone for an anxious depressed patient with a history of alcoholism or sedative-hypnotic abuse.

It is also good to keep in mind that almost all of the treatment that is summarized in this report took place before the publication of the third edition of the *American Psychiatric Association Practice Guideline for Major Depressive Disorder*,<sup>4</sup> which elevated the adjunctive use of SGAs to one of the empirically validated options for antidepressant nonresponders. It is likewise true that clinical practices are continuously evolving at a pace that is faster than guideline development as evidence pertaining to new treatment strategies accumulates. In the case of use of SGAs such as aripiprazole, quetiapine, and olanzapine for nonpsychotic depression, it simply was not known at the start of the last decade what were the best doses of these medications, whether used as adjuncts or as monotherapies. Thus, the relative futility of use of higher doses of quetiapine or adjunctive aripiprazole for patients with nonpsychotic

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depression was not known until later in the decade, when clinical observations dovetailed with the results of the clinical trials<sup>12</sup> and analyses of pharmacy databases.<sup>13</sup>

A final point stems from the harsh reality that the depressive disorders are heterogeneous conditions that not uncommonly fail to respond to “good care”; some depressed patients have illnesses that do not respond to any approved form of pharmacotherapy. For these patients, clinicians sometimes must pick treatments for which no guideline-concordant options exist. As about 40% of the antipsychotic-treated cohort had a depressive disorder for which an antipsychotic was indicated, and about one-quarter of the nonpsychotic depressed patients received antipsychotics in a manner that could be considered “guideline concordant” (ie, adjunctive therapy with appropriate doses of quetiapine or aripiprazole after nonresponse to several adequate courses of antidepressant), it can be estimated that the maximum overprescription rate for antipsychotic therapy in this cohort was no higher than 6% of all of the depressed patients. Given the likely error rate for diagnoses (ie, the patient actually had a disorder for which an antipsychotic was indicated and the clinician simply recorded the wrong diagnosis) and arguable “gray area” indications for use of low-dose antipsychotics noted above, the number of cases that might be considered to be truly actionable cases may well be much smaller.

### Mitigating Risks and Improving Quality Assurance

Even for treatment of schizophrenia, for which the indications for antipsychotic therapy are clear and the risks associated with the older medications are well-established, vigilant monitoring and assertive management of side effects of the SGAs are widely recognized as indicators of good patient care, particularly with respect to minimizing weight gain and metabolic complications during longer-term therapy.<sup>3,13</sup> Longitudinal documentation of weight and abdominal circumference, coupled with periodic screening of fasting glucose and hemoglobin A<sub>1c</sub> levels, are now considered to be the standard of care<sup>3,13</sup> and are routinely selected as indicators for quality assurance monitoring. As concomitant therapy with antidepressants and mood stabilizers may further increase metabolic burden associated with longer-term SGA therapy,<sup>3</sup> clinicians prescribing these medications to patients with nonpsychotic depressive disorders must implement the same practices to mitigate risks. The settings that they work in should similarly implement quality assurance monitoring. At a more practical level, it is fortunate that so much of the metabolic burden of antipsychotic therapy can be estimated by weight gain, because this inexpensive “marker” of risk can be ascertained by psychiatrists and psychiatric nurses as reliably as by the most expert endocrinologist.

Although the risk of tardive dyskinesia is quite low in studies of adjunctive SGA therapy of nonpsychotic depressive disorders, there is some risk of this dreaded complication of antipsychotic therapy—perhaps as high as 4 cases per thousand patients per year of treatment.<sup>3</sup> It is

therefore incumbent upon prescribers to document lifetime history of antipsychotic therapy and the presence or absence of involuntary movements at the outset of treatment and to continue to monitor for the emergence of early signs of tardive dyskinesia during ongoing therapy. Given the disfiguring effects and ominous prognostic implications of tardive dyskinesia, antipsychotic therapy should be tapered and stopped at the first signs of dyskinetic movements, and alternate strategies of therapy should be explored whenever possible.

### An Alternate Vision of the Future

The report by Gerhard et al<sup>6</sup> documents that a relatively small percentage of the presumably nonpsychotic, nonbipolar depressed adult outpatients in the Medicaid database received guideline-discordant care with antipsychotic medications. As noted above, clinicians who have the privilege to prescribe these medications and the systems of care entrusted to oversee their treatment must ensure that guidelines are followed as appropriate, deviations are documented and explained, and patient safety is ensured by regular monitoring and vigorous intervention whenever practicable. That said, Gerhard and colleagues are silent about the treatment received by the other 1.3 million or so depressed patients in this database who did not receive therapy with an SGA. What was their fate? The findings of the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) project,<sup>14</sup> which began to be published while these data were being collected, suggest that up to 40% of this treatment-seeking, Medicaid-insured population of depressed outpatients may not have responded to up to 1 year of conventional pharmacotherapy. This means that at least 400,000 of the depressed patients in this database were likely to have developed treatment-resistant depression de novo, yet did not receive the opportunity to benefit from a course of therapy with an SGA added an adjunct to an antidepressant. As 25%–50% of the patients treated with adjunctive SGA therapy typically respond in controlled clinical trials,<sup>15</sup> it is conceivable that at least 100,000 patients would have been “saved” from treatment-resistant depression if these therapies had been systematically incorporated into treatment algorithms in community care settings. If these assumptions are correct, we can hope that efforts to systematically improve the care of patients with more difficult to treat depressive disorders by more vigorously “rolling out” newer therapy options have the potential to do much more good than harm.

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