The Appropriateness of Routine Medication Treatment for Schizophrenia

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Objective: Although national guidelines specify appropriate strategies for the treatment of schizophrenia, this disorder presents challenges to clinicians and health-care organizations. To improve care, it is useful to understand how often patients receive appropriate treatment. Most research evaluating treatment was performed when first-generation antipsychotic medications were the modal treatment. Given that most prescriptions are now for second-generation medications, this study describes current clinical problems and the appropriateness of treatment in routine practice.

Method: Between 2002 and 2004, a random sample of patients (n = 398) were interviewed at baseline and 1 year at 3 Department of Veterans Affairs mental health clinics. Symptoms and side effects were assessed. Analyses examined whether prescribing were consistent with guidelines in patients with significant psychosis, depression, parkinsonism, akathisia, tardive dyskinesia, or elevated weight. Results: Few patients met criteria for depression, parkinsonism, or akathisia. A total of 44% of patients had significant psychosis, 11% had tardive dyskinesia, and 46% were overweight. Medication was appropriate in 27% of patients with psychosis, 25% of patients with tardive dyskinesia, and 2% of patients with elevated weight. Management of elevated weight improved modestly over time. Treatment was more likely to improve for patients whose psychiatrists had more than 12 patients with schizophrenia in their caseload. Conclusion: Compared with the 1990s, outpatients are more likely to have significant psychosis. The rate of appropriate treatment of psychosis is unchanged. Weight gain has become a prevalent side effect, yet treatment is rarely changed in response to weight. There is a need for interventions that improve management of psychosis and weight.

Keywords: antipsychotics/community mental health/drug side effects/quality measurement/health service research/quality of care/weight management

Introduction

Clinical research in schizophrenia has supported the development of national practice guidelines and treatment recommendations, including the American Psychiatric Association's (APA) Practice Guideline,1 the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations,2 and the Texas Medication Algorithm Project.3 Appropriate medication management reduces relapse and hospitalization and improves functioning and quality of life.1,4 However, available medications have important side effects and may not fully control symptoms. Also, researchers have found large gaps between actual treatment and recommended medication practices.5 This problem with treatment “appropriateness” is widely acknowledged6; however, most research on the appropriateness of care was performed when the majority of prescriptions were for the first-generation antipsychotic medications. Although first- and second-generation medications have similar average efficacy (except for clozapine), they have very different side effect profiles.7,8 In clinical trials of second-generation agents, extrapyramidal side effects (EPS) are less common than with first-generation agents, while weight gain is more common.9 A very high proportion of new prescriptions are now for second-generation agents. It is not clear how the remarkable dissemination of this new medication class has affected the appropriateness of medication treatment, nor how this dissemination should change efforts to improve care.

In schizophrenia, medication prescribing and treatment appropriateness can be affected by a variety of organizational, clinician, and patient factors.10,11 Organizational factors can include formulary restrictions, lacking a clozapine clinic, or scheduling short patient visits during which psychiatrists do not have time to adequately discuss side effects or medication changes with patients.6 Clinician factors contributing to inappropriate care can include low

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levels of competence (ie, values, knowledge, skills) or inadequate assessment.12 Patient factors can include refusal to accept a recommended medication change or poor adherence with prescribed medications.13,14

Numerous studies have found that routine treatment for schizophrenia varies markedly from evidence-based recommendations.5 Most of this research has not included direct patient assessment and has instead relied on medical records. Because medical records in schizophrenia contain little reliable and valid information on clinical status,15 researchers have been unable to systematically assess the extent to which care is concordant with most treatment guidelines.16 By necessity, they have been limited to examining domains that can be measured with computerized data, such as the dosage of antipsychotic medications. In the 1990s, researchers found that about one-third of outpatients are prescribed medication within the recommended dosage range.17–19 The relevance of this approach to the second-generation agents is not clear because these agents lack many of the dose-related side effects of the first-generation agents. An alternative approach evaluates the appropriateness of treatment using assessment of patients’ clinical status. This approach assesses the extent to which treatment responds to the clinical needs of individual patients.20 Before second-generation medications became the dominant treatment, one such study of appropriateness found that 17% of patients had severe psychotic symptoms and no appropriate medication change, while 27% of patients had severe side effects and no appropriate medication change.21

This study uses measures of treatment appropriateness that make use of clinical assessment and applies these methods to clinics that are primarily using second-generation antipsychotic medications. To determine the extent to which treatment changes over time, appropriateness is evaluated at baseline and 1 year later. Also, one of the most consistent findings in quality of care research is that when treatment is complex, high volume clinicians provide better treatment.21,22 This may be due to provider specialization or selective referral to expert providers. This association is examined here for schizophrenia. Data were obtained from a research project at 3 large Department of Veterans Affairs (VA) mental health clinics, starting in 2001. The appropriateness of medication management was defined using national guidelines, updated with recent leading literature reviews, and was consistent with previous definitions.21 The resultant appropriateness criteria examined key aspects of medication prescribing that are likely to have a large effect on patient outcomes.

Methods

Study Design

“Enhancing QUality-of-care In Psychosis” (EQUIP) was a longitudinal project that included evaluation of routine treatment for schizophrenia.23,24 As part of EQUIP, data were collected during 2002 and 2003 at 3 large VA clinics in Southern California: the West Los Angeles, Long Beach, and Sepulveda mental health clinics. The West Los Angeles and Long Beach clinics serve populations of patients in 2 different urban areas. The Sepulveda clinic serves a suburban area. Patient sampling was designed so that results could be generalized to the overall population with schizophrenia at each clinic. Patients at the clinics were eligible if they (1) were at least 18 years old, (2) had a diagnosis of schizophrenia or schizoaffective disorder as determined by an abbreviated version of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID),25 and (3) had at least one mental health clinic visit during a 5-month sampling period. We used real-time, visit-based sampling21 to identify a random sample of adults that met criteria. At each clinic, during a 5-month period in 2002–2003, a random sample of eligible patients was approached regarding enrollment. To ensure that visit frequency did not affect the probability of being selected, patients were eligible only at their first visit during the enrollment period.

Fifty-one percent of eligible patients consented to participate (n = 398). A total of 158 patients were enrolled at Clinic 1, 140 were enrolled at Clinic 2, and 100 were enrolled at Clinic 3. Institutional Review Board approval was obtained for the study. Written informed consent was obtained after the study had been fully explained. Patients were interviewed in person at baseline and 1 year later. During this 1-year period, the project did not affect treatment at the sites. Data on medication prescribing were obtained from computerized databases.

Measures

The SCID and Brief Psychiatric Rating Scale (BPRS) were performed by masters or doctoral level clinical research interviewers who were trained to a high level of reliability. Each completed an established training and quality assurance program.26,27 Interviewers were also trained to assess akathisia using the Barnes Scale28 and tardive dyskinesia (TD) using the Abnormal Involuntary Movement Scale.29 Body Mass Index (BMI) was calculated from weight and height, which was measured during the interview. The total number of patients with schizophrenia in each psychiatrist’s practice was estimated by multiplying the number of study subjects in their practice by the inverse of the rate at which patients at their clinic were sampled for the study.

Criteria for Evaluation of Appropriateness

Criteria for inappropriate care were based on a previous project that used a comprehensive literature review, national treatment recommendations, and an expert panel.21 The previous medication management criteria for psychotic symptoms, akathisia, parkinsonism, and
TD are used in this study. In the current project, management of elevated weight was added as a criteria given the weight gain liability of second-generation antipsychotics. Because much of the relevant research on weight gain was performed after development of the APA and PORT guidelines, weight criteria were based also on recent literature reviews and expert panels.3,9,30,31 the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and other studies have found that switching to an antipsychotic medication with less weight gain liability results, on average, in substantial weight loss.32 Although research on adjunctive medications to control weight is inconsistent, we considered this strategy to be appropriate to ensure that no possibly effective treatments were missed. A criterion was also added for management of depression, based on treatment recommendations from the Schizophrenia PORT.2

The medication management criteria are (1) patients with significant psychotic symptoms should have had an increase in antipsychotic medication dosage or have started a new antipsychotic medication within the past 3 months or been treated with clozapine (a medication with greater efficacy); (2) patients with significant akathisia or parkinsonism should have had a reduction in the dose of antipsychotic medication, a switch to a different antipsychotic medication, or a change or addition of a side effect reducing medication during the previous month; (3) patients with significant TD should have had a reduction in the dose of antipsychotic medication within the past 3 months or have been treated with quetiapine or clozapine (medications that cause little or no TD); (4) patients with significantly elevated weight should have (a) been treated with an antipsychotic medication with little or no weight gain potential (ziprasidone, aripiprazole, or a first-generation medication other than chlorpromazine or thioridizine) or (b) been switched to a medication with less weight gain potential or been prescribed an augmenting weight loss medication within the past 3 months; and (5) patients with significant depression and no significant psychosis should have started treatment with an antidepressant medication or had an increase in dosage of antidepressant medication within the past 3 months.

Measurement of Appropriateness of Medication Treatment

We operationalized “significant” symptoms and side effects using information from the patient baseline and follow-up interviews. Cut points were set high enough to ensure that symptoms and side effects above the cut point would be clinically meaningful and likely to affect outcomes. Patients were categorized as having significant psychotic symptoms if their BPRS ratings were “moderately severe” or greater for hallucinations, suspiciousness, unusual thought content, or conceptual disorganization. Patients were categorized as having significant akathisia if they met Barnes28 criteria for moderate, marked, or severe akathisia; significant parkinsonism if they responded “a great deal” to items regarding muscle stiffness and slowing of movements; and significant TD if the Abnormal Involuntary Movement Scale ratings met clinical criteria described by Schooler and Kane.33 Patients were categorized as being significantly overweight if they had (a) a BMI > 30 or a BMI > 27 plus diabetes, hypertension, or cardiovascular disease and (b) had not lost 8% or more of prior weight in the past 6 months.9,30 Patients were defined as having significant depression if their BPRS rating was “moderately severe” or greater on depression and they did not experience significant psychotic symptoms (as defined above).

Participants were classified as receiving overall inappropriate medication management if they met criteria for poor symptom management or poor side effect management in any of the following 4 domains: psychotic symptoms, TD, elevated weight, and depression. The akathisia/parkinsonism domain was excluded due to the small number of people who experienced akathisia (1%, n = 4) or parkinsonism (5%, n = 19). Medication appropriateness was based on automated prescription data and did not take into consideration provider recommendations to patients or patient adherence with prescribed medications.

Statistical Analyses

Data were analyzed using chi-square tests for proportions and Pearson correlations. Repeated-measures logistic regressions were used to examine the appropriateness of care over time as well as clinic by time interactions. Two-tailed tests of significance were used and differences were considered statistically significant at P < .05.

Results

Participants

Study participants (n = 398) were primarily male (92%), averaged 51.8 ± 9.6 years old, and had been ill for an average of 24.5 ± 11.4 years. Sixty-one percent of participants were white, 27% were African American, 7% were Hispanic, and 5% were from other ethnic groups. Most (72%) were unemployed, and approximately half of the sample had never married (50%). Of the 398 participants, 88% (n = 351) completed the follow-up interview. Attrition analyses revealed that completers did not differ significantly from noncompleters in regard to age, gender, ethnicity, employment status, or baseline symptom severity.

Appropriateness of Medication Management

At baseline, 73% of patients were prescribed a second-generation antipsychotic medication, 17% were prescribed a first-generation medication, and 10% were simultaneously prescribed medications from both classes. Second-generation medication prescriptions were for
The Appropriateness of Treatment for Schizophrenia

Table 1. Comparison Between Clinics of the Number of Subjects With Symptoms, Side Effects, and No Appropriate Management of These Problems

<table>
<thead>
<tr>
<th>Treatment Domain</th>
<th>Clinic 1 (n = 158), n (%)</th>
<th>Clinic 2 (n = 140), n (%)</th>
<th>Clinic 3 (n = 100), n (%)</th>
<th>Total (n = 398), n (%)</th>
<th>( \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant psychosis</td>
<td>72 (45.6)</td>
<td>58 (41.4)</td>
<td>46 (46.0)</td>
<td>176 (44.2)</td>
<td>0.71</td>
</tr>
<tr>
<td>No appropriate management of psychosis</td>
<td>50 (31.6)</td>
<td>42 (30.0)</td>
<td>36 (36.0)</td>
<td>128 (32.2)</td>
<td>0.77</td>
</tr>
<tr>
<td>Moderate or severe tardive dyskinesia</td>
<td>20 (12.7)</td>
<td>10 (7.1)</td>
<td>12 (12.0)</td>
<td>42 (10.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>No appropriate management of tardive dyskinesia</td>
<td>16 (10.1)</td>
<td>8 (5.7)</td>
<td>8 (8.0)</td>
<td>32 (8.0)</td>
<td>0.67</td>
</tr>
<tr>
<td>Weight problem</td>
<td>76 (48.1)</td>
<td>61 (43.6)</td>
<td>47 (47.0)</td>
<td>184 (46.2)</td>
<td>0.73</td>
</tr>
<tr>
<td>No appropriate management of weight</td>
<td>72 (45.6)</td>
<td>61 (43.6)</td>
<td>47 (47.0)</td>
<td>180 (45.2)</td>
<td>0.16</td>
</tr>
<tr>
<td>Significant depression</td>
<td>4 (2.5)</td>
<td>5 (3.6)</td>
<td>2 (2.0)</td>
<td>11 (2.8)</td>
<td>0.75</td>
</tr>
<tr>
<td>No appropriate management of depression</td>
<td>2 (1.3)</td>
<td>3 (2.1)</td>
<td>2 (2.0)</td>
<td>7 (1.8)</td>
<td>0.78</td>
</tr>
<tr>
<td>No appropriate medication management in one or more domains</td>
<td>108 (68.4)</td>
<td>87 (62.1)</td>
<td>73 (73.0)</td>
<td>268 (67.3)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

\( P > > .05 \) for all domains.

risperidone (31% of patients), olanzapine (24% of patients), quetiapine (19% of patients), ziprasidone (3% of patients), and clozapine (7% of patients). Aripiprazole had not yet been approved during the Clinic 1 and Clinic 2 interviews and was not yet available on formulary during the Clinic 3 interviews. As shown in table 1, 128 participants (32%) had inappropriate management of psychotic symptoms, and 7 (2%) had inappropriate management of depressive symptoms. In regard to side effects, 32 (8%) had inappropriate management of TD, and 180 (45%) had inappropriate management of weight. Overall, 268 participants (67%) received inappropriate medication management in one or more domains. There were no significant differences between the 3 clinics in the prevalence of symptoms or side effects or the appropriateness of medication management.

Repeated-measures logistic regression was utilized to determine if the appropriateness of medication management changed over time and to characterize clinic by time interactions. The appropriateness of management for psychotic symptoms did not change over time (\( \chi^2_1 = 0.07, P = .79 \) and \( \chi^2_2 = 0.67, P = .41 \), respectively) nor were there any clinic by time interactions (\( \chi^2_2 = 0.59, P = .74 \) for psychosis and \( \chi^2_2 = 0.49, P = .78 \) for depressive symptoms). The appropriateness of management of TD also did not change over time (\( \chi^2_1 = 0.02, P = .88 \)). However, there was a significant time by clinic interaction indicating no change in the appropriateness of management of TD at Clinic 1, a decline in appropriateness at Clinic 2 and an improvement in appropriateness at Clinic 3 (\( \chi^2_2 = 6.6, P < .05 \)). Management of elevated weight improved over time (from 45% to 35% poor care; \( \chi^2_2 = 19.6, P < .0001 \)), though there was no clinic by time interaction (\( \chi^2_2 = 4.84, P = .09 \)). Overall medication management improved over time (from 67% to 53% poor care; \( \chi^2_1 = 28.0, P < .0001 \)), and there was a significant time by clinic interaction (\( \chi^2_2 = 12.4, P < .001 \) with an improvement of 15% in Clinic 1, 3% in Clinic 2, and 28% in Clinic 3.

Psychiatrist Specialization and the Appropriateness of Medication Management

Some psychiatrists had practices that included many more patients with schizophrenia, typically because they were specializing in the treatment of this disorder. The number of patients with schizophrenia in each psychiatrist’s practice varied from 1 to 456, with a median of 12 patients per psychiatrist. The number of patients with schizophrenia in a psychiatrist’s practice was not significantly associated with the appropriateness of care they delivered at baseline (\( r = 0.10, P = .51 \)). However, when we examined psychiatrist specialization in relation to change in appropriateness of care over time, we found that compared with those psychiatrists with 12 or fewer patients with schizophrenia, psychiatrists with more than 12 patients were significantly more likely to improve their care over time (\( \chi^2_2 = 19.7, P < .001 \)). Of the 18 psychiatrists who treated more than 12 patients with schizophrenia, 14 psychiatrists (78%) provided better care to their patients over time, 1 (6%) provided worse care, and 3 (17%) did not change. In contrast, of the 26 psychiatrists who treated 12 or fewer patients with schizophrenia, 3 (12%) provided better care over time, 6 (23%) provided worse care, and 17 (65%) did not change. Most resident trainees (\( n = 16, 84\% \)) were in the low volume group. Of the 19 residents, 5 (26%) provided better care over time, 5 (26%) provided worse care, and 10 (47%) did not change.

Discussion

Over the past decade, the widespread dissemination of second-generation antipsychotic agents has resulted in
major changes in treatment for schizophrenia. This study estimated the prevalence of significant symptoms and side effects and the prevalence of appropriate medication management at three clinics. Figure 1 presents these findings in comparison to a similar study conducted during 1996, when most patients were prescribed first-generation antipsychotic medication.21 With regard to side effects, a decade ago clinically significant akathisia and parkinsonism were present in about a quarter of patients, but these problems are now rare. TD is also less common now but is still present in 11% of patients. Second-generation agents cause much less TD than first-generation agents,34,35 and current TD could be mostly due to prior exposure to first-generation agents. On the other hand, elevated weight is now a very common problem. Forty-six percent of patients at these clinics were significantly overweight. Nearly all these patients were on medications that cause weight gain and were receiving medication management that did not change in response to their weight problem. With regard to psychotic symptoms, we found that significant psychosis was more common than a decade previously. The cause of this increase is unclear. It could be due to the reduced availability of hospitalization in treating psychotic patients36 or an improved ability to maintain patients with psychosis in the community.

These results reinforce concerns that weight has become the most important side effect of antipsychotic medications. Researchers have found that clinicians are aware of weight and related metabolic consequences of antipsychotic medication; however, this awareness has not translated into routine monitoring of metabolic side effects.37–39 This study finds that clinicians are also rarely changing medication in response to weight gain. Obesity increases the risk for diabetes, cardiovascular morbidity, and death.9 Other medical consequences include hypertension, strokes, gallstones, osteoarthritis, sleep apnea, and colon, breast, and endometrial cancer.30–45 Given the problems associated with elevated weight, national expert panels have recommended that treatment changes be considered for patients with schizophrenia who have BMI > 25, for women who have a waist size of 35 inches or greater, and for men who have a waist size of 40 inches or greater.9,30 Antipsychotic agents differ substantially in their weight gain liabilities, and changing medication to an agent with less weight gain potential results, on average, in significant weight loss.31 Also, weight control programs that emphasize nutrition, exercise, and behavioral change can stabilize or reduce weight in patients with schizophrenia.46–49

This study is one of the first to look longitudinally at the appropriateness of treatment for schizophrenia. We found that management of side-effects improved somewhat over time for individual patients. On the other hand, management of psychotic symptoms did not improve over time, suggesting that new strategies are needed for this problem. The CATIE study and treatment guidelines support greater use of clozapine.50 Although clozapine is the best available treatment for persistent and non-responsive psychosis, it is underutilized. Only 26 (6.5%) participants in this study were prescribed clozapine during the year in which they were evaluated. Prescription of clozapine can be challenging for psychiatrists who are not trained in the use of this medication, and care is often not organized in a way that makes clozapine easy to use.

This study is also one of the first to study the prevalence of severe depression and the appropriateness of its treatment in schizophrenia. We found that 11% of patients had depression that was moderately severe or greater. Most of these patients had severe psychosis. Given the efficacy of clozapine for refractory psychosis
and related mood symptoms, more frequent use of this medication could be an effective strategy for improving depression in this population.

This study has important limitations. Medication prescribing and treatment appropriateness in schizophrenia could be affected by a variety of organizational, clinician, and patient factors. We did not assess these factors and therefore cannot explain the underlying causes of inappropriate care or why treatment appropriateness changed over time. For example, clinicians could have become increasingly aware of the problems related to elevated weight, or, alternatively, they may have become more persuasive in getting patients to accept appropriate medication changes. Further, while treatment guidelines define treatments that will, on average, result in the best outcomes for patients, there are patients for whom these changes are not clinically indicated. Because data on prior clinical status were unavailable, it is possible that patients had previously received appropriate treatments, and they were not helpful. However, given the low levels of use of clozapine and medications with low weight gain liability, this seems unlikely. Another possibility is that clinicians may be reluctant to switch patients to medications with less weight gain potential due to fear of exacerbating symptoms. However, research indicates that these switches are usually well tolerated. Development of benchmarks for best practices would clarify the extent to which care should be improved. And the development of stronger interventions to improve care would benefit from further research to clarify patient, clinician, and organizational barriers to improving treatment.

Finally, this study was performed at three VA medical centers in southern California, and replication is needed. We do not know the extent to which these results generalize beyond a primarily male VA population or to other systems of care. Prior research has found small, inconsistent differences between the quality of VA and non-VA care for schizophrenia.21,52 Also, while results were similar across these three diverse urban and suburban areas, other clinics may have formulary restrictions or other barriers to treatment access that could affect the care they provide.

Consistent with research from the 1990s, this study finds important problems with the quality of treatment for schizophrenia. However, problems in care have changed substantially. The emphasis of efforts to improve care will need to shift from improving management of EPS and neurologic side effects to a focus that includes weight gain and its associated complications. With regard to symptoms, efforts to better manage psychosis need to be redoubled.

Schizophrenia can be a challenging disorder to evaluate and treat. At these clinics, psychiatrists who specialized in the treatment of schizophrenia had more improvement in their care over time. However, much greater improvement in care is needed. This may require attention to a range of organizational, clinician, and patient factors that impede the delivery of appropriate treatment. We do not yet know how to best improve the quality of care in this disorder nor what benchmarks indicate that best practices are being provided. Quality improvement research will be critical to answering these questions. Researchers should partner with clinicians and policy makers, study novel treatments and approaches to reorganizing care, and determine how to best implement improved treatment and outcomes in this population.

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