Rethinking Antipsychotic Formulary Policy

R.A. Rosenheck1,2,3, D.L. Leslie2,3, Susan Busch7, Ethan S. Rofman4,5, and Michael Sernyak2,3

2Yale Medical School, New Haven, CT; 3Northeast Program Evaluation Center (182), Veterans Affairs Connecticut Health Care System, 950 Campbell Ave, West Haven, CT 06516; 4Veterans Affairs New England Health Care System, Bedford, MA; 5Boston University Medical School, Boston, MA

In this commentary, we review recent research suggesting that (a) second-generation antipsychotics (SGAs) may be no more effective than first-generation antipsychotics (FGAs), (b) the reduced risk of EPS and tardive dyskinesia with SGAs is more weakly supported by the research literature than has been appreciated, and (c) benefits may be offset by greater metabolic risks of some SGAs and their substantially greater cost. Bearing in mind, as well, that risperidone, currently the least expensive SGA, will soon be available as an even less expensive generic drug, we propose a new algorithm for maintenance antipsychotic therapy. We further outline a cautious implementation procedure that relies on standardized documentation and feedback, without a restrictive formulary that would limit physician choice. The algorithm outlined here and the process for its implementation are intended as a stimulus for discussion of potential policy responses, not as a finalized proposition.

Key words: schizophrenia/antipsychotic medication/public policy

Second-generation antipsychotic (SGA) medications have almost entirely supplanted first-generation antipsychotics (FGAs) in the long-term treatment of schizophrenia and are increasingly used in treatment of other psychiatric disorders. Early research suggested that SGAs were more effective than FGAs1,2 and posed substantially less risk of neurological side effects, especially tardive dyskinesia (TD).3 While many mental health systems have no formal antipsychotic formulary policy, the widely known Texas Medication Algorithm Project,4 American Psychiatric Association guidelines on the treatment of schizophrenia,5 and empirical data on provider behavior6 all suggest that current de facto policy favors virtually exclusive use of SGAs.

Annual expenditures on SGAs in the United States totaled $11.6 billion in 2005,7 a sum greater than the $8.5 billion estimated total income of all 47 000 US psychiatrists8,9 and about 10% of all US mental health expenditures.10 The overall US health care system is in crisis, with per capita health expenditures twice those of other industrialized nations11 and health care quality indicators only two-thirds as high as a set of standardized benchmarks.12 Prioritization of high-cost treatments like SGAs is only rational if they yield superior health outcomes compared with other medications to a degree that merits their additional cost.

Recent studies, consistent with past Cochrane reviews13,14 have raised questions about both the greater effectiveness and lower side effect risks of SGAs, while affirming their greater total cost.15–18 In addition, risperidone, currently the least expensive SGA,19 will soon become available as a generic at even lower cost. A reconsideration of antipsychotic formulary policy, taking account of recent research, as well as costs, seems due.

In this commentary, we first review recent research on SGAs. We then propose a modified algorithm for maintenance antipsychotic therapy, and, finally, outline a process for its implementation based on a procedure that requires structured documentation of the rationale for using nongeneric medications with active data sharing. Policy development is complex because it requires a balanced approach to competing goals (eg, effectiveness, tolerability, efficiency, and consumer and provider choice). Stimulated by new research and the prospect of the first generic SGA, we hope to initiate discussion of possible responses to these new circumstances.

Recent Research

Effectiveness and Tolerability

In 2003, a 12-month VA Cooperative Study unexpectedly found no difference in effectiveness or most side effects between olanzapine and haloperidol in patients with chronic schizophrenia. These results, it was suggested, differed from those of previous studies because haloperidol was given with prophylactic anticholinergics.13

More recently, the 18-month CATIE study found no significant advantage for any of 4 SGAs as compared

1To whom correspondence should be addressed; tel: 203-937-3850, fax: 203-937-3433, e-mail: Robert.Rosenheck@Yale.Edu.
with perphenazine, an intermediate potency FGA, on measures of symptoms, neurologic side effects, quality of life, employment, or neuropsychological functioning, although patients continued olanzapine treatment longer. One quarter of those assigned to perphenazine completed 18 months of treatment with no change in medication, a percentage no smaller than 3 of the 4 SGAs.

CATIE has been the subject of several critiques, but a detailed response shows that virtually all the noted methodological limitations applied equally to the studies that showed SGAs to have advantages over FGAs. If such methods were sound enough to convince physicians of the benefits of SGAs, studies of similar populations using similar methods may be sound enough to support contrary views. The use of moderate to high doses of haloperidol without prophylactic anticholinergics in earlier studies may have given an undue advantage to the SGAs.

CATIE findings were further echoed by CUtLASS, a government-funded U.K. trial, which also found no advantage of SGAs over FGAs on symptoms, side effects, or quality of life. CUtLASS has also been a subject of extensive controversy, but while space prohibits addressing each critique here, what has clearly stimulated debate is the perception that independent government studies challenge the conclusions of earlier, largely industry-sponsored, research.

First-episode patients, however, were not included in any of the new studies and are typically 10–20 years younger than chronic patients. Two recent studies of such patients have shown mixed results. A 12-week study comparing olanzapine (9.1 mg/d) and haloperidol without prophylactic anticholinergics but at modest doses (4.4 mg/d) favored olanzapine on symptom outcomes, neurological side effects, and time to discontinuation, although olanzapine patients had greater weight gain. A longer, 1-year, study found no difference between risperidone (3.3 mg) and low-dose haloperidol (2.9 mg) on symptoms or time to first discontinuation, but risperidone showed less EPS and more weight gain. While dosing in these studies was more modest than in other haloperidol trials and they favor SGAs, their relevance for policy is uncertain because the generalizability of the results to FGAs other than haloperidol is unknown. A Cochrane review of first-episode studies reported that "whether the use of new generation antipsychotics really makes the treatment less off putting and enhances long-term compliance is unclear."

While differences in side effects and symptom outcomes vary from study to study, and subclinical EPS may not be detected by available measures, differences in results are generally small in magnitude. While controversial, it seems likely that some patients now on SGAs could be just as successfully treated with generic or soon-to-be generic antipsychotics, with a change to on-patent SGAs when clearly indicated.

Cost and Cost-Effectiveness
Paralleling the VA trial, the cost-effectiveness component of CATIE found that average monthly health care costs were $300–$500 greater with SGAs than perphenazine, with no advantage on symptoms or quality of life. A review of cost-effectiveness research prior to CATIE also found no evidence of cost savings or greater cost-effectiveness for SGAs. None of the many commentaries on CATIE or CUtLASS have questioned the robustness of these cost differences, which range from $2400–$10 000/year across studies. The US General Accounting Office has further concluded that the lower cost of risperidone justifies formulary policies that gave it priority over other SGAs because it was clinically equivalent.

Unpublished data from MarketScan private insurance claims show that only 44% of patients who were prescribed SGAs have a diagnosis of schizophrenia or bipolar disorder (data available from first author), and an older VA study also found most SGA use to be off label. A recent review of 84 published studies found a lack of high-quality evidence to support off-label use of SGAs, which is thus likely to yield even less benefit per dollar expended.

These shifts in the literature, while unanticipated, are not surprising. Reviews of research on SGAs and other medications show that they are most likely to demonstrate superiority over older treatments in studies conducted or sponsored by their manufacturers, the predominant source of studies during the years when drugs are first marketed. The Director of APA’s Division of Research recently noted in response to CUtLASS that “clinicians have long recognized that SGAs were no more effective than FGAs in reducing psychotic symptoms.”

Metabolic Side Effects
There has also been growing evidence of greater risk of weight gain, diabetes, and metabolic syndrome with some SGAs, especially olanzapine and clozapine, a concern that also applies to less extensively studied low potency FGAs and intermediate potency FGAs at higher doses.

Tardive Dyskinesia
Another recent review, however, suggested lower annual TD risk with SGAs (0.8%) as compared with FGAs (5.4%). It identified three 1-year randomized trials comparing SGAs and FGAs on TD risk in which patients were followed for an average median of 8.8 months. Taken together, these studies were not substantially different in duration from CATIE, which found no significant differences on a similar measure of TD, and in which patients assigned to perphenazine or to the best performing SGA, olanzapine, participated for a median of 5.6 and 9.2 months, respectively.
The authors of the TD review\(^3\) also note that their results could have been biased by the fact that all 3 head-to-head FGA-SGA comparison trials involved moderate-high doses of haloperidol. A meta-analysis of 31 randomized controlled trials found no greater risk of EPS between low potency FGAs and SGAs other than clozapine,\(^43\) and 4 recent epidemiologic studies questioned whether SGAs have any lower TD risk than FGAs,\(^44\)–\(^46\) even in elderly populations.\(^46\)

Recovery from TD can be as high as 78% in the first year,\(^47\) although it may decline to as little as 15% in later years,\(^47\) but recent studies involving clozapine\(^48\) and olanzapine\(^49\) suggest that recovery from TD can be promoted by these drugs, thus reducing the risk of long-term impairment with FGAs.

These perspectives on long-term TD outcomes are consistent with FDA policy that requires the package insert of each SGA to state that whether there are differences in risk of TD among antipsychotic drugs is unknown. The risk of TD is highest in elderly patients but quasi-experimental studies suggest that risperidone, soon to be available in generic form, poses a lower risk of TD, at least as compared with haloperidol, in older people.\(^50\),\(^51\)

It thus appears that SGAs may be no more effective and substantially more expensive than FGAs and that side effect differences are complex, vary across individual drugs, and do not clearly favor either class. We believe that cost differences deserve special attention because they are clear, robust, and substantial, while evidence of effectiveness differences are limited, and evidence of side effect differences, while strong in older studies, now seem more variable and may offset each other in net effect. We are unaware of any counter argument that SGAs are worth their $11.6 billion annual cost or any specific justification for inefficient use of resources in the case of these particular medicines.

**Proposed Treatment Sequence**

We propose an antipsychotic algorithm that would not force any patient to change medication but could foster incremental changes in antipsychotic prescribing that would increase efficiency without reducing effectiveness or safety. We classify antipsychotic medications into 4 groups conceptualized as being used sequentially when either initiation of antipsychotic therapy is indicated or a change is required.

**Group 1**

First-line treatments would include risperidone and intermediate potency FGAs. Perphenazine performed as well as all SGAs on clinical outcomes and side effects in the CATIE trial and showed no differences from aripiprazole in a trial of patients who had previously been unresponsive to olanzapine or risperidone.\(^52\) Other intermediate potency FGAs (eg, loxitane or thiothixine) are similarly likely to pose less risk of TD than the high potency FGA, haloperidol, used in much previous research. It could be argued that high potency FGAs, if used at low doses, would be equivalent to intermediate potency FGAs, but there are no recent trials to support this perspective. Anticholinergics would not need to be used prophylactically with moderate doses of intermediate potency FGAs.

**Group 2**

Because clozapine is uniquely indicated for refractory schizophrenia, it should be offered to patients who have failed 2 or 3 previous antipsychotic trials, and many think it is underused. Generic clozapine is now available at low cost, although weight gain and metabolic risk is of concern and some patients may not accept the required blood monitoring.\(^53\)

**Group 3**

The third line of treatment would include aripiprazole, ziprasidone, or quetiapine, patented SGAs, that seem to pose less risk of weight gain than olanzapine and that differ from each other in their side effect profiles.

**Group 4**

The fourth-line treatment would be olanzapine (because of its additional risk of weight gain and high cost and the lack of robust evidence of greater effectiveness) as well as FGAs not included in group 1 (both low potency FGAs such as haloperidol and high potency FGAs such as chlorpromazine).

Long-acting intramuscular risperidone, now the most expensive SGA therapy, is not specifically included in any of the 4 groups because clinical trials comparing it with oral therapy are not yet available. Data comparing depot FGAs with either long-acting intramuscular (IM) risperidone or with oral SGAs are also not available. The high cost and undemonstrated benefit of long-acting IM risperidone, and the high risk of neurological side effects with depot FGAs, argue for their inclusion as group 3 or 4 drugs, requiring documented justification as described below.

**Risk Communication and Monitoring**

All antipsychotic drugs can have serious side effects. Patient understanding should be documented concerning: (a) risk of TD with all drugs including the need for semi-annual AIMS testing, (b) risk of agranulocytosis with clozapine including required blood monitoring, and (c) risk of weight gain and diabetes with semi-annual monitoring of indicators of metabolic syndrome. Lower doses should be used in first-episode patients and elderly patients.

**Implementation**

Because medication nonadherence can be a serious problem for people taking antipsychotic medication,\(^54\)
procedures that might discourage adherence should be avoided and therapy should be individualized when indicated.

We propose a practice monitoring/information gathering procedure to support implementation of this algorithm. When a patient is initiated on therapy with medications in groups 3 or 4 or with long-acting IM risperidone, a brief structured form (available from the authors on request), would document why that drug was specifically chosen rather than one of those in group 1 or 2. The form would record sociodemographic characteristics, diagnoses, risk factors for TD and metabolic disease, previous antipsychotic medication failures, and clinical reasons for selecting the proposed agent—all important considerations for selecting medications. This requirement is less stringent than preauthorization or restrictive formularies but would provide a weak incentive to prescribe group 1 or 2 drugs to avoid a small documentation burden. It also would provide information on the judgments of prescribing clinicians for ongoing review and discussion.

In integrated systems like VA that operate internal pharmacies, completion of a checklist could be required before a new antipsychotic agent could be prescribed other than those in groups 1 or 2. In other systems, retrospective review of medical records could be used to monitor compliance with the policy. Concerns about untoward delays in changing medications may be allayed by a study that showed staying with a current medication may be more advantageous than switching to a new one.55

An important component of this policy would be tracking of quality indicators such as changes in rates of hospitalization, medication discontinuation, or incidence of TD to identify untoward effects.

Agencies attempting to implement a policy such as this should explain the shifts in recent research and details of this proposal to providers, stakeholders, consumers, and their families through open discussion.56

Feedback on risk monitors, changing prescribing patterns, and information gathered on monitoring forms should be used for ongoing review and mutual learning among providers, administrators, and consumers. Conventional medical records do not lend themselves to this kind of systematic review.

What we propose is thus not driven by prior authorization, utilization review, capped prescription quantities, closed formularies, tiered copayments, or mandatory disease management systems but focuses rather on standardized documentation and feedback with academic detailing.57 Whether this kind of procedure will actually change practice substantially or result in savings is unknown and deserves empirical study. The immediate goal is limited to increasing awareness of current practices and recent research findings.

Conclusion

In recent years, many treatments once thought to be highly advantageous, have been revealed by new indepen-
dent research to be substantially less so. Vioxx, hormone replacement therapy for menopausal symptoms, calcium channel blockers for hypertension, and radical mastectomy for breast cancer are only a few prominent examples. The algorithm proposed here and the process for its implementation are one possible response to changing circumstances and may provide a starting point for renewed discussion.

Funding

This work was supported by the VA New England Mental Illness research, Education and Clinical Center, West Haven, CT.

Acknowledgments

We would like to thank Alexander Miller, MD, Shitij Kaupur, MD, and Miklos Losonszy, MD for helpful suggestions. Rosenheck had received research support from Eli Lilly, Janssen Pharmaceutica, Astra-Zeneca, and Wyeth. He has been a consultant to GlaxoSmithKline, Bristol Myers Squibb, and Janssen Pharmaceutica.

References

1. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry. 2003;60:553–564.


