Principles of Antipsychotic Prescribing for Policy Makers, Circa 2008. Translating Knowledge to Promote Individualized Treatment

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Abstract

Findings from 2 pivotal government-funded studies of comparative antipsychotic effectiveness undermine assumptions about the marked superiority of the more expensive second-generation "atypical" medications in comparison to the less expensive first-generation "typical" drugs. Because this assumption was the basis for the almost universal recommendation that these newer antipsychotics be used preferentially resulting in a 10-fold increase in state governmental expenditures on this class of medications over the past decade, a reassessment of policy is called for. To address the issue, the Medical Directors Council of the National Association of State Mental Health Program Directors critically reviewed findings of these studies in the context of other data and considered policy implications in the light of the obligations of state government to make available best possible and individually optimized treatment that is cost-effective. The Medical Directors Council unanimously adopted a set of recommendations to promote appropriate access, efficient utilization, and best practice use. We present our policy statement, in which we provide a succinct background, articulate general principles, and describe a set of 4 broad recommendations. We then summarize our understanding of the current state of knowledge about comparative antipsychotic effectiveness, best antipsychotic practice, and considerations for state policy that represent the basis of our position statement.

Keywords: antipsychotic / policy / schizophrenia / treatment / effectiveness / cost-effectiveness / best practice / states / costs

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National Association of State Mental Health Program Directors Medical Directors' Statement on

Comparative Effectiveness of Antipsychotic Medications and Individualized Treatment

Background

Over the past decade, there has been a significant change in patterns of antipsychotic practice, with the newer, more costly, and believed-to-be-more effective "atypical" agents replacing the older "typical" antipsychotic medications. While all these medications are Food and Drug Administration (FDA) approved for the treatment of schizophrenia in adults, where their use has been best studied, they are often utilized "off-label" for treatment of a wide variety of other conditions. (Some agents have additionally received FDA approval for other indications and/or populations). Although our review focuses on the use of antipsychotics in schizophrenia, many observations may also be relevant to the use of these agents in other conditions.

The recent publication of the findings of 2 major government-funded studies (Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE], Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study) of comparative antipsychotic effectiveness in schizophrenia has caused uncertainty among patients, clinicians, and policy makers about the relative utility of atypical and typical antipsychotic agents. To address the issue, National Association of State Mental Health Program Directors (NASMHPD) medical directors critically reviewed the findings of these studies in the context of other data. Over the past 2 years, the Medical Directors Council repeatedly reviewed the evolving evidence, sought to understand the studies' findings, and discussed policy implications. The principal investigator of CATIE (Jeffrey Lieberman, MD) participated in a full-day discussion of CATIE in July 2006. Subsequently, findings and implications were discussed at monthly medical directors' conference calls and 3 additional NASMHPD Medical Directors Council meetings (October 2006, May 2007, and December 2007). Review drafts were provided to psychiatry researchers active in the field and their input considered and incorporated. Observations were also presented to the NASMHPD Commissioners in July 2006 and December 2007. It should be noted that the findings and recommendations are solely those of the NASMHPD Medical Directors Council, and nothing in this report should be construed as recommending a particular medication for use by individual patients. In our statement, we utilize commonly used colloquial terms (typicals and atypicals) for these first- and second-generation classes of antipsychotic medications.

Based on our review, we present the following summary of findings and set of recommendations. We first enumerate broad principles that should guide policy approaches to antipsychotic utilization and then discuss specific policy recommendations.

General Principles of Antipsychotic Access, Efficient Utilization, and Prescribing

1. Treatment with antipsychotic medication, like any other treatment, should be individualized in order to optimally promote recovery.

2. Treatment with antipsychotic medication should be as effective, safe, and well tolerated as possible.
3. Treatment with antipsychotic medication should consider personal preference and vulnerabilities.
4. Treatment with antipsychotic medication should provide value in terms of improved quality of life to the consumer.
5. Treatment choices should be informed by the best current evidence and must evolve in response to new information.
6. Cost considerations should guide antipsychotic medication selection once the preceding principles are met.

Policy Recommendations Based on the Current State of Knowledge
The following policy recommendations should be considered in light of the complexity of antipsychotic prescribing in clinical practice and the expectation for individualized treatment; they are not to be considered specific practice guidelines.

Ensure Appropriate Access

Antipsychotic medications should be available and utilized as clinically appropriate on an individualized basis. Efficacy, safety, tolerability, personal preferences and vulnerabilities, and cost considerations should guide antipsychotic selection. Given significant individual variability in response, ultimately all marketed antipsychotic medications should be available to patients who require treatment with them.

Ensure Efficient Utilization

The cost of antipsychotic medications is an important factor, and controlling this cost will help to protect access. Cost-effective utilization of antipsychotic medications can be promoted in the context of an unrestricted "open formulary" or in the context of a preferred drug list (PDL); both these approaches have strengths and weaknesses.

A. An open formulary with unrestricted access to all antipsychotic medications is clinically desired because it allows unfettered clinical decision making without any additional administrative burden but has the disadvantage of eliminating cost competition in procuring these medications. In an open formulary system, the ability to limit cost and constrain practice by limiting formulary options is also relinquished.
B. Clinically adequate access can also be ensured by utilizing a PDL that provides open access to a range of antipsychotic medications with substantial clinical differences; however, access to any antipsychotic must ultimately be available,

through a responsive, user friendly, and timely process. Prior authorization and step therapy are two of the mechanisms utilized in conjunction with a PDL approach. While facilitating a greater degree of systemic influence on individual practice, these mechanisms generally add administrative burdens and costs. With a PDL, 2 key conditions are necessary to facilitate individualized antipsychotic use.

1. Patients should have few, if any, obstacles to getting any antipsychotic on which they are currently stable or on which they have done well previously. To assure this, all pharmacy benefit programs should adhere to the following 3 protections:

   a. If a medication listed as "nonformulary" is considered clinically appropriate for an individual patient (based on past response or other considerations), prior authorization procedures should be simple and flexible.
   b. If an antipsychotic medication listed as "nonformulary" is known or found to be safe and effective for a given individual, it should continue to be available for that patient; "grandfathering" is the recommended practice for individuals stabilized on a nonformulary antipsychotic medication to minimize risk of relapse and support continuity of care.
   c. Patients should not be forced to switch medications due to changes in formulary policy, prior authorization, or change in the payer responsible for the benefit. This will require either flexible prior authorization within an individual benefit or detailed account coordination of formulary and PDL design across pharmacy benefit plans in the same region.
   2. A PDL should provide initial first-line access to a choice of antipsychotic agents that have substantial clinical differences that are generally predictable across individual patients. The evidence currently available indicates that important such differences exist in weight gain, extrapyramidal side effects, sedation, other adverse effects, availability of long-acting dose forms, and, for clozapine only, efficacy in treatment of psychosis. Therefore, choices of PDL medications, based on current information about antipsychotic medications, should include at a minimum
   1. at least one of the relatively weight-neutral atypicals,
   2. one or more medium-potency typicals,
   3. at least one of the relatively sedating atypicals,
   4. a high-potency atypical,
   5. one or more high-potency typicals with long-acting formulations,
   6. clozapine,
   7. one or more low-potency typicals.

The above policy recommendations should not be construed as support for policies of:

1. step therapy requiring a trial of a typical before having access to atypicals;
2. having only a single atypical as an open access, first-choice agent;

3. requiring a trial on one of the above 7 categories before having access to the other 6.

Promote Best Practice Use of Antipsychotic Medications

Differences in treatment outcomes are as dependent on how antipsychotic medications are prescribed and patient adherence to the medication as on differences between medications. Because actual clinical use of antipsychotic medications diverges widely from evidence-based practice, states should systematically promote best psychopharmacological treatment practices by utilizing a combination of approaches such as

i. developing and disseminating best practice guidelines, including recommendations about optimal antipsychotic dosing, trial duration, monitoring of treatment response (including use of defined standardized rating instruments and side effect tracking protocols), and switching considerations and strategies;
ii. making point-of-care clinical information tools available to clinicians to inform best practice;
iii. monitoring actual practice and implementing a hierarchy of interventions to identify, constrain, and guide less established and "high-risk" practices;
iv. encouraging patient adherence by promoting:
a. shared decision making,
b. recovery-oriented approach,
c. community case management,
d. education of the patient and family.

Improving prescribing practices should be the major focus of any program to manage the utilization of antipsychotic medications. It has been our experience that improving the quality of antipsychotic prescribing saves funding that can then be redirected to other treatment needs.

Ensure Timely Availability and Dissemination of Necessary Clinical Trial Information

There is often a significant lag between the identification of an important clinical question and the implementation of a well-designed study to address that question. In addition, there are often significant lags between conclusion of clinical trials and complete dissemination of all its findings and between the publication of important clinical trials

and the translation of findings of that research into practice. There is a great need for independent, well-designed trials that address clinically relevant questions that can guide best practice regarding the use of psychiatric medications. The states, as guarantors of the public good and as the biggest payer for antipsychotic medications, have an obligation to ensure the timely conduct of pertinent clinical trials, independent of the pharmaceutical industry, that can guide the efficient and effective use of pharmacotherapy to promote individual recovery. Because existing mechanisms for research into these questions are inadequate, NASMHPD, in conjunction with Substance Abuse and Mental Health Services Administration, Centers for Medicare and Medicaid Services, National Institute of Mental Health, and other groups, should develop such a mechanism. It should be noted that the federal government and states collectively spend about 9 billion dollars per year on antipsychotic medications; we believe that it would be wise to invest a small percentage of that amount in ongoing, well-designed and impartial research on the appropriate use of these medications, including ways to maximize the principles put forth here.

The Current State of Knowledge About Antipsychotic Effectiveness and Prescribing From All Available Studies

1. Atypical antipsychotic medications are not universally or consistently more effective in treating symptoms of psychosis than typical antipsychotic medications.[1–6]
2. In contrast to their relatively similar efficacy in treating positive symptoms, there are substantial differences among both typical and atypical antipsychotic agents with regard to their propensity to cause extrapyramidal, metabolic, and other adverse effects. Atypical antipsychotics generally have a lower liability to cause extrapyramidal symptoms[1,6–8] including tardive dyskinesia, and some atypicals have a higher rate of metabolic side effects[8–10] than typicals.
3. Atypical antipsychotic medications were thought to be more effective than typical antipsychotic medications in improving negative and cognitive symptoms,[7,11–14] but the existence and extent of this advantage is questionable.[15–17]
4. The use of modest doses of some typical antipsychotic medications may reduce (or eliminate in some patients) the difference in the risk of motor side effects between atypical and typical antipsychotic medications.[2,8] Typical antipsychotic medications may be a suitable treatment option for some patients, particularly those at low risk for motor side effects.
5. Clozapine consistently outperforms all other antipsychotic medications, both typical and other atypical, in the management of treatment-resistant schizophrenia.[8,18–21]
6. There are no consistent differences in treatment efficacy among various atypical antipsychotic medications other than clozapine; any such differences, if they exist, are likely to be small in magnitude.[8]
7. Research publications on individual antipsychotic medications frequently tend to overemphasize the relatively minor differences in efficacy between these medications; these differences can often be attributed to differences in study design.[8,22,23]

8. There is no best medication or best dose for all patients; the choice of an antipsychotic medication and its dose, and subsequent decisions about changes in treatment, require careful initial consideration and ongoing, shared decision making between the patient and clinician.7,8,24,25
9. Antipsychotic dosing is a key variable influencing the effectiveness of treatment.7,8,24
10. Treatment of any individual patient with an antipsychotic medication requires balancing efficacy and tolerability.
11. All patients on an antipsychotic medication, atypical or typical, should be carefully monitored for both metabolic and motor side effects because each medication has a different side effect profile and each patient has different vulnerabilities and preferences.7,8,25,26
12. Switching antipsychotic medications in schizophrenia carries significant risk and should be undertaken carefully.27,28 Continuation of an agent in the absence of desired benefit and/or occurrence of significant adverse effects, however, is also inappropriate; in the context of inadequate efficacy and/or safety-tolerability, carefully considered and informed switching to a suitable alternative agent should be considered.7,8,29,30
13. Although there is an extensive database to guide optimal antipsychotic therapy, there are many important gaps in this database.8
14. There is a significant lag between identification of important clinical questions and implementation of well-designed studies to address such questions. Furthermore, there is often a lag between completion of studies and publication of their findings, leading to a misrepresentation of the world of existing data. Additionally, there is often a significant lag between the publication of important clinical trials and the translation of findings of that research into practice.8,22
15. The role of the state mental health system is to make available the best possible services to individuals with severe mental illness to enable them to lead maximally productive and meaningful lives.8,31–35 Toward this end, public mental health policy involves several balancing acts: (1) provide "all" maximally effective services in the context of limited resources; (2) articulate clear practice standards in the context of scientific uncertainty; (3) effectively guide good practice without interfering with the doctor-patient locus of clinical decision making; and (4) harmonize often conflicting objectives of multiple stakeholders (patients, providers, families, etc).36

Footnotes

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