Outcomes, Costs, and Policy Caution

A Commentary on the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1)

SCHIZOPHRENIA IS among the most serious psychiatric illnesses, causing both personal suffering and impaired functioning. Almost 90% of people with this illness are not employed, and many rely on family assistance and public support to pay for their health care and daily living expenses. In 1990, the Americans With Disabilities Act sought to increase work opportunities and reduce disability. However, between 1994 and 2003, recipients of Social Security Administration disability benefits for schizophrenia increased by 35% from 400 000 to 550 000, double the rate of increase of cardiovascular disability and 3 times the 11% growth in the adult population (Pamela Mazerski, associate commissioner, Social Security Administration, written communication, 2004).

See also pages 1069 and 1079

During these years, the dissemination of second-generation antipsychotic (SGA) medications has been the most hopeful development in the medical treatment of this illness. Dozens of studies have described reduced adverse effects, better compliance, and greater symptom reduction (especially for negative symptoms and depression), and some have shown lower costs than older medications. In 1994, the year risperidone was released, annual domestic expenditures on antipsychotic medication totaled $1.4 billion and less than 5% of patients received SGAs. A decade later, 6 different SGAs are available in the United States. Almost 90% of patients with schizophrenia receive these new drugs, with costs exceeding $10 billion annually, 70% paid through Medicaid.[1] While researchers have attempted to differentiate the effectiveness of individual SGA medications,[2] guidelines tend to treat them as a class, and their enthusiastic reception appears to have been a "class" phenomenon, with each drug experiencing increased annual sales every year following its release. High expectations for these agents are reflected in daily wholesale prices for the treatment of schizophrenia ($6-$12/d) that are 4 to 6 times the daily costs of newer antidepressants ($2-$3.50/d), the most widely prescribed on-patent psychotropic drugs, and as much as 100 times the cost of some first-generation antipsychotics (FGAs).[3]

In response, primarily, to the promise of reduced adverse effects, first-line use of SGAs has been advocated by guidelines from the American Psychiatric Association,[4] the United Kingdom's National Institute for Health and Clinical Excellence,[5] the Texas Medication Algorithm Project,[6] and the Expert Consensus Guideline Series in the Treatment of Schizophrenia, which observed as early as 1999 that SGAs were rendering conventional antipsychotics obsolete.[7] These recommendations recently received empirical backing from an important meta-analysis of 124 studies that concluded that 4 widely used SGAs (clozapine, olanzapine, risperidone, and amisulpiride) were more effective than FGAs, although effect sizes for olanzapine, risperidone, and amisulpiride were small by conventional standards (0.21-0.29) and 6 other SGAs did not show superiority to FGAs.[2]

It was thus unexpected that the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1), a large (N=227), randomized clinical trial from the United Kingdom, with an unusually high 12-month follow-up rate of 81%, found no advantages of SGAs over FGAs on standard measures of quality of life (the primary outcome) or on discontinuation rates, symptoms, or adverse effects.[8] Nor were there any savings on health costs, even after excluding the greater costs of the SGAs themselves.

Several methodological features that might account for these findings deserve comment: (1) the study compared physician's choice of any SGA to choice of any FGA, rather than comparing specific agents; (2) both physicians and patients were unblinded to treatment assignment (although efforts were made to keep raters unbiased); and (3) sulpiride was the most commonly chosen FGA, an FGA similar in name to the SGA amisulpiride (neither of which is available in the United States). Some of these design features may be viewed as strengths. The novel design of CUtLASS 1 is closer to "real-world practice" than typical monotherapy trials because treatments are always unblinded and numerous drugs are available in real practice. This flexible design also yielded higher 12-month follow-up rates than previous studies. Although researchers have focused on differentiating the SGAs from one another, both practice guidelines and physician behavior suggest that they are treated as a class in practice and thus may deserve evaluation as a class as they are in CUtLASS 1.

CUtLASS 1 also applied an exceptional array of sophisticated analytic methods, including multiple imputation to address missing data, and tested minimally significant clinical differences to properly sup-

port the conclusion that, in this study, at least, FGAs are not inferior to SGAs. In contrast to the reliance on potentially biased analytic strategies in many earlier studies, most notably, use of last observation carried forward,[9] these methods represent an advance for the field.

A serious limitation, however, is that only 59% of patients continued taking their originally assigned medication for the full year. However, overall differences in completion rates taking the initial drug were not significantly different between FGAs and SGAs, and a 12-week analysis of "on protocol" cases showed the same pattern of results as the trial overall. The authors further argue that the pharmacologic features of sulpiride, a "pure" D2 antagonist that has been available since the mid-1960s, are more akin to those of FGAs than SGAs. Because rigorous drug evaluation was rare 50 years ago, a 1999 Cochrane review of the sulpiride literature failed to find substantial evidence that it was superior even to placebo, let alone either FGAs or SGAs.[10] Generalizability of CUtLASS 1 results to other FGAs is thus uncertain, but sulpiride was not an unfair FGA drug for comparison with SGAs since it has nothing clinically to distinguish it from FGAs and was the physicians' most common choice.

Perhaps the most important contribution of CUtLASS 1 is that 80% of patients who entered the trial had been taking FGAs prior to randomization. A problem that complicates interpretation of SGA research is that subjects who entered studies in the early years of their availability often did so because they were dissatisfied with their FGA medication and were thus likely to benefit from "something new," as compared with controls, who were often assigned FGAs to which they had previously been unresponsive. Reciprocally, patients who agree to enter more recent studies of SGAs, now that they are the most widely used antipsychotics, are more likely be dissatisfied with their SGA medication and thus may be more likely to benefit from "something old" that they had not been exposed to recently, if ever. Because SGAs have been less dominant in UK markets than in the United States, the majority of patients entering CUtLASS 1 were taking FGAs prior to randomization. Although we do not have data on their lifetime experience with SGAs, the "no difference" findings in CUtLASS 1 are thus not likely to be explained by overrepresentation of SGA nonresponders among study recruits.

While the results of CUtLASS 1 differed from those of many SGA studies, they echo the findings of 2 recent, large, long-term effectiveness studies that, like CUtLASS 1, were carried out under government auspices—a 12-month Department of Veterans Affairs Cooperative Study of 309 patients randomly assigned to olanzapine or haloperidol administration[11] and the 18-month National Institute of Mental Health–funded Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial that compared 1460 patients assigned to 4 different SGAs and the FGA perphenazine.[12]

The Department of Veterans Affairs Cooperative Study found no statistically significant differences between haloperidol and olanzapine on time to all-cause discontinuation, symptoms, quality of life, or pseudoparkinsonian symptoms.[11] Careful comparison of 6-week dropout data suggested that the use of prophylactic anticholinergics with haloperidol improved the effectiveness of this generally unpopular FGA drug and might explain the difference of these results from studies cited by Davis et al,[2] two thirds of which compared SGAs with haloperidol without prophylactic anticholinergics.[13]

The CATIE study, similarly, found no significant differences in time to all-cause discontinuation, the primary outcome, or on any neurological adverse effect between each of 4 different SGAs and perphenazine, an intermediate-potency FGA.[12] While both the Department of Veterans Affairs trial and CATIE found advantages for olanzapine on some secondary outcomes (especially akathisia and neurocognition in the Department of Veterans Affairs trial), both also found increased weight gain and potential risk of metabolic syndrome.

The authors of all 3 of these trials reported surprise and consternation over the differences between their findings and the existing literature. While each study has discernable limitations, taken together, they cannot be easily dismissed. A basic assumption of clinical research is that the results of carefully conducted clinical trials of the same agents in the same illness should not be grossly inconsistent. Support for research cannot be justified if the results only pertain to the specific samples and methods used in each study.

A synthesis of the results of these studies is sorely needed and can, perhaps, be deduced from 2 observations. First, even in the large meta-analysis,[2] the effect sizes for SGAs other than clozapine are small for 3 widely used drugs and not significantly different from zero for 6 others. Second, in the 3 recent practical trials, small methodological differences in sample selection, choice of comparison drug, or dosing—differences that did not seem substantial to study designers at the outset—apparently resulted in unexpected study results and conclusions. We might assume that the effects of a substantially beneficial treatment would not flip-flop with modest differences in study design. Reciprocally, we might conclude that when such apparently minor methodological differences do tilt the results in opposite directions, differences between agents may be very small, if they exist at all. Since both FGAs and SGAs do show robust and consistent advantages over placebo, we can be confident that basic methods and measures used in our field are not seriously flawed. The effect size reported for haloperidol vs placebo in the Davis et al meta-analysis[2] was significant and moderate in magnitude at 0.60.

Much, however, remains unknown. Research is not conclusive on crucial long-term effects of SGAs on tardive dyskinesia (TD) or metabolic risk factors. A recent review concluded that SGAs may pose less risk of TD than FGAs but acknowledged that supporting trial data are limited.[14] Some recent reports suggest the risk of TD with SGAs may have been underestimated[15-17] and a

meticulous replication of a 1985 study of TD at 1 community mental health center found no overall reduction in TD prevalence in 2003 in spite of widespread use of SGAs.[18] Furthermore, the expected release of presumably lower-priced generic risperidone, in 2007, may bring an unheralded shift in market behavior with the advent of far cheaper SGAs.

In the face of substantial cost differences between FGA and SGA treatments and small, inconsistent differences in effectiveness and adverse effects in clinical trials, some may be tempted to conclude from this research that the benefits of SGAs have not justified their costs and that "fail first" or other pharmacy benefit policies should be implemented to foster more selective and judicious use of these expensive drugs. While all research findings, not just the most recent findings, deserve consideration in policy decisions, ethicists have urged extensive and cautious deliberation among stakeholders before major policy changes are implemented.[19] While the publication of CUtLASS 1 and other recent studies[20] has questioned previously held certainties, these unexpected empirical findings should not lead to a precipitous turn away from policies that support open formularies for psychotropic drugs. Data from clinical trials are only 1 type of information of relevance to public discourse. A comprehensive public dialogue is needed prior to policy action and should involve patients, health care professionals, researchers, industry representatives, and other stakeholders. Policy change may eventually be warranted, but potentially polarizing decisions are best delayed until thoughtful public deliberation gives a chance for comprehensive review, consensus building, and shared understanding.

Unfortunately, the United States currently lacks institutions that are either responsible for, or capable of, convening such public discussions or for guiding clashing parties to mutually acceptable agreement. The mandate of the Food and Drug Administration does not extend to comparing the value of approved treatments with one another, and the Institute of Medicine typically addresses global policy issues through one-time reports rather than ongoing deliberations. Congressional hearings on recent, well-publicized drug failures have been occasions for vigorous finger-pointing rather than thoughtful cost-benefit or policy analysis. Private and public insurers, who have the most to gain from vetting controversial, if rational, drug policies, operate in isolation from one another, with no corpus of precedent to draw from or add to. We are thus left with brief sound bites, glossy print ads, and adversarial rhetoric about "fail-first policies," "price gouging," and "closing down the pipeline to future innovation." What we need is trustworthy leadership for nuanced consensus building. The cost and potential effectiveness of health care technologies are reaching new heights and are increasingly influenced by both private economic incentives and public health interests. Institutions for sustained public health policy deliberation are needed now more than ever.[21]

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1. Duggan M. Do new prescription drugs pay for themselves? the case of second-generation antipsychotics. *J Health Econ*. 2005;24:1-31.
2. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry*. 2003;60:553-564.
3. *1999 Drug Topics Red Book*. Montvale, NJ: Medical Economics Co; 1999.
4. *Practice Guideline for the Treatment of Patients With Schizophrenia*. 2nd ed. Washington, DC: American Psychiatric Association; 2004:16.
5. Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia. May 2002. National Institute for Health and Clinical Excellence Web site. http://www.nice.org.uk/. Accessed March 1, 2006.
6. Miller AL, Hall CS, Buchanan RW, Buckley PF, Chiles J, Conley RR, Crismon ML, Ereshefsky L, Essock SM, Finnerty M, Marder SR, Miller D, McEvoy J, Rush AJ, Saeed SA, Schooler NR, Shon S, Stroup S, Tarin-Godoy B. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2003 update. *J Clin Psychiatry*. 2004;65:500-508.
7. Treatment of schizophrenia 1999: the expert consensus guideline series. *J Clin Psychiatry*. 1999; 60(suppl 11):3-80.
8. Jones PB, Barnes TRE, Davies L, Dunn G, Lloyd H, Hayhurst KP, Murray RM, Markwick A, Lewis SW. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry*. 2006; 63:1079-1087.
9. Lavori PW. Clinical trials in psychiatry: should protocol deviation censor patient data? *Neuropsychopharmacology*. 1992;6:39-48, discussion 49-63.
10. Soares BG, Fenton M, Chue P. Sulpiride for schizophrenia. *Cochrane Database Syst Rev*. 2000; (2):CD001162.
11. Rosenheck R, Perlick D, Bingham S, Liu-Mares W, Collins J, Warren S, Leslie D, Allan E, Campbell EC, Caroff S, Corwin J, Davis L, Douyon R, Dunn L, Evans D, Frecska E, Grabowski J, Graeber D, Herz L, Kwon K, Lawson W, Mena F, Sheikh J, Smelson D, Smith-Gamble V; Department of Veterans Affairs Cooperative Study Group on the Cost-Effectiveness of Olanzapine. Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia. *JAMA*. 2003;290:2693-2702.
12. Lieberman JA, Stroup TS, McEvoy J, Swartz M, Rosenheck R, Perkins D, Keefe RSE, Davis S, Davis CE, Lebowitz B, Severe J, Hsiao J; the CATIE Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia: primary efficacy and safety outcomes of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial. *N Engl J Med*. 2005; 353:1209-1223.
13. Rosenheck RA. Efficacy vs effectiveness of second generation antipsychotics: haloperidol without prophylactic anticholinergics as a comparator. *Psychiatr Serv*. 2005;56:85-92.
14. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *Am J Psychiatry*. 2004;161:414-425.
15. Halliday J, Farrington S, Macdonald S, MacEwan T, Sharkey V, McCreadie R. Nithsdale schizophrenia surveys 23: movement disorders. *Br J Psychiatry*. 2002;181:422-427.
16. Lee PE, Sykora K, Gill SS, Mamdani M, Marras C, Anderson G, Shubnan KI, Stukel T, Normand S-L, Rochon P. Antipsychotic medication and drug-induced movement disorder: a population-based cohort study in older adults. *J Am Geriatr Soc*. 2005;53:1374-1379.
17. Rochon PA, Stukel TA, Sykora K, Gill S, Garfinkel S, Anderson GM, Normand S-LT, Mamdani M, Lee PE, Li P, Bronskill SE, Marras C, Gurwitz JH. Atypical antipsychotics and parkinsonism. *Arch Intern Med*. 2005;165:1882-1888.
18. Woods S. Tardive dyskinesia dead or alive? Paper presented at: Institute on Psychiatric Services; October 6, 2005; San Diego, Calif.
19. Daniels N, Sabin J. *Setting Limits Fairly: Can We Learn to Share Medical Resources?* New York, NY: Oxford; 2003.
20. Heres S, Davis J, Maino K, Jetzinger E, Kissling W, Leucht S. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. *Am J Psychiatry*. 2006;163:185-194.
21. Reinhardt UE. An information infrastructure for the pharmaceutical market. *Health Aff (Millwood)*. 2004;23:107-112.