The cost of second-generation antipsychotics in the treatment of schizophrenia is about $10 per day, more than ten times the cost of generic first-generation antipsychotics and three to four times the cost of patented antidepressants (1). Total sales of second-generation antipsychotics reached $11.5 billion in the United States in 2006 (2), over $100 per household. Whether these expenditures are justified and what, if anything, might be done to reduce them are issues of substantial public concern (3).

Cost-effectiveness analysis and consumer choice
Cost-effectiveness analysis is a scientific method for determining whether the increased cost of new treatments is justified by their relative benefits. Most commercial goods are purchased on the basis of consumer choice in private markets without a need for scientific evaluation. An important assumption about such markets is that consumers have adequate information on which to base their choices. Such information is far less accessible in health care markets. As a result, patients largely rely on their physicians for guidance. Physician opinion, however, is often shaped by industry-sponsored research (4–6) and marketing (7), especially when new drugs are brought to market. Cost-effectiveness analysis conducted by independent researchers seeks to provide data on “relative” health care value, or the cost of additional health gains with new treatments compared with the best available alternatives.

Cost-effectiveness analysis, policy, and politics
Because cost-effectiveness analysis considers costs and outcomes in a single analysis, it offers the most comprehensive empirical estimate of treatment value—critical information for shaping policy. But cost-effectiveness research is only one of many inputs to choice of health care policy. First, alternative policies representing diverse courses of action must be outlined. Such policies affect different sets of stakeholders: patients, family members, professional groups, insurance and pharmaceutical companies, and, ultimately, taxpayers. Political decision making, in turn, represents a transition from scientific fact and policy review to collective action and is shaped by interest group politics (8), regulatory law (9), and broad social values—domains in which emotional symbolism and narrow stakeholder interest carry increasing weight (10).

This commentary has three objectives: first, to summarize recent research on the cost-effectiveness of second-generation antipsychotics; second, to review the diverse policy op-

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tions available for drug cost-containment; and third, to map the wider political landscape in which antipsychotic policy is shaped. We thus seek to contrast cost-effectiveness analysis (scientific data), with policy development (conceptualization of alternative choices), and political action (the responses of decision makers).

Cost-effectiveness of second-generation antipsychotics

To put the $11.5 billion annual domestic expenditure on second-generation antipsychotics into perspective, it is noteworthy that the additional cost of using these drugs rather than first-generation antipsychotics—about $10 billion—is substantially greater than the $5.5 billion total annual income of all 47,000 U.S. psychiatrists (11, 12). This amount could fund 150,000 case managers—enough to provide intensive evidence-based treatments like assertive community treatment or supported employment to 1.5 million additional consumers—or could support three times the total number of social workers currently employed in the United States (13).

Early research

Early research on second-generation antipsychotics suggested that these medications are more effective than their predecessors (14), pose less risk of neurological side effects (especially tardive dyskinesia) (15), and save enough in inpatient costs to pay for themselves (16).

Effectiveness and tolerability

Cochrane reviews, however, do not support these conclusions (17), and in 2003 a 12-month Department of Veterans Affairs (VA) cooperative study of 309 inpatients unexpectedly found no significant differences between olanzapine and haloperidol on measures of symptoms, quality of life, or most side effects (18). One explanation for these unexpected findings was that haloperidol was given in the VA trial with prophylactic anticholinergics, whereas most industry-sponsored trials had used haloperidol without such medicines (19) and at higher doses than recommended by the Food and Drug Administration (FDA) (20), which posed a high risk of neurological side effects that could be mistaken for negative symptoms of schizophrenia.

More recently a series of reports from the 18-month Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) indicated that even though patients used olanzapine longer than two other second-generation antipsychotics (21), none of four second-generation antipsychotics (olanzapine, risperidone, quetiapine, or ziprasidone) showed any statistically significant advantage over the first-generation antipsychotic perphenazine on measures of symptoms, neurologic side effects, quality of life, employment, violent behavior, or neuropsychological functioning (22–24). CATIE has been challenged because follow-up rates were lower than in briefer studies, study duration was limited to 18 months, patients had chronic schizophrenia, and those with tardive dyskinesia were excluded from assignment to the randomization stratum that received perphenazine. However, a detailed literature review showed that the design and implementation of CATIE was no more flawed in these respects, and less flawed in some, than studies that showed second-generation antipsychotics to be superior to older drugs (25).

CATIE findings were reinforced by the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUTLASS 1), a government-funded trial in the United Kingdom, which also found no advantage of second-generation antipsychotics over first-generation drugs on symptoms, side effects, or quality of life (26). Most recently, a post-CATIE industry-sponsored trial also found no meaningful difference between the latest second-generation antipsychotic, aripiprazole, and perphenazine (27, 28).

Metabolic side effects

There has also been growing concern that some second-generation antipsychotics (especially olanzapine and clozapine) increase the risk of weight gain, diabetes, and metabolic syndrome (29), risks that may offset the benefit of any reduced risk of tardive dyskinesia (30).

Tardive dyskinesia

Reduced risk of tardive dyskinesia remains an area of potential benefit for newer drugs. A 2004 review estimated that the annual risk of this syndrome with first-generation antipsychotics was 4.6% greater than with second-generation antipsychotics (5.4% versus 8%) (15) but noted that the results could have been biased because the major trials all involved moderate to high dosages of haloperidol and may thus not be generalizable to other first-generation antipsychotics. These trials were not substantially longer than CATIE, which found no benefits for the newer drugs on similar measures (21). Recent epidemiologic studies also question whether second-generation antipsychotics have any lower risk of tardive dyskinesia than first-generation antipsychotics (31–33), even in elderly populations (34).

Another recent analysis with prevailing estimates found that the cost of avoiding one case of tardive dyskinesia by using second-generation antipsychotics ranged from $52,000 to $135,000 per year (15), or from $149,000 to $683,000 per quality-adjusted life year (35), which is three to 13 times the ceiling of $50,000 per quality-adjusted life year used by many industrial countries to determine whether a treatment is cost-effective (36).

Cost-effectiveness

The VA trial found no reductions in health service use with olanzapine, which was associated with increased total health care costs (including drugs) of $3,000 to $10,000 per year (18). A comprehensive review of cost-effectiveness research before CATIE also found no evidence of cost savings or greater cost-effectiveness for second-generation antipsychotics (37). CATIE itself found second-generation antipsychotics to have greater costs (that is, $2,400–$6,000 greater per year) and no clinical advantages over perphenazine (22). CUTLASS found first-generation antipsychotics to be more cost-effective than second-generation antipsychotics (38).
which promote bargaining between drug manufacturers; pricing mechanisms, and providers, primarily through formulary policies, affect patients by reducing high-cost drug use (45–47), discouraging unjustifiably expensive prescribing practices. Less intrusive provider-oriented approaches include presentation of independent research reviews, educational interventions, academic detailing, or disease management systems. Although all of these mechanisms seek to discourage use of high-cost medications except when specifically indicated, they also introduce a potential risk that access to beneficial treatments will be blocked for some patients.

Cost-sharing clearly has been shown to reduce high-cost drug use (45–47), but data on the application of such policies to antipsychotics are lacking. Studies of implementation of threeteried formularies showed little advantage over first-generation antipsychotics. Optimal practice with medications for off-label conditions, such as Alzheimer’s disease and posttraumatic stress disorder, may be even less cost-effective than suggested by recent research on use for schizophrenia.

Why have research results changed?
A recent editorial suggested that although the results of CATIE were disappointing, they were not unexpected because drugs in both classes work by the same mechanism (42). Meta-research on second-generation antipsychotics (4,5) and other medications (6) has found that new drugs are most likely to outperform older drugs in studies sponsored by their manufacturers, the primary source of information when they are first marketed and when enduring impressions are consolidated.

Policy options
Although second-generation antipsychotics thus may offer little advantage over first-generation antipsychotics on average, some patients may do better with one or another second-generation medication than with an older antipsychotic. Optimal practice would encourage use of newer medications for only such patients. Unfortunately no laboratory tests or clinical evaluation can objectively identify patients who are uniquely responsive to second-generation antipsychotics, and relatively blunt cost-containment policies offer the major options.

A recent review (43) identified three types of strategies for prescription drug cost containment: utilization management, which affects patients and providers, primarily through formulary policies; pricing mechanisms, which promote bargaining between fiscal intermediaries; and government regulations, which most directly affect payments to manufacturers.

Utilization management
The most restrictive utilization management strategies either entirely exclude some expensive drugs from a formulary or impose limits on the total number of prescriptions that can be prescribed. Less restrictive approaches, such as step therapy or prior-authorization policies, restrict access to a drug or drug class unless otherwise less costly or safer medications have been tried and failed or some other justification is presented. Such approaches have been strongly recommended in the treatment of hypertension, where research showed that generic drugs, as with first-generation antipsychotics, are no less beneficial than newer medications (44).

Tiered formularies, which require differential cost-sharing for generic drugs, preferred brand-name drugs, and nonpreferred brand-name drugs, also have been used to create financial incentives for patients to use less expensive, but medically equivalent, drugs. Cost-sharing can be in the form of a copayment (a fixed dollar amount per prescription, regardless of drug price) or coinsurance (a percentage of total drug price).

Other utilization strategies are directed more to providers than to patients. In physician profiling, data are compiled on individual physicians’ prescribing of high-cost drugs or polypharmacy, and either administrative feedback or economic incentives are used to discourage unjustifiably expensive prescribing practices. Less intrusive provider-oriented approaches include presentation of independent research reviews, educational interventions, academic detailing, or disease management systems. Although all of these mechanisms seek to discourage use of high-cost medications except when specifically indicated, they also introduce a potential risk that access to beneficial treatments will be blocked for some patients.

Cost-sharing clearly has been shown to reduce high-cost drug use (45–47), but data on the application of such policies to antipsychotics are lacking. Studies of implementation of threeteried formularies showed little advantage over first-generation antipsychotics (48) or stimulants among children (49), but a draconian intervention that imposed a three-per-month payment limit on prescriptions under Medicaid was associated with an increase in emergency room use and partial hospitalization among people with serious mental illnesses, offsetting all drug cost savings (50). There is insufficient evidence for or against utilization management policies for antipsychotics.

Pricing mechanisms
The second broad class of cost-control policies involves pricing mechanisms, such as the establishment of purchasing pools in which multiple providers jointly negotiate with manufacturers for lower prices (43). Pricing mechanisms predominantly affect negotiation between drug manufacturers and health plans, with larger potential prescription volumes increasing the bargaining power of purchasers. But the ultimate leverage for purchasers is the threat that utilization management strategies, such as those described above, will be used to limit access to a manufacturer’s drugs. Thus even competitive pricing mechanisms may ultimately impose burdens on prescribers and patients. The VA has successfully used its substantial purchasing power to lower drug costs (51), as has an interstate Medicaid purchasing pool (52).

The prices of second-generation antipsychotics may be especially high, say three to four times those of newer antidepressants (1), in part because over 70% of all sales have been paid by Medicaid historically (39). By law, the price Medicaid pays for a drug is based on a formula that uses the average manufacturer price charged to non-Medicaid purchasers and the lowest price given to any such purchaser in the United States. This creates unintended incentives for the pharmaceutical industry to charge higher wholesale prices for drugs such as second-generation antipsychotics because they are not typically purchased directly by consumers (that is, only third parties face their high prices) (53).
Medicare and transitioned from Medicaid to private Medicare Part D plans in 2006 may further increase prices of antipsychotics. Persons with dual eligibility constituted a significant proportion of Medicaid beneficiaries receiving antipsychotics, and their exit reduces the bargaining power of state Medicaid programs for the remaining beneficiaries (54). The dispersed enrollment of the dually eligible beneficiaries across several Medicare Part D plans within each state also limits the bargaining power of any single plan. The Part D requirement that all drugs in the second-generation antipsychotic class be covered by all plans substantially limits price negotiations.

**Government regulation**

The final set of policies primarily affects manufacturers and includes direct price regulation, mandated volume rebates, accelerated conversion of patent drugs to generic status, direct-to-consumer advertising, and reimportation of less expensive medicines from other countries (43). These approaches are far less disruptive for providers or patients and are likely to enhance, rather than reduce, drug access. In regard to pricing policies, Medicaid rebates have lowered drug costs but have been countered, as noted above, by increased prices (53,55). By lowering corporate income such regulations risk reducing investment in the development of new drugs (56,57), with possible adverse effects in the long run. Price regulation appears to be most stringent in countries that lack a significant domestic drug manufacturing sector, such as the Netherlands, France, Germany, and the United Kingdom all regulate drug prices despite a strong industrial pharmaceutical presence (58). The possibility that price controls could limit the need for utilization management strategies and improve access deserves further study, but opposition to price controls in the United States is strong and broad based.

**Stakeholder interest and politics**

Although many appropriate policy alternatives are thus available, a recent cross-national study showed a general reluctance to use cost-effectiveness analysis to influence policy in the United States compared with other industrial countries (36). Americans seem to distrust cost-effectiveness analysis, perhaps fearing that it could lead to harmful restrictions. Governments in the United Kingdom, Canada, and Australia, in contrast, generally do not pay for treatments that cost more than U.S. $50,000 per quality-adjusted life year (36).

Responses to the CATIE trial vividly reflect the differing perspectives of major competing stakeholders. Press releases from the American Psychiatric Association and from leading patient and family advocates have expressed alarm that the results of CATIE would lead to restrictive formulary policies that would limit the freedom of physicians to prescribe or the right of consumers to have access to all approved medications. None of these stakeholders would support preferential use of less expensive first-generation antipsychotics before more expensive drugs. Although none argued against recent research showing that second-generation antipsychotics are no more cost-effective than first-generation antipsychotics, they take the implicit position that rights of access should take priority over regulations promoting cost-effectiveness.

A *New York Times* editorial (59), in contrast, concluded that CATIE showed that “the system for approving and promoting drugs is badly out of whack” and that “the nation is wasting billions,” and a *Washington Post* report concluded that “physicians, patients and policymakers can be blindsided by self-interested research by drugmakers” (60). But these expressions of dismay were also unaccompanied by calls for limits on use of more expensive drugs.

Manufacturers of second-generation antipsychotics, in contrast, noted advantages that CATIE showed for their specific products (61), and some CATIE results have been used, albeit selectively, in their advertising campaigns. At least one company has been alleged to operate a program through which it offers to pay for quality management data reviews for state mental health agencies in exchange for a commitment that no formulary restrictions are placed on its product (62).

State Medicaid agencies, which historically paid 70% of costs for second-generation antipsychotics, have been largely silent on recent research. Costs for this class of drugs are clearly a concern for both Medicaid and for Medicare Part D, and prior authorization, copayments, and other restrictions are increasingly used in these programs (63,64). In some cases access to individual second-generation antipsychotics has been restricted (65), but no policy has been implemented for systematically limiting use of the class as a whole. One state Medicaid official described psychotropic drugs as “the third rail of formulary policy,” uniting the interests of left-leaning patient advocates with those of pharmaceutical industry interests (66). This may explain why the Medicaid response to recent research on newer antipsychotics has been muted.

Some psychiatrists have expressed dismay that they were misled by industry (67,68) or have expressed renewed confidence in first-generation antipsychotics (69), but policy proposals suggesting change to the status quo for antipsychotic formularies or drug pricing have been few (70). The Texas Medication Algorithm Project group recently decided that second-generation antipsychotics should not necessarily be prescribed in preference to first-generation drugs in chronic schizophrenia (71). Some of the important CATIE findings have only recently been published (22–24) and may require more time to influence policy.

The most compelling responses to CATIE have been anecdotal. Physicians, consumers, and family members have reported in various settings that regardless of research findings, the benefits of second-generation antipsychotics are clear to them, and the imposition of any limits on these medications would cause grave harm. A powerful rhetoric of deprivation argues that if all drugs are not available, some patients will suffer unduly. The probabilistic estimates of clinical trials pale beside the imagery of tragically impaired lives. Successes of older drugs go unreported because such stories are not considered news.

Attitudes of mental health groups toward medications (72), including second-generation antipsychotics, are po-
ularized, and it has been suggested that conflicts between patient, family, and provider groups are stronger in the mental health community than elsewhere (73). A 1991 survey of U.S. congressional staff concerning the relative political effectiveness of the mental health and developmental disabilities communities concluded that the developmental disabilities community was more effective because it was less divided (74). Dry cost-effectiveness data are not likely to attract the attention of parties contending over broader policy issues, such as whether medications should be used at all.

One final policy option that might limit the dominance of industry research and foster studies like CATIE that provide additional independent information to public policy discussions would establish a new federal agency or funding pool that would carry out independent trials comparing different FDA-approved drugs with each other (75). Such an agency could be funded through taxes on profits of blockbuster drugs, such as those with sales of more than $1 billion per year, without undermining corporate incentives to innovate (76).

Despite offering the public, physicians, and policy makers better data for judging price appropriateness, such studies would not, by themselves, improve the cost-effectiveness of practice. That will remain a matter of health system administration, policy, and politics.

Conclusions
Recent independent research suggests that higher expenditures on second-generation antipsychotics are not justified by their relative clinical benefits. Also, alternative policy options are available that would favor more selective and more efficient antipsychotic use; however, such policies are not likely to be implemented for want of political support. Expenditures on antipsychotic drugs are likely to remain high with limited health benefit.

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References
73. Stockdill JW: A government manager’s view of mental health advocacy groups. Administration and Policy in Mental Health 20:45–56, 1992