Effectiveness Versus Efficacy of Second-Generation Antipsychotics: Haloperidol Without Anticholinergics as a Comparator

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Over the past decade, second-generation antipsychotic medications have become the first-line treatment for schizophrenia. Placebo-controlled studies have unambiguously demonstrated their effectiveness and safety, and they have expanded the range of pharmacotherapeutic options for patients, families, and clinicians. Furthermore, because of the low rate of extrapyramidal side effects, the need for anticholinergic medications is dramatically lower than with first-generation agents, resulting in greater ease of use.

Second-generation agents are costly, with $7.5 billion in U.S. sales in 2003. However, their expanded use has been supported by the results of randomized controlled trials and meta-analyses that have shown reduced risk of treatment discontinuation, greater improvement in symptoms, and fewer side effects than with first-generation antipsychotics (1–3).

Last year my colleagues and I published results from a Department of Veterans Affairs (VA) Cooperative Study comparing olanzapine and haloperidol—a first-generation agent—that unexpectedly found far more limited benefits for olanzapine in these outcome domains, apparently because anticholinergic medication was prescribed to the haloperidol group prophylactically rather than on an as-needed basis (4). In subsequent months I have had the opportunity to discuss these results at professional meetings and with colleagues, consumers, and consumers' family members, many of whom led me to scholarly publications and Food and Drug Administration (FDA) documents that have helped reconcile what were apparently contradictory findings. In this forum I survey these issues as I currently understand them to encourage further discussion and debate.

Of 124 studies that were considered in the largest meta-analysis of second-generation antipsychotics (2), 82 (66 percent) used haloperidol as a comparator, in all but four cases without prophylactic anticholinergics. Published literature that originated before the second-generation-antipsychotic era urged use of prophylactic antiparkinsonian medication, especially with drugs such as haloperidol, because some extrapyramidal side effects, described as akinesia or akinetic depression that are responsive to anticholinergics, can emerge without telltale parkinsonian features. Thus these symptoms can be indistinguishable from negative symptoms of schizophrenia and depression (5–13). Because they are unrecognized, they are unlikely to be treated with anticholinergics and may be exacerbated by increased dosages of antipsychotics.

In this review I consider whether the widespread use of haloperidol without prophylactic anticholinergic medications has given second-generation antipsychotics an overall advantage in studies that compare the efficacy of first- and second-generation antipsychotics. The assessment of relative efficacy in clinical research must be differentiated from the assessment of relative effectiveness (14). Although efficacy studies in psychopharmacology assess the effect of a molecule of interest on specific symptoms, effectiveness studies assess the impact of treatment packages that may involve bundled combinations of interventions, delivered as they would optimally be used in real-world practice. Thus it is possible that second-generation antipsychotics have greater efficacy than haloperidol when haloperidol is used in isolation, without prophylactic anticholinergics, but are no more effective when haloperidol is provided with prophylactic anticholinergic treatment, or when they are compared with low-potency first-generation antipsychotics that have a lower risk of extrapyramidal side effects.

A three-part review

This review first presents a detailed comparison of the contrasting methods and results of the VA Cooperative Study (4) and the International Collaborative Trial (ICT) (15,16), the largest and most influential trial to compare olanzapine and haloperidol and one that has spawned numerous articles in the peer-reviewed literature and whose methods have been replicated in many if not most subsequent trials of second-generation an-

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tipsychotics. Prophylactic anticholinergics were not used in the ICT.

I then review the literature on akinesia, an extrapyramidal syndrome that resembles the negative symptoms of schizophrenia (5–13). This literature helps explain the contrast between the robust outcomes favoring second-generations antipsychotics in three landmark trials of second-generation antipsychotics and haloperidol (15,17,18), as contrasted with the limited benefits for positive symptoms.

Finally, I reconsider the three most recent meta-analyses of trials of second-generation antipsychotics (1–3) to determine whether their conclusions may have been affected by the use of haloperidol without prophylactic anticholinergics in a majority of studies.

The VA Cooperative Study and the ICT

The VA Cooperative Study was a 12-month randomized clinical trial (N=309) that found no evidence of olanzapine's superiority in adherence (time to medication interruption for any reason), in positive or negative symptoms of schizophrenia, in parkinsonian side effects, in multiple measures of quality of life, or in cost (4). No differences were found in use of any concomitant or off-protocol medications, and there were no differences in symptoms or quality of life when off-protocol observations were excluded. Lower frequency of mild akathesia and modestly better memory and motor function with olanzapine were balanced by more frequent reports of weight gain as well as annual health care costs that were $3,000 to $9,000 higher per patient (4).

These findings were quite different from those of the landmark ICT (N=1,966), in which olanzapine and haloperidol were compared over six weeks, with an extension phase of up to one year (15), and significantly greater benefits were found for olanzapine in almost all symptom and side-effect domains, using virtually the same measures as the VA study.

Although dosages of medication were not substantially different in the two trials (13 to 15 mg for both drugs over the year of treatment) (4,15), VA patients were about eight years older on average (46.5±8.7 compared with 38.3±11.4) and were overwhelmingly male (96 percent), and 21 percent had a current substance use disorder (an exclusion criterion in the ICT). Analyses of the VA data, excluding patients with current substance abuse, did not alter the findings, nor did analyses that excluded patients who were older than 44 years. Baseline total scores on the Positive and Negative Syndrome Scale (PANSS) were about four points lower in the VA sample (86.4±15.4 compared with 90.8±19.5), and entry criteria pertaining to refractoriness were not applied in either study.

Comparison of the proportions of patients who completed the first six weeks of treatment, when study designs were almost identical, shows no appreciable differences between the two studies among patients who were assigned to receive olanzapine (68 percent in VA compared with 67 percent in the ICT). In contrast, among those who were assigned to receive haloperidol, a far greater proportion completed six weeks of treatment in the VA trial than in the ICT (71 percent compared with 47 percent). The most viable explanation of this 24 percent difference is the use of prophylactic benztropine in the VA study. Even though patients who received haloperidol in the ICT had access to anticholinergics on an as-needed basis—and about half were reported to have received such medications (15)—it appears that these agents were not used sufficiently to prevent substantial early discontinuation of treatment. One would have expected VA patients who were receiving haloperidol to have had more problems with extrapyramidal side effects because most were male and were eight years older than the patients in the other study (19).

Although the use of prophylactic anticholinergics could readily explain the differences between studies in overall treatment discontinuation and extrapyramidal side effects, it could not obviously explain differences in symptom outcomes or in treatment discontinuation attributed to lack of effectiveness.

Other design differences were that the VA study continued to collect data for all patients, even after the patients changed medications, whereas the ICT stopped data collection at the time of medication change and analyzed the available data by using the last observation carried forward (LOCF) method, whereby each patient's last observation is counted as his or her end point. Because patients who receive an effective treatment for six weeks are likely to show more improvement than patients who are treated for shorter periods, simply because they have more time to improve, early discontinuation in the haloperidol group, although most likely to have been caused by extrapyramidal side effects, biases symptom results in favor of olanzapine.

Although early haloperidol discontinuation and use of the LOCF method in the ICT may thus explain the greater reduction in symptoms among patients who received olanzapine, it does not explain the fact that 32 percent of the patients who received haloperidol in the ICT were judged by their clinicians to have discontinued medication because of lack of effectiveness, compared with only 21 percent of the patients who received olanzapine ($p<.001$). Could clinicians have mistakenly identified lack of effectiveness as the reason for drug discontinuation if the actual reason was undertreated extrapyramidal side effects?

Akinesia in the absence of prophylactic anticholinergics

Clinical reports and controlled trials suggest that one kind of extrapyramidal side effect—akinesia—can readily be mistaken for refractory symptoms of schizophrenia, especially negative symptoms and depression, without being accompanied by telltale parkinsonism (5–13). The term "akinesia" is used in these studies to address a constellation of symptoms that is broader than the narrow neurologic use. In their 1969 textbook, Klein and Davis (5) presented a classic description of treatment without prophylactic anticholinergics: "Frequently these patients did not manifest extrapyramidal disorder but

showed lack of spontaneity, inability to participate in social activities, general akinesia and complained of feeling lifeless and drowsy. At that point the introduction of antiparkinsonian medication regularly resulted in marked increase in the patient's spontaneity and feeling of capacity to engage in activity." In a 1987 review, Van Putten and Marder (6) similarly concluded that "akinesia may be the most toxic behavioral side effect of antipsychotic drugs" and added, "It is notoriously difficult to differentiate schizophrenic apathy and blunting from akinesia," a conclusion that has been affirmed by others (7,8,10).

To illustrate the clinical presentation of akinesia without frank parkinsonism, Rifkin and associates (9) described eight cases in which patients who were apparently depressed, socially withdrawn, or demoralized experienced a rapid recovery after having anticholinergics prescribed. In an observational study, Van Putten and May (11) reported that 30 percent of 92 hospitalized patients with schizophrenia experienced akinesia that was responsive to treatment with anticholinergics. More recently, Bermanzohn and Siris (12) presented a series of cases in which noncompliance with anticholinergic medication was associated with onset of akinetic depression that was reversed when anticholinergic treatment was resumed.

To experimentally evaluate the risk of akinesia, Rifkin and colleagues (10) recruited 55 patients who were being treated with a first-generation antipsychotic and procyclidine with no evidence of extrapyramidal side effects. In a double-blind discontinuation study, these patients were randomly assigned to receive active procyclidine (N=18) or placebo (N=37) for three weeks. None of the patients who received active procyclidine experienced any clinical changes. Of the 37 patients who were randomly assigned to receive placebo, seven (19 percent) developed akinesia without other evidence of extrapyramidal side effects, ten (27 percent) developed extrapyramidal side effects without akinesia, and three (8 percent) developed both akinesia and other manifestations of extrapyramidal side effects.

Thus, in a trial that did not use prophylactic anticholinergic medications, even if all cases of manifest parkinsonism had been promptly and effectively treated, 19 to 30 percent of the patients who were assigned to first-generation antipsychotics could develop treatable akinesia without any other evidence of extrapyramidal side effects, and their treatment might be erroneously judged ineffective. Given that patients in the experimental study by Rifkin and colleagues (10) were assigned to receive a variety of high- and low-potency antipsychotic medications, rates of disk-

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inesia could be even higher in studies such as the ICT in which all control patients were assigned to receive haloperidol, a drug associated with an especially high risk of extrapyramidal side effects (19).

Differential effects on positive, negative, and depressive symptoms

Because the inactivity, withdrawal, and depression associated with drug-related akinesia are more likely to be confused with negative symptoms of schizophrenia and depression than with positive symptoms (5–13), we might expect especially impressive advantages for second-generation antipsychotics in these domains in studies that offered anticholinergics only as needed. Among the three most influential studies that have compared atypical antipsychotics and haloperidol are the ICT (15,16,20), Marder and Meibach's 1994 trial of risperidone (17), and the study by Csernansky and colleagues (18) of relapse with risperidone. In all three studies, haloperidol was provided without prophylactic anticholinergics, and LOCF analysis was used. All studies showed more early treatment discontinuation with haloperidol and significantly less improvement in symptoms. The studies also indicated substantially greater benefit of second-generation antipsychotics for negative symptoms and depression than for positive symptoms.

Although the ICT reported a significant difference between olanzapine and haloperidol in negative symptoms ($p=.03$), as well as a modest effect size (.21), differences between the two agents in positive symptoms were only marginally significant ($p<.06$), with a small effect size (.14). The greatest benefit for olanzapine was for depressive symptoms ($p<.003$, effect size=.33) (15). Claims for the direct effects of olanzapine on negative symptoms (20) and depression (16) thus may actually reflect untreated akinesia among the controls who received haloperidol. Because akinesia in the absence of parkinsonian symptoms is not identifiable on measures of extrapyramidal side effects (5,6,9,10), efforts to model the effects of the second-generation agent independent of extrapyramidal side effects (20) cannot adequately address this potential confound.

In Marder and Meibach's study (17), risperidone (6 mg) was associated with two times as much improvement as haloperidol for positive symptoms (effect size=.34), but gains were significantly different from placebo for both drugs. In contrast, for negative symptoms, risperidone was associated with 11 times as much improvement as haloperidol (effect size=.44), and only the gains associated with risperidone were significantly different from those associated with placebo. Schooler (21), in a further analysis of data from this trial, also

Table 1

Difference in risk of poor outcome among patients with schizophrenia in studies that compared second-generation antipsychotics and haloperidol with and without prophylactic anticholinergic medication[a]

Outcome	Second-generation			First-generation			Difference	
	Total sample	Adverse outcome		Total sample	Adverse outcome			
		N	%		N	%	%	ratio
With anticholinergic								
Relapse	60	11	18	28	4	14	–4	1.28
Treatment failure for any reason	25	6	24	14	1	7	–17	3.36
Dropout due to side effects	25	4	16	14	1	7	–9	2.24
Without anticholinergic								
Relapse	960	137	14	538	123	23	9	.62
Treatment failure for any reason	1,306	687	53	631	442	70	17	.75
Dropout due to side effects	960	107	11	538	84	16	5	.71

[a] Based on a meta-analysis conducted by Leucht and colleagues (1)

concluded that apparent differences between haloperidol and risperidone for negative symptoms were actually attributable to differences in extrapyramidal side effects.

In the study by Csernansky and colleagues (18) of relapse with risperidone, only 18 percent of patients who received haloperidol received anticholinergics at all, even though dosages averaged 11.7±5 mg of haloperidol per day, and 37 percent of the patients received more than 15 mg per day. The most plausible explanation for this very low use of anticholinergics (in the ICT 50 percent of haloperidol patients received anticholinergics) is that unrecognized akinesia adversely affected symptom and functional assessments and led to misclassification as relapse. Comparison of the median number of days of treatment shows that patients who received risperidone had 126 days' (about four months') more treatment than patients who received haloperidol.

This large difference, in turn, could account for the significant ($p<.05$) LOCF differences favoring risperidone on four of five PANSS symptom factors. Notably, the two PANSS symptom factors on which the haloperidol group showed the largest deterioration from baseline—and on which the risperidone group, in contrast, showed net improvement—were the negative symptom and anxiety-depression factors of the PANSS, both of which could reflect akinesia from undertreated extrapyramidal side effects. For positive symptoms, in contrast, there was virtually no deterioration among patients receiving haloperidol but substantial improvement among patients receiving risperidone—most likely because they were exposed to four more months of treatment.

The research on akinesia reviewed above (5–13) suggests that results favoring second-generation antipsychotics are most likely attributable to a design triad of undertreated akinesia, early discontinuation of treatment among patients receiving haloperidol, and use of LOCF analysis.

In contrast with these studies, an earlier multisite VA study of clozapine and haloperidol among patients with treatment-refractory schizophrenia—one of the few studies that used prophylactic anticholinergics and avoided the biases of LOCF analysis—showed significant benefits associated with clozapine for both positive and negative symptoms with gains of similar magnitude (–6 percent for positive symptoms over haloperidol and –8 percent for negative symptoms at 12 months) (22).

Meta-analyses of atypical antipsychotics

If, as I have suggested, the use of haloperidol without prophylactic anticholinergic medication may generate results that spuriously favor second-generation antipsychotics, further examination of recently published meta-analyses that have reported greater efficacy of second-generation antipsychotics may be informative (1–3). Readers should be cautioned that citation of studies from these meta-analyses can be confusing, because one citation may report on as many as three different studies (23), and three different citations may address different outcomes from the same study (22,24,25).

The first meta-analysis examined outcomes from 11 randomized trials that compared the risk of adverse outcomes in a sample of 2,032 patients (1). Second-generation antipsychotics were associated with a lower risk of relapse than first-generation antipsychotics (15 percent and 23 percent, respectively), treatment failure for any reason (49 percent compared with 66 percent), and dropout due to adverse events (11 percent compared with 15 percent). Although five second-generation antipsychotics were used in these studies (amisulpride [26,27], clozapine [25,28–30], olanzapine [23], risperidone [18,31], and sertindole [32]), monotherapy with haloperidol was the comparator in all but one (28), and prophylactic anticholinergics were used in only two (24,30). Thus 91 percent of studies in this meta-analysis used haloperidol as the comparator, and only 20 percent of these prescribed prophylactic anticholinergics.

Remarkably, data from the two studies that used haloperidol with prophylactic anticholinergics (both involving comparison with clozapine) document a greater risk of relapse with clozapine than with haloperidol (18 percent compared with 14 percent) as well as a greater rate of treatment failure for any reason with clozapine (24 percent compared with 7 percent) and of early discontinuation of treatment (16 percent compared with 7 percent) (Table 1). Only when haloperidol was used without prophylactic anticholinergics was risk of relapse less with second-generation antipsychotics than with haloperidol (14 percent compared with 23 percent), as was the risk of treatment failure for any reason (53 percent compared with 70 percent) and of dropout (11 percent compared with 16 percent).

In a second meta-analysis, Davis and colleagues (2) computed effect sizes from clinical rating scales in a sample of 124 studies that included 18,272 patients and showed superior efficacy of second-generation antipsychotics compared with first-generation antipsychotics, especially for clozapine, amisulpride, risperidone, and olanzapine (2). Of these studies, 66 percent used haloperidol as the comparator, but only four could be identified that used prophylactic anticholinergics (24,33–35).

Three studies included by Davis and colleagues (2) found that even with prophylactic anticholinergics, haloperidol was less effective than clozapine—two among adults (24,35) and one among children (33). A four-group study that used haloperidol with prophylactic anticholinergics in one group showed greater symptom improvement with both clozapine and olanzapine but not with risperidone (34). However, the authors of that study concluded that these results could not be taken as evidence of the inferiority of haloperidol, because the study "included patients who had failed to respond to haloperidol" while excluding "those who showed a clear failure to clozapine, olanzapine or risperidone." The authors go on to comment, "This selection bias, shared with many other studies, would be expected to result in data that tend to show superior efficacy of atypical antipsychotics" (34). These flaws limit the study's relevance to this discussion and, perhaps, should have been grounds for excluding the study from the meta-analysis. However, the authors' suggestion that this exclusion bias is not uncommon is of concern, especially given that such bias is not explicitly addressed in the meta-analysis or in any other individual studies that we have been able to review.

A third recent meta-analysis (3) recognized that the predominant use of haloperidol as a comparator might favor second-generation antipsychotics, especially in the risk of extrapyramidal side effects (19). That meta-analysis examined 31 trials, involving 2,320 patients, that compared second-generation antipsychotics with low-potency first-generation antipsychotics, those with the least risk of extrapyramidal side effects and thus most similar to the combination of haloperidol and prophylactic anticholinergics. It concluded that there were no differences between second-generation antipsychotics and low-potency first-generation antipsychotics in rates of treatment discontinuation at any dosage, or in extrapyramidal side effects at 600 mg chlorpromazine equivalent or less. Second-generation antipsychotics, particularly clozapine, showed greater efficacy than low-potency first-generation antipsychotics, although when three studies that used subtherapeutic dosages of thorazine (less than 300 mg per day) were excluded (remaining N=1,505), the overall advantage of second-generation antipsychotics was not statistically significant.

The results of this final meta-analysis are consistent with the view that there is no advantage to second-generation antipsychotics in either adherence or extrapyramidal side effects compared with treatment approaches that appropriately address the risk of extrapyramidal side effects. Nor is there any advantage in terms of effectiveness when extrapyramidal side effects are clinically addressed or when low-potency first-generation antipsychotics are given in adequate dosages.

Discussion

A fundamental principle of cost-effectiveness analysis is that new interventions should be tested against the next-best alternatives (36). A trial that compares a new treatment with a hobbled comparator gives an unfair advantage to the newer agent and provides less useful guidance for practice. Most trials of second-generation antipsychotics have used haloperidol without prophylactic anticholinergic medication as the comparator. Although these are legitimate studies of efficacy (the impact of a molecule, in isolation, on specified clinical phenomena), they are less informative on the subject of effectiveness (the advantage of an agent over the next-best choice as used in optimal real-world practice). Here I have presented three types of evidence that the findings of efficacy studies that used haloperidol without prophylactic anticholinergics overestimated the advantages of second-generation antipsychotics, with the possible exception of clozapine.

First, we compared two large studies of olanzapine and haloperidol that came to opposite conclusions (4–15), evidently because one used prophylactic anticholinergics and the other did not.

Second, research was reviewed showing that akinesia without evident parkinsonism can be clinically indistinguishable from negative symptoms of schizophrenia or depression and, as a result, can be treated effectively only with prophylactic anticholinergics. Data from three landmark trials (15,17,19) that found distinct advantages for atypical antipsychotics in negative symptoms and depression most likely reflect undertreated akinesia among patients who received haloperidol but who did not receive prophylactic anticholinergics.

Finally, we reviewed the three most recent meta-analyses of second-generation antipsychotics, which included more than 130 trials (1–3). Including the recent VA study (4), these meta-analyses bring to just eight the number of valid comparisons of second-generation antipsychotics and first-generation antipsychotics with prophylactic anticholinergic treat-

ment, six of which involved haloperidol. Four of eight analyses found no significant benefits for second-generation antipsychotics—two involving olanzapine (4,37) and two clozapine (25,30). Four that did show significant benefit for second-generation antipsychotics all involved clozapine (24,33,35,38), the most efficacious agent in the meta-analysis conducted by Davis and colleagues (2) and one that is widely regarded as unique among the second-generation antipsychotics. When the reviewed studies are considered together, about two-thirds gave an unfair advantage to second-generation antipsychotics by comparing these agents with haloperidol without prophylactic anticholinergics, and the remainder, using low-potency first-generation antipsychotics, did not find robust advantage for second-generation antipsychotics.

It must be acknowledged that although most experts have advocated the use of prophylactic anticholinergics (5,10–13,39), some suggest that this decision should be made on a case-by-case basis (use of haloperidol would be a strong indication) (40,41), and one panel cautioned against prophylactic use of anticholinergics (42). The use of prophylactic anticholinergics appears to have become less common in ordinary practice, even with first-generation antipsychotics. The evidence reviewed here lends support to the argument in favor of their use, especially with high-risk medications such as haloperidol, although they can themselves cause unpleasant side effects and cognitive impairment.

Second, differences in results between the two large trials (4,15) may also reflect differences in historic recruitment conditions. Fair comparison with older drugs may have been difficult at the time of the ICT, because many recruitable study participants would have already had poor results with haloperidol, whereas none would have had poor results with olanzapine. These circumstances differ from the nonequivalent entry criteria described by Volavka and colleagues (34), because they change naturally with time (34). Among participants in the recent VA trial, 40 percent were being treated with second-generation antipsychotics before study entry, 37 percent with haloperidol, and the others with other first-generation agents, a far more balanced array. Although recruitment differences might partially explain differences in results, the differences between results for positive contrasted with negative symptoms in major trials are most consistent with underuse of anticholinergics among controls receiving haloperidol, resulting in akinesia.

Third, although the evidence presented here suggests that the benefits of second-generation antipsychotics for symptoms and quality of life may have been overestimated in past studies, a comprehensive reevaluation of second-generation antipsychotics must also consider other outcomes. Some studies have shown modest advantages of second-generation antipsychotics in terms of akathisia and cognition (4) as well as a lower risk of tardive dyskinesia (18,43,44). A recent review of one-year studies (45) suggested that second-generation antipsychotics are associated with a reduced risk of tardive dyskinesia but noted serious limitations, including the fact that only three studies used a concurrent first-generation-antipsychotic comparator, all used relatively high dosages of haloperidol, and many patients did not complete the trials.

These benefits must be evaluated against increased weight gain, diabetes and metabolic problems (46), and greater medication costs, with little or no savings elsewhere (4,47–49). Economic studies showing net savings in the ICT (50) had follow-up rates of less than 25 percent at 12 months, and cost estimates are especially vulnerable to distortion by use of LOCF methods, because costs decline steadily after trial entry. Although this review has identified a potential bias against comparator treatments in two-thirds of previous studies, it has not determined whether this bias accounts for all the reported efficacy advantages of second-generation antipsychotics, or does so only partially, as seems especially likely in the case of clozapine.

Consistent with our findings, an unpublished internal memo written in August 1996 by the director of the division of neuropharmacological drug products of the FDA concluded that the ICT data did not support the conclusion that olanzapine is more efficacious than haloperidol. Thus far, the FDA has not approved such a claim for any second-generation antipsychotic. A subsequent FDA memo explained that the reason for this judgment was that "some of the so-called negative signs and symptoms of that illness [schizophrenia] are indistinguishable from the pseudoparkinsonian signs and symptoms that are known side effects of antipsychotic drugs like haloperidol," an argument quite similar to the line of reasoning presented here.

Conclusions

It is unsettling when carefully and well-conducted research studies come to different conclusions, and it is hoped that this discussion may help resolve these apparent contradictions and constructively encourage designers of future clinical trials to thoughtfully consider whether to use prophylactic anticholinergics with first-generation antipsychotics. Although we can never know what the results of past studies would have been had prophylactic anticholinergics been used, we can look forward to results of important new studies, such as the National Institute of Mental Health–funded Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (51) schizophrenia trial that uses trilafon as the first-generation-antipsychotic comparator, a medication with less tendency to cause extrapyramidal side effects than haloperidol. Although anticholinergics were not used prophylactically in CATIE, concerted efforts are being made to follow all patients for the full duration of the trial through a series of structured medication changes, and LOCF is not proposed as a method of analysis (52).

It is important, in concluding, to reemphasize that the discussion presented above pertains only to the comparison of second-generation antipsychotics and first-generation antipsychotics in published clinical trials. All parties agree the second-gen-

eration antipsychotics are safe and effective treatments for schizophrenia. Effectiveness trials do not conflict with efficacy trials but rather build on them, elaborating their meaning for practice.

Generalizable knowledge often accumulates slowly, through unexpected twists and turns, and public policy is inevitably guided both by the imperfect state of clinical science and by economic constraints. However, a long and distinguished clinical tradition demands that individual treatment decisions be based on the particular knowledge shared by the health care professional and the patient and must always be driven by the unique circumstances of each encounter. ♦

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