Antipsychotic Trials in Schizophrenia

The CATIE Project

Edited by

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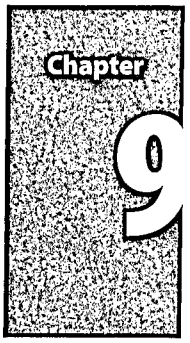

Extrapyramidal side effects

Stanley N. Caroff, Del D. Miller, and Robert A. Rosenheck

From the beginning of the use of chlorpromazine and other neuroleptic drugs, signs of parkinsonism (e.g., tremor, rigidity, and bradykinesia) were observed as frequent side effects and, despite numerous studies to the contrary, were considered to be inextricably linked to therapeutic antipsychotic effects [1,2]. Within a few years, investigators also observed an association between these drugs and abnormal involuntary movements that came to be known as tardive dyskinesia (TD) [3,4]. These and other drug-induced extrapyramidal side effects (EPS) can be mistaken for or worsen primary psychotic symptoms, are sometimes irreversible or lethal, often necessitate additional burdensome side effects from antiparkinsonian agents, can be disfiguring and stigmatizing, and have been shown to influence compliance, relapse, and rehospitalization [1,5,6]. As a result, EPS dominated concerns about tolerability of antipsychotic drugs for decades, and their elimination served as a major impetus for new drug research and development.

In 1988, clozapine was found to have broader efficacy in schizophrenia with negligible EPS, stimulating the search for other antipsychotics with improved tolerability [7]. The drugs that were introduced after clozapine came to be known as atypical or second-generation antipsychotics (SGAs) while the earlier drugs were now called typical or first-generation antipsychotics (FGAs). Industry-sponsored clinical trials suggested that SGAs were superior to FGAs in the treatment of schizophrenia, reducing psychotic symptoms and causing fewer EPS [8–20]. Cumulative evidence supporting reduced liability for EPS with SGAs contributed to the widespread dominance of these drugs in the marketplace and fostered the concept of "atypicality" in the mechanism of action of the new drugs [21–25].

Further studies mostly confirmed a reduced risk of EPS with SGAs but also raised questions about the degree or significance of the advantages of SGAs seen in earlier trials. Although haloperidol, as the most widely prescribed FGA, was a reasonable choice as a comparator in industry-sponsored trials because of its widespread use, several reviews and meta-analyses suggested that the relative advantages of SGAs in reducing EPS liability were diminished when lower doses or lower-potency FGAs are used, or if prophylactic antiparkinsonian drugs are administered [21,26–33]. In view of these conflicting findings, the CATIE schizophrenia trial offered an opportunity to address the lingering controversy over the significance of the relative liability for EPS between first- and second-generation antipsychotics.

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Initial analysis of EPS in the CATIE schizophrenia trial

The rationale, design, methods, and statistical analysis of the CATIE trial have been described previously and in Chapters 1 and 2 [34–36]. Here, only features of CATIE that are relevant to interpretation of EPS findings are briefly summarized. CATIE was designed to address the overall effectiveness of SGAs versus a mid-potency FGA, perphenazine, based on treatment discontinuation for any cause. The key secondary outcomes were the specific reasons for discontinuation including inefficacy or intolerability. Among the latter was the influence of EPS on tolerability and effectiveness.

Patients were initially assigned randomly to receive olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone under double-blind conditions (Phase 1). The daily mean modal doses were 20.1 mg for olanzapine, 20.8 mg for perphenazine, 543.4 mg for quetiapine, 3.9 mg for risperidone, and 112.8 mg for ziprasidone. Patients with TD ($n = 231$, 15% of the sample) were excluded from randomization to perphenazine and were assigned to one of the four SGAs (Phase 1A). Ziprasidone was added to the trial after 40% of the patients had been enrolled. Comparisons involving perphenazine were limited to patients without TD and comparisons involving ziprasidone limited to patients randomized after ziprasidone was added. Patients who discontinued their first treatment were invited to participate in subsequent phases of the trial, which will be discussed in a later section of this chapter. The data presented in this and the following section on the initial and second analyses of EPS deal only with Phases 1 and 1A.

Baseline data revealed that the CATIE sample represents a chronic and moderately symptomatic population of middle-aged patients with schizophrenia who have experienced long-term treatment with antipsychotics, which are important considerations in interpreting EPS findings and generalizability to other patient samples. Patients had received antipsychotic drugs for a mean of 14.4 years, starting at a mean age of 24 years. A total of 72% of patients were receiving antipsychotics at baseline, and 56% were on SGAs.

There were significant differences among drugs in time to discontinuation for any cause, time to discontinuation for inefficacy, and duration of successful treatment, with median time on drug of 9.2 months for olanzapine, 4.6 months for quetiapine, 4.8 months for risperidone, 5.6 months for perphenazine, and 3.5 months for ziprasidone.

The study showed no significant difference between treatment groups in time to discontinuation due to intolerable side effects overall ($p = 0.054$). However, the rates of discontinuation due to side effects differed significantly ($p = 0.04$), with risperidone showing the lowest and olanzapine the highest due to metabolic effects of the latter drug. In contrast, more patients discontinued perphenazine owing to EPS (8% versus 2% to 4% for the SGAs, $p = 0.002$) (Table 9.1). Quetiapine was associated with a higher rate of anticholinergic effects (31% versus 20% to 25%, $p < 0.001$), and conversely, quetiapine had the lowest and perphenazine the highest rate of concomitant use of anticholinergic drugs (3% versus 10%, $p = 0.01$).

There were no significant differences among groups in the incidence of parkinsonism, akathisia, or TD assessed by rating scale measures of severity (Table 9.1). Parkinsonism was defined as a mean score of one or more on the Simpson-Angus Extrapyramidal Signs Scale (SAS), indicating at least mild severity of parkinsonism [37]. Scores of three or more on the global assessment of the Barnes Akathisia Rating Scale (BAS) were chosen to indicate at least moderate severity of akathisia [38]. Finally, scores of two or more on the Abnormal Involuntary Movement Scale (AIMS) global severity score were chosen to indicate at least mild severity of dyskinesia [39]. In Table 9.1, all values listed for each EPS category are for

Table 9.1. Initial analysis of CATIE outcome measures related to EPS [34]

Outcome	Olanzapine	Quetiapine	Risperidone	Perphenazine	Ziprasidone	*p* Value
Discontinuations due to extrapyramidal symptoms*						
	8/336 (2)	10/337 (3)	11/341 (3)	22/261 (8)	7/185 (4)	0.002
Extrapyramidal side effects*‡						
Parkinsonism	16/240 (7)	10/247 (4)	20/238 (8)	15/243 (6)	6/129 (5)	0.50
Akathisia	12/234 (5)	12/248 (5)	12/240 (6)	16/241 (7)	13/132 (10)	0.19
TD	32/236 (14)	30/236 (13)	38/238 (16)	41/237 (17)	18/126 (14)	0.23
Anticholinergic side effects*€						
	79/336 (24)	105/337 (31)	84/341 (25)	57/261 (22)	37/185 (20)	<0.01
Anticholinergic medications added*						
	25/336 (7)	11/337 (3)	32/341 (9)	26/261 (10)	14/185 (8)	0.01

Notes: *Number/total number of patients (%).
‡Parkinsonism percentages = the number of patients with an SAS mean score $\geq$ 1, with a mean score < 1 at baseline and at least one post-baseline assessment; Akathisia percentages = the number of patients with a BAS global score $\geq$ 3, with a global score < 3 at baseline and at least one post-baseline assessment.
TD percentages = the number of patients with an AIMS global score $\geq$ 2, with a global score < 2 at baseline and at least one post-baseline assessment. Patients with TD at baseline (assigned to Phase 1A) were excluded from all EPS assessments.
€Urinary hesitancy, dry mouth, constipation.

patients who did not have that corresponding EPS at baseline, had at least one post-baseline assessment, and were without TD at baseline, i.e., data excludes patients from Phase 1A who were restricted from receiving perphenazine. These data differ from the original report in which SAS and BAS data included patients who had TD at baseline [34]. However, there were no significant differences observed regardless of whether or not TD patients were included in the analysis.

In summary of the initial trial analysis, there were no significant differences between perphenazine and SGAs in the proportion of patients exhibiting parkinsonism, akathisia, and TD, in contrast to previous studies using haloperidol as the representative FGA. However, more patients discontinued perphenazine (8%) than SGAs (2% to 4%) as a result of EPS, and perphenazine (10%) had a high rate of concomitant anticholinergic drug use relative to SGAs (3% to 9%).

Second analysis of EPS in the CATIE schizophrenia trial

Given the somewhat unexpected lack of significant differences in EPS found in the initial analysis, a second in-depth analysis of the CATIE schizophrenia trial data was undertaken to more rigorously assess and compare the incidence of treatment-emergent dystonia, parkinsonism, akathisia, and TD associated with SGAs and perphenazine, excluding subjects with each respective condition at baseline and using more sensitive diagnostic criteria for specific EPS symptoms [40]. Both survival analysis and mixed models were applied to each side effect.

EPS were measured using six items of the SAS for parkinsonism, the global clinical assessment item of the BAS for akathisia, and the first seven items from the AIMS as a

measure of TD. Data on concomitant medications, reasons for treatment discontinuation, and reported adverse events were also used to identify the occurrence of any EPS reactions. Two of the authors (D.M. and S.C.) conducted a blind adjudication of physician reports to classify cases in which treatment was discontinued or concomitant medications were added for each of the four EPS side effect symptoms.

Dystonia was identified if it was given as the reason for adding concomitant medications or discontinuation of antipsychotic medications, or reported as an adverse event.

Patients were considered to have met criteria for parkinsonism if they scored 1 (mild) on at least two of the six SAS items or 2 (moderate) on one of the items (initial analysis required a mean score ≥ 1). Cases of parkinsonism were further identified if they were taking an antiparkinsonian medication or discontinued their antipsychotic medication due to parkinsonism. The summary score of all six SAS items was also used as a continuous measure.

Patients were considered to have met criteria for akathisia if they scored at least 2 (mild) on the BAS global item, if akathisia was specifically given as the reason for starting any medication, or if they discontinued their antipsychotic medication due to akathisia (initial analysis required a global score ≥ 3). The summary score of the BAS global item was also used as a continuous measure.

Patients were considered to have met criteria for TD if they met Schooler-Kane (S-K) criteria, i.e., if they scored 2 (mild) on at least two AIMS items or 3 (moderate) on one of the items at two or more assessments (initial analysis required a global score of ≥ 2) [41]. Analyses were also conducted using modified S-K criteria such that meeting the AIMS criteria on only one assessment was required, i.e., "probable" TD. The summary score of all seven AIMS items was also used as a continuous measure. TD was also diagnosed if it was the reason given for adding any medication or discontinuing antipsychotic medication.

Analyses of the incidence of the four EPS were conducted only on subpopulations that did not meet criteria for that side effect at the time of baseline assessment. For TD, patients were excluded from the analysis if they met modified S-K criteria at baseline, or were identified as having borderline TD, which was defined by not meeting the full modified S-K criteria but having at least one AIMS item score of mild, reporting a history of TD, taking medications for TD, or being placed in Phase 1A. A supportive analysis was repeated in which all borderline patients were included.

A second set of analyses involved repeated measures analysis of continuous measures representing change in severity of the three syndromes from baseline. Patients meeting criteria for each syndrome at baseline were not excluded from these analyses but baseline scores of the dependent measure were included as covariates in each analysis. Analyses of incidence of side effects were conducted first without adjustment for potential baseline predictors of each syndrome and then in models that included socio-demographic and other baseline measures that were significantly associated with the dependent measure. The statistical plan used for treatment group comparisons followed the same methods as in the original publication from CATIE and described in Chapter 2 [34,36,40].

Dystonia

Dystonia occurs mostly in young males and was commonly associated with FGAs in the past [42,43]. Over 95% of dystonic reactions occur within the first 5 days of treatment, with

an incidence rate of 2% to 5%, although some reports suggest higher rates when more potent drugs are used parenterally. In published trials, haloperidol had up to four times greater risk of causing dystonia than SGAs [8,10,44].

By comparison, there were only six cases of acute dystonia reported in the CATIE study (6/1,460 or 0.4%) that were not present at baseline, four of which resulted in treatment discontinuation. Of these six cases of dystonia, none were receiving olanzapine, one was receiving perphenazine, one was receiving quetiapine (discontinued), one was receiving risperidone (discontinued), and three were receiving ziprasidone (two discontinued).

Parkinsonism

The risk of parkinsonism has been associated with increasing age, female gender, and increased dose and potency of antipsychotics [42,43]. It typically develops in days to weeks, with 50% to 75% of cases occurring within 1 month and 90% within 3 months. The incidence is variable depending upon risk between studies but has been estimated to occur in about 10% to 15% of patients treated in routine practice with FGAs. In randomized trials, haloperidol has been associated with two to four times the risk of parkinsonism compared with SGAs (22% to 38% versus 4% to 14%) [8,10,12,14,44–46].

In the second CATIE analysis, examination of the proportion of patients showing no evidence of parkinsonism at baseline who met at least one of the three criteria for parkinsonism during the subsequent follow-up period revealed no substantial differences between treatment groups (Table 9.2). Statistical analysis, using piecewise exponential regression of the probability of having a parkinsonian event showed no statistically significant difference between treatment groups. Covariate-adjusted 12-month event rates were notable at 37% to 44% among the four SGAs and 37% for the FGA perphenazine. The Kaplan-Meier survival plot illustrates both the substantial incidence of parkinsonian events, particularly in the first month, and the convergence of treatment groups (Figure 9.1). Finally, mixed model analysis of change in parkinsonian symptoms from baseline for all treated patients, as measured with the SAS, also showed no statistically significant group differences. Analyses of maximum change in SAS score and incidence of parkinsonism events after the first month of treatment also found no statistically significant differences.

Table 9.2. Second analysis of observed EPS events for patients without the events at baseline [40]

Extrapyramidal event	Olanzapine	Quetiapine	Risperidone	Perphenazine	Ziprasidone
Any parkinsonian event	70/201 (35)*	55/187 (29)	71/191 (37)	48/160 (30)	31/98 (32)
Any akathisia event	52/238 (22)	42/250 (17)	61/244 (25)	51/207 (25)	26/130 (20)
Tardive dyskinesia (S-K)	2/182 (1)	8/179 (5)	4/179 (2)	6/183 (3)	3/89 (3)
Tardive dyskinesia (mS-K)	20/216 (9)	19/222 (9)	21/220 (10)	26/221 (12)	10/120 (8)

Notes: *Number/total number of patients without the extrapyramidal symptom at baseline (%).
Any parkinsonian event includes meeting SAS score criteria, discontinuing treatment, or adding a medication for parkinsonism.
Any akathisia event includes meeting BAS score criteria, discontinuing treatment, or adding a medication for akathisia.
S-K = Schooler Kane criteria; mS-K = Modified Schooler Kane criteria requiring only one post-baseline assessment [41].

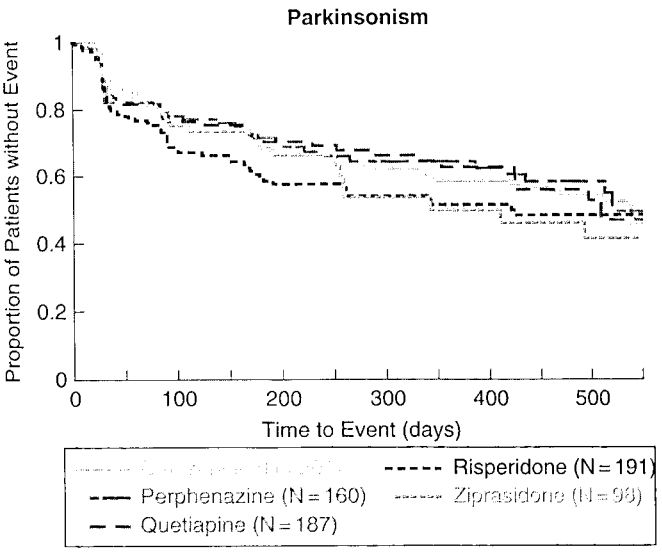

Figure 9.1. Kaplan-Meier survival curve of time until parkinsonism event for people with no parkinsonism at baseline. See plate section for color version. [40] Reprinted with permission of The British Journal of Psychiatry.

Analysis of incidence of adding medications found an overall difference ($p = 0.029$ for primary data set 1), with addition of antiparkinsonian medications most likely for risperidone patients (6.7%) and least likely for quetiapine patients (1.0%). In addition, analyses of incidence of discontinuation for parkinsonism suggested there was a lower rate of discontinuation for quetiapine and ziprasidone ($p < 0.05$ for all four data sets, although exact logistic regression methods were statistically significant only for data set 3).

Akathisia

Akathisia is another common EPS that occurs in all age groups associated with increasing dose and potency of antipsychotics [42,43]. It develops in 50% of cases within 1 month and 90% of cases within 3 months. Incidence rates vary between 5% and 50% across studies of FGAs, but it occurs in about 20% of patients in routine practice. In published trials, akathisia developed at an incidence rate of about two to seven times higher with haloperidol (15% to 40%) compared with SGAs (0% to 12%) [8,10,12,14,44–46].

In the CATIE study, examination of the proportion of patients who met at least one of the criteria for akathisia among those who had no evidence of akathisia at baseline, showed no substantial difference between treatment groups (Table 9.2). Poisson regression analysis of the probability of meeting any of the three criteria for akathisia revealed no significant difference between groups. Covariate-adjusted 12-month event rates ranged from 26% to 34% for the SGAs and 35% for perphenazine. The Kaplan-Meier plot graphically shows the close grouping of survival curves across treatment groups (Figure 9.2), and mixed model analysis of change from baseline on the BAS global rating similarly revealed no statistically significant group differences, but did suggest a general decline in akathisia over time. Analysis of maximum change in BAS global ratings found no statistically significant differences ($p = 0.071$), although perphenazine had the largest estimated change (0.44) and olanzapine had the lowest (0.22). Analyses of incidence of adding medications for

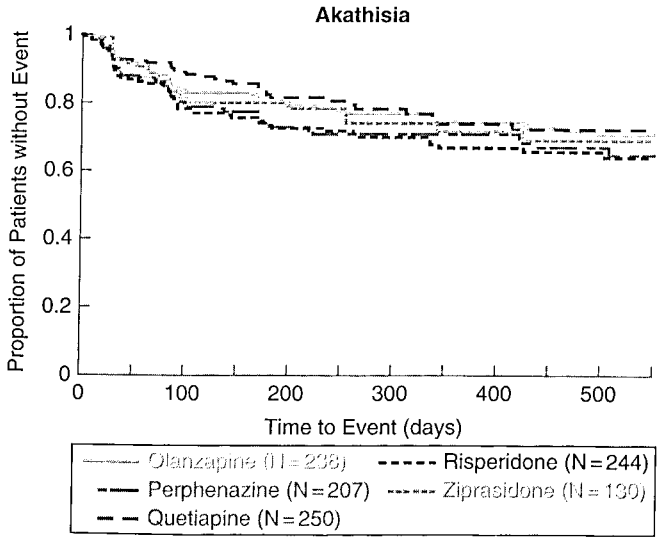

Figure 9.2. Kaplan-Meier survival curve of time until akathisia event for people with no akathisia at baseline. See plate section for color version. [40] Reprinted with permission of The British Journal of Psychiatry.

akathisia found no significant differences ($p = 0.056$), although perphenazine (8%) and risperidone (6%) had higher rates of medications added compared with quetiapine (2%). No significant differences were noted for analyses of discontinuation for akathisia.

Tardive dyskinesia

The onset of TD occurs insidiously over 3 months or more of treatment and has been associated with increasing age, possibly dose and potency as well as long-term exposure to FGAs [47,48]. Studies of FGAs have reported an incidence of 4% to 5% per year, reaching 15% to 30% in the elderly, and a prevalence of about 20% to 25% [47–49]. In contrast, studies with SGAs have suggested a significantly lower risk of TD [17,19,33,50,51].

Data from patients who had no evidence of TD at baseline show a small proportion of patients met full S-K TD criteria during Phase 1 treatment (1.1% to 4.5% receiving SGAs and 3.3% receiving perphenazine (Table 9.2). The proportion of patients who met modified S-K TD criteria ranged from 8.3% to 9.6% with SGAs and 11.8% for perphenazine. The other two measures of TD events (patient discontinuations and concomitant medications) were met by only 1% or fewer cases in all treatment groups. Poisson regression reveals no statistically significant difference between treatment groups on either TD indicator. Covariate-adjusted 12-month event rates for S-K TD ranged from 0.7% to 2.2% among the SGAs and 2.7% for perphenazine. Kaplan-Meier survival curves show both the infrequent incidence of TD and the overlapping of treatment groups (Figure 9.3), while mixed model analysis of change in TD symptoms from baseline, based on the AIMS total score, also showed no statistically significant group differences. Analyses of incidence of TD events for patients with either no or borderline TD at baseline, and maximum change in AIMS total score also found no statistically significant differences between treatment groups.

In summary, using a broad variety of more stringent measures of dystonia, parkinsonism, akathisia, and TD, the analysis of incidence rates and continuous measures from CATIE shows no significant differences between any SGA and perphenazine, or between

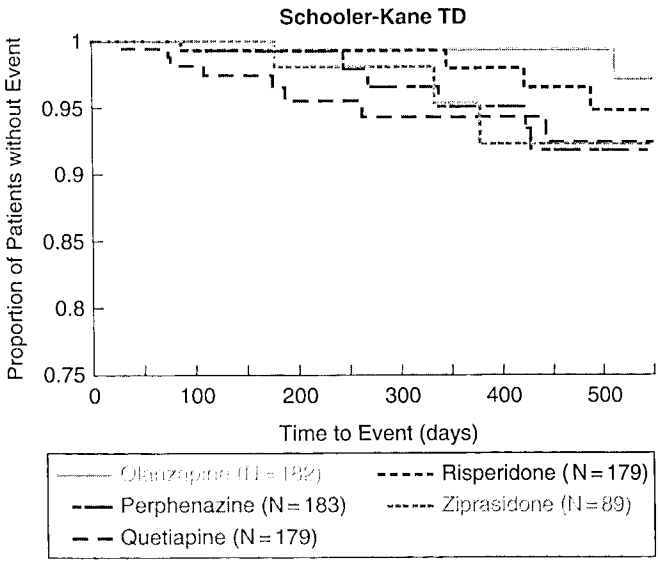

Figure 9.3. Kaplan-Meier survival curve of time until Schooler-Kane TD for people with no TD at baseline. See plate section for color version. [40] Reprinted with permission of The British Journal of Psychiatry.

any pair of SGAs. In this analysis, we utilized more sensitive criteria for parkinsonism and akathisia than in the analyses reported by Lieberman *et al.* [34], and we thus found a much higher incidence of these side effects, whereas we used more specific and standardized criteria for TD resulting in a lower incidence than in the initial analysis; in neither case did the criteria result in any significant differences in the incidence of specific EPS symptoms. However, there were differences among the secondary measures of adding concomitant medications and discontinuations for parkinsonism and less so for akathisia, with quetiapine least likely to cause either outcome, and perphenazine or risperidone more likely to do so in some instances.

Analysis of EPS in subsequent phases of the CATIE schizophrenia trial

In the CATIE trial, patients who discontinued medications assigned in Phase 1 or 1A could enter Phase 2. If the patients received perphenazine during Phase 1, they could enter Phase 1B to receive olanzapine, risperidone or quetiapine [52]. If they again discontinued treatment in Phase 1B, they could enter Phase 2. Patients entering Phase 2 from either Phase 1, 1A or 1B, could enter one of two pathways; the efficacy pathway (Phase 2E), which was designed for patients who discontinued previous treatment because of inefficacy, compared open-label clozapine to double-blind treatment with olanzapine, risperidone, or quetiapine [53]; or the tolerability pathway (Phase 2T), which was designed for patients who discontinued previous treatment due to intolerability, compared double-blind treatment with ziprasidone, olanzapine, risperidone, or quetiapine [54]. Measures of EPS based on scale scores were the same as in the initial CATIE trial analysis.

Among 444 patients who discontinued an SGA in previous phases and entered Phase 2T, olanzapine and risperidone proved more effective than quetiapine and ziprasidone based on longer time until discontinuation for any reason [54]. This ranking of relative effectiveness

held true for patients who discontinued previous drugs for inefficacy. However, among patients who discontinued previous drugs for intolerability, time until discontinuation was longest for risperidone but the differences were not significant. There were no differences in the incidence of EPS between drugs based on rating scale scores or reasons for discontinuations.

Among 99 patients discontinuing SGAs in previous phases for lack of efficacy and entering Phase 2E, clozapine was more effective than olanzapine, risperidone, and quetiapine based on longer time to treatment discontinuation for any reason [53]. This was true for discontinuations for lack of efficacy, but there were no significant differences in discontinuations because of intolerable side effects. There were no significant differences in EPS, but quetiapine was associated with significantly more anticholinergic side effects.

In Phase 1B, 114 patients who previously had been randomized to perphenazine received olanzapine, risperidone, or quetiapine [52]. Although there were no differences between the drugs in the incidence of EPS based on scale scores or reasons for discontinuing treatment, quetiapine and olanzapine were more effective than risperidone as reflected in all-cause discontinuations. There were no differences between drugs for discontinuations due to inefficacy, intolerability, or patient choice considered separately. However, among patients who earlier discontinued perphenazine because of intolerability, twice as many discontinued risperidone (85%) compared with quetiapine (40%). In addition, none of these patients discontinued quetiapine because of intolerability compared with 64% receiving olanzapine and 69% receiving risperidone. Finally, among 19 patients who discontinued perphenazine specifically because of EPS, twice as many discontinued risperidone for any reason (83%) compared with quetiapine (38%) or olanzapine (40%). Therefore, in Phase 1B, among patients who had not responded well to perphenazine previously, quetiapine was more effective than in other phases, and risperidone was less effective. Stroup *et al.* speculated that patients in Phase 1B represented a subgroup of patients who were sensitive to and less tolerant of the high affinity dopamine D2 receptor mediated neurological effects of perphenazine and risperidone, and did better on quetiapine, which is least like perphenazine in this regard [52].

Clinical correlates of TD at baseline from the CATIE schizophrenia trial

As reviewed above, there were no significant differences between perphenazine and SGAs in the rate of development of TD studied prospectively in any phase of the CATIE trial. However, CATIE also afforded a unique opportunity to re-examine cross-sectional clinical correlates associated with TD at baseline in a large and well-defined population. Previous studies have suggested an association with increasing age, female gender, longer duration of antipsychotic treatment, higher ratings of negative symptoms and thought disorder, greater cognitive impairments, presence of acute EPS, and diabetes [47,48].

To re-examine these correlations, patients at baseline were divided into TD and non-TD groups [55]. Probable TD was defined by use of S-K criteria, except a history of 3 months of drug exposure was not required and the diagnosis was derived only from the AIMS ratings at baseline [41]. Patients who had no history of TD and who had no AIMS item rated greater than 1 on the baseline AIMS examination comprised the non-TD group. Patients who had a history of TD but did not meet modified S-K criteria and subjects who had one AIMS item rated 2 were considered indeterminate and were excluded from the analyses. The methods of statistical analysis were previously described [55].

Table 9.3. Clinical correlates of TD in baseline data from the CATIE schizophrenia trial [55]

	TD (N = 212)	Non-TD (N = 1098)	*p* Value
	Mean ± SE	Mean ± SE	
Age (years)	47.2 (0.6)	38.9 (0.3)	<0.0001
Years since first antipsychotic	21.5 (0.7)	12.8 (0.3)	<0.0001
AIMS (total)	7.6 (0.3)	0.3 (0.02)	<0.0001
SAS	0.40 (0.03)	0.16 (0.01)	<0.0001
BAS	2.06 (0.14)	0.78 (0.04)	<0.0001
Neurocognitive composite (Z-score)	−0.19 (0.05)	0.02 (0.020)	0.772
PANSS			
Total	78.2 (1.2)	75.1	0.001
Positive	19.4 (0.4)	18.3	0.058
Negative	20.2 (0.4)	20.1	0.013
General psychopathology	38.6 (0.7)	36.7	0.003
Gender (% male)	78%	74%	0.224
Current antipsychotic			0.051
None	26%	27%	
SGA only	47%	60%	
FGA (± SGA)	28%	14%	
Current anticholinergic use	28%	14%	0.009
Diabetes	13%	9%	0.682
Hypertension	41%	33%	0.405
Substance abuse	42%	37%	0.0032

Abbreviations: SAS = Simpson-Angus Extrapyramidal Signs Scale, BAS = Barnes Akathisia Rating Scale, AIMS = Abnormal Involuntary Movement Scale, PANSS = Positive and Negative Syndrome Scale; FGA = first-generation antipsychotic; SGA = second-generation antipsychotic.

Of the 1,460 patients in the CATIE trial, 212 met modified S-K criteria for probable TD and 1,098 had neither a history nor current evidence of TD (Table 9.3). Sixty-eight patients who had a chart history of TD but did not currently meet modified S-K criteria, and 80 patients who had no history of TD but had one AIMS item rated 2, were considered indeterminate, and were excluded from the analyses. Patients with probable TD were found to be significantly older, and had been treated with an antipsychotic significantly longer, were more likely to be currently treated with an FGA, and to be currently treated with an anticholinergic agent. However, since these are cross-sectional data, we cannot infer that these are causal relationships. Gender, race, and ethnicity were not differentially distributed between patients with TD versus those without TD. Patients with diabetes or hypertension did not have higher rates of TD.

Having a substance abuse disorder was significantly associated with having TD after adjusting for significant covariates and when stratified by age. In addition, we also found that both alcohol ($p = 0.023$) and drug abuse/dependence ($p = 0.0032$) were significantly associated with TD in covariate-adjusted analyses. We also found that the relationship with cocaine abuse/dependence showed a trend toward being associated with TD ($p = 0.057$), stimulant abuse/dependence was significantly associated with TD ($p = 0.013$), and opiate ($p = 0.88$) and marijuana ($p = 0.33$) abuse/dependence were not associated with TD.

Although TD was associated with neurocognitive impairment in unadjusted analysis, the relationship lost significance after adjustment for covariates and investigator site. When we examined individual neurocognitive factors, the pattern remained the same. Patients with TD had higher levels of psychopathology (Positive and Negative Syndrome Scale [PANSS] total score) [56] even after the covariates and investigator site were included in the analysis.

The severities of parkinsonism and akathisia were significantly related to TD in unadjusted models and after covariate adjustment.

In conclusion, our results confirm previously suggested relationships between age, duration of treatment with an antipsychotic, treatment with FGAs, treatment with an anticholinergic agent, presence of acute EPS, increased psychopathology, current substance abuse, and the presence of TD. Of note, the correlation between TD and FGAs at baseline contrasts with the lack of differences between perphenazine and SGAs observed in the prospective outcome data of the study. This could be explained by the long-term effect of past exposure to high doses of more potent D2 receptor antagonists, like haloperidol, in patients prior to entry in the study, whereas the mid-potency antipsychotic perphenazine was less likely to induce dyskinesias during the shorter trial period itself. Moreover, data on TD from the randomized, controlled prospective phases of CATIE provide a more rigorous test of the causal nature of the association between TD and drug class compared with the cross-sectional analysis of the correlation at a single point in time. Finally, we found no support for the hypothesis that diabetes or hypertension increase the risk for TD, or that TD is associated with cognitive impairment. This suggests that older patients with schizophrenia who have a long duration of treatment with potent FGAs, who experience EPS, are treated with anticholinergic agents, have higher ratings of psychopathology, and who are current substance abusers are at higher risk for developing TD.

Methodological limitations of the CATIE trial in relation to EPS

The strengths of the CATIE study include its large sample size, diverse representation of clinical settings, independence from industry sponsorship, and the head-to-head comparison of four SGAs and a representative FGA. Based on the sample size and event rates for EPS, the study had 80% power to detect with a p value < 0.05, a 15% difference between any two treatment groups for parkinsonism events, a 14% difference for akathisia, and a 7% difference in TD.

Nevertheless, there are a number of design features to consider in interpreting the findings on EPS and generalizability of the study data to other patient populations. First, the use of perphenazine, an intermediate potency FGA given at modest doses, was likely at least partially responsible for the lack of difference in the incidence of treatment-emergent EPS seen between the FGA and SGA groups in the study that might have been expected if haloperidol had been used as the FGA. The daily mean modal dose for the perphenazine

group was 20.8 mg/day. Using the dose equivalency of 4:1 (perphenazine to haloperidol) proposed by Kane *et al.* [57], this would be equivalent to a dose of 5.2 mg/day of haloperidol, which is lower than was used in the initial trials for the SGA agents. At this dose, perphenazine was no less effective than olanzapine, quetiapine, risperidone, and ziprasidone measured as time to discontinuation of treatment for any cause [34]. Similarly, there were no differences between perphenazine and SGAs on measures of symptoms or quality of life, or on neurocognitive functioning [25,58,59].

Second, since most subjects in the trial had received antipsychotic medications for many years, the patients may be less likely to develop EPS than the general population of persons with schizophrenia, especially those with first-episode psychosis. In addition, it is possible that, for subjects who developed TD during the trial, the onset of TD could have been related to prior antipsychotic exposure. However, previous studies that showed advantages of SGAs over FGAs usually were conducted on patient samples of similar age and duration of illness, so these sample characteristics may not account for the differences in findings [60].

Like other studies comparing the incidence of TD in patients treated with FGAs and SGAs, some subjects may have been experiencing withdrawal dyskinesia or unmasking of TD related to switching from one antipsychotic to another. The majority of subjects in the CATIE schizophrenia trial switched antipsychotics at baseline. It is possible that the antipsychotic prior to entry into the study or the antipsychotic that they were randomized to may have had an influence on the rates of withdrawal dyskinesia although investigators were allowed to cross-titrate the previous and new antipsychotics for up to a month. In fact, we saw very few cases of TD within the first month of the trial, and our findings did not change substantially whether we included the data from the 1-month visit or not, suggesting that withdrawal dyskinesia did not significantly affect our findings.

Another potential limitation of the study was the relatively short duration of exposure to each drug due to high switch rates. Nonetheless, the duration of exposure was similar to or longer than those in prior studies with SGAs [19,60]. Our findings were corrected for duration of exposure, and it is unlikely that the results for parkinsonism and akathisia were affected by the duration of exposure as they tend to occur early in treatment.

Another substantial difference between the CATIE data and previously reported trials was that patients with a history of TD at baseline were excluded from analyses that compared SGAs and perphenazine. The CATIE design is more consistent than previous studies with the basic principle of risk assessment research which states that patients who already have the outcome being studied should be excluded from the study cohort [61]. Such patients already *are* "cases" and thus cannot be at any risk of *becoming* "cases" and add uninformative variance that biases results toward the null. The exclusion of TD patients from our statistical analysis allowed *more* precise comparison of treatment-emergent TD incidence than in studies that included mixed samples. It has previously been reported that there is a relationship between the development of parkinsonism, akathisia, and TD. Various investigators have shown that antipsychotic-induced parkinsonism and/or akathisia are associated with a higher risk of developing TD [52–55], and the baseline analysis of the CATIE data showed a significant correlation of parkinsonism and akathisia with TD [22,55,62–65] However, inclusion of acute EPS as a covariate in adjusted analyses of the incidence of TD did not alter the lack of significance between treatment groups.

We also excluded subjects who were experiencing parkinsonism and akathisia at baseline from the corresponding analysis comparing the incidence of treatment-emergent parkinsonism and akathisia to avoid potential biases. Although we feel that this was the best method for

comparing rates of EPS, our findings may not directly relate to patients who are already experiencing an EPS on their current antipsychotic agent. It is also possible that patients with TD at baseline who were only randomized to an SGA may have been at a greater risk for developing parkinsonism and akathisia, which could potentially bias these results. However, in analyses between perphenazine and SGAs in the incidence of acute EPS, patients receiving perphenazine were compared only with patients receiving SGAs who were not in Phase 1A, i.e., patients with TD were excluded from these analyses. Moreover, there were no significant differences between antipsychotics in the incidence of acute EPS in the initial CATIE trial analyses regardless of whether patients with TD were included or not [34].

Another limitation of the study was that, as with most randomized trials of antipsychotic medications, training for the scales used to rate EPS and TD was not as rigorous as training for ratings of psychopathology. Given that the trial was double-blind, this fact should have influenced all treatment groups equally. Another issue related to scale scores concerns criteria used in the study to define EPS events. The S-K criteria for TD based on the AIMS scale have been standardized and widely used in antipsychotic trials, and the rate of TD events found in the CATIE study based on S-K criteria are comparable to previous results ranging from 1.1% to 4.5% [41]. Use of modified S-K data or use of an AIMS global score of 2 or more in the initial CATIE analysis yielded substantially higher rates of dyskinesia (8.3% to 11.8% and 13% to 17%, respectively) [34,40]. In any case, the criteria were applied uniformly to all treatment groups in double-blind fashion, and we found no significant differences regardless of the criteria used.

With respect to acute EPS, there is a lack of standardization among trials in diagnostic criteria. Most previous studies report data either on comparative analysis of continuous measures of rating scale scores between treatments or spontaneous adverse reports without specified symptom criteria. In contrast, we applied pre-defined criteria for identifying EPS events similar to the method used by Schooler and Kane for TD [41]. In the initial analysis, parkinsonism was defined by an SAS mean score of 1 or more post-baseline (4% to 8%), whereas in the second analysis, parkinsonism was defined by more sensitive criteria of 1 or more on two items or 2 on one item of the SAS (28.1% to 32.5%). Similarly, akathisia was defined initially by a BAS global score of 3 or more post-baseline (5% to 9%), whereas in the second analysis akathisia was defined by a lower threshold of 2 or more on the BAS (15% to 23%). For both parkinsonism and akathisia, treatments were also compared by discontinuations, concomitant medications, and continuous measures of scale scores. Regardless of the criteria used, there were no significant differences between treatments. However, results may be difficult to compare to other trials if different methods for case ascertainment were used.

There is a need for standardization of the definition of "caseness" for acute EPS similar to the current consensus on TD. For example, the need for further study of the sensitivity and specificity of EPS criteria is underscored by the findings in Phase 1B, during which the patients seemed to be affected by the shared neurological properties of perphenazine and risperidone, even though no differences were found using the less sensitive criteria for EPS employed in the initial CATIE study analysis [34,52].

Conclusions

Using a variety of measures of dystonia, parkinsonism, akathisia, and TD, the analysis of incidence rates and continuous measures from CATIE shows no substantial or statistically significant differences between modest doses of the intermediate potency FGA

perphenazine and four SGAs in patients with chronic schizophrenia requiring maintenance antipsychotic treatment.

However, there was evidence from secondary measures scattered through phases of the trial suggesting that subtle differences in extrapyramidal effects between the drugs, which correlate with D2 dopamine receptor affinity, were noted by patients and their doctors, although these findings could be explained by chance due to multiple comparisons. For example, in the initial analysis, perphenazine was associated with more discontinuations for all EPS effects combined, and perphenazine-treated patients received the most concomitant anticholinergic drugs and quetiapine-treated patients the least. In the second analysis, the overall rate of parkinsonian events was not different between drugs, but there was a lower rate of discontinuations due to parkinsonism for quetiapine and ziprasidone, and addition of anticholinergic drugs was most likely for risperidone and least likely for quetiapine. Finally, in Phase 1B, among patients who discontinued perphenazine, quetiapine was significantly more effective and less likely to be discontinued because of intolerability than risperidone, and this was especially true for patients who discontinued perphenazine because of EPS and intolerability in general.

Nevertheless, the conclusion that must be drawn from the CATIE study is that there were no significant differences in primary outcome measures of acute EPS and TD overall, while at the same time perphenazine was shown to be not significantly different in overall effectiveness compared with olanzapine, risperidone, quetiapine, and ziprasidone. Therefore, one could surmise that the advantages of SGAs over haloperidol used without anticholinergics in the incidence and significance of acute EPS and TD shown in previous trials are diminished when modest doses of a low or mid-potency antipsychotic like perphenazine are used as the representative FGA. This is entirely consistent with data emerging from other recent studies [21,26–32]. Furthermore, this implies that haloperidol cannot be considered paradigmatic of all FGAs in comparison with SGAs, and therefore, the dichotomy between first- and second-generation drugs and the concept of SGA "atypicality" based on EPS liability may be misleading. It can be compellingly argued that antipsychotic drugs should be conceptualized as a single drug class with a spectrum of risk for treatment-emergent EPS dependent upon dopamine D2 receptor affinity and patient susceptibility.

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Chapter 17

Conclusion and implications for practice and policy

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The CATIE schizophrenia trial was among the largest, longest, most comprehensive, studies of psychotropic medication ever undertaken. The federal government and NIMH made a major investment in CATIE because schizophrenia is a major cause of disability and even small benefits could have important ramifications for patients and their families and savings for the country. Antipsychotics under patent protection usually cost $10 or more per day of treatment. Much of their huge annual cost falls to taxpayers since most people with schizophrenia and other severe mental illnesses receive their health care or health insurance through the public sector. There was thus understandable interest in evaluating the effectiveness and cost-effectiveness of these medicines. As we conclude this volume, the following five key questions remain:

- What, in sum, are the major results of this large complex study?
- Do these results alter what we know about these medications when they are considered in the context of the literature of this field and clinical practice?
- Do methodological limitations temper the credibility of the study findings?
- How has CATIE been received by stakeholder communities and has it changed clinical practices?
- What are the implications of CATIE findings for clinical practice, for mental health policy, and for psychiatric education?

Summary of results

The important methodological strengths of the CATIE trial are the following: 1) that all treatment choices were made through random assignment, ensuring that differences in outcomes between drugs were caused by the drugs themselves and not by other confounding differences between treatment groups; 2) that all assessments were made under double-blind conditions to ensure that no rater biases in favor of one drug or another could distort the assessment of primary and secondary outcomes; and 3) the study was conducted in a wide range of "real-world" sites and enrolled a broad sample of subjects with clinical characteristics that allow for the generalizability of the study's results. The results highlighted below, with a few exceptions, all rest on this firm methodological foundation.

Primary outcome

On the primary outcome, time to all-cause discontinuation, olanzapine did better than the other treatments, with some variability across the different phases of the study. In Phase 1,

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patients continued on olanzapine for significantly longer than on risperidone or quetiapine. In Phase 2T, among patients who had not tolerated the second-generation antipsychotic (SGA) to which they were first assigned, olanzapine and risperidone were both superior to quetiapine and ziprasidone. Among patients who had discontinued perphenazine (Phase 1B), both olanzapine and quetiapine did better than risperidone. In Phase 2E, among patients whose first drug did not prove efficacious, patients assigned to clozapine stayed on their treatment longer than those assigned to quetiapine or risperidone, but there was no significant difference between clozapine and olanzapine. However, Phase 2E was not conducted under double-blind conditions, and this could have given clozapine an advantage since it is widely believed by clinicians to be the most effective drug in patients who have not responded to other medications. It is all the more impressive, therefore, that patients did not stop taking olanzapine significantly sooner than clozapine in this phase of the study.

On the primary outcome of CATIE, therefore, olanzapine was superior to other agents, with the possible exception of clozapine. What was most surprising in these results was that the first-generation antipsychotic (FGA), perphenazine, appeared similar in effectiveness to three of the four SGAs to which it was compared (risperidone, quetiapine, and ziprasidone). When CATIE was designed, it was expected that all of the SGAs would be better tolerated than perphenazine, and at least some would be more effective. Some of the study investigators were so confident of these results that they questioned whether there was any need to include one of the older drugs in the study at all. This input led to the decision not to include perphenazine in subsequent phases of the trial.

A caveat to the superiority of olanzapine that was determined in post hoc analyses is that, in spite of the use of random assignment, both olanzapine and risperidone had an advantage at baseline over the other drugs on the primary outcome. Substantial numbers of patients randomly assigned to these medications had actually been taking them previously and thus were assigned to stay on the same medication they had been taking prior to the trial. While many experts would have thought that switching to a new medication would be advantageous [1], analysis of CATIE data showed that, for patients on risperidone and olanzapine, switching to a new medication led to worse outcomes on the measure of time to all-cause discontinuation [2]. While the effect of changing medications in schizophrenia has not been extensively studied, CATIE patients who stayed on their pre-CATIE medication stayed on their assigned medication longer than those who switched. When this advantage was eliminated by excluding "stayers" from the analysis, the advantage of olanzapine was attenuated but still present.

Secondary outcomes

The results of CATIE extend well beyond the primary outcome. The primary outcome of CATIE, time to all-cause discontinuation, integrates several important goals of treatment (e.g., reduced symptoms, improved quality of life, greater tolerability) without being a direct measure of these outcomes. Although the ultimate goal of pharmacotherapy is not that a patient continues on medication for as long as possible, the CATIE primary outcome was expected to both reflect and result in other important outcomes such as superior efficacy, fewer side effects, and greater global satisfaction among both patients and their clinicians. Numerous direct measures of these outcomes were also collected at regular intervals during the trial, and for the most part, confirmed the findings on the primary

outcome. With the exceptions of weight gain, measures of glucose and lipids, and cost, there were few differences between any of the treatments on these myriad measures, as follows:

- On measures of change in psychopathology, olanzapine was significantly superior to risperidone and quetiapine, but differences were of small magnitude (Chapter 3).
- On measures of psychosocial functioning including social relationships, role functioning (e.g. work or housekeeping), there were no significant differences between any treatments at any of several times points that were examined (Chapter 5).
- On neurocognitive measures, which are viewed as the most direct measures of brain function, there were no differences between treatments after 2 months. Perphenazine was superior to olanzapine at 18 months, but this difference was small in magnitude (Chapter 6).
- On multiple standardized measures of side effects including akathisia, pseudoparkinsonism, and tardive dyskinesia (TD), there were also no significant differences between treatments (Chapter 9). However, patients assigned to perphenazine were more likely to discontinue that medication because of extrapyramidal side effects (EPS) (8% for perphenazine vs. 4% for ziprasidone and 2% for olanzapine) and to receive more adjunctive anticholinergics for EPS (10% for perphenazine vs. 3% for quetiapine and 7–9% for the other medications).
- However, when considering all patients who discontinued medication due to adverse effects, there was no significant difference between perphenazine and any of the other drugs.
- As one might expect from the lack of robust difference on the previous measures, there were also no significant differences between treatments on days of employment, family burden, or violent behavior (Chapters 7, 8, and 12).
- Finally on a measure of quality adjusted life years (QALYs), which combines symptom and side effect indicators, the preferred outcome measure in cost-effectiveness analysis, perphenazine did significantly better than risperidone, but the difference was small (0.016 on a 1–100 scale) and there were no other significant differences between other treatments on either QALYs or on three other patient-centered measures of quality of life.
- Patients assigned to olanzapine showed significantly greater weight gain per month than other treatments. Weight gain was observed with risperidone and quetiapine, the magnitudes were far smaller, and perphenazine and ziprasidone were associated with weight loss.
- Olanzapine, and to a lesser extent quetiapine, were associated with increases in blood glucose and triglycerides, suggesting a clinically meaningful increase in cardiovascular risk for patients.
- Finally, cost findings showed that virtually none of the higher costs of the patented drugs was offset by reductions in other types of health service use. Even after including the cost of patented drugs prescribed to perphenazine patients after their initial medication switch, total monthly costs for the perphenazine group were $300–$500 lower than for the newer antipsychotics, or $3,600–$6,000 less per year.

Summary

On the primary outcome, the essential finding of CATIE is that patients continued on olanzapine longer than on other drugs, although this finding was not statistically significant in comparisons with perphenazine and ziprasidone. However, the superiority

of olanzapine on time to all-cause discontinuation did not translate into any advantage on a broad array of secondary outcome assessments of health status and quality of life. In addition, potential clinical advantages of olanzapine may be offset by weight gain and increased risk of cardiovascular disease. Perhaps the most important finding of the study, because it was unexpected, was that perphenazine did no worse than any other study medication on any measure of clinical status, quality of life, or tolerability. Due to its substantially lower cost, perphenazine was the most cost-effective treatment in CATIE and cost-benefit analysis showed there to be little uncertainty about this overall result.

CATIE in the context of other research

While we were engaged in the conduct of the CATIE study, colleagues around the world were carrying out related studies, reviews, and analyses of published data that bear on the interpretation of the CATIE results. In 2003 and again in 2009, meta-analyses suggested that four SGAs, clozapine, olanzapine, risperidone, and amisulpride (which is not marketed in the United States) were more effective at reducing symptoms of schizophrenia [3,4] than older drugs, although several other atypicals did not show such superiority. It was also widely believed that newer drugs uniformly caused fewer neurological side effects, with an especially lower risk of TD [5]. Some studies also reported that these drugs could save enough in inpatient costs to pay for their considerable costs even while under patent protection [6]. Through the 1990s, a number of prominent industry-sponsored trials had evoked great enthusiasm, especially for olanzapine and risperidone [7–9].

Other reviews and meta-analyses, including those conducted by the independent Cochrane Collaborative in recent years, have not supported the conclusion that SGAs are superior to FGAs [10]. A systematic overview and meta-regression analysis published in 2000 found that the superiority of SGAs over FGAs was largely attributable to comparisons with high doses of haloperidol [11] and concluded that they were not generally superior to FGAs. As early as 1996, an attempted meta-analysis of risperidone trials, found a "bewildering array of disaggregation (when results from a multicentre trial are presented in several publications) as well as . . . redundant reporting," [12, p. 1024] which, along with changing authorship of the same data, was thought to perhaps misleadingly "give an artificial impression of wide support for the efficacy of the drug." [12 p. 1025].

Then, in 2003, a 12-month, multi-site, Veterans Administration (VA) Cooperative Study found no significant differences between olanzapine and haloperidol on measures of symptoms, quality of life, or most side effects [13]. One possible explanation for these unexpected findings (in addition to the dose effect subsequently presented by Geddes *et al.* [11] was that haloperidol was given with prophylactic anticholinergics. About two-thirds of industry-sponsored trials had used haloperidol without such medicines [14], and often at higher than FDA recommended doses [15], posing a high risk of neurological side effects that could be mistaken for negative symptoms of schizophrenia or depression, a suggestion that was consistent with the meta-analysis by Geddes *et al.* [11]. In stark contrast to these findings, however, an additional meta-analysis by Davis *et al.* [16], found no effects associated with extrapyramidal symptoms, use of prophylactic anticholinergics, industry sponsorship, or study quality, and made no mention of the disaggregation or redundant reporting found previously.

In 2005, the first CATIE publication reporting study results [17] again found little or no advantage of four SGAs over perphenazine. Soon thereafter, the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1), a prominent government-funded 12-month trial in the United Kingdom, similarly found no advantage of second-generation antipsychotics over first-generation drugs on symptoms, side effects, or quality of life [18].

These three government-sponsored trials [13,17,18] also found no cost savings in health service use associated with SGAs and that the greater costs of these drugs resulted in increased costs to society. The VA trial found olanzapine increased total health care costs (including drugs) by $3,000–10,000/patient/year [13]. CATIE found all SGAs to have significantly greater costs than perphenazine by $2,400–$6,000/year (see Chapter 4), and CUtLASS found FGAs to be more cost-effective than second-generation antipsychotics, which were still under patent protection [19].

A review of cost-effectiveness research prior to CATIE reported no evidence of cost savings or greater cost-effectiveness for SGAs [20]. A naturalistic analysis of data from California Medicaid, furthermore, found that the six-fold increase in antipsychotic spending for schizophrenia attributable to SGAs did not generate savings in other health care costs and concluded that the drugs did not "pay for themselves" [21]. Thus, the cost and cost-effectiveness data are far less mixed than the clinical outcome data, with the older generic drugs having an advantage because of the clearly higher cost of SGAs under patent protection.

What the three recent independent studies seemed to have in common was that they were large, randomized, double-blind, clinical trials conducted under the auspices of government agencies and used somewhat different comparators from prior trials. More recently an industry-sponsored trial that compared aripiprazole and perphenazine in patients who had failed to respond to olanzapine or risperidone also found no substantial benefit for the newest SGA over perphenazine [22,23].

Most recently, a large multisite study of first-episode psychosis comparing SGAs to low dose haloperidol [24] found that SGAs had lower rates of treatment discontinuation than haloperidol but did not differ on measures of psychopathology. This report was followed by a study of adolescent schizophrenia comparing molindone (the intermediate potency FGA that causes the least weight gain), olanzapine, and risperidone and found comparable therapeutic efficacy among the three medications, whereas olanzapine followed by risperidone produced substantially greater weight gain and increase in metabolic indices [25]. Finally, two large meta-analyses reported findings that were generally consistent with the CATIE study and the lack of substantial and consistent differences in effectiveness between the SGAs and FGA medications save clozapine [4,26].

Summary

Although we are faced with conflicting results from numerous clinical trials and meta-analyses published in major journals, the CATIE results are consistent with and reinforce much of what is known about pharmacotherapies for chronic schizophrenia. First, the findings of CATIE do not represent an anomalous event reflecting "just one trial" that stands out from most others. Rather, there have been a number of large randomized trials that have reported results similar to those of CATIE, even for neurological side effects.

Second, consideration of the magnitude of effects shows that the results of CATIE are not substantially different even from the large meta-analysis that favored some SGAs [3,16].

Thus, even the results of studies that appear to be in conflict with CATIE are actually not very inconsistent in that no studies have found even moderately large effect sizes for SGAs as compared to FGAs [3,4,26].

Third, CATIE and related studies, taken together, suggest that differences between SGAs and FGAs are either negligible or so small that they may fluctuate from study to study, perhaps in response to small differences in choice of comparator, study design, or in the population studied. Some have declared that there is little remaining justification for even considering FGAs and SGAs to be distinctive drug classes [4,27]. The CATIE results found considerable heterogeneity among the newer medications. CATIE thus is best seen as having re-framed the way we understood previous findings that, when examined closely, consistently show either no or small differences between FGAs and SGAs.

Methodological limitations

However, the CATIE study was not without methodological limitations that have been highlighted in many commentaries and that require review. These limitations can be summarized under eight headings: 1) low follow-up rates, 2) inadequate study duration, 3) idiosyncratic sample characteristics, 4) unusual outcome measures, 5) exclusion of patients with TD from the randomization that included perphenazine, 6) choice of study drugs and doses, 7) biasing differences in treatments used before randomization, and 8) inadequate statistical power to determine equivalence of treatments and an overly complex design resulting in suboptimal statistical power for some drug comparisons. Many of these limitations have been addressed in detail previously [28], and we will briefly summarize the principal points here.

Follow-up rates

Although the 18-month follow-up rates on initially assigned treatments in CATIE were only 18%–36% across treatments, CATIE actually achieved higher follow-up rates on the initially assigned treatment at comparable time points to most of the studies that had established the efficacy of SGAs. For example, at 8 weeks, CATIE follow-up rates on the initially assigned study drug were 69%–77% across treatments [17], somewhat better than the 67% follow-up rate for olanzapine patients in the International Collaborative Trial at only 6 weeks [8] and substantially superior to the 52%–56% follow-up rates at 8 weeks among patients assigned to risperidone in the major registration trial of that drug [7]. Data presented from a 28-week study of olanzapine, show follow-up rates of 42%–59% across groups at 28 weeks, not substantially different from the 40%–60% follow-up rates at the equivalent time point in CATIE [29].

In one study, the risperidone relapse trial [9], 12-month follow-up rates were substantially better than in CATIE with over 70% of risperidone patients and almost 60% of haloperidol patients still participating at 12 months. Unlike CATIE, however, this study specifically targeted stable patients with PANSS scores that were lower by a clinically significant amount (10 points).

Study duration and longer-term outcomes

Although longer than other studies, CATIE may not have been long enough to compare long-term side effects such as TD, diabetes, and cardiovascular morbidity that develop from cumulative treatment exposure [30]. The risk of weight gain and probably diabetes

with some SGAs is well-established, especially for olanzapine and clozapine [31]. Olanzapine showed dramatic increases in weight, blood glucose, and triglycerides in CATIE, although the study was too short and too small to evaluate differences in incident cases of diabetes.

TD, a sometimes permanent movement disorder that often affects the mouth and tongue, is of greater concern since a lowered risk of this disorder may remain an important advantage of SGAs. A recent comprehensive review of past studies could identify only four 1-year randomized trials of TD [32]. These trials included 1,707 patients who were followed for an average median of 8.8 months across the studies. These studies, taken together, were not substantially different in duration from CATIE, in which patients assigned to perphenazine and to the best performing SGA, olanzapine, participated for a median of 5.6 and 9.2 months, respectively. While CATIE may not have been as long as desirable for a study of TD, it was not much shorter than the studies that are cited as suggesting SGA benefits on this outcome, and thus its "no difference" findings may be no less informative. A critical point is that CATIE used perphenazine at moderate doses rather than haloperidol, which is noted for causing EPS and TD.

Sample characteristics

When findings are unexpected, as in CATIE, it is natural to wonder whether some idiosyncratic feature of the sample may have obscured benefits of the SGAs. Available data, however, suggest that participants in CATIE were broadly comparable to those in seven other major trials of SGAs with similar mean age (41 years in CATIE vs. 36–43 in other trials) and duration of illness (16.6 years in CATIE vs. 14.7–16.3 in other trials), and no indication of greater "chronicity" or "refractoriness." Mean baseline PANSS total symptoms scores in CATIE averaged 76.1 (SD = 18.2), notably lower than both the 87.5 (SD = 15.4) mean score in the major registration trial of olanzapine [8] and the 92.2 (SD = 16.7) mean score in the comparable study of risperidone [7], but higher than the 65.0 (SD = 15.9) score in the "stable" cohort recruited for the risperidone relapse study [9].

Comparative data from two large non-experimental outcome studies of schizophrenia in the general population, presented previously [33 p. 492–493], showed similarities on gender, age, and education, symptoms levels, and quality of life, although CATIE had a lower proportion of minority patients. Comparisons have also been reported with data from the Schizophrenia PORT survey of 745 randomly sampled patients treated for schizophrenia in Ohio and Georgia [34] and further demonstrate that the CATIE sample was broadly representative of Americans with chronic schizophrenia.

It is important to acknowledge, however, that first-episode patients and geriatric patients were not a focus in CATIE and deserve additional study.

Choice of outcome measures

The primary outcome measure, time to all-cause treatment discontinuation, and the main effectiveness in the cost-effectiveness analysis, QALYs, have not been commonly used in clinical trials of schizophrenia. But the presence of more standard measures of symptoms, quality of life, and side effects, all of which gave similar results, suggests that the results of CATIE cannot be explained by the choice of measures. Time to all-cause

treatment discontinuation stands out as a measure of a drug's enduring acceptability that reflects efficacy and tolerability and that has the distinct statistical advantage of having no missing data.

Exclusion of patients with tardive dyskinesia from the randomization that included perphenazine

The initial reason for excluding patients with TD from randomization to perphenazine was the belief among senior scientific advisors to the NIMH, in 2000, that patients with TD should not be exposed to any FGA. Within the non-TD stratum (85% of the sample), however, patients had an equal and unbiased chance of being assigned to each of the five available treatments—the essential feature of any randomization.

In view of the unexpected CATIE findings of no significant group differences on measures of tardive dyskinesia, it is relevant to reiterate a basic principle of risk assessment research—that patients who already have the outcome being studied should be excluded from the study cohort [35, page 88–89; 36 p. 82]. Since such patients already are "cases," they are not at risk for becoming "cases" and add uninformative variance that biases results toward the null. The exclusion of TD patients thus allows more precise comparison of TD incidence in CATIE than in studies that included mixed samples.

Choice of medications and doses

The central feature of the dosing regimens used in CATIE is that they were designed to allow flexible adjustment by physicians according to the clinical needs of each patient. Concern has been expressed that the mean modal dose of olanzapine was higher than in typical practice at the time of the CATIE study and that dosing of risperidone and ziprasidone were somewhat lower than in typical practice [37,38]. Since dosing was determined according to the individualized clinical judgment of each psychiatrist, and was thus based entirely on the manifest clinical needs of individual patients, it would seem that differences in outcome were not likely to have been attributable to differences in permissible dosing, but this possibility cannot be ruled out.

Concern has also been expressed that perphenazine was used at unusually low doses to avoid neurological side effects [37]. The mean modal dose of perphenazine in CATIE (20.8 mg) is toward the upper end of the recommended outpatient dose range (24 mg), and CATIE participants were outpatients for 95% of the trial. Because it is a mid-potency drug, perphenazine may be more representative of the class of FGAs than high-potency haloperidol, especially as it was used in many past FGA-SGA trials—at high doses and without prophylactic anticholinergics to prevent EPS.

Differences in pre-randomization treatment

As noted above, about 40% of CATIE patients were treated prior to study entry with either of two study drugs (olanzapine or risperidone) [17]. Thus, while most patients were assigned to a change in medication, about 20% of those assigned to olanzapine or risperidone were assigned to the same medication they had been taking before entering the study. The re-analysis of CATIE data showed that those who stayed on their prior medication did better on the primary study outcome [2] and that, when these patients were excluded, the

differences between treated patients were attenuated, although the same general patterns in time to all-cause discontinuation were preserved.

Inadequate statistical power

The statistical analysis of the primary results of CATIE, which adjusted for multiple comparisons, found olanzapine superior to quetiapine and risperidone but not perphenazine and ziprasidone even though the median time to discontinuation was no longer for perphenazine or ziprasidone [17]. There was lower power to detect differences involving the perphenazine and ziprasidone arms of the study because individuals with TD were excluded from randomization to perphenazine and because ziprasidone was added to the protocol late and fewer participants took these drugs. As the CATIE study was originally conceived as a study to determine superiority of the SGAs, and was not statistically powered to determine equivalence or non-inferiority, the findings of no differences between perphenazine and the SGAs cannot be considered definitive in that regard.

While several design features in CATIE have been identified as potential methodological limitations, many of these turn out to have either not been important weaknesses or were in fact relative strengths after careful comparison with other studies. The remaining limitations are not substantially different from limitations that characterize the studies that highlighted the advantages of SGAs. Although many observers have pointed to methodological limitations to explain why CATIE results were different than some expected [37–40], the results of CATIE were, in fact, not as dramatically different from those that preceded it as has been portrayed.

Reception/reaction in the professional community and initial impact on prescribing

Science is often portrayed as an edifice built by individual investigators, one brick, or one study, at a time. However, medical science, in particular, is more aptly described as the collaborative construction of a learning community, which includes researchers, clinicians, pharmaceutical companies, health providers, consumers and their families, and other interested parties (e.g., insurers). An important part of the appraisal of a major research study such as CATIE is its reception by the community to which it was broadly addressed.

Initial critiques

The initial responses to CATIE were surprise, skepticism, and concern. For many involved in the world of antipsychotic pharmacotherapy, the CATIE results, with their implication that most SGAs had little advantage over an FGA in effectiveness and no advantage on neurological side effects came as a surprise. Some psychopharmacologists who had championed the SGAs over the years and many of whom had conducted landmark studies, emphasized the methodological limitations addressed earlier in this chapter, which they thought limited both the validity and generalizability of the results [37–40]. A common refrain was that treatment should always be individualized and development of more effective treatments is sorely needed. The fact that only 24% (range 18%–36%) of patients completed 18 months of treatment without changing medications was widely taken as evidence of the ineffectiveness of current treatment, although such a conclusion was one

that CATIE was not designed to evaluate since there was no placebo treatment condition. Informally, many commented that CATIE was "just one study" and was not an occasion for revising the accepted assessment of SGAs.

Some of the strongest reactions were those of professional organizations and consumer groups whose press releases expressed less concern with the unexpected results of CATIE, and more apprehension that insurance companies and government funders would use (or perhaps misuse) the CATIE results to impose harmful restrictions on the ability of physicians to prescribe drugs as needed by individual patients on the basis of their unique needs. The Director of the American Psychiatric Association's Division of Research noted in response to CUtLASS that "clinicians have long recognized that SGAs were no more effective than FGAs in reducing psychotic symptoms" [40] but nevertheless cautioned against abrupt changes in practice or policy.

Early acceptance

Other researchers, perhaps reflecting the underlying consistency of CATIE with an emerging current of opinion [41], recognized that this major study in fact confirmed what many had suspected in recent years, that a fundamental reconsideration of SGAs was needed to guide both clinical practice and policy [42–45]. The president of the American Psychiatric Association expressed personal anger that the profession seemed to have been misled by corporate marketing [46].

The CATIE trial received widespread coverage by the press. An editorial in the *New York Times* [47] concluded that CATIE showed that "the system for approving and promoting drugs is badly out of whack" and that "The nation is wasting billions..." A *Washington Post* article on CATIE reported that "patients and policymakers can be blindsided by self-interested research by drugmakers" [48]. There were, however, no calls for draconian limits on access or any other policy initiatives. It is notable in this respect that CATIE was published almost exactly 1 year after Vioxx was withdrawn from the market because of concerns about its safety, a year in which a spate of books by highly respected physicians had been published documenting many apparently misleading methods used to promote patent medications to US physicians [49–52]. Although limited attention was focused on SGAs in these books, they reflected a climate that was more likely to accept empirical results that questioned established beliefs about patent medicines.

Shifting consensus

With time, as additional reports from CATIE showed that the initial pattern of results was repeated in clinical domains such as neurocognitive functioning, symptoms, quality of life, violent behavior, and employment, a consensus of opinion came to accept the study's results. In the Fall of 2007, the Texas Medication Algorithm Project (TMAP) group concluded that there was no reason to prefer SGAs over FGAs in chronic schizophrenia, although with considerable difference of opinion they continued to recommend SGAs in first-episode illness [53]. The Medical Directors of the National Association of State Mental Health Program Directors also completed a policy report which began by concluding that recent research had shown that SGAs should not be assumed to be markedly superior to FGAs and that new policy approaches are needed. In addition, in November 2007, following discussions with the FDA in which the CATIE results [54] figured prominently, Eli Lilly strengthened its warning about adverse metabolic consequences in their labeling.

Almost 3 years after the original CATIE paper was published, the May 2008 issue of the APA journal *Psychiatric Services*, was devoted almost entirely to current perspectives on antipsychotic medications and included a special section devoted to the CATIE study. Commentaries from experts and stakeholders seemed to uniformly accept the findings of CATIE, even on the subject of TD [55]. While the debate over the scientific meaning of CATIE seemed to have produced a new consensus, debate about issues like TD risk continues, and discussions about the implications of the CATIE consensus for changes, practice, and policy are just beginning.

Changes in prescribing

There have been only two studies of changes in prescribing practices of antipsychotics since the first CATIE publication. One study of antipsychotic prescription use in the VA showed declining use of olanzapine beginning about 2002, well before CATIE was published, and stabilization of the use of conventionals for about 15% of patients after 2003 [56]. A total of 1.8% of VA patients with schizophrenia were prescribed perphenazine during the year before CATIE was published and 1.8% in the year after. One other study also showed little change in patterns of FGA prescriptions before and after CATIE [57]. Citrome and colleagues reported that prescriptions for both clozapine and perphenazine increased among individuals with schizophrenia in inpatient units operated by the New York State Office of Mental Health in the year after the original CATIE report was published [58].

Summary

While initial reactions of surprise and skepticism were accompanied by an inclination to minimize the importance of the CATIE study, because of both methodological limitations and concern about restrictive formulary policies, a more recent consensus has emerged that has largely accepted the CATIE findings. While agreement on the science progressed over the initial years after the results were published, influence on practice was slower, and the debate about policy implications will be ongoing.

Implications for clinical practice

While clinical trials provide the most rigorous understanding of the benefits and risks of various treatments for populations of patients, they can only guide, not dictate, clinical practice since treatment must always be individualized for each unique patient. The results of CATIE, however, can help practicing clinicians tailor treatment for their patients. We single out seven issues as of particular relevance for practice.

Use of intermediate potency FGAs

The CATIE results suggest that the armamentarium for treating schizophrenia can be expanded to include perphenazine as well as three other intermediate potency drugs: loxitane, molindone, and thiothixene. The intermediate potency FGA perphenazine, when used at modest doses appeared to be as effective and to have no substantially greater neurological side effects than SGAs.

Clinical cost considerations

Whether cost should ever play a role in the clinical care of individual patients is controversial [59], but an important implication of CATIE is that clinicians should inquire as to whether each patient, or their family, is paying out-of-pocket for their medicines. About 20% of patients treated in CATIE had no health insurance, and the results of CATIE suggest that far less expensive treatment options are available, when needed, with similar effectiveness. Cost-saving strategies for patients who have either private or government insurance are left to the discussion of public policy options.

Minimizing metabolic adverse effects

Second, the substantial and distinct increase in metabolic risk with olanzapine and to a lesser extent quetiapine, should make them lower preference agents, but especially for those who are obese, or who are at high risk, by family history or blood chemistries, for diabetes or cardiovascular disease. The greater time to all-cause discontinuation for olanzapine did not translate into gains in quality of life, neurocognition, employment, or reduced violence; thus, the robust and sustained increase in metabolic risks for this drug may outweigh the limited evidence of relative benefit.

Clozapine for refractory illness

Among patients who have persistent psychotic symptoms in spite of adequate antipsychotic trials, clozapine may be useful because of its distinct advantages for refractory symptoms. However, clozapine also incurs an increased risk of weight gain, suggesting that caution is indicated for patients who are obese or at risk for diabetes or cardiovascular diseases. Effective strategies to mitigate metabolic side effects are needed.

Potential hazards of switching

One of the more unexpected findings of CATIE is that switching to a new drug may result in poorer outcomes than staying on the same drug [2]. It is widely believed that patients who do not respond to one treatment may have a better response to another, even when there are no demonstrated differences in effectiveness in head-to-head trials [1]. While the findings from CATIE tend to undermine that widely held belief, additional studies of this issue are needed. Perhaps more watchful waiting is indicated in the use of antipsychotic therapy.

Applicability to use of SGAs in illnesses other than schizophrenia

The greatest area of growth in the use of antipsychotics in recent years has not been in the treatment of schizophrenia but in bipolar disorder, the second illness for which most SGAs have received FDA approval, and in the off-label (i.e., not FDA approved) treatment of affective disorders, post-traumatic stress disorder, and dementia [60,61]. While a separate CATIE study found little evidence of benefit of SGAs as compared to placebo in treating agitation and psychosis in Alzheimer's disease [62], it is unclear how generalizable the results of CATIE are to the use of SGAs in bipolar disorder and in many other conditions for which they are currently prescribed. Narrowly considered, CATIE results would only apply to schizophrenia, but it would seem reasonable to apply data on side effects to other

illnesses, although the generalizability of efficacy data has not been widely discussed. This is an important challenge since it is unlikely that studies like CATIE will ever be conducted on the many off-label uses of antipsychotics.

Implications for mental health policy and psychiatric education

Mental health policies are formal rules intended to shape behavior of administrators and clinicians within defined jurisdictions, whether government funded agencies, private health care systems, or insurance plans. While psychiatric care represents the application of medical science to the treatment of unique individuals, one at a time, mental health policies are intended to affect the behavior of many providers and patients simultaneously. Such policies are implemented when there are strong grounds for wanting to change behavior on a large scale and when it would be inefficient or impractical to do so through educational initiatives or case-by-case persuasion. The hazard of implementing policy initiatives in health, and especially in mental health care, is that they may reduce attentiveness to the unique needs of each individual patient.

In the previous section, we identified eight issues in clinical practice that could be shaped by the findings of CATIE along with other recent research. None of these issues would seem to be appropriate targets for a mental health policy because virtually all apply to highly individualized aspects of care. Several of the clinical implications discussed above, such as inquiring about insurance coverage for pharmacy benefits, or watchfully waiting before a medication change, would be cumbersome to monitor, and both costly and intrusive to enforce. Off-label polypharmacy with multiple antipsychotics has been a reasonable target for mental health policy in some state Medicaid programs, but these issues were not specifically addressed by CATIE.

Perhaps of greatest policy relevance are the cost and cost-effectiveness results of the CATIE study. CATIE, CUtLASS, and the earlier VA trial all suggested that the new drugs do not generate savings sufficient to offset their higher costs, and in view of their limited benefits, the cost of their use for the vast majority of patients with schizophrenia may not be a rational practice. The research reviewed here indicates there are likely many patients with schizophrenia who are treated with SGAs who could be treated just as successfully with an FGA. Now that risperidone is off-patent, there is now at least one lower cost SGA.

While it seems desirable to adopt policies that would increase the use of less expensive treatments when more expensive treatments are not medically necessary, it is challenging to identify specific policies that would achieve this goal without provoking a concern from stakeholder groups (e.g. clinicians, consumers, and advocacy groups) and posing a risk that some patients would be unintentionally deprived of needed access to more expensive drugs. The most immediately applicable approaches to this challenge are utilization management policies. Policies that would affect pricing mechanisms or changes in the government regulation of pharmaceuticals would not be specific to SGAs and will not be considered here (but see Hoadley) [63].

Utilization management

The most restrictive utilization management strategies would either exclude some expensive drugs from a formulary, or impose limits on the total number of prescriptions that can be prescribed. These approaches pose the greatest risk to patients with schizophrenia and cannot be recommended.

Less restrictive approaches such as step therapy or prior authorization would also restrict access to a drug or drug class unless other less costly or safer medications had been tried first and proved to be ineffective or intolerable. Such approaches have been strongly recommended in the treatment of hypertension where research showed generic drugs, like some FGAs, are no less beneficial than newer medications [64]. But recent studies have shown little cost savings from pre-authorization policies that limit access to some but not all SGAs [65], and there is some suggestion of poorer adherence when one such policy was implemented in Maine [66]. Prior authorization has been vigorously criticized by professional and consumer groups [67] and by some health services researchers [68,69].

Tiered formularies that require differential cost-sharing for generic, preferred brand-name, and non-preferred brand name drugs have also been used to create financial incentives for patients to use less expensive, but medically equivalent, drugs. Prescription cost-sharing can be in the form of a copayment (i.e., a fixed dollar amount per prescription filled, regardless of drug price) or coinsurance (i.e., a percentage of total drug price). Studies of implementation of three-tiered formularies have shown little adverse effect on utilization of antidepressants [70] or stimulants among children [71], 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, offsetting all drug cost savings in patients with schizophrenia [72]. These approaches are less relevant to patients with schizophrenia who are often poor and whose medications are most often funded entirely by government agencies that do not charge co-payments.

More acceptable utilization management strategies are directed to providers rather than patients. In physician profiling, data are compiled on individual doctors' prescriptions for high cost drugs and/or polypharmacy, and either administrative feedback [68] or economic incentives are used to discourage costly prescribing practices. Less intrusive provider-oriented approaches include disease management, independent research reviews, educational interventions, or academic detailing based on provider-specific data [23] that impose less risk that needed drugs will not be available, but they are less likely to change provider behavior.

While the scientific evidence from CATIE and other studies suggests that it would be desirable and justifiable to realize greater efficiencies in the use of antipsychotic medications, there is insufficient evidence on the effects of any antipsychotic utilization policy to support the needed consensus of stakeholders [67]. As State Medicaid programs experiment with various arrangements [73], it can be hoped that safe and effective policies will emerge.

Issues for medical education

It has unfortunately not been unusual in recent years for treatments that, like SGAs, were initially believed to represent major advances to be found subsequently to be less effective or to have more serious adverse side effects than had been appreciated. Among the more widely publicized treatments of this type are Vioxx®, hormone replacement therapy for symptoms of menopause, the fen-phen combination of diet pills, and Neurontin® for migraine and bipolar disorder. In many cases, these reversals appear to have been a result of overzealous marketing and there has been growing concern about the influence of industry on the medical profession through gifts, sponsored symposia, office-based detailing, speakers' bureaus, and even, indirectly, through direct-to-consumer advertising [50,52]. More serious are concerns that the integrity of medical science has been

jeopardized by the publication of ghost-written articles by commercial writers in leading medical journals [74], the suppression of negative trials [75], and by the disaggregation of data into multiple publications with different authors [12,76].

In response to these and other concerns, the clinical trials registry was implemented, and both AMA and PHRMA have adopted ethics guidelines for the interactions between industry representatives and physicians. These initiatives have not, however, solved this knotty problem and the Institute of Medicine recently convened a new committee on Conflict of Interest in Medical Research, Education and Practice to recommend additional approaches. A recent public hearing emphasized that, at a minimum, residents as well as more senior physicians, nurses, and other mental health professionals should be educated to think critically about industry-sponsored studies, continuing education programs, and marketing campaigns [77]. The story of research on SGAs over the past two decades, culminating in the CATIE trial and the large independently sponsored studies of the comparative effectiveness of antipsychotic drugs which followed, provide an illustrative example and perhaps a cautionary tale that may be useful in such educational initiatives.

A final word

With the publication of this volume, the complete results of CATIE have become available for the first time from a single accessible source. It is well known that changes in medical practice come slowly [78]. CATIE has helped to establish a new scientific foundation for the use of antipsychotic medications in psychiatric practice and we will all be experiencing the as yet unforeseen consequences of this new knowledge for many years to come.

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