Discontinuing and Switching Antipsychotic Medications: Understanding the CATIE Schizophrenia Trial

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A new standard in effectiveness research on schizophrenia medications has been established by the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. The study used an innovative approach to determining relative effectiveness of medications by using time until medication discontinuation or switch as the primary outcome criterion. The study is perhaps best known for the overall high proportion of subjects (74%) meeting all-cause discontinuation (ACD) criteria within the 18-month time frame of being assigned to their phase 1 antipsychotic. However, some of the drawbacks of the ACD approach are not well understood, in part because of unfamiliarity with the way ACD was assessed and problems with the use of hierarchical criteria to establish the primary reason for medication discontinuation. Using the time until ACD as an endpoint cannot by itself capture the complexity of the trajectory of a patient's response to a new medication. In particular, it is quite plausible that switching medications upon entering CATIE phase 1 would reduce some symptoms, which then would lead to a greater desire to make another medication switch. Using ACD criteria, a comparison with CATIE subjects who coincidentally remained on treatment with their preswitch medication would make it seem that switching was detrimental when in fact it could have been helpful. Another major limitation of the ACD was omitting the recording of the reason for stopping study medication whenever the ACD was considered to be a "patient-decision" discontinuation. This means that patient-initiated discontinuations could never be classified as a tolerability discontinuation. Since the ACD was done by the patients' clinicians, this approach may have underestimated the proportion of side effect discontinuations whenever the patient disagreed with his or her clinician. Moreover, retaining the "patient-decision" discontinuation subgroup in the attributable risk estimates of tolerability discontinuations further minimizes the attributable risk estimate of the role of side effects relative to other causes of discontinuation. For these assumptions to be valid would require the very optimistic assumption that CATIE clinicians never underestimated tolerability concerns in their patients. Otherwise, this mutually exclusive approach will lead to significant underestimation of the proportion of CATIE discontinuations caused by tolerability problems. It can be argued that excluding the "patient decision" subgroup from the attributable risk estimate of role of tolerability in medication discontinuation is a better approach to mitigate against these biases. A reanalysis using an adjusted N of 1061 evaluable subjects changes the attributable portion of tolerability discontinuations from 14.9% to 38.5%. Regarding specific side effect–medication pairs of interest, the attributable risk of extrapyramidal symptoms as a reason for discontinuing perphenazine increases from 8% to 21%, and weight-related discontinuations from olanzapine from 9% to 28%. Therefore, the clinical implications of the CATIE phase 1 findings may depend, in part, on the underlying assumptions of the ACD outcome measure.

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The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study, sponsored by the National Institute of Mental Health, is a landmark accomplishment. It will undoubtedly set a new standard for future effectiveness research in the psychopharmacology of antipsychotic treatment of schizophrenia. The innovative design is one of its major strengths in that it breaks new ground in understanding treatment patterns that occur once the narrow constraints of most other clinical trials of antipsychotics are removed from the equation. Nonetheless, these innovations also make the CATIE methodology less familiar to many of the readers, and the absence of a track record of other studies using similar outcome criteria makes it harder to assess the consistency of the results across other treatment settings. Readers are probably familiar with the very high rate of medication discontinuation or medication switching that occurred within the phase 1 follow-up period of the CATIE study. At the

18-month study completion point, most of the study participants were not taking their initial CATIE antipsychotic medication. In fact, 1061 of the 1432 patients elected to try another medication or discontinue their participation in the study altogether.[1] This high rate was reported as the primary outcome measure, or "all-cause discontinuation rate" (ACD), which was 74% of the original sample.

To understand the actual clinical implications of the high discontinuation rate from the phase 1 CATIE study, it is very important to understand the precise way in which the reasons for ACD were determined. While the ACD criteria are described in the original report,[1] it seems that the implications of the approach used are not fully understood by many clinicians. To help readers understand the CATIE results, this article will review the primary outcome measure of the CATIE study in considerable detail, and discuss how some of the assumptions used in estimates of reasons for discontinuation affect the interpretation of the CATIE phase 1 results.

RATIONALE FOR USING MEDICATION DISCONTINUATION AS AN OUTCOME MEASURE

The primary outcome measures for phase 1 of the CATIE study were related to discontinuation of the initial CATIE antipsychotic study medication.[1] The primary outcome measure was "the discontinuation of treatment for any cause, a discrete outcome selected because stopping or changing medication is a frequent occurrence and major problem in the treatment of schizophrenia . . . [and it is] a global measure of effectiveness. . . ."[1(p1211)] It is important to note that the initial report of ACD time-until-discontinuation measure did not distinguish between patients who stopped their antipsychotic and refused to try another from those who discontinued the specific medication and agreed to switch to another antipsychotic medication. The secondary ACD outcome was an assessment of the reason the medication was discontinued: "the specific reasons for the discontinuation of treatment (e.g., inefficacy or intolerability owing to side effects such as weight gain, extrapyramidal signs, or sedation as judged by the study doctor)."[1(p1211)]

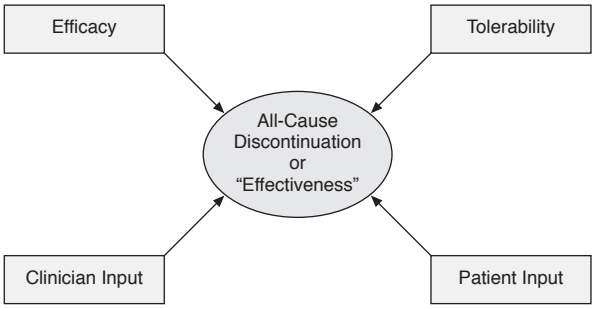
The decision to use ACD as the primary approach to testing differences between antipsychotic medications reflected the desire of the investigators to move closer to outcomes that are more relevant to doctors and patients than the traditional symptom rating scales used in direct head-to-head efficacy studies that compare one antipsychotic with another. This innovative approach helped solve a major problem in using symptom or illness severity criteria as a primary outcome measure for an effectiveness study like CATIE. In an illness such as schizophrenia, the perception of degree of "response" to the medication is usually not based on the score from a rating scale. Likewise, "tolerability" does not always reflect the severity of a side effect as an "adverse event" or its quantitative severity on a rating scale, nor does it always depend on an "out of range" laboratory value. While relevant, "tolerability" in day-to-day practice is better reflected by factors such as the individual's distress from a side effect; other factors influence whether or not continued treatment in the face of such side effect distress is acceptable. Important factors that contribute to the decision of acceptability include the opinions about medication that are held by the patient's significant others, the efforts by which the doctor can address the side effect problem, and the degree of conviction that doctor or patient has about alternative medications or treatments that might be effective with potentially fewer side effects.

Psychopathology and change in symptom severity are often assessed using objective measures with established reliability and validity, such as the Positive and Negative Syndrome Scale (PANSS). In most studies of patients with schizophrenia, however, these rating scales are the measure by which treatment effectiveness is judged. In the real world, the decision as to whether a drug is suitable is based on a wide variety of factors that are not contained in a structured symptom rating scale. Also, the satisfaction with the current treatment plan is assessed repeatedly and informally in the course of treatment and, like most decisions in life, depends in large part on perceived alternative choices. In any event, the patient, clinician, and other stakeholders then decide whether the benefits of the medication are greater than the problems arising from continued symptoms or from distressing side effects. Sometimes the doctor and patient will agree; sometimes not. This composite decision-making process is reflected in the ACD outcome measure. The ACD is a composite measure that represents a decision to change or discontinue antipsychotic medication.[2] Figure 1 shows how the ACD encompasses 4 components: lack of drug efficacy, problems with drug tolerability, clinician decision, and patient decision.

Note that these components do not necessarily show the weighting of these factors, or who is the primary decision-maker when the medication is discontinued. The wisdom in using ACD as an outcome is that it does capture the end result of these many individual factors, each of which is hard to measure by itself.

But it still is important to understand that solving one set of methodology problems may inadvertently create other methodology problems. One potential drawback in the ACD outcome is that it used a mutually exclusive approach to categorizing reasons for discontinuation. Therefore, the ACD cannot capture all of the individual factors leading up to the decision to remain on the current regimen, stop, or switch. Moreover, the trajectory of changes in medication efficacy, side effects, and patient and clinician attitude is not recorded. The ACD outcome does not tell us when the decision was made, how strong the beliefs and attitudes are, or how changing attitudes and expecta-

Figure 1. Components of the All-Cause Discontinuation Measure[a]



[a]Based on Stroup and colleagues.[2]

tions might have influenced this outcome. The next section explores this issue in greater detail, and discusses the clinical implications of various scenarios that might lead to an ACD event.

THE DECISION TO DISCONTINUE: ACD IS NOT ALWAYS A BAD OUTCOME

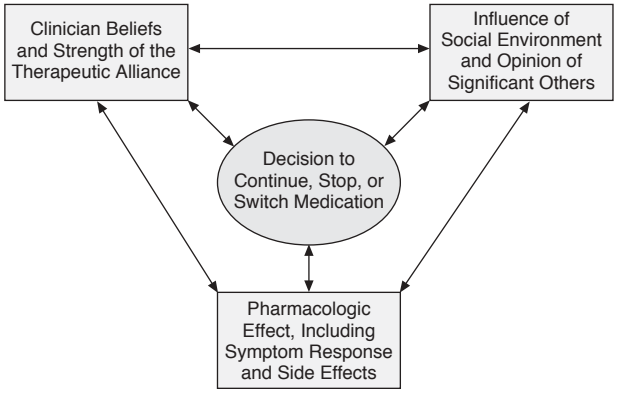
The effectiveness design of the CATIE study rightly emphasizes the broad range of patients who were allowed to enter this trial. Nonetheless, the very nature of the study meant that all patients entering the CATIE study had to be dissatisfied enough with their current or past medications that they were willing to try to change medications. In addition, a central aspect of the informed consent discussion was about the flexibility of the medication assignment; namely, both the patient and the doctor retained the option to change medications a second time if the first CATIE study medication was unsatisfactory. At the outset, the mindset was one of achieving improvement. Given that full remission is not expected within the cohort, it is hardly surprising that patients and doctors would want to try another agent before the end of the study period.

But how do we interpret a discontinuation or a switch? Is ACD always a negative outcome? The decision to stay on treatment with or change antipsychotic medications may depend on multiple influences and considerations. Many of these relate to value judgments on what is acceptable, which in turn are based on past experience, range of options available, and information about these options. Presumably, the setup of the CATIE study design meant that every person who went into the study shared the following: (1) each patient already had a past experience with at least one antipsychotic, usually an atypical; (2) each patient was not completely satisfied with the current medication, with sufficient motivation to warrant a change in medication; (3) the past history of each patient was such that one of the CATIE study medications was not already clearly indicated or contraindicated (otherwise the patient would have been excluded); and (4) if the initial choice of medication was not satisfactory, the patient or clinician would have the option of trying another antipsychotic without jeopardizing their access to study medication or the therapeutic relationship with the local CATIE clinical team. The net results of these factors were (1) to somewhat restrict the range of therapeutic outcomes that might be expected to occur and (2) to select patients and clinical situations in which the expectation was to change medications, and then change again if necessary. The point here is not to criticize the study design, in which such tradeoffs had to occur, but to underscore that the "unexpected" small differences between medications and the high switching rates may not have been so surprising after all—admittedly with the benefit of hindsight, that is. Or, consider that if a person gets better following one switch in medication, perhaps the person would be more interested in switching to yet another medication, compared with someone who did not benefit from an initial change in medication and is discouraged by the lack of improvement. Given the inclusion criteria, then, it is hardly surprising that many of the same individuals would eventually want to try another medication later on.

Because of the need to compare the different antipsychotic medications with each other, there had to be a way to come up with objective quantifiable criteria that could be used fairly across all medications. For this purpose, it probably was the correct decision to classify an ACD outcome as always representing a failure of that particular antipsychotic medication. In other words, there were important and valid research questions that required a uniform outcome assessment for a head-to-head comparison. The drawback is that the ACD event was not invariably a "bad" outcome and in fact often reflected a medication trajectory that most patients and clinicians might think of as an indicator of better effectiveness, not an effectiveness failure. How could ACD be a marker of good response? First and foremost, the CATIE trials were trials of choice and switching. Like voting for a political candidate, the decision of who to vote for is influenced by opinions of others and the perception of the alternate choices (see Figure 2).

Because CATIE was not one study but a series of 3 sequential studies, there were other choices. Patients or their clinicians were encouraged to switch into another medication phase of the CATIE study without any penalty whatsoever. One could still remain in the study after a phase 1 ACD event and go on to try another agent in the clozapine or ziprasidone arms of CATIE phase 2 and again for CATIE phase 3. In fact, most patients, after their CATIE phase 1 ACD evaluation, agreed to stay in the CATIE study and switched to another antipsychotic medication under the auspices of the CATIE phase 2

Figure 2. A Dynamic Model of Factors That Influence Decision to Continue, Stop, or Switch Antipsychotic Medication



study. Most of these phase 1 patients who changed to another CATIE medication had remained on their initial medication assignment long enough to allow the participants (patients and their doctors) time to consider whether to switch to another option and try again. Therefore, for some of the CATIE 2 discontinuations, switching could have been part of a recovery approach to the illness such that after achieving one level of response, the patient continues to seek further improvements in the hope that another medication would offer a still better chance for further gain.

The final ACD does not capture the trajectory of clinical effects during each person's treatment in the course of the CATIE phase 1 study. Changes in functional status in relation to symptom expression also are not accurately reflected in the ACD statistic, and the all-cause measure does not account for the effect of symptomatic improvement with secondary functional changes for the individual. Prior to entering the study, the patient had a certain level of symptoms that corresponded to a certain low level of function. If the patient begins treatment with the study drug and a response is achieved, some of the symptoms would be decreased. If the patient then decides to push himself or herself to a new functional level by obtaining a job or entering into a new relationship, some symptoms may recur or intensify. The patient may interpret this—erroneously—as a treatment failure and decide to switch or discontinue the medication. In assessing the pharmacologic response of a medication, both direct and indirect effects must be taken into account. The direct effects impact on symptoms, whether in the positive or negative symptom realm. The indirect effects impact on the coping response to environmental issues and stresses. Functional recovery in the social and vocational realms is an indirect effect and is fundamental to the recovery process.

Clinical Implications When Changing Antipsychotic Medication for Efficacy

In a narrative study of 90 patients who had responded to an atypical antipsychotic, Jenkins and Carpenter-Song found that the recovery process was slow and often grueling: "The usually long (several years) and excruciating process of trying a series of medications was typical in this sample of persons who had struggled with schizophrenia-related conditions for 2 decades."[3(p389)] Table 1[4] shows in greater detail some of the possible psychological responses a patient may have to a successful medication intervention, in which "success" is defined as a clinically significant and desired improvement in a persistent symptom over and above the level of symptom response achieved by the prior (preswitch) antipsychotic.

As one might expect from any major life event, some psychological responses are more adaptive than others. An adaptive response to symptom reduction may result in greater engagement in the therapeutic process, improved social relationships and vocational functioning, greater emotional awareness, and a sense of purpose in life. A maladaptive response might result in denying the illness and rejecting the need for treatment. There may be an overestimation of one's abilities and subsequent withdrawal, with a sense of failure and rejection. A new medication that results in positive symptom reduction might then be followed by a maladaptive response to the improvements.

One example of a maladaptive response is when the patient stops medication after doing better in the mistaken belief that the illness has gone away entirely.[4] This latter scenario would show up in the CATIE phase 1 data as a patient-initiated ACD event. While it certainly is true that the chain of events leading to medication discontinuation began with initiating the new antipsychotic, it would not be fair to conclude in this instance that the antipsychotic "doesn't work." Many recovery-oriented clinicians would consider such an event to be a setback on a longer trajectory that might well end up with a much better outcome eventually. In fact, it seems reasonable to assume that any clinically significant improvement in persistent symptoms in an illness with a symptom course that grinds on for years will produce a mixture of adaptive and maladaptive emotional responses. In turn, the outcome from these indirect responses may well depend in part on the preparedness of the treating clinicians to help the patient negotiate these psychological issues.

In summary, it is very important clinically to be able to sort out direct pharmacologic effects of a new antipsychotic medication from the indirect psychological effects that are sure to follow any symptom response. The most important point to realize about the CATIE study is that the ACD outcome is not able to provide such guidance. Other qualitative studies that assess the time course of a broad range of influences may be able to supplement this limitation of the CATIE study.

Table 1. Patient Responses to Successful Medication Intervention[a]

Maladaptive Responses		Indirect Psychological Effect From Symptom Reduction Following Medication Switch		Adaptive Responses
Rejecting treatment	←	Resolution of persistent positive symptoms	→	Engaging further in treatment process
Doing too much too soon	←	Improved motivation or energy	→	Moving toward better functioning
Wanting to return to psychic numbness	←	Improved mood and affective response	→	Becoming more aware of emotional issues
Withdrawing after experiencing rejection	←	Improved socialization	→	Greater engagement in relationships
Existential despair	←	More awareness of self	→	Regaining a sense of purpose in life

[a]Adapted with permission from Weiden et al.[4]

Table 2. Impact of Data Approach on Estimation of Attributable Risk of CATIE Discontinuations Caused by Tolerability[a]

Eligibility Criteria Chosen for "Rate for Exposed"	Evaluable Cohort From Initial Phase 1 Cohort, N (%)	Percentage of Cohort Discontinuing for "Tolerability"			
		All Tolerability (N = 213)	EPS-Related (N = 58)	Weight-Related (N = 58)	Sedation-Related (N = 26)
Entire randomized cohort	1432 (100)	14.9	4.1	4.1	1.8
Subgroup who discontinued study medication (any reason)	1061 (74.1)	20.1	5.5	5.5	2.4
Subgroup for whom tolerability-related reason was a possible choice	553 (38.6)	38.5	10.5	10.5	4.7
Clinician and patient agreed on a "tolerability" discontinuation	213 (14.9)	100.0	27.2	27.2	12.2

[a]Original data were reported in Lieberman et al.[1] The reanalysis shown in this table is original to this article.
Abbreviations: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness, EPS = extrapyramidal side effects.

THE IMPACT OF SIDE EFFECTS IN CAUSING MEDICATION DISCONTINUATION

Limitations of the CATIE 1 ACD Method in Estimating the Role of Side Effects

A common interpretation of the initial phase 1 CATIE results regarding the role of side effects as a cause for medication discontinuation is that (1) side effects were a relatively uncommon cause of medication discontinuation, accounting for just under 15% of the total reasons for medication discontinuation, and (2) the side effect differences between the medications, while detectable, did not lead to noticeable differences between antipsychotic medications in terms of discontinuation risk. Even when differences were found, such as greater rates of discontinuation from extrapyramidal side effects (EPS) in the perphenazine group or from weight gain in the olanzapine group, the maximum contribution to discontinuation in these cases was still under 10%. I strongly disagree with these conclusions. I believe that the phase 1 CATIE data themselves provide a strong case that the role of side effects as a primary cause for medication discontinuation is much larger than implied in the original 2005 report of CATIE phase 1 results.[1] What follows is an alternative approach to understanding the ACD secondary data as they pertain to understanding tolerability discontinuations.

Recall that the secondary goal of CATIE phase 1 was to learn about "the specific reasons for the discontinuation of treatment (e.g., inefficacy or intolerability owing to side effects such as weight gain, extrapyramidal signs, or sedation as judged by the study doctor)."[1(p1211)] From an epidemiologic perspective, this is technically known as an "attributable fraction" or "attributable risk" analysis. *Attributable risk* is defined as the "proportion of the disease occurrence that would be potentially eliminated if exposure to risk factor were eliminated."[5] Mathematically, this is calculated using the following equation:

$$\text{Attributable fraction} = \frac{(\text{Rate for exposed}) - (\text{Rate for unexposed})}{\text{Rate for exposed}}$$

The problem with the ACD measure for estimating the attributable fraction of tolerability discontinuations is that the "rate for exposed" population for the estimate of discontinuations for tolerability reasons is actually much lower than was used in the estimates presented in the CATIE phase 1 report.[1] The explanation has to do with the details of the way reasons for discontinuation were categorized.

The ACD approach works very well when the doctor agrees with a patient to change medication because of a side effect. Whenever a CATIE phase 1 patient decides to stop or switch medication and the doctor disagrees, the specific reason as reported by the patient as being most relevant in this decision is not captured or recorded on the ACD form. The patients' reasons are considered and included in the analysis when the doctor agrees with the patient, but this is not the case when patients discontinue their CATIE medication against the advice of their doctor. These discontinuations are captured as "patient decision," but in these cases, the reason for the patient discontinuation is not included in the phase 1 discontinuation report. For example, if a patient decides to stop medication in part because of weight gain, EPS, or sedation, this would be

recorded as a "tolerability" discontinuation on the ACD measure only if the doctor agrees with the patient. If the doctor disagrees, the distress from the side effect is never captured as a cause of discontinuation, which is then recorded as a "patient decision" on the ACD form without including the side effect. Thus, any time a patient stops CATIE study medication against the doctor's wishes, this individual could never be counted in the attributable fraction estimate of the role of medication tolerability in a decision to discontinue that medication. The net effect is that the CATIE outcome results probably underestimate the impact of side effects in influencing patient decisions to discontinue their medication. Since the ACD was done by the patients' clinicians, this approach may have underestimated the proportion of side effect discontinuations whenever the patient disagreed with the clinician.

Moreover, retaining the "patient-decision" subgroup in the attributable risk estimates of tolerability discontinuations further minimizes the attributable risk estimate of the role of side effects relative to other causes of discontinuation. For these assumptions to be valid would require the very optimistic assumption that CATIE clinicians never underestimated tolerability concerns in their patients. This assumption is seriously challenged not only by the literature on this topic[6,7] but by the relative complacency of the same CATIE clinicians (including the author) when it came to addressing potentially serious dyslipidemias that arose during the course of phase 1 treatment. If we assume that clinicians may have underestimated the impact of other side effects, this mutually exclusive approach will lead to significant underestimation of the proportion of CATIE discontinuations caused by all tolerability problems.

It can be argued that excluding the "patient decision" subgroup from the attributable risk estimate of the role of tolerability in medication discontinuation is a better approach to mitigate against these biases. A reanalysis using an adjusted N of the subgroup of 553 of 1061 phase 1 discontinued subjects whose ACD showed agreement between patient and clinician changes the attributable portion of tolerability discontinuations (N = 213) from 14.9% to 38.5%. The overall effects of changing the base population used for the attributable fraction estimates are shown in Table 2.

Not surprisingly, this same approach would change the attributable fraction estimates of the role of specific side effects in causing discontinuations of specific antipsychotic medications studied. These estimates, along with the subgroups used to make these estimates, are shown in Table 3. Regarding specific side effect–medication pairs of interest, the attributable risk of EPS as a reason for discontinuing perphenazine increases from 8% to 21%, and weight-related discontinuations from olanzapine from 9% to 28%. Therefore, the clinical implications of the CATIE phase 1 findings may depend, in part, on the underlying assumptions of the ACD outcome measure.

Table 3. Attributable Risk Estimate of Side Effect as a Cause of Discontinuation Using the Evaluable ACD Cohort[a]

CATIE Phase 1 Subgroup With a Primary Mutually Agreed ACD Category	Entire Evaluable Subgroup (N = 553)		CATIE Phase 1 Subgroups According to Study Medication Assignment[b]									
			Olanzapine (N = 110)		Perphenazine (N = 105)		Quetiapine (N = 141)		Risperidone (N = 125)		Ziprasidone (N = 72)	
Specific mutually agreed reasons	% Within All Mutually Agreed Reasons	Proportion by Specific Tolerability Reason (%)	% Within All Mutually Agreed Reasons	Proportion by Specific Tolerability Reason (%)	% Within All Mutually Agreed Reasons	Proportion by Specific Tolerability Reason (%)	% Within All Mutually Agreed Reasons	Proportion by Specific Tolerability Reason (%)	% Within All Mutually Agreed Reasons	Proportion by Specific Tolerability Reason (%)	% Within All Mutually Agreed Reasons	Proportion by Specific Tolerability Reason (%)
Mutually agreed primary reason for discontinuation was tolerability, N (%)	213 (38.5)		62 (56.4)		40 (38.1)		49 (34.8)		34 (27.2)		28 (38.9)	
EPS-related	10.5	27.2	7.3	12.9	21.0	55.0	7.1	20.4	8.8	32.4	8.3	21.4
Weight-related	10.5	27.2	28.2	50.0	2.9	7.5	8.5	24.5	4.8	17.6	9.7	25.0
Sedation-related	4.7	12.2	6.4	11.3	6.7	17.5	6.4	18.4	2.4	8.8	0.0	0.0
Any other tolerability reason	12.8	33.3	14.5	25.8	7.6	20.0	12.8	36.7	11.2	41.2	20.8	53.6

[a]Original data were reported in Lieberman et al.[1] The reanalysis shown in this table is original to this article.
[b]Only those subjects who discontinued study medication with a mutually agreed ACD rating were included in this analysis.
Abbreviations: ACD = all-cause discontinuation, CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness, EPS = extrapyramidal side effects.

Figure 3. Estimated Changes in Weight, Metabolic, and Endocrine Parameters After Changing Antipsychotic Medications[a,b,c]

Preswitch Antipsychotic	Postswitch Antipsychotic: Conventional[d]	Olanzapine	Quetiapine	Ripseridone	Ziprasidone	Aripiprazole[e]
Conventional[d]		↑↑ Weight ↑↑ Lipids ↓ Prolactin	↑ Weight ↑ Lipids ↓ Prolactin	↑↑ Weight ≈ Lipids ↑ Prolactin	≈ Weight ≈ Lipids ↓ Prolactin	≈ Weight ≈ Lipids ↓ Prolactin
Olanzapine	↓↓ Weight ↓↓ Lipids ↑ Prolactin		↓ Weight ↓ Lipids ≈ or ↓ Prolactin	↓ Weight ↓ Lipids ↑↑ Prolactin	↓↓ Weight ↓↓ Lipids ≈ Prolactin	↓↓ Weight ↓↓ Lipids ≈ or ↓ Prolactin
Quetiapine	↓ Weight ↓↓ Lipids ↑ Prolactin	↑ Weight ↑ Lipids ≈ Prolactin		≈ Weight ≈ or ↓ Lipids ↑↑ Prolactin	↓ Weight ↓ Lipids ≈ Prolactin	↓ Weight ↓ Lipids ≈ Prolactin
Risperidone	↓ Weight ≈ Lipids ≈ or ↓ Prolactin	↑ Weight ↑↑ Lipids ↓↓ Prolactin	≈ Weight ≈ or ↑ Lipids ↓↓ Prolactin		↓ Weight ≈ or ↓ Lipids ↓↓ Prolactin	↓ Weight ≈ or ↓ Lipids ↓↓ Prolactin
Ziprasidone	≈ Weight ≈ Lipids ↑ Prolactin	↑↑ Weight ↑↑ Lipids ≈ Prolactin	↑ Weight ↑ Lipids ≈ Prolactin	↑ Weight ≈ or ↑ Lipids ↑↑ Prolactin		≈ Weight ≈ Lipids ≈ or ↓ Prolactin
Aripiprazole[e]	≈ Weight ≈ Lipids ↑ Prolactin	↑↑ Weight ↑↑ Lipids ≈ Prolactin	↑ Weight ↑ Lipids ≈ Prolactin	↑ Weight ≈ or ↑ Lipids ↑↑ Prolactin	≈ Weight ≈ Lipids ≈ Prolactin	

[a]Data from Lieberman et al.[1] unless otherwise noted.
[b]These are estimates-based differences between preswitching and postswitching values, with the latter being obtained at least 2 weeks after monotherapy with the postswitch antipsychotic.
[c]Table symbols refer to the estimated magnitude of preswitch and postswitch differences, with "≈" indicating no change, single arrows indicating increase or decrease, and double arrows indicating a common and clinically significant problem.
[d]Here, "conventional" refers to high-potency conventional antipsychotics such as haloperidol or fluphenazine. Low-potency conventional antipsychotics will have greater weight gain liability.
[e]Data on aripiprazole were not obtained from the CATIE study but are based on other "switch" studies[14–20] that show a similarity to the profile of ziprasidone in terms of effect on weight and metabolic side effects.

Clinical Implications of Underestimating the Role of Side Effects

The clinical implication is that depending on how the data are interpreted, the CATIE study differences in side effect profiles across the range of antipsychotic medications may be a more important factor in influencing the decision to stay on a medication, or to discontinue the medication, than is commonly believed.[8–10] These findings also speak to the difficulties in coming up with an accurate or valid understanding of the causal role of side effects in medication discontinuation. In other words, studies comparing patient preferences with clinician preferences routinely show that clinicians do not estimate the burden of distressing side effects as highly as do their patients.[11,12] The clinician may be better placed to understand the consequences of medication discontinuation, whereas these consequences of relapse may have lost salience for patients who have been stable for awhile on their medication regimen. On the other hand, clinicians are not the ones who have to endure distressing side effects day in and day out. In my opinion, there is a great danger in interpreting the CATIE results to mean that the burden of EPS during treatment with the conventional antipsychotics is not as great as was believed. The CATIE study shows that even giving lower doses of a moderate-potency conventional antipsychotic to a cohort of patients who by entry criteria have not been extremely sensitive to EPS in the past will demonstrate significant differential effects of EPS on medication discontinuation rates.

Failure to Consider Medical Risks in ACD Outcome

Another important limitation of the ACD approach to understanding the role of tolerability problems has to do with trends in the acceptance of certain side effects among clinicians. The lack of clinical reactivity to the metabolic disturbances that arose during the phase 1 CATIE study is discussed in the article by Newcomer in this supplement.[13] The fact is that doctors did not often initiate discontinuation of the assigned phase 1 CATIE medication, despite the availability of laboratory evidence documenting serious exacerbation of medical risk factors for cardiovascular disease. Common sense tells us that finding should hardly be used as "evidence" that the propensity for some antipsychotic medications to cause dyslipidemia is not important when it comes to effectiveness outcomes. However, strictly speaking, if using the a priori definition that effectiveness of the medication is

shown by the rate of discontinuation, the technical conclusion is that dyslipidemia is not important.

A more sensible interpretation is that at the time the CATIE study was conducted, doctors were not as proactive about these problems as they should have been. Because dyslipidemias do not overtly cause the distress that is commonly seen with EPS, sexual dysfunction, or weight gain, clinicians need to be even more alert to the possibility of metabolic disturbances when changing from one antipsychotic to another. Figure 3 summarizes some important metabolic and endocrine effects that frequently occur as a result of changing antipsychotic medications. Physicians need to be especially vigilant in educating their patients about these effects because there seems to have been excessive complacency with some of these problems.

CONCLUSIONS

Despite decades of research, our many treatments for schizophrenia remain only partially effective in ameliorating the symptoms of this disease. The CATIE trials, primarily designed to compare currently available agents to each other with regard to efficacy and side effects, are perhaps most remarkable for their high discontinuation rates. These rates are reflected in the high proportion of patients switching or not adhering to their medication. The availability of the many atypical antipsychotics with varying clinical and side effect profiles allows for increased choice for the patient and clinician. In evaluating the ACD, the clinician must be aware of the multiple factors in a drug discontinuation or desire to switch. For example, changes in functional levels interplay with a patient's symptoms and may secondarily result in a drug termination or change. It is only in this broadened context that we will be able to obtain a comprehensive overview of the many facets of how the individual with schizophrenia functions and thereby maximize our treatments.

Most of all, the ACD contains some hierarchical decision criteria that constrain the interpretability of the reasons why a medication was stopped. Whenever the patient and doctor agree that a medication switch is indicated, the ACD form enters this discontinuation as being a clinician decision, and then the ACD form asks the doctor to further categorize the switch decision as either "efficacy" or "tolerability." Depending on which assumptions are chosen, the ACD estimates on attributable risk of reasons for discontinuation are quite different. The clinical implications of this approach are also very important: that side effects may actually be a much more common reason for discontinuation of the phase 1 CATIE medication, and that the EPS burden of perphenazine and the weight-related burden of olanzapine may be greater than what was implied in the primary CATIE report.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), fluphenazine (Prolixin, Permitil, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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