# Mid-Term and Long-Term Efficacy and Effectiveness of Antipsychotic Medications for Schizophrenia: A Data-Driven, Personalized Clinical Approach

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**ABSTRACT**

***Objective:*** Our aim in this article is 2-fold: first, to examine the mid-term to long-term data on efficacy, from controlled and naturalistic and other studies, in order to determine if they are consistent with the quantitative meta-analyses of mostly short-term, randomized controlled trials Our second (and most important) aim is to use these and other data to provide guidance about the potential relationship of these differences among antipsychotics to the individual patient's own experience with antipsychotic drugs in the process of shared decision-making with the patients and their significant others.

***Data Sources:*** A search of PubMed, Embase, and PsychINFO was conducted for articles published in English between January 1, 1999, and April 2011, using the search terms *double-blind* AND *randomized* AND *olanzapine* AND (*ziprasidone* OR *risperidone* OR *quetiapine* OR *haloperidol* OR *fluphenazine* OR *perphenazine* OR *aripiprazole*).

***Study Selection:*** Studies with a duration 3 months or longer, including patients with schizophrenia or schizoaffective disorder, reporting survival analysis for all-cause discontinuation and relapse or dropout due to poor efficacy were selected.

***Data Extraction:*** We extracted the number of patients relapsed due to poor efficacy and hazard rates for relapses.

***Data Synthesis:*** Overall, the efficacy patterns of both controlled effectiveness and observational long-term studies closely parallel the efficacy observed in the short-term, controlled studies. The results of Phase 1 Clinical Antipsychotic Trials of Intervention Effectiveness are very similar to, but not identical with, the controlled short-term efficacy studies, the European First-Episode Schizophrenia Trial, and naturalistic studies. The mid-term and long-term data suggest that olanzapine is more effective than risperidone and that both of these are better than the other first- and second-generation antipsychotics except for clozapine, which is the most efficacious of all. Further large differences emerged regarding the specific mid-term and long-term safety profiles of individual antipsychotics.

***Conclusions:*** Despite intraclass differences and the complexities of antipsychotic choice, the second-generation antipsychotics are important contributions not only to the acute phase but, more importantly, to the maintenance treatment of schizophrenia.

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In discussing "the path to personalized medicine," Margaret Hamburg and Francis Collins write, "The challenge is to deliver the benefits of this work to patients.…Together, we have been focusing on the best ways to develop new therapies and optimize prescribing by steering patients to the right drug at the right dose at the right time."[1(p301)]

Schizophrenia requires lifetime management. Unfortunately, the majority of treatment research has focused on short-term studies rather than on the disease management over the long-term course. Over the past 2 decades, a pressing clinical question is, how much better (if at all) are the second-generation antipsychotics (SGAs) compared to the first-generation antipsychotics (FGAs)? A related question is, which individual agents are most efficacious? This controversy surrounding choice of best drug (or class) for the average patient is partially fueled by the experts' beliefs and their personal interpretation of the data,[2] which disregard many important differences between individual drugs within both SGA and FGA categories,[3] creating confusion. Part of the disagreement depends on how clinically important a change of a Positive and Negative Syndrome Scale (PANSS) point (or effect size unit) is.

Our aim in this article is 2-fold: first, to examine the mid-term (3 months to less than 1 year) to long-term (12 months or longer) data on efficacy, from controlled[4] and naturalistic and other studies, focusing on intuitive and pragmatic, clinically meaningful and important outcomes,[5] in order to determine if they are consistent with the quantitative meta-analyses of mostly short-term, randomized controlled trials.[6–12] Our second (and more important) aim is to use these data (as well as other data from the literature) to provide guidance about the potential relationship of these differences among antipsychotics to the individual patient's own experience with antipsychotic drugs in the process of shared decision-making with the patient and his or her significant others.

## METHOD

Before describing our analysis, there are a number of biases, ie, design issues, in long-term studies that need to be considered. One, when a drug is more effective than a comparator or a placebo, patients drop out of the trial in uneven numbers due to relapse or poor efficacy, introducing a systematic bias. We aimed to control this bias, using survival analysis and capturing the mid-term and long-term phase of these trials. Two, we also excluded those trials that included patients who were switched from a randomized medicine to clinician's choice, as this severely compromised randomization.[10] (We recognize that such a design is valuable for certain aspects of service research but not in the present case.) An example of this bias is when patients who drop out because of relapse while taking haloperidol are switched to a more efficacious

**Clinical Points**

- Mid-term and long-term data suggest that some antipsychotics are more effective than others when treating schizophrenia over the long run. They include clozapine, olanzapine, and risperidone.
- Each antipsychotic has a unique side effect profile, with greater or less propensity for weight gain, but in general second-generation antipsychotics have fewer extrapyramidal symptoms and less tardive dyskinesia than first-generation antipsychotics over the long run.
- As much as possible, individualize medication, psychotherapy, and rehabilitation treatment choices, ie, share the decision-making with each "patient–significant other unit." For many chronic patients over time, efficacy and improved function are more important than possible future side effects.

drug (such as clozapine), and the better results are due to this more effective drug's contaminating the assessment of the efficacy of haloperidol. Three, since many patients are dropped from clinical trials as they relapse because the drug is not effective, other patients whom the drug helped remain, making all the drugs seem to have the same efficacy. In this situation, the patients for whom the drug did not work are no longer in the trial. Consequently, we also excluded outcome data based on (or driven by) only those who completed long-term maintenance trials. We did this because, if one drug is more efficacious than the other, there will be fewer patients taking the less effective drug in the trial at completion, thus introducing a systematic bias. Since only responders remain, drug differences are eliminated, including statistics done per patient-months, since only responders have accrued many patient-months. Completer data also eliminate side-effect differences for those side effects leading to dropouts.

### Literature Search

Published studies eligible for this analysis were identified through a search of clinical trials in PubMed, Embase, and PsychINFO (January 1, 1999, through April 2011 and limited to articles written in English) using the following terms: *double-blind* AND *randomized* AND *olanzapine* AND (*ziprasidone* OR *risperidone* OR *quetiapine* OR *haloperidol* OR *fluphenazine* OR *perphenazine* OR *aripiprazole*).

### Study Selection

Studies with a duration 3 months or longer, including patients with schizophrenia or schizoaffective disorder, reporting survival analysis for all-cause discontinuation and relapse or dropout due to poor efficacy were selected.

### Data Extraction

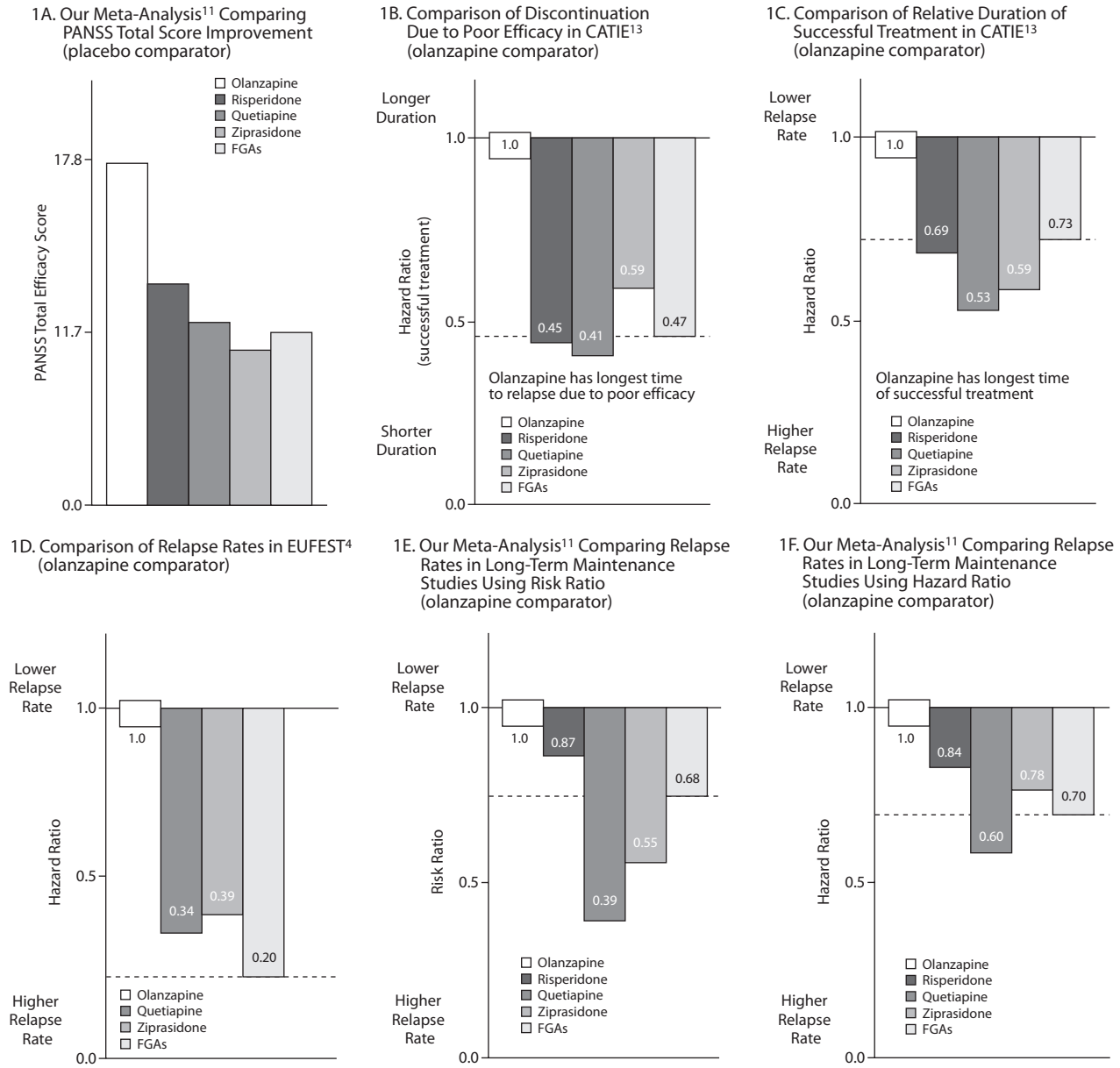
We extracted the number of patients relapsed and hazard rates for relapses.

In this report, we have added new studies and updated a prior meta-analysis[8,9,11,12] of relapse prevention data from long-term maintenance studies that focused on all-cause discontinuation in schizophrenia. We present a graphic display (Figure 1A) of the efficacy comparison of short-term studies of the mean effect size (weighted for sample size) of our previous meta-analyses of FGA vs placebo,[12] FGA versus SGA, and SGA vs SGA,[8,9] by adding the mean of the FGA versus placebo comparison[12] to that of the effect sizes of the other 2 meta-analyses[8,9] to integrate all the studies, expressing the efficacy differences versus placebo. We expressed these differences as PANSS points, which have some intuitive clinical meaning, so that the results can be compared to the longer-term studies. We did not estimate the variance or statistical significance, nor did we take into account all drug-drug differences. This is just a visual representation of the original 3 meta-analyses so that the reader can see the rank ordering of the findings present in a simple form.

Since the focus of this article is on the mid-term to long-term data, we performed 2 new meta-analyses on these same studies, used in Beasley et al[11] (approximating the raw data present in the original studies, calculating the risk ratio for relapse and hazard ratio [HR] for time to relapse using Comprehensive Meta-Analysis software [Biostat, Englewood, New Jersey]). Since we are comparing the results of this meta-analysis with the results of Phase 1 of Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE),[13] we did not include CATIE in the calculation. Unfortunately, because time to relapse was not always available, we performed a meta-analysis calculating risk ratios for relapse rates and all-cause discontinuation for completeness as well, using valid but less-sensitive measures available on more studies using olanzapine as the common comparator. We have presented the results from CATIE,[13] the European First-Episode Schizophrenia Trial (EUFEST),[4] and our meta-analysis in graphics, so that it is easy to compare and contrast the results in order to form a gestalt (Figure 1B–1F). Since the meta-analysis of acute efficacy used different comparators, we integrated these into effect sizes based on the mean effect sizes, per number of subjects. Note that efficacy differences in maintenance trials can be conceptually divided into initial improvement and relapse prevention produced by the experimental drugs versus comparator. The former is captured in the acute trials, the latter is not, and so we emphasize relapse as our primary outcome. The outcome is clinically based on the judgment that the patient has relapsed, has deteriorated, or has such a poor response that the patient needs to be dropped for clinical reasons. All of these outcomes are clinically important and easily intuitively understandable.

As to cognition, we believe that this parameter is important, but the studies have important methodological limitations, such as exclusion of patients who (1) could not complete the cognitive tasks, (2) dropped out due to poor efficacy, or (3) experienced practice effects. Therefore, with few exceptions, we did not attempt to integrate this area into our discussion.[14,15]

**Figure 1. Efficacy Comparisons of First- and Second-Generation Antipsychotic Drugs Versus Olanzapine or Placebo[a,b]**




[a]Based on intent-to-treat, last-observation-carried-forward data from our 3 meta-analyses,[8,9,12] the mean PANSS total scores being weighted by sample size.
[b]The dotted line in each figure is for visual orientation illustrating how the FGA medications compare to other medications.
Abbreviations: CATIE = Clinical Antipsychotic Trials in Intervention Effectiveness, EUFEST = European First-Episode Schizophrenia Trial, FGA = first-generation antipsychotic, PANSS = Positive and Negative Syndrome Scale.

## RESULTS

### Effectiveness Outcomes Using All-Cause Discontinuations

We present the results of our meta-analysis of long-term all-cause discontinuation studies[11] but modified these to include all FGAs as one group (Figure 2A) versus CATIE[13] (Figure 2B), using olanzapine as a comparator. We found the same pattern of results as in the short-term studies, namely, that olanzapine is associated with fewer all-cause discontinuations than the other antipsychotics. The graph of the hazard function indicates more all-cause discontinuations with other drugs compared to olanzapine, the standard comparator used. (The HR expresses the relative rate of an outcome, here all-cause discontinuation, of drugs compared to a common standard arbitrarily given the score of 1. This provides an index of the relative rates of relapse over the course of the trial.) Since 2 drugs are being compared, drug A can cause one-half the rate of discontinuations as drug B, or B drug can cause one-half the rate of discontinuations as Drug A. One number is the reciprocal of the other. For example, risperidone can cause 0.75 (or three-fourths) the number of all-cause discontinuations as olanzapine, or olanzapine can cause 1.33 times as many discontinuations as risperidone.


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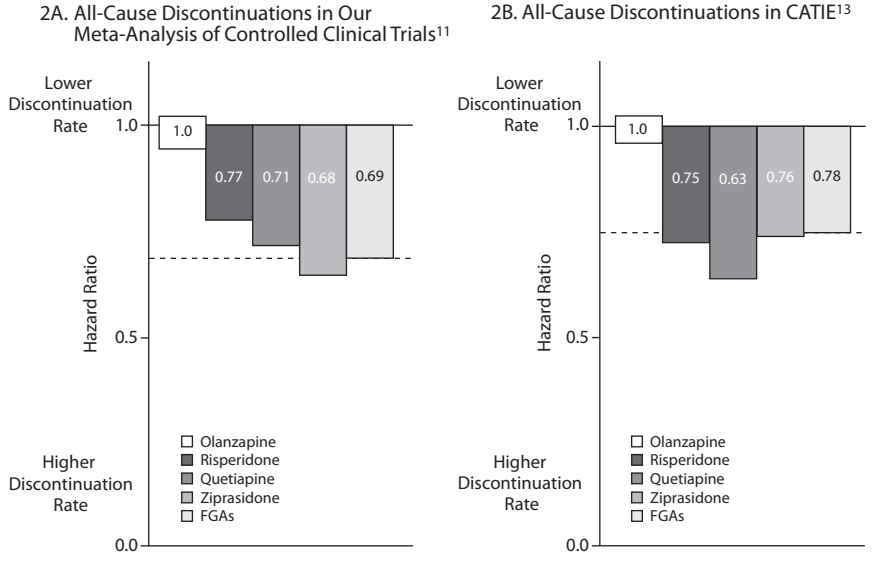
**Figure 2. Efficacy Comparisons of First- and Second-Generation Antipsychotics Versus Olanzapine in Our Meta-Analysis and CATIE Using All-Cause Discontinuation[a,b,c,d]**




[a]Hazard ratio expresses the relative rate of all-cause continuation against a standard that is arbitrarily given the score of 1.
[b]These graphs express the relative rate of all-cause discontinuation.
[c]The dotted line illustrates how the FGA medications compare to the other medications.
[d]Olanzapine has longest time to relapse due to poor efficacy.
Abbreviations: CATIE = Clinical Antipsychotic Trials in Intervention Effectiveness, FGA = first-generation antipsychotic.

Survival analysis is frequently presented as time to reach a certain criterion. For example, the median time to relapse for drug A would be longer than that for drug B. Figure 2A shows our meta-analysis of the controlled clinical trials of all-cause discontinuation (± 95% CI) using olanzapine as a comparator (HR: olanzapine [comparator] = 1.00; risperidone = 0.77 [95% CI, 0.63–0.9; $P = .005$]; quetiapine = 0.71 [95% CI, 0.53–0.95; $P = .02$]; ziprasidone = 0.68 [95% CI, 0.53–0.76; $P < .001$]; FGAs = 0.69 [95% CI, 0.55–0.90; $P < .001$]). Figure 2B shows the all-cause discontinuation in CATIE—these 2 graphs express the relative rate of all-cause discontinuation. For example, for quetiapine, an HR of 0.63 indicates that quetiapine has a mean of 63% fewer patients who remain unrelapsed (HR: olanzapine [comparator] = 1.00; risperidone = 0.75 [95% CI, 0.62–0.90; $P = .002$]; quetiapine = 0.63 [95% CI, 0.52–0.76; $P = < .001$]; ziprasidone = 0.76 [95% CI, 0.60–0.97; $P = .03$]; FGAs = 0.78 [95% CI, 0.63–0.96; $P = .02$]).

## Efficacy Outcomes

The efficacy results from our meta-analysis of acute studies expressed in the more intuitive and, we think, more meaningful PANSS points are provided in Figure 1A. (A 10-point change in PANSS points corresponds to 0.4–0.5 effect size [standard mean difference] units, depending on the standard deviation of PANSS used, here 25 or 20.[6–9]) The principal efficacy results of CATIE,[13] discontinuations due to poor efficacy, are presented in Figure 1B (olanzapine [comparator] = 1.00; risperidone = 0.45 [95% CI, 0.34–0.64; $P = .001$]; quetiapine = 0.41 [95% CI, 0.29–0.57; $P < .001$]; ziprasidone = 0.59 [95% CI, 0.37–0.93; $P = .03$]; FGAs = 0.47 [95% CI, 0.31–0.70; $P < .001$]) and the other CATIE efficacy outcome, duration of successful treatment, in Figure 1C. (olanzapine [comparator] = 1.00; risperidone = 0.69 [95% CI, 0.55–0.87; $P = .002$]; quetiapine = 0.53 [95% CI, 0.43–0.67; $P < .001$]; ziprasidone = 0.59 [95% CI, 0.58–0.94; $P < .02$]; FGAs = 0.73 [95% CI, 0.57–0.93; $P = .01$]). The hazard rate for dropout due to poor efficacy in EUFEST[4] is plotted in Figure 1D (olanzapine [comparator] = 1.00; quetiapine = 0.34 [95% CI, 0.18–0.68, $P < .001$]; ziprasidone = 0.39 [95% CI, 0.17–0.92; $P < .001$]; FGAs = 0.20 [95% CI, 0.10–0.38; $P < .001$]). In this meta-analysis, risk ratios for relapse are shown in Figure 1E (risperidone = 0.87 [95% CI, 0.62–1.2, not significant]; quetiapine = 0.39 [95% CI, 0.25–0.63, $P = 10^{-4}$]; ziprasidone = 0.55 [95% CI, 0.37–0.83, $P = .004$]; FGAs = 0.68 [95% CI, 0.50–92, $P = .02$]). The HR for relative relapse rate while taking ziprasidone, quetiapine, risperidone, and FGAs versus olanzapine as a common comparator was (Figure 1F) risperidone = 0.84 (95% CI, 0.78–0.90, $P < 10^{-6}$), quetiapine = 0.60 (95% CI, 0.54–0.66, $P < 10^{-8}$), ziprasidone = 0.79 (95% CI, 0.72–0.85, $P < 10^{-8}$), and FGAs = 0.70 (95% CI, 0.55–90; $P = .005$[16–24]).

The pattern of these analyses is very similar to that in CATIE but not identical. The meta-analysis of Leucht et al[7] found risperidone more effective at preventing relapse than the comparator FGA. In a single study, Csernansky et al[25] found that risperidone reduced the relapse rate to about one-half that of haloperidol, and Marder et al[26] found a small difference in the same direction.

Meta-analytic studies of clozapine versus FGAs clearly show clozapine to be more efficacious than FGAs.[6,27–29] The clozapine phase of CATIE (in which patients were randomized to clozapine, but it was given non-blindly)[13,30] and the clozapine phase of the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS)[31] both found clozapine to be more effective than other antipsychotic drugs. CUtLASS[31] was widely interpreted as demonstrating that inexpensive medications cost less than expensive medications. Given the design problems—one of which was that individual drugs were not randomized, no other major conclusions of CUtLASS can be made with confidence.

## Naturalistic Studies

The Schizophrenia Outpatient Health Outcomes (SOHO) study,[32] a 3-year, observational, naturalistic study from 10 European countries, also found that olanzapine and clozapine had relatively better outcomes than other drugs on a wide range of effectiveness outcomes: response, relapse,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remission, and treatment discontinuation. A very recent report from SOHO study authors found a small but clinically relevant superiority of SGAs over FGAs in subjective well-being, extending previous positive findings of different effects on quality of life.[32] Two controlled industry service delivery studies showed an efficacy advantage of risperidone compared to typical antipsychotics.[33,34] Two long-term naturalistic studies found that switching from FGAs to SGAs resulted in better treatment compliance and psychosocial functioning.[35–37] One study has failed to confirm these findings.[38] Although the lack of an FGA control group does not permit us to rule out a positive effect of time or study participation,[39] there are some controlled studies of depot FGAs versus oral FGAs showing that the depot formulation slightly reduces the number of relapses compared to oral drugs,[40] while effectiveness studies (using the mirror image design) show that depot medication reduces relapses by three-fourths in a real-world setting.[41]

### Data From the Longer-Term Extension Phase of Controlled First-Episode Studies

First-episode studies generally find FGAs to be about equal in efficacy to SGAs in the short term, although some studies did find differences between the 2 groups.[42] We examined the long-term, first-episode studies to see if any differences between drugs surfaced, not in the first few weeks of treatment but rather after a year or 2. We found a number of trends for differences: (1) one study found that olanzapine produced a higher remission rate than haloperidol (57.3% versus 44%, $P < .04$)[43]—furthermore, haloperidol had an increased reduction in the amount of gray matter volume, whereas the olanzapine group did not, suggesting a potential neuroprotective factor for olanzapine or a potential neurotoxic effect of haloperidol[44]; (2) another study found greater efficacy in the olanzapine group in comparison with risperidone and a nonsignificant difference favoring olanzapine over haloperidol[45]; (3) another study[46] showed a shorter median time to clinical response with significantly fewer relapses in the risperidone group than the haloperidol group, with the median time to relapse being 466 days for risperidone versus 205 for haloperidol, $P = .008$[46]; (4) a fourth study showed greater neurocognitive benefit with olanzapine than with haloperidol or risperidone[47]; and (5) finally, Marder et al[26] found that risperidone produced greater sustained improvement in anxiety, depression, and the general symptom index than haloperidol but that there was no difference in relapse rates.

### Longer-Term Studies: Side Effects

We present a semiquantitative chart indicating our assessment of side effects in Table 1.[48] The results of our meta-analysis for anticholinergic use for EPS are presented in Figure 3A (placebo comparator) and 3B (haloperidol comparator), for akathisia as measured by Barnes Akathisia Scale ratings are presented in Figure 3C,

**Table 1. Severity of Adverse Effects in First- and Second-Generation Antipsychotic Drugs[a]**

| Adverse Effect | Mechanism | Dose-/Titration-Dependence | Aripiprazole | Clozapine | Olanzapine | Quetiapine | Risperidone | Ziprasidone | Haloperidol | Perphenazine |
|---|---|---|---|---|---|---|---|---|---|---|
| Anticholinergic | $M_{1-4}$ blockade | ++ | 0 | +++ | ++ | 0/+ | 0 | 0 | 0 | 0/+ |
| Acute parkinsonism | $D_2$ blockade | +++ | + | 0 | + | 0 | ++ | + | +++ | ++ |
| Akathisia | ? $D_2$ blockade and $\alpha_1$, 5-HT interaction | +++ | ++ | + | + | + | + | +/++ | +++ | ++ |
| Cerebrovascular event | ? $D_2$-mediated hypercoagulability | 0? | ?[b] | ?[b] | ?[b] | ?[b] | ?[b] | ?[b] | ?[b] | ?[b] |
| Diabetes | Weight gain, ? direct effects | 0? | 0/+[b] | +++ | +++ | ++ | + | 0/+[b] | 0/+[b] | + |
| ↑Lipids | Weight gain, ? direct effects | 0? | 0/+[b] | ++ | ++ | + | + | 0/+[b] | 0/+[b] | + |
| Neutropenia | ? | +? | 0/+ | ++ | 0/+ | 0/+ | 0/+ | 0/+ | 0/+ | 0/+ |
| Orthostasis | $\alpha_1$ blockade | +++ | 0/+ | +++ | ++ | ++[c] | + | 0 | 0 | + |
| ↑Prolactin/sexual dysfunction | $D_2$ blockade | +++ | 0 | 0 | +/++ | 0 | +++ | + | ++ | ++ |
| ↓Prolactin | $D_2$ agonism | +? | ++ | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ↑QTc interval | Cardiac ion channel effects | +? | 0/+[b] | +[d] | 0/+[d] | +[d] | +[d] | ++[d] | 0/+[d] | +[d] |
| Sedation | $H_1$ blockade | +++ | 0/+ | +++ | ++ | ++[c] | + | 0/+ | 0/+ | + |
| Seizures | ? | +++ | 0/+ | ++[b] | 0/+ | 0/+ | 0/+ | 0/+ | 0/+ | 0/+ |
| Tardive dyskinesia | ? $D_2$ receptor desensitization | ++ | 0/+[b] | 0 | 0/+[e] | 0/+ | 0/+ | 0/+[c] | ++ | +/++ |
| Withdrawal dyskinesia | $D_2$ blockade rebound | +++ | ++ | 0 | 0/+ | + | + | + | ++ | +/++ |
| Weight gain | $H_1$, $D_2$, 5-$HT_{2C}$ blockade | 0? | + | +++ | +++ | ++ | ++ | + | + | ++ |

[a]Adapted with permission from Correll.[48] [b]Insufficient long-term data to fully determine the risk. [c]Less at higher doses. [d]Relevance for the development of torsades de pointes not established. [e]Less than 1% per year in adults who were often pretreated with first-generation antipsychotics.

Abbreviations: α = alpha-adrenergic receptor, D = dopaminergic receptor, H = histaminic receptor, M = muscarinic receptor, 5-HT = serotonergic receptor.

Symbols: 0 = none, 0/+ = minimal, + = mild, ++ = moderate, +++ = severe, ↑ = increased, ↓ = decreased.



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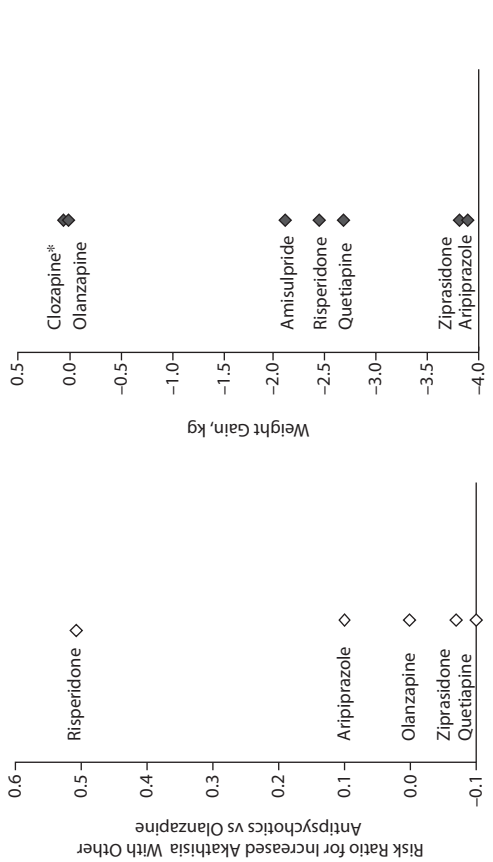
**Figure 3. Meta-Analysis of Extrapyramidal Symptoms, Akathisia, and Weight Gain Associated With Other Second-Generation Antipsychotic Drugs Compared to Olanzapine**




[a]Antiparkinsonian drugs were administered presumably because patients developed extrapyramidal side effects during the trial.[12]
[b]Antiparkinsonian drugs were administered presumably because patients developed extrapyramidal side effects during the trial.[8]
[c]Risperidone caused the most akathisia, with ziprasidone, quetiapine, and aripiprazole causing about the same degree of akathisia as olanzapine.
[d]Weight gain with olanzapine versus the other second-generation antipsychotics is shown in Figure 3D.[49] Since olanzapine is the comparator, it has a risk ratio of zero to itself. A negative number indicates less weight gain than olanzapine. Clozapine caused a very slight and statistically insignificant increase in weight; and the other antipsychotics caused substantially less weight gain, with ziprasidone and aripiprazole causing almost 4 kg less weight gain than olanzapine; quetiapine and risperidone caused less weight gain than olanzapine but more than ziprasidone and aripiprazole.
*The weight gain caused by clozapine was slight and not statistically significant compared to olanzapine.

and for weight gain are presented in Figure 3D. Weight gain was greatest in patients treated with olanzapine and clozapine, with a 2- to 4-lb weight gain with risperidone and quetiapine, and least in patients treated with aripiprazole, ziprasidone, and some FGAs, using olanzapine as a comparator.[49] Although it is clearly possible that there may be direct dose-dependent metabolic effects with olanzapine, clozapine, and quetiapine,[49–51] we would generally assume that the differential effect of drugs on weight gain parallels the liability for metabolic abnormalities.[52–60] Exceptions to this rule of parallel weight and metabolic effects are the relatively greater lipid effects with quetiapine than with risperidone, despite similar weight gain potential[49,61] and the relatively lower lipid[61] and, possibly, glucose effects with aripiprazole.[51,62] Unfortunately, reliable comparative data regarding actual cardiovascular morbidity and mortality outcomes across antipsychotics are lacking, largely due to a relatively long lag time between cardiometabolic risk accumulation and cardiovascular endpoints, as well as frequent switching in severely mentally ill patients.

Another long-term concern, tardive dyskinesia, does not seem to differ significantly among SGAs (Table 1), with a 1-year incidence risk reduced up to 600% compared to FGAs.[64] However, more comparative long-term data are needed to substantiate the uniform risk reduction among SGAs. Prolactin elevation, with its potential effects on sexual dysfunction and adherence, as well as its potential long-term implications for bone density and fracture risk,[65,66] sedation, and general anticholinergic burden,[67] can also affect overall functioning.

## DISCUSSION

Our review of the mid-term to long-term data suggests that the efficacy pattern both of controlled effectiveness and observational long-term studies closely parallels the efficacy observed in the short-term controlled studies. The results of CATIE are very similar, but not identical, to, those in the controlled efficacy studies mentioned earlier and similar to EUFEST[4] as well as other naturalistic studies.[68] Although there are few efficacy differences that appear in the initial phase of the blinded first-episode studies, there is suggestive evidence that efficacy differences appear in their long-term

phase and that these are also consistent with both double-blind and naturalistic long-term studies. The only exception is risperidone, in which the dose used in CATIE Phase I was probably inadequate, although this drug showed better efficacy in Phase II compared with the other drugs.[30,69] (The fixed-dose randomized-blinded studies show that 2 mg of risperidone is 50% less efficacious than 4 mg, a finding that is consistent with a controlled-maintenance dose study.[26,69–71]) About 40% of the patients in the CATIE studies received 3 mg or less of risperidone.[13]

### Industry Bias

We have found that open-label studies systematically favor the sponsors' drug.[9] While the interpretation of results from well-controlled clinical trials can favor the sponsors' drugs due to selective emphasis on favorable findings,[72] we found no consistent significant sponsorship bias in the actual numeric findings.[73]

### Implications of the Data for Long-Term Management

As mentioned, this is the first meta-analysis of mid-term to long-term outcome data focusing on the newer antipsychotics in the literature. As such, we have used these data as a springboard to make clinical treatment recommendations for long-term management. Where controlled evidence exists, we have referenced it.

### Shared Decision-Making

As much as possible, decisions on what drug to use should be based on shared decision-making among patients, their significant others, the physician, and other members of the team, a practice favoring a fully informed consent.[74,75] Kon[76] notes that shared decision-making is a continuum moving from a decision at one end, when the patient or agent solely drives the decision, to the opposite end, when the physician drives the decision, such as an urgent condition for which the physician must act immediately. Not uncommonly, the physician has to make the final decision, based on an inadequate history and the current clinical state of the patient. Shared decision-making is a process that requires time and skill, and active listening is essential.[77,78] However, given the cognitive deficits and often limited insight of the patients (and sometimes their families), obtaining a useful history can be problematic. The physician's contributions are vital. For example, some patients may not appreciate the long-term consequences of weight gain or metabolic abnormalities on life expectancy.

Some of the controversy is on how to balance cost differential against the projected risk estimate or poor health based on weight gain. Differences against an efficacy advantage of *x* PANSS points or *y* effect size units, relapse, or very poor efficacy are an easily understood, clinically relevant outcome.

Not all patients experience every side effect or experience a side effect to a similar degree. Patients may be concerned about a common side effect but feel embarrassed or reluctant to talk about it (eg, sexual dysfunction, gynecomastia, the effects of weight gain on appearance, dysphoria, or sedation). Uncommon but severe or medically dangerous side effects can be very important. The choice of drug for any patient undergoing long-term treatment implies a previous experience, as most patients usually have been taking various drugs over a period of many years, so it is possible to begin to tailor the drug to the patients. Furthermore, patients may value different properties of the drug. The controversy about which are the "best" drugs is partly based on values; when one value is seen as the sole determinant of choice, drug differences in other areas are minimized or not recognized in order to reduce cognitive dissonance.[2] Nevertheless, we do not treat groups of patients on which these differences are based but individuals who might not even have been well-represented in the available evidence-based trials. However, individual antipsychotics, FGAs or SGAs, are *not* all alike: Figure 3 and Table 1 reveal that they differ in weight gain and metabolic risk potential, sedation, EPS potential, prolactin elevation and sexual dysfunction, QTc interval prolongation, availability of depot or oral formulations, and pharmacology. We think that knowledgeable clinicians will show much more agreement and will be more balanced when focusing on a decision about a particular patient, in a particular setting, and with a particular history than when judging different medications globally.

## Clinical Recommendations for the Long-Term Treatment of Schizophrenia

These treatment recommendations are partially based on the data presented above, the literature, and our clinical experience:

- Patient preferences vary as to the state of the illness—in the acute phase, many patients focus as much (or more) on side effects as on efficacy, as commonly they do not have illness insight and are usually not convinced that they need treatment. They do not want disabling side effects like severe dystonia or parkinsonism, which increase in importance over time. In the chronic, long-term phase of the illness, especially when they have continuing, intrusive positive symptoms like delusions, command hallucinations, or referential thinking, many patients are more likely to want relief from these disabling symptoms and may value the efficacy of a particular medication *if it helps them*. During the long-term, chronic phase of treatment, they may focus on issues of gaining work or having more friends, outcomes that are linked to efficacy in ways that many patients may not fully appreciate. Saying it another way, many patients (and usually their families) want to feel better, even function better, and have a better quality of life. It is not that they are unconcerned about side effects, but rather they may be more prepared to live with the side effects if they function even modestly better. However, even this assessment cannot be generalized, as not infrequently patients lack illness insight and focus on adverse effects of medications that they



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feel they do not need and that they do not see as being helpful.
- Further, one should try to avoid a drug the patient does not like. Physicians are responsible for contributing their expertise to the process of choosing a medication, balancing issues such as the longer-term potential and problems and risks with an especially effective antipsychotic for the particular patient. As such, we must involve both patients and families. Hopefully, pharmacogenetics will be increasingly helpful.[79] But if the patient and prescriber agree that efficacy is most important in the long-term treatment, then we suggest that use of risperidone, olanzapine, or amisulpride (not registered in the United States) should be considered first and, of course, clozapine later. (Studies comparing very inadequate low-dose clozapine to SGAs are not helpful because of the confounding of dose.[9])
- Serious consideration should be given to long-term treatment with ziprasidone or aripiprazole, due to their low incidence of side effects, but caution is indicated if the patient does not have a good response to these drugs in the first 4 to 6 weeks. While the acute studies of aripiprazole do not always provide support that aripiprazole is as efficacious as olanzapine for acute treatment, one randomized, double-blind maintenance study found patients who completed the first 6 weeks of the long-term maintenance treatment study to have little difference in dropout rates due to poor efficacy between olanzapine and aripiprazole.[16] More data are needed about this issue. On the other hand, some have argued that, since patients are ill for the rest of their lives and efficacy is relative (and established on the basis of group means), one must first try the medication with the *fewest* side effects,[61,62] only switching to a higher-risk agent in patients who do not reach sufficient efficacy. We think it is better to make such decisions about efficacy or a side effect sooner rather than later to avoid patients' deteriorating and breaking family ties and to avoid the accumulation of potentially harmful long-term effects. One cannot assume that all patients respond at exactly the rate of group means.
- All antipsychotics work best on positive symptoms, but they do have modest beneficial effects on the negative and general symptom cluster.[8] Nonetheless, some SGAs (compared to FGAs) have a slightly better efficacy on negative or general symptoms cluster (but these symptoms clearly remain a problem in many patients). This is (in part) because there are fewer extrapyramidal symptoms (EPS) and less tardive dyskinesia with SGAs.[78,80] These outcome differences are small, but when viewed in the context of functioning (in an outpatient setting for chronic patients), between 30 to 40, ie, a 10-point range, on a 100-point global assessment of functioning scale, a 5-point change can be significant for an individual patient. A relapse or worsening to such a degree that the patients must have a different treatment is a clinically meaningful outcome. One can argue about the clinical significance of changes of a few PANSS points.
- For patients with severe positive symptoms in the chronic phase, eg, hallucinations and agitation, olanzapine, amisulpride, and risperidone (and of course clozapine) seem to be most efficacious overall. Data on the efficacy of combinations of antipsychotics have not been consistent.[78]
- For patients who have high denial/lack of insight (and perhaps for many others who are ambivalent about whether they are sick), long-acting injectables may be the treatment of choice, as they make noncompliance transparent. It is unclear if long-acting injectable SGAs have efficacy advantages over FGAs. The central issue is to increase compliance to avoid relapse—since the more episodes a patient has, the longer it takes to get back to baseline.[78]
- Over the long run, do not keep switching if a medication gives a reasonable (for that patient) partial response from baseline decompensation levels, unless relevant side effects mandate treatment discontinuation. Be aware—it is extremely difficult to get back to pre–first-episode baseline function.
- Do not use antipsychotic polypharmacy instead of clozapine,[78] as clozapine is the most effective antipsychotic in resistant or partially responsive patients.[78]
- The mood stabilizers and antidepressants do not add much, except in selected patients with comorbid major affective disorder.[80] Antidepressants may reduce negative symptoms[81] but are not indicated when demoralization (not severely lowered mood) is the prominent symptom—here psychotherapy is the treatment of choice.[82]
- Outcomes such as vocational and social functioning can be enhanced with psychosocial interventions,[75] which should be phased in over time once the "right" medication is in place.
- The strongest predictor of early discontinuation of a drug was the perception that the medication was of poor benefit, ie, the patients who initially perceive benefit from the medication are much more likely to take their drug for long periods of time.[83]
- For patients who are apathetic or sluggish, for example, a trial of a less-sedating medication, ziprasidone or aripiprazole, is preferentially indicated, even given potential efficacy considerations mentioned above.
- For patients who already have cardiovascular risk factors (overweight, obesity, hypertension, lipid abnormalities, insulin resistance, prediabetes, diabetes, or metabolic syndrome) and those at high risk for the development of cardiovascular disorders (eg, family history of cardiovascular risk factors or disorders or early cardiac death), consider agents with lower cardiometabolic risk, such as aripiprazole, ziprasidone, or high- or mid-potency FGAs.
- The potential long-term consequences of weight gain and metabolic abnormalities are associated with

premature death.[84] This is why, for some patients, cardiometabolic risk might trump potential efficacy differences (which were at effect sizes of 0.1–0.3 in short-term studies comparing different SGAs as well as SGAs with FGAs [except for clozapine, which had an effect size advantage of 0.5 versus FGAs]).[9] These adverse effects are associated primarily with the use of clozapine and olanzapine. On the other hand, there is a recent study[85] showing mortality reduction with clozapine and other antipsychotics—as well as the classic studies showing that clozapine lowers the risk of suicide.[86]

- Children, adolescents, and first-episode patients are more susceptible to substantial weight gain while taking either FGAs or SGAs,[87,88] but the relative propensity differences across medications still remain similar. The battle of the bulge should begin with the first episode. Patient Outcomes Research Team guidelines recommend[78] that olanzapine should be second-line in young and first-episode patients, but this is not an absolute proscription. Psychoeducation about maintenance of meaningful activity levels, healthy lifestyle, and diet is critical. Some advocate starting with low-risk agents.[62] If patients gain weight rapidly, this will most often become apparent in the first 2 to 6 weeks. Because of the potentially serious consequences of the weight gain, like diabetes, stroke, heart disease, it is important to address cardiovascular risk before the patients gain excessive weight,[89] by switching drugs,[90] implementing lifestyle changes, and addition of medications that can attenuate weight gain.[91]
- We emphasize, "Know thyself": the clinicians must carefully assess the capacity of their particular center and the patient to monitor and cope with clinically important side effects. If the patient has the capacity to accept and successfully adhere to weight loss interventions, diet, exercise, and the management of other potentially relevant side effects, this may impact on the choice of antipsychotic drugs.[75,92]
- In general, SGAs as a class are associated with a lower frequency of EPS and anticholinergic use than both high- and mid-potency FGAs, but, here again there are differences among drugs within class.[9,93] In addition, many studies document that some patients have a dysphoric reaction to certain medications, particularly medications that produce EPS, and may dislike these medications.[94] As such, clinicians personalize treatment based on (1) anecdotes favoring switching from an FGA to an SGA for efficacy reasons (clinicians rarely switch back to FGAs, although it does happen and can work), (2) anecdotes suggesting that the subjective sense of well-being is improved,[95] ie, "the lights are turned on"[96] by SGAs, as well as (3) some data suggesting that patient satisfaction seems to be better when taking some SGAs than FGAs,[9] (4) drugs with fewer EPS and less tardive dyskinesia may be associated with better compliance—clozapine and quetiapine have the least EPS/tardive dyskinesia. For the patient who experiences EPS while taking, for example, risperidone or haloperidol at therapeutic doses, the drug is a probable non-starter. Clinicians should very carefully monitor neurologic side effects, particularly in patients treated with high-potency FGAs but also in those treated with risperidone and paliperidone. (5) Potential clinical manifestations of prolactin elevation, ie, sexual and reproductive system functioning,[97,98] need to be monitored and taken into account when choosing antipsychotics.
- There is evidence from CATIE[99] that individualized treatment works best. For those patients who were switched from olanzapine to risperidone or vice versa, the discontinuation rate was lowest for those patients who then were assigned to stay on their previous medication therapy in comparison to those who switched medicines. Nevertheless, the differences between olanzapine and risperidone remained the same, regardless of the switch condition. There was no significant interaction. Once those patients who remained on the medication they had been assigned at baseline were removed, the all-cause discontinuation rates and median time to discontinuation were as follows: (1) olanzapine: 68% and 7.7 months, respectively; (2) perphenazine: 75% and 5.6 months, respectively; (3) risperidone: 76% and 4.7 months, respectively; (4) quetiapine: 82% and 4.7 months, respectively; (5) ziprasidone: 80% and 3.5 months, respectively. There were no significant treatment group differences remaining for all-cause discontinuation, when patients rerandomized to the antipsychotic they took at baseline and patients with tardive dyskinesia were removed, so pairwise comparisons were not evaluated, even though the power was reduced by only 10%.

### Cost

Finally, if cost is an issue, use FGAs—although oral risperidone is now off-patent, olanzapine will be shortly, and others soon will follow. This change in cost will soon help mitigate the FGA versus SGA arguments based on economic reasons. Moreover, it needs to be considered that medication costs must be balanced against the much greater costs of hospitalization that have been associated with relapses.

## CONCLUSION

Neither FGAs nor SGAs are a homogenous group, either regarding efficacy or side effects, particularly on an individual patient level. We have detailed our clinical suggestions by way of being specific regarding what individualizing treatment means. For example, try to avoid a drug that patients do not like. Just as all drugs are not alike, neither are all patients. Selection is not a single balance sheet that drives attitudes to treatment and compliance—it is different for each patient depending on his or her preferences and past exposure. As such, we must involve both patients and families in the treatment decisions. Despite intraclass differences and the



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complexities of antipsychotic choice, the SGAs are important contributions to treatment, and most psychiatrists, let alone patients and their families, would probably not want to do without them.[2]

***Drug names:*** aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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