All Antipsychotics Are Equal, but Some Are More Equal Than Others

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One of the "atypical" features of second-generation antipsychotics (SGAs) that was quickly appreciated by clinicians and patients shortly after their introduction was that these medications were shown to elicit fewer extrapyramidal side effects than the first-generation antipsychotics (FGAs). Early head-to-head comparisons of some first-line SGAs with FGAs in patients with schizophrenia also demonstrated better efficacy in terms of overall symptom reduction in studies comparing risperidone[1] and olanzapine[2] with haloperidol. However, later studies failed to demonstrate the superiority of SGAs over FGAs in effectiveness or safety.[3,4] Recent meta-analyses[5,6] have provided important insights into these questions, and we will aim to interpret their results as they apply to the current controversy about SGA versus FGA use in the treatment of schizophrenia.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE),[3] one drug representing FGAs (perphenazine) was compared with 4 SGAs (olanzapine, quetiapine, risperidone, and ziprasidone). The time to the discontinuation of treatment for any cause was the principal measure of effectiveness.

Perphenazine did not show statistically significant inferiority to any of the 4 SGAs on time to all-cause discontinuation (or on time to discontinuation due to intolerable side effects). Perphenazine was (nonsignificantly) superior to quetiapine, risperidone, and ziprasidone in terms of time to all-cause discontinuation. When calculating number needed to treat (NNT) for the outcome of all-cause discontinuation, the advantage of perphenazine over quetiapine can be quantified as a statistically significant ($p < .05$) NNT of 15, compared with a NNT of 13 for risperidone versus quetiapine and a NNT of 6 for olanzapine versus quetiapine (see Figure 6 in Citrome[7]).

The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1) tested the hypothesis that SGAs (other than clozapine) will result in greater improvement of quality of life than FGAs in patients with schizophrenia who require a change in treatment.[4] The 227 participating subjects were randomly assigned to receive open-label treatment with either an FGA or SGA (other than clozapine), with the choice of individual drug made by the managing psychiatrist prior to randomization. The FGAs included 15 preparations; the SGAs, 5 (risperidone, olanzapine, amisulpride, zotepine, and quetiapine). Sulpiride was the most commonly prescribed FGA (49% of patients in the FGA arm). Despite the similarity in their names, amisulpride has little in common pharmacologically with sulpiride.[8] Olanzapine was the most commonly prescribed SGA (46% of patients in the SGA arm). After 1 year of treatment, participants in the FGA arm showed a trend toward greater improvements in Quality of Life Scale and symptom scores. The authors concluded that there is no disadvantage in terms of quality of life, symptoms, or cost in using an FGA rather than a non-clozapine SGA.

These 2 articles[3,4] were criticized on methodological grounds.[9] Nevertheless, after their publication, it has been suggested that "SGAs other than clozapine may offer few, if any, advantages over FGAs, especially agents of intermediate potency."[10(p515)] If this is true, there would be few, if any, reasons to prescribe the expensive SGAs (other than clozapine), since the cheap FGAs could do the same job.

However, a recent large Finnish study has looked at the problem of comparative effectiveness from a different angle.[11] The subjects were members of a nationwide cohort of 2230 consecutive adults hospitalized in Finland for the first time because of schizophrenia or schizoaffective disorder. Initial use of monotherapy medication after discharge from hospital was recorded for the 10 most commonly used antipsychotic drugs. Drug-purchasing data were used to form all groups. The outcome measures were rates of all-cause discontinuation of antipsychotic, rates of rehospitalization, and mortality. There was considerable variation in relative risks of all-cause discontinuation and of rehospitalization, particularly among the oral formulations of FGAs. The superior performance of perphenazine depot was probably due to the inherently better compliance associated with slow-release injections. Clearly, the availability of a depot formulation is an important factor in choosing an individual antipsychotic. There was an overlap in the relative risk for rehospitalization between FGAs and SGAs. These data illustrate the point that pooling the FGAs into one group and contrasting that group with a pooled SGA group in an analysis is not clinically meaningful.

The variation among the SGAs was confirmed by a recent meta-analysis.[5] Total score on the Positive and Negative Syndrome Scale (PANSS) was the primary outcome measure. The meta-analysis evidenced the superiority of olanzapine to aripiprazole, quetiapine, risperidone, and ziprasidone and the superiority of risperidone to quetiapine and ziprasidone. Secondary analyses indicated that these differences were due to improvement in positive symptoms rather than negative symptoms. The weighted mean differences in PANSS points (total score) were not large, ranging from 1.9 (95% CI = 0.6 to 3.3) (olanzapine versus risperidone) to 8.3 (95% CI = 5.6 to 11.0) (olanzapine versus ziprasidone), favoring olanzapine. The authors concluded that in clinical practice, "small efficacy superiorities must be weighed against large differences in side effects and cost."[5(p152)]

Another recent meta-analysis compared SGAs with various FGAs (mostly haloperidol).[6] Four of the SGAs (amisulpride, clozapine, olanzapine, and risperidone) showed superior efficacy against overall symptoms (including positive and negative symptoms) in comparison with FGAs, whereas the other SGAs (aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine) did not. SGAs showed fewer extrapyramidal side effects than haloperidol. However, with the exceptions of aripiprazole and ziprasidone, SGAs induced more weight gain than haloperidol (but not more than low-potency FGAs). There were also differences among SGAs in their sedative effects. The authors conclude: "Because the SGAs differ in…efficacy, side effects, cost…and pharmacology…they do not form a homogeneous class and neither do FGAs. Improper generalization creates confusion and as a result the classification might be abandoned."[6(p40)]

In addition to the heterogeneity among the SGAs (and FGAs), there is substantial heterogeneity in terms of individual patient response to any of these medications. History appears to be destiny if one examines the different phases of the CATIE trial.[12] Depending on the phase of CATIE, different antipsychotics had different rankings for overall effectiveness. Olanzapine had advantages in terms of all-cause discontinuation and efficacy (assessed by PANSS total score change), particularly in phase 1. Quetiapine (and olanzapine) had advantages in terms of all-cause discontinuation in phase 1B among patients in whom

perphenazine treatment had failed, with stronger effect sizes as measured by NNT compared to phase 1. Clozapine was superior to risperidone and quetiapine for patients who discontinued an SGA in phase 1 (or 1B) because of "inefficacy." Risperidone had advantages in terms of overall tolerability in phases 1, 2E, and 2T. Ziprasidone had the most benign metabolic profile and in phase 2T was associated with a higher likelihood of weight loss for patients who gained greater than 7% of their initial body weight in phase 1. Regarding switching, a caveat raised by a reanalysis of the Phase 1 data[13] was that patients randomly assigned to olanzapine and risperidone who were continuing with their baseline medication (the "stayers") had significantly longer times until all-cause discontinuation than did those assigned to switch antipsychotics. However, the authors did concede that the original pattern of results remained when the "stayers" were omitted from the analyses.

Finally, there is some evidence that antipsychotics differ in their effects on cognition in schizophrenia,[14,15] although more recent evidence suggests otherwise.[16,17]

What are the clinical implications of these findings? First, the early belief that SGAs (as a group) are more efficacious than the FGAs is no longer tenable. Does it mean that the SGAs other than clozapine offer few, if any, advantages over FGAs? We do not think so. It appears that some SGAs are more efficacious than the FGAs, whereas other SGAs are not. Also, some FGAs such as perphenazine may be more efficacious than some SGAs. Thus, the merits of each drug should be judged independently of the traditional dichotomous SGA-FGA classification. The clinician's choices have now widened to again include some low-dose FGAs, perhaps with concomitant anticholinergic treatment to reduce extrapyramidal side effects.

Second, the small to medium-sized differences among antipsychotics in efficacy in terms of symptom reduction (concerning mostly positive symptoms) need to be considered in the context of side effects and cost. Schizophrenia is a long-term illness that not only lowers the quality of life but also increases mortality. Do the risks associated with increased weight and disturbance of glucose and lipid metabolism caused by a more effective drug such as olanzapine outweigh the risk of suboptimal treatment of schizophrenia with a less effective drug that does not have these side effects? Similar questions can be asked about other medications with other side effects such as elevated prolactin level, extrapyramidal symptoms, and tardive dyskinesia (TD). Although lower incidence of TD in comparison with FGAs was reported for clozapine,[18] risperidone,[19] and olanzapine,[20] cases of TD can develop with SGAs.

These questions can only be answered on the basis of clinical assessment of an individual patient's situation. The assessment must include, to the extent possible, a discussion with the patient, who should be able to express his/her preferences. History of response, or lack thereof, or of intolerability, will limit the choices available to offer.

Finally, the clinician should keep in mind that the relatively small differences between agents reported in clinical trials and meta-analyses are mean differences that may underestimate the differences between individuals. It is therefore necessary to empirically test agents in individual patients. This in turn requires good monitoring of response and side effects.

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