

Recent Advances in the Antipsychotic Treatment of People with schizophrenia

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Antipsychotic medications are the primary class of drugs used in the pharmacological treatment of schizophrenia. Over the past five years, there have been hundreds of studies published on the antipsychotic treatment of schizophrenia (1), including three large pragmatic studies: the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (2); the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) (3); and the European First-Episode Schizophrenia Trial (EUFEST) (4). These pragmatic studies are the largest studies conducted to date that compare first generation antipsychotic medications (FGAs) and second generation antipsychotic medications (SGAs) in people with first-episode and multi-episode schizophrenia. The results of these and other studies provide important new information on the antipsychotic treatment of people with schizophrenia.

Treatment of Multi-episode Schizophrenia. The primary question concerning the antipsychotic treatment of people with treatment-responsive, multi-episode schizophrenia is whether there is sufficient evidence to recommend the preferential use of SGAs versus FGAs. The answer to this question is dependent upon the careful evaluation of the cost/benefit ratio of the individual agents that make up each of these two major classes of antipsychotics. The CATIE (2) and CUtLASS (3) pragmatic clinical trials examined the comparative efficacy and safety of FGAs and SGAs. In both of these studies, the study sample included participants who were experiencing an acute exacerbation of their illness, as well as individuals who were changing their medications because of inadequate response to or intolerable side effects from prior antipsychotic treatment. In the CATIE study, risperidone, olanzapine, quetiapine and ziprasidone were compared to the first generation antipsychotic: perphenazine. The olanzapine group had a significantly longer time to discontinuation than those who received risperidone, quetiapine, ziprasidone and perphenazine, though the differences between olanzapine and ziprasidone and olanzapine and perphenazine were no longer significant after correction for multiple comparisons. There was no significant difference among olanzapine, risperidone and perphenazine on the Positive and Negative Syndrome Scale (PANSS) total score. In the CUtLASS study, antipsychotic medications were classified into FGA and SGA groups and were compared by group. There were no significant FGA versus SGA group differences for PANSS total score or the positive or negative syndrome subscale scores. These studies suggest that there are limited positive symptom efficacy differences, except for possibly olanzapine, between FGAs and SGAs. There continues to be no data to support a change to a SGA for those people who experience adequate symptom control and minimal side effects with an FGA (1).

In terms of the costs of these agents, there are four major side effects to consider when choosing among the first and second generation agents: 1) extrapyramidal symptoms (EPS), including tardive dyskinesia (TD); 2) weight gain and associated metabolic effects; 3) prolactin elevation and associated sexual side effects; and 4) QTc prolongation. FGAs and SGAs do not differ as a class on these side effects, rather there may be marked differences within a class for a particular side effect. In general, the high potency FGAs are most likely to cause EPS and TD, whereas clozapine has a very low

risk for both of these side effects (1); olanzapine and clozapine are more likely to cause weight gain, glucose elevation, and lipid abnormalities than other SGAs and medium and high-potency FGAs (5,6); risperidone and its metabolite, paliperidone, and high-potency FGAs are more likely to cause prolactin elevation than other FGAs and SGAs, with aripiprazole the least likely to cause prolactin elevation (1); and thioridazine and ziprasidone are the most likely to cause QTc prolongation (7).

In light of the largely comparable efficacy and variable risk of side effects among the different FGAs and SGAs, the choice of antipsychotic medication should be based on individual preference; prior treatment response and side effect experience; adherence history; relevant medical history and risk factors; and long-term treatment planning (1).

Treatment of First-Episode Schizophrenia. In people with first-episode psychosis, early treatment with antipsychotic drugs is associated with significant symptom reduction. There have been several important new studies that have addressed the question of whether there are specific antipsychotics that should be preferentially used in this population. In the EUFEST study, an open-labeled, 1-year randomized trial, treatment discontinuation was greatest for participants randomized to haloperidol compared to those receiving any of four SGAs: amisulpiride (not available in the United States); olanzapine; quetiapine; and ziprasidone (4). However, there were no significant group differences in the PANSS or Calgary Depression Scale (CDS) total scores or quality of life scores. In an 8-week study of people with early-onset schizophrenia and related spectrum disorders (aged 8 - 19), there were no significant differences among molindone, risperidone and olanzapine in response rates or symptom reduction (8). In studies comparing multiple SGAs, there have been no differences in overall symptom scores and response rates among treatment groups (9).

There are a number of studies that suggest that olanzapine may be especially problematic when used in this population. In particular, olanzapine has been shown to have the highest liability for weight gain when compared to most other FGAs and SGAs. In the head-to-head comparison with quetiapine and risperidone, olanzapine was associated with up to two times the increase in weight at 12 and 52 weeks (9). In the 8-week study of people with early-onset schizophrenia, olanzapine was associated with significant increases in weight, fasting insulin, cholesterol, and LDL cholesterol compared to risperidone and molindone (8). Therefore, in the absence of any evidence of enhanced therapeutic benefits, the association of olanzapine with significant metabolic risks suggests that olanzapine should not be considered as a first-line treatment for individuals experiencing their first episode of schizophrenia (1).

Treatment-Resistant Schizophrenia. Clozapine is the only antipsychotic that has been shown to be effective in people who have failed to adequately respond to FGAs. Two new studies suggest that clozapine is more effective than other SGAs in people who have failed to adequately respond to either a FGA or SGA (10,11). The CATIE Phase 2E study compared clozapine (open-label), olanzapine, risperidone, and quetiapine (10). Clozapine had a longer time to all cause discontinuation than any of the other drugs, with the comparison between clozapine and quetiapine and clozapine and risperidone statistically significant. Clozapine had a significantly longer time to discontinuation due to lack of efficacy than all three drugs. Clozapine produced greater improvements in PANSS total and positive syndrome subscale scores, with the difference in PANSS total scores significant for clozapine versus quetiapine and risperidone, but not olanzapine. In

the CUtLASS 2 trial, open-label clozapine was compared to a group of other SGAs, including olanzapine, quetiapine, and risperidone, and produced significantly greater reductions in the PANSS total score than these other agents (11). There continues to be limited evidence that any of the other SGAs are effective in this population.

A number of other pharmacological approaches have been used for the treatment of partially-responsive or treatment-resistant schizophrenia, including antipsychotic polypharmacy, adjunctive anticonvulsants, and electroconvulsive therapy (ECT). In people who failed to adequately respond to clozapine, the addition of a second antipsychotic has received partial support. Risperidone has been the most frequently studied agent (1), with three studies finding an effect of risperidone for global psychopathology or positive symptoms (12-14), but two studies failed to find any benefit (15,16).

Adjunctive lithium and the anticonvulsants: carbamazepine and valproic acid/valproate have been previously evaluated for the treatment of residual positive symptoms and found to have limited benefit (17,18). There are several recent studies that have examined the therapeutic potential of adjunctive lamotrigine to clozapine. Two studies reported a significant benefit of adjunctive lamotrigine for positive symptoms, including hallucinations, and general psychopathology measures (19,20), whereas a third study failed to find any benefit of the combination (21).

ECT may have a role in the treatment of people with treatment-resistant schizophrenia (1). One recent study used a prospective open-label design to examine ECT versus treatment as usual for people with treatment-resistant schizophrenia (22). The groups consisted of people who were either non-responsive to clozapine or refused clozapine treatment. The ECT treated group exhibited significant improvements on measures of global psychopathology, but not on measures of specific symptom domains. A recent review suggests ECT plus antipsychotic medication is a safe and effective option for people with treatment-resistant schizophrenia (23). However, currently there is not sufficient evidence to warrant a new treatment recommendation for the use of ECT for treatment-resistant individuals.

In summary, there is modest support for the use of adjunctive high-potency antipsychotics for people who failed to adequately respond to clozapine. ECT may also be useful for the treatment of the person who has been partially-responsive to clozapine or other antipsychotic medications. There is little evidence to support the use of adjunctive lithium or anticonvulsants for this population, though further study is required to determine whether lamotrigine may be of benefit.

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