Evidence for Using Atypical Antipsychotics in Psychosis

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Conventional antipsychotics have been used as treatment for schizophrenia and other psychotic illnesses for 50 years. While they offer relief for most schizophrenic symptoms, many people have been intolerant of or unresponsive to conventional antipsychotic treatment. Because atypical antipsychotics provide relief against schizophrenic symptoms with a better side effect profile than conventional antipsychotics, some feel that atypical antipsychotics should be considered a first-line treatment. Others believe that atypicals should mainly be used for patients who are intolerant of conventional antipsychotics. Long-term studies and studies on patients' subjective well-being indicate that atypical antipsychotics may be superior to conventional antipsychotics in treating schizophrenia.

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Since their introduction in the 1950s, conventional antipsychotics have been used as a treatment in schizophrenia. While conventional antipsychotics, such as haloperidol, have been proven effective in treating the positive symptoms of schizophrenia—delusions, hallucinations, and incoherence—they have not been as effective against the negative symptoms, such as affective flattening, alogia, or avolition. Conventional antipsychotics have also been known to have severe side effects including sedation, anticholinergic toxicity, reversible drug-induced movement disorders such as extrapyramidal symptoms (EPS), and persistent motor side effects such as tardive dyskinesia (TD).[1] Subsequently, a substantial group of schizophrenic patients in the United States have been intolerant of or unresponsive to conventional antipsychotic treatment.

With the introduction of clozapine in 1989, patients with schizophrenia intolerant or partially responsive to conventional antipsychotics had a second-line treatment. While conventional antipsychotics treat schizophrenia by blocking central dopamine-2 (D_2) receptors, atypical antipsychotics also block the serotonin receptors; this mechanism of action may explain why these agents have efficacy against negative symptoms.[1] The introduction of atypical antipsychotics also provided patients with treatments that have mild side effects. However, some argue that atypical antipsychotics should remain a second-line treatment for schizophrenia due to similar efficacy to conventional agents in some acute studies.[2] In terms of overall efficacy, though, the question is whether atypical antipsychotics are more effective and tolerable in the long-term. How a patient feels is the true measure of the effectiveness of an antipsychotic. Results of long-term studies that measure patients' well-being over time suggest that atypical antipsychotics are both more effective and better tolerated than conventional antipsychotics.

EFFICACY

Psychosis

In 2000, Geddes et al.[2] conducted a systematic overview and meta-regression analysis of atypical antipsychotics. Forty-seven of the 52 trials studied were short-term trials (a median follow-up of 6.5 weeks). The meta-analysis examined studies comparing atypical antipsychotics—amisulpride, clozapine, risperidone, olanzapine, quetiapine, and sertindole—with conventional antipsychotics—haloperidol or chlorpromazine. (Neither amisulpride nor sertindole is currently available in the United States.) Although patients taking conventional antipsychotics developed more extrapyramidal side effects than those taking the atypical antipsychotics, conventional antipsychotics were still recommended for continued first-line use in the treatment of schizophrenia due to their lower cost. The investigators found that in many of the trials, haloperidol was used in dosages greater than 12 mg/day. As the dosage of haloperidol increased, there was a greater likelihood that the atypical agent would be superior. When haloperidol was observed in doses of 12 mg/day or less, efficacy was similar. Geddes et al. concluded that because haloperidol demonstrated an improved side effect profile at lower

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doses, the superior efficacy of atypical antipsychotics could not be proved. Atypicals were shown to have a reduced risk of motor side effects such as EPS in all comparative studies with conventional antipsychotics and were therefore recommended for use in patients who had a history of motor side effects or did not respond to conventional antipsychotics. This advantage should be seen in EPS.

Many researchers[3] dispute the conclusion of Geddes et al.[2] Another meta-analysis[3] measured the efficacy and safety of risperidone, olanzapine, sertindole, and quetiapine as compared with conventional antipsychotics, mainly haloperidol. In this meta-analysis, double-blind randomized controlled trials with duration periods of 3 to 12 weeks were included. The study reviewed mean changes in Brief Psychiatric Rating Scale (BPRS) scores, total scores on the Positive and Negative Syndrome Scale (PANSS), number of negative symptoms, number of patients requiring at least one dose of antiparkinsonian medicine, and number of dropouts due to treatment failure or adverse effects. Atypical antipsychotics and haloperidol were all found to be more effective in reducing BPRS scores than placebo. Sertindole and quetiapine were found to be as effective as haloperidol, while risperidone and olanzapine were found to be significantly more effective than haloperidol, as assessed by BPRS scores. All antipsychotics were found to reduce the number of negative symptoms from baseline. Haloperidol was associated with a need for antiparkinsonian medication, a marker for motor side effects such as EPS, even at reduced dosages, while the atypical antipsychotics appeared to be similar to placebo in the need for antiparkinsonian medicine to treat these side effects. Dropout due to lack of efficacy was less frequent among patients taking antipsychotics when compared with those taking placebo. Only olanzapine was demonstrated to be significantly superior to haloperidol in terms of failures of treatment and adverse side effects. Quetiapine was also shown to have fewer dropouts with regards to adverse effects. Again, in terms of EPS, atypical antipsychotics had an important advantage. Although as a group atypical antipsychotics demonstrated efficacy compared with haloperidol, the effect size was not at a level that would be considered applicable to clinical practice. However, unlike Geddes et al.,[2] the researchers concluded that the more tolerable side effect profile of the atypicals is a strong argument in favor of their first-line use.

In long-term studies, however, the overall improved efficacy of atypical antipsychotics can be seen more clearly than in the acute studies. Csernansky et al.[4] reported a long-term double-blind study of risperidone and haloperidol. Patients in the study were diagnosed with schizophrenia or schizoaffective disorder according to the DSM-IV. Accepted doses in the 365 participants were 2 to 8 mg/day of risperidone (mean ± SD = 4.9 ± 1.9) and 5 to 20 mg/day of haloperidol (mean ± SD = 11.7 ± 5.0). The median duration that patients remained in the trial was 364 days for risperidone-treated patients and 238 days for haloperidol-treated patients. There was a statistically significant difference in the estimated risk of relapse, 34% in the risperidone group and 60% in the haloperidol group ($p < .001$). Relapse was defined by either psychiatric hospitalization, an increase in the level of psychiatric care, or an increase of 25% or more from baseline in total score on the PANSS. The mean decreases in the PANSS scores were 3.9 with risperidone and 1.4 with haloperidol. In 5 of the 6 factor scores on the PANSS—total, positive symptoms, negative symptoms, disorganized thoughts, and anxiety-depression—risperidone was associated with a significant decrease. Antiparkinsonian medication was prescribed for more patients receiving haloperidol (17.6%) than risperidone (9%). An increased rate of TD was found among haloperidol patients (2.7% compared with 0.6% for risperidone patients). At the end of the 12 months, risperidone was found to have a significantly reduced risk of relapse and to be better tolerated than haloperidol. Risperidone was also noted to have steadily increasing efficacy over the course of treatment.

Other long-term studies also show a decreased risk of relapse among patients taking atypical antipsychotics. One maintenance study[5] reviewed maintenance phases of 3 acute studies[6–8] comparing olanzapine and haloperidol in 3 dose ranges. Patients enrolled in the studies had to have responded to acute-phase therapy with a total BPRS score decrease greater than 40% from baseline and had to have been outpatients during their last acute phase. One study was from the North American Double-Blind Olanzapine Trial[6] while the other 2 were from the International Double-Blind Trial.[7,8] The maintenance phase of the North American Trial compared olanzapine at mean doses of 12.1 mg/day with haloperidol at 14 mg/day, and placebo.[5] The maintenance phase of one international trial compared olanzapine (mean dose = 11.5 mg/day), haloperidol (mean dose = 16.4 mg/day), and a low dosage of olanzapine (1 mg/day) instead of placebo.[5] The maintenance phase of the other international trial used mean dosage levels of 13.9 mg/day for olanzapine and 13.2 mg/day for haloperidol.[5] The pooled results of the 3 studies showed 50.5% of olanzapine-treated patients without relapse and 8.6% discontinuing because of adverse side effects, versus 42% of haloperidol-treated patients without relapse and 11.1% discontinuing because of adverse side effects.[5]

Mood

While atypical antipsychotics have been shown to be more effective in the long-term rather than short-term studies, the true measure of efficacy is how a patient feels. The anxious-depression factor in schizophrenia rating scales is an indicator of the patient's mood. Several studies show that atypical antipsychotics are more effective than conventional antipsychotics in treating anxious depression.

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A meta-analysis[9] was conducted on 4 randomized, double-blind, multicenter registrational trials of olanzapine.[6–8,10] Patients were assigned to haloperidol, olanzapine, or placebo for a period of 6 weeks. Comparisons were made between placebo and haloperidol, placebo and olanzapine, and haloperidol and olanzapine. Efficacy was measured through BPRS and total scores of PANSS as well as scores of the 5 factors of the PANSS. In the first study,[6] 335 patients were assigned to either 5 ± 2.5, 10 ± 2.5, or 15 ± 2.5 mg/day of olanzapine, 15 ± 5.0 mg/day of haloperidol, or placebo. The second study[10] consisted of 152 patients taking a fixed dose of 1 or 10 mg/day of olanzapine or placebo. The third study[7] was an international study consisting of 431 patients on the same doses as the first study except that 1 mg/day of olanzapine was used instead of placebo. The last study,[8] also an international study, observed 1996 patients taking 5-mg/day doses of olanzapine and haloperidol with the option to increase up to 20 mg/day. The combined results of the 4 studies showed that olanzapine was significantly more effective than haloperidol in 3 of the 4 items on the anxiety/depression scale.

In the Csernansky et al.[4] study comparing patients taking risperidone and haloperidol, patients taking risperidone showed significant improvement in anxiety-depression scores from the baseline at the completion of the study.

The pooled results of two 8-week North American risperidone trials[11] compared the effects of risperidone, haloperidol, and placebo in 513 men and women diagnosed with chronic schizophrenia according to the DSM-III-R. Patients were randomly assigned to a fixed dose of 2, 6, 10, or 16 mg/day of risperidone, 20 mg/day of haloperidol, or placebo. Haloperidol and placebo were shown to reduce symptoms of anxiety and depression in schizophrenic patients on the PANSS scale. Risperidone was associated with significant improvement in the anxiety-depression items of the PANSS. Risperidone also demonstrated superior efficacy on the depression, anxiety, and tension items when compared with haloperidol. Risperidone, which was used at doses higher than those currently recommended, target doses of 4 to 6 mg/day for patients with schizophrenia, also demonstrated efficacy at the 2-mg/day level. (Table 1).

Table 1. Recommended Dosage for Atypical Antipsychotics in Schizophrenia[a]

Drug	Manufacturer's Recommended Dosage, mg/d	Administration
Clozapine	300–450	bid
Risperidone	2–6	Once daily
Olanzapine	10	bid
Quetiapine	300–400	bid or tid

[a]Data taken from package inserts.[18–21]

Negative Symptoms

While all antipsychotics show relief for positive symptoms of schizophrenia, it is unclear if they have the same effect on negative symptoms—affective flattening, alogia, and avolition. Atypical antipsychotics appear to be more effective than conventional agents in the treatment of negative symptoms.

The Leucht et al.[3] meta-analysis demonstrated the efficacy of a wide variety of atypical antipsychotics. The antipsychotics used in this study were olanzapine, risperidone, quetiapine, sertindole, and haloperidol. All antipsychotics demonstrated statistically significant reductions in negative symptoms from baseline compared with placebo. Olanzapine and risperidone were shown to be superior to haloperidol in the pooled results of atypicals compared with haloperidol. While many studies demonstrate some improvement in negative symptoms with conventional antipsychotics, the North American risperidone trials[11] reported an increase in negative symptoms among patients receiving haloperidol. Patients taking 2 mg/day or 6 to 16 mg/day of risperidone demonstrated a statistically significant reduction in negative symptoms.

Cognitive Function

Recent studies show that atypical antipsychotics may substantially benefit cognitive function of patients with schizophrenia and schizoaffective disorder. One review[12] described improvement in cognitive function among patients receiving clozapine, risperidone, and olanzapine. Clozapine was found to improve verbal fluency and attention. Evidence also indicates that clozapine may have the potential to improve some types of executive functioning and verbal learning and memory. Statistically significant improvements with risperidone were found on some measures of perceptual/motor processing, reaction time, executive function, working memory, verbal learning and memory, and motor function. Olanzapine was found to have significant efficacy in improving reaction time, executive function, verbal learning and memory, and verbal fluency.

Atypical and conventional antipsychotics may be similar in efficacy when treating the positive symptoms of schizophrenia, but atypicals have been demonstrated to be more effective when treating patients' mood and cognitive function. Negative symptoms, which conventional antipsychotics are not effective in treating, have also been shown to be improved with atypical antipsychotic treatment. However, the differences in their effect on negative symptoms are small and may not be apparent to clinicians.[5]

Safety

The efficacy of atypical antipsychotics is evident in long-term studies that show the improvement of patients' subjective well-being. Many antipsychotics provide relief

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from the symptoms of schizophrenia, but this relief comes with added health risks. Atypical antipsychotics provide safer alternatives to the typical agents that are associated with a higher risk of both reversible and persistent drug-induced movement disorders.

Symptoms of reversible drug-induced movement disorders include tremors, Parkinson-like symptoms, and akathisia.[13] One study[14] found that 75% of patients administered haloperidol developed akathisia within 1 week. Most patients with schizophrenia are prescribed antiparkinsonian medications to combat these side effects. However, studies[2,3] show a reduced amount of reported EPS and use of antiparkinsonian medications among patients prescribed atypical antipsychotics.

In the Leucht and coworkers meta-analysis,[3] haloperidol was found to have a higher risk of EPS as compared with atypical antipsychotics. The risk of EPS was statistically significant for haloperidol when rated against placebo. Risperidone, quetiapine, olanzapine, and sertindole were all found to be similar to placebo in the amount of antiparkinsonian medication needed for patients. Likewise, in the Csernansky et al. study,[4] rates of antiparkinsonian medication use were significantly higher with haloperidol than with risperidone.

My coworkers and I[11] conducted a study of risperidone and haloperidol and also found the risk of EPS higher among patients taking haloperidol. The risk of EPS was measured by the Extrapyramidal Symptom Rating Scale and the number of patients receiving antiparkinsonian medication. Patients receiving 16 mg/day of risperidone and haloperidol demonstrated a higher risk of suffering from EPS compared with those taking placebo. Patients receiving 6 mg/day of risperidone displayed EPS similar to those of patients receiving placebo.

Even the Geddes et al.[2] study recommended the use of atypical antipsychotics for treating schizophrenic patients suffering from reversible motor side effects. Risperidone at 4 to 16 mg/day was found to lessen the likelihood of dystonia and dyskinesia when compared with haloperidol. Sertindole was also found to have a 16% reduction in akathisia over 10 mg/day of haloperidol.

Persistent drug-induced movement disorders such as tardive dyskinesia are other side effects of antipsychotic medication. TD can be defined as continuous rhythmic movements, and it has been estimated that about 4% to 5% of the younger patient population will develop TD with conventional antipsychotics.[15] The percentage of patients suffering from TD increases with patients' age.[16] However, atypical antipsychotics have been shown to reduce the number of patients suffering from TD.

In a 9-month open-label study, Jeste and colleagues[16] observed patients with TD who took either haloperidol or risperidone. Sixty-one risperidone patients were matched with 61 haloperidol patients. The patients had to meet 3 TD risk factors: age (mean age was 66.2 years for patients taking risperidone and 66.1 years for patients taking haloperidol), diagnosis (patients had to be diagnosed as requiring neuroleptic drugs based on the DSM-III-R or DSM-IV scale), and length of exposure to a neuroleptic (minimum exposure was 1 month). Researchers measured TD through the Abnormal Involuntary Movement Scale, modified Simpson-Angus Scale for EPS, 18-item BPRS, and the Mini-Mental State Examination. At the conclusion of the trial, haloperidol-treated patients showed a higher risk for TD than risperidone-treated patients.

Another study, involving clozapine, included patients who specifically suffered either from schizophrenia or from schizoaffective disorder.[17] Patients who could not tolerate or did not respond to conventional agents were switched to clozapine. Twenty-eight patients, without a history of TD, were treated for 1 year and measured with the Simpson Dyskinesia Scale. Only 2 of the 28 patients were diagnosed with mild TD at the end of the study.

The low rates of reversible and persistent motor side effects, such as EPS and TD, with atypical antipsychotics indicate that these agents may provide improved treatment over the long term for patients suffering from schizophrenia. Safely dosing these agents can help minimize adverse effects.

CONCLUSION

The goal in treating schizophrenia is to find a medication regimen that will not only treat the obvious symptoms of the illness but will also promote improvement in the way patients feel. Research comparing older and newer antipsychotics in areas such as relapse prevention, neurocognition, subjective response, and tolerability strongly support the use of atypical antipsychotics.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperidal).

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

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