Treatment of Special Populations With the Atypical Antipsychotics

Collaborative Working Group on Clinical Trial Evaluations

Atypical antipsychotics have become the treatment of choice for patients experiencing a first episode of schizophrenia. In addition, they are often prescribed for conditions such as bipolar disorder and dementia. While clinical trials have not yet established the efficacy of the atypical antipsychotics for these uses, a number of reports offer preliminary evidence that the atypical antipsychotics may be beneficial for affective disorders, substance abuse disorder, senile dementia, and pathologic aggression. Atypical agents may be particularly effective and tolerable in elderly patients who are especially susceptible to the adverse effects of conventional antipsychotic medication. Lower dosages are more necessary for the elderly than for younger adults. Current evidence suggests that clozapine is the most effective atypical antipsychotic for neuroleptic-resistant patients. Risperidone, olanzapine, and quetiapine may also be effective in a subset of these patients.

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The atypical antipsychotics—clozapine, risperidone, olanzapine, and quetiapine—are rapidly becoming the treatments of choice for schizophrenia. Most of these new medications offer distinct advantages over conventional neuroleptics, including improvement in negative symptoms, fewer extrapyramidal symptoms, and less tardive dyskinesia, as well as a reduction of other adverse effects. Among the novel neuroleptics, risperidone and olanzapine have become the first-line treatment for schizophrenia in many a clinician's armamentarium. Clozapine is approved for treatment-resistant and neuroleptic-intolerant schizophrenia only; however, 30% of patients with schizophrenia are treatment-resistant even by narrow criteria, and many of these patients respond better to clozapine than to olanzapine or risperidone and should be given a trial of clozapine. Quetiapine, introduced in 1997, is also indicated to be a first-line drug.

The remarkable effectiveness of the atypical antipsychotics in the treatment of schizophrenia tends to overshadow the fact that only 33% of risperidone prescriptions are written for schizophrenic patients; the remainder of these prescriptions are written for patients with illnesses such as bipolar disorder, dementia, and other medical conditions (Figure 1).

Like the other atypical antipsychotics, risperidone (introduced in 1994) and olanzapine (introduced in 1996) have been on the market for a comparatively brief period. Clinical trials of sufficient number and precise enough focus to answer important questions dealing authoritatively with off-label use have not yet been conducted. Nevertheless, a number of reports offer suggestions of the effectiveness of atypical antipsychotics in a variety of medical conditions considered off-label (Table 1).[1] Because there are few studies examining the efficacy of olanzapine and quetiapine in off-label use, this paper will examine such use and the evidence supporting it only for clozapine and risperidone.

PATIENTS WITH AFFECTIVE DISORDERS

Affective disorders have traditionally been treated with antidepressants, but there is evidence to suggest that the atypical antipsychotics like risperidone that target 5-HT_2 receptors may also be effective in treating mood symptoms. Keck et al.[2] conducted a retrospective chart review to identify predictors of risperidone response in patients with schizophrenic, schizoaffective, and psychotic mood disorders. They examined the records of 144 patients who had received at least 2 weeks of risperidone treatment; each patient had been diagnosed with schizophrenia, schizoaffective disorder, bipolar disorder, or major depression with psychotic features, according to DSM-III-R criteria. They found that the therapeutic effects of risperidone were in evidence more often in younger, less chronically ill patients than in their older, more chronically ill counter-

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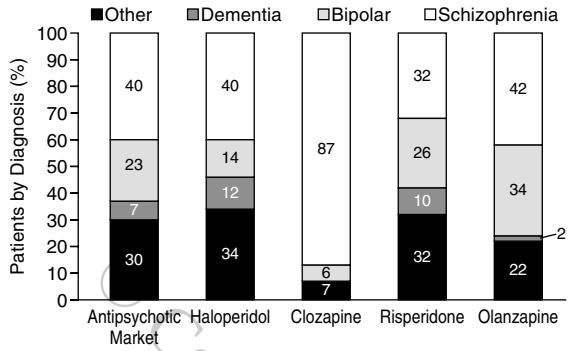
Figure 1. Antipsychotic Market Distribution by Diagnosis*



*Data from IMS America/NDTI, October 1997.

Table 1. Off-Label Uses of Atypical Antipsychotic Drugs*

Bipolar disorders[a]
Psychotic depression[a]
Dementia[a]
Drug-induced psychoses
Delusional disorder
Parkinson's disease[a]
Psychoses not otherwise specified
Brain injury
Delirium
Obsessive-compulsive disorder
Personality disorders (particularly schizotypal and borderline)
Mental retardation
Stuttering
Pervasive developmental disorders

*Data from reference 1.
[a]Clozapine efficacy established.

parts. Patients with schizoaffective disorder, depressive type, responded to risperidone more often than patients with schizophrenia, whose response, especially if they had been hospitalized for more than 1 year, was poor. Even so, 11% of inpatients hospitalized for more than 1 year and 26% of inpatients hospitalized for more than 10 weeks improved while taking risperidone. While this response rate is less than the 30% to 40% of treatment-refractory patients reported to respond to clozapine, 5 patients who responded to risperidone had been unresponsive to clozapine.

Tohen and Zarate[3] reviewed studies of the effectiveness of risperidone as a treatment for bipolar disorder. Hillert et al.[4] first found evidence that risperidone might reduce psychotic and affective symptoms in patients diagnosed with DSM-III-R major depression with psychotic features or schizoaffective disorder, depressive type. Singh et al.[5] and Gilmer et al.[6] found positive results in risperidone-treated patients with HIV-related manic psychosis. Sajatovic et al.,[7] however, found no improvement in 5 risperidone-treated schizoaffective bipolar patients.

PATIENTS WITH SUBSTANCE ABUSE DISORDER

Misra and Kofoed[8] report the case of Mr. A, a 45-year-old man who had been taking methamphetamine for 12 years. Four months before hospitalization, he experienced hallucinations, his first psychiatric symptoms. He was hospitalized for 3 days after he drove his truck through fresh concrete at the behest of accusatory and command auditory hallucinations, which also urged him to stop using cigarettes and methamphetamine. After being released, Mr. A continued to experience auditory hallucinations and to complain of insomnia, impulsivity, and paranoia. He displayed a neutral mood and constricted affect. His thoughts were disorganized and blocked. A mental and physical examination disclosed depression, disorganized thinking, avoidance, and alienation but no clinically significant organic disorder. Mr. A consented to take 1 mg of risperidone b.i.d. His hallucinations, delusions, and paranoia diminished within 3 days. After 1 week, he showed improvement in mood, affect, organization of thought, delusional beliefs, memory, attention, insight, and judgment. Auditory hallucinations and delusions stopped after risperidone was increased to 1.5 mg b.i.d. Two weeks into treatment, when Mr. A stopped taking risperidone, the auditory hallucinations returned. He craved methamphetamine and resumed smoking. One week later he resumed risperidone treatment, and the hallucinations and craving for methamphetamine quickly stopped. His insomnia, impulsivity, and anhedonia also improved. With increases in amphetamine use since 1991 particularly in mind, the authors suggested further investigations.

Smelson et al.[9] performed an open preliminary study to investigate whether cocaine-withdrawn patients taking risperidone would evince more neuropsychological improvement than a cocaine-withdrawn control group. Of 24 cocaine-withdrawn patients, 13 were administered a battery of psychological tests—the Digit Symbol subtest from the Wechsler Adult Intelligence Scale–Revised, Trails Part A and B, and the Grooved Peg Board Test—and invited to begin taking risperidone. Eleven patients were administered the same tests but were not offered risperidone; these patients acted as a control group. Both groups were retested after 7 days.

The first 1 mg/day dose of risperidone was titrated to at least 1 mg b.i.d. but no more than 2 mg b.i.d. While the control group showed no significant differences from baseline to follow-up, the group taking risperidone showed significant improvement from baseline to follow-up on mean scores of the Digit Symbol ($p < .01$), Trails part A ($p < .001$), and Grooved Peg dominant ($p < .003$) and nondominant tests ($p < .002$). This open study found improved neuropsychological impairment in withdrawn cocaine-dependent patients taking risperidone. Further studies should address the potential of risperidone for improving cognitive deficits accompanying cocaine abuse

with larger samples, random assignment of subjects, placebo controls, more detailed neuropsychological tests, and biological measures.

ELDERLY PATIENTS

A group particularly susceptible to the adverse effects of conventional antipsychotic medications, the elderly population presents special problems to the clinician. Unwelcome side effects can include falls and fractures resulting from orthostatic hypotension, delirium, acute extrapyramidal symptoms or tardive dyskinesia, and anticholinergic side effects, including urinary retention, constipation, or acute glaucoma.[10]

In their survey of the treatment of late-life psychosis, Zayas and Grossberg[11] evaluated the efficacy of clozapine. Seven of 12 patients discontinued the medication. Patients taking clozapine must have their cellular blood counts monitored regularly; total white count and neutrophil count must be monitored as well. The authors recommend that patients fail 2 trials of conventional antipsychotics before beginning a regimen of clozapine.[11] Pitner et al.[12] found that 2 of 4 patients with psychotic symptoms found relief from these symptoms with clozapine, although falls, symptomatic bradycardia, and delirium were observed side effects. Oberholzer et al.,[13] evaluating 18 patients with dementia, reported that 4 patients discontinued clozapine because of side effects. In their study of elderly women, Chengappa et al.[14] found a better response to clozapine than to typical antipsychotics in 2 patients. They reported the most common side effects as postural hypotension, excess salivation, and sedation; 1 patient developed agranulocytosis.

Zarate et al.[10] examined a group of 122 hospitalized psychogeriatric patients with psychiatric diagnoses including dementia (52.5%), major depression with psychotic features (16.4%), bipolar disorder, manic or mixed, with psychotic features (13.1%), and schizophrenia (8.2%). Seventy-seven percent of these patients had at least one comorbid medical illness, which complicated their clinical management. Patients received a mean ± SD daily dose of 1.6 ± 1.1 mg of risperidone. It is important to note that, of the 117 patients who gave reasons for taking risperidone, 58.2% cited lack of previous response to other psychotropic medications. Results were evaluated using the 7-point Clinical Global Impressions-Improvement (CGI-I) scale: 46 (82.1%) of 56 patients diagnosed as having dementia with agitated or psychotic features were rated as "much improved," "improved," or "minimally improved." Overall, 23.6% of the patients were rated "much improved," 36.1% were rated "improved," 25.9% were rated "minimally improved," 10.2% were rated as "unchanged," 3.7% were rated "worse," 0.9% were rated "much worse," and 0% were rated "very much worse." Adverse effects, which occurred in 39 (32.0%) of the sample, included hypotension and new extrapyramidal side effects such as tremors, bradykinesia or rigidity, and akathisia. Twenty-two subjects dropped out due to adverse events or lack of efficacy. Zarate and colleagues found risperidone effective and generally well tolerated[10] in this group of elderly patients, noting that "there is little information regarding [risperidone's] effectiveness and safety in the elderly, particularly in the large population of psychogeriatric patients with comorbid medical disorders who require other medications."[10(p311)]

Madhusoodanan et al.[15] studied the safety of risperidone in 103 geriatric patients (mean age = 71 years) diagnosed with schizophrenia (75%) or schizoaffective disorder (25%). The patients started taking 0.5 mg of risperidone b.i.d., which could be increased to 3 mg/day during the first week and thereafter in increments of 0.5 mg b.i.d. to a maximum of 6 mg/day. Adverse events reported most often were dizziness (22%), insomnia (17%), agitation (15%), somnolence (15%), and injury (12%). Thirty-three percent of the patients were taking antiparkinsonian medication. Mean total and subscale Positive and Negative Syndrome Scale (PANSS) scores improved substantially, with patients receiving doses of less than or equal to 3 mg/day of risperidone improving more than those receiving doses of greater than or equal to 3 mg/day. The authors found that risperidone was well tolerated and effective in the population studied.

Thorpe[16] conducted a literature review of the treatment of psychotic disorders in late life. Symptoms such as delusions in late life can have a number of causes, from a primary psychotic disorder to another medical or psychiatric disorder. The prevalence of psychosis increases with age, disproportionately so among women, for a number of reasons, from age-related deterioration and cognitive impairment to the emergence of premorbid paranoid personality traits. Genetics plays a role, and the use of medications is a major contribution to psychotic disorders in the elderly. Many older people fail to seek mental health care for psychosis due to skepticism about the system and decreased physical mobility. Cognitive impairment can mean a decreased understanding of their treatment options.

Risperidone demonstrates strong binding at 5-HT_2 receptors and an affinity for D_2 receptors. It is well tolerated in the elderly. Compared with haloperidol, it has reduced risk of extrapyramidal side effects and tardive dyskinesia, to which the elderly are particularly susceptible. Add its low anticholinergic toxicity and the usefulness of risperidone in treating elderly patients is evident.

Particular treatment problems are presented to the clinician by Parkinson's disease in elderly patients. Dopaminergic agents are usually indicated, but these agents frequently cause psychotic symptoms. Agents that block dopamine, on the other hand, worsen mobility and tremor. Clozapine has proven effective in a number of cases. It is very well tolerated with regard to motor effects in this group,[17] but other side effects may limit its use. Risperi-

done has not been generally found to be tolerable in this population. The data are mixed with regard to olanzapine.

While noting limited success with neuroleptics in eradicating the hallucinations that accompany Charles Bonnet syndrome, Thorpe[16] suggests that risperidone may be more efficacious than conventional neuroleptics in treating this disorder. Howard et al.[18] report the successful treatment of this syndrome with low doses of risperidone.

Conventional antipsychotics will continue to play a role in the treatment of psychosis in the elderly, but must be used carefully and their effects closely monitored. The atypical neuroleptics, including clozapine and risperidone, may have a special role in particular patient populations. Clozapine is useful in treatment-resistant populations. The other atypical antipsychotics—risperidone and olanzapine—are alternatives for treating the geriatric population. All these drugs must be used cautiously in the frail and elderly population.

Dementia frequently affects the elderly population. Brecher et al.[19] conducted a multicenter, double-blind study testing the effects of risperidone on psychosis and aggressive behavior in patients with dementia. A total of 625 patients diagnosed with dementia of the Alzheimer's type, vascular dementia, or mixed dementia were treated with 0.5, 1, or 2 mg/day of risperidone for 12 weeks. While 52% of placebo patients were treatment responders on the basis of a reduction in BEHAVE-AD scores of 30% or greater, 53%, 60%, and 65% of patients receiving 0.5, 1, and 2 mg/day of risperidone, respectively, were also treatment responders. Risperidone (1 and 2 mg/day) also demonstrated an antiaggressive effect. Adverse effects occurred most often in patients taking 2 mg/day of risperidone; the frequency of adverse effects in patients taking 1 mg/day resembled that of the patients taking placebo. Brecher and colleagues concluded that risperidone substantially improved symptoms of psychosis and aggressive behavior in severely ill patients with dementia.[19] They further suggested that risperidone would be useful in outpatients with higher psychosis scores than those of the study group.

Bulow[20] reported on an 80-year-old man with Parkinson's disease, peptic ulcer disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, osteoarthritis, and prostate hyperplasia. Mr. A was taking both prescription (cimetidine, theophylline, glyburide, prazosin) and over-the-counter (ibuprofen, acetaminophen, and diphenhydramine) medications. His family brought him to the clinic after he became withdrawn, restless, and mistrustful of family and neighbors. Mr. A grew worse after he had been prescribed 0.5 mg b.i.d. of haloperidol and 0.5 mg lorazepam every 6 hours or as needed for agitation. He had difficulty walking, sustained frequent falls, and was verbally aggressive and abusive. Mr. A was then prescribed 0.5 mg of risperidone b.i.d. and was placed in a residential care facility. After 2 weeks, Mr. A's gait had improved, his paranoia had diminished, and the verbal abuse had stopped. After 2 additional months, the paranoia had resolved, and Mr. A's demeanor and interactions with other patients were improved. Risperidone was tapered, and the patient required no psychotropic medications 6 months later.

Clinical symptoms in late-life schizophrenia often confound conventional wisdom on the subject. The notion that positive and disorganized symptoms disappear in late life has been brought into question by several recent studies. Davidson et al.[21] found, for example, that the scores in the 40th percentile on the PANSS were registered by some of the oldest patients in their study. Jeste et al.[22] found that late-onset schizophrenia patients had more instances of paranoid subtype than the early-onset patients studied. In addition, late-onset patients exhibited higher levels of premorbid functioning than did early-onset patients.

OTHER OFF-LABEL USE

Fava,[23] conducting a review of the literature evaluating the psychopharmacologic treatment of pathologic aggression, pointed out that anger and pathologic aggression are phenomena common to a varied assortment of psychiatric and neurologic disorders. Because both human and animal models support the role of several systems of neurotransmitters in the modulation of aggression, researchers have investigated the effects of psychotropic drugs on this behavior. Czobor et al.[24] reported that risperidone may be useful for patients who show overt physical aggression. The authors examined the effects of risperidone, haloperidol, and placebo, as measured by the hostility item of the PANSS, in 139 patients with a diagnosis of DSM-III-R schizophrenia. They found that risperidone-treated patients had greater improvement in hostility unrelated to changes in psychosis than patients treated with the comparators.

Despite the wide use of conventional antipsychotics to treat aggression, little evidence supports their use in patients without active psychosis. For aggressiveness and hostility among patients with unipolar depression and anger attacks, antidepressants are the treatment of choice. As serotonin has been implicated in aggressive behavior, drugs that affect serotonin are strong candidates for treatment. Other drugs such as lithium, anticonvulsants, benzodiazepines, and β-blockers appear to be effective in different neuropsychiatric populations. Several drugs appear to be effective in the treatment of pathologic aggression, but polypharmacy and inconsistent results across conditions that have aggression as a common symptom complicate the identification of these agents. Further study, particularly of agents affecting the serotonergic system, is indicated.

TREATMENT-RESISTANT PATIENTS WITH SCHIZOPHRENIA

Green et al.[25] noted that even though the reduction of symptoms generally defines treatment success in schizo-

phrenia, new antipsychotic medications could potentially affect even neurocognitive deficits. They conducted a randomized, double-blind comparison of treatment with risperidone and haloperidol that assessed the verbal working memory of 59 treatment-resistant patients. Thirty patients received risperidone, and 29 received haloperidol. During the first 4 weeks of the study (the fixed-dose phase), patients received either 6 mg/day of risperidone or 15 mg/day of haloperidol. During the second 4 weeks, treating psychiatrists were allowed to adjust dosages in either direction. Verbal working memory, derived from 2 indices of the Digit Span Distractibility Test, was measured at baseline and after 4 weeks of both fixed- and flexible-dose treatment, under both distracting and nondistracting conditions. Risperidone treatment improved verbal working memory significantly more than haloperidol across testing conditions and study phases. When the effects of benztropine treatment, changes in psychotic symptoms, and changes in negative symptoms were controlled, the treatment effect remained significant ($p < .002$).

Risperidone treatment of schizophrenia appears to affect working memory more favorably than treatment with a conventional neuroleptic, and at least part of the difference appears due to the direct effect of the drug, possibly through antagonism of the 5-HT_{2A} receptor. The Green et al. study[25] suggested that future schizophrenia treatment goals could include improving neurocognitive abilities, which would improve the disease outcome. Harvey[26] pointed out that the deficits in cognitive functioning commonly associated with schizophrenia are generally thought to be a predictor of poor disease outcome, as cognitive impairments often accompany severe negative symptoms and impairments in adaptive functioning. Cognitive functioning deficits are thought to be caused by other features of the disease, such as severe hallucinations or delusions, poor motivation, or iatrogenic effects of treatment. However, the remission of positive symptoms after an acute episode is not accompanied by an improvement in cognitive functioning.

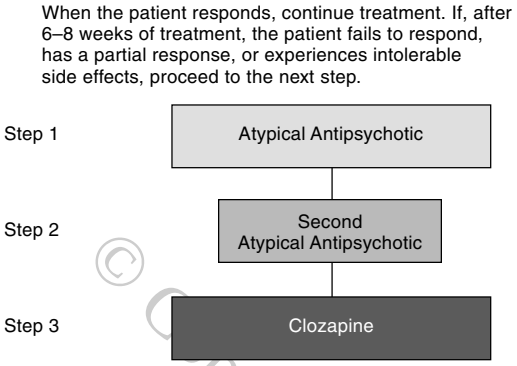
Clozapine, as noted earlier, is eschewed as a first-line treatment option because of potentially fatal side effects. However, the agent is efficacious for treatment-resistant schizophrenia and is in fact only indicated for such patients.[27] There is evidence to suggest that risperidone may be effective in treating refractory patients. Smith et al.[28] studied 25 schizophrenia patients who had been hospitalized more than once, had been inpatients treated with conventional neuroleptics for at least 1 year during the current hospitalization, and who had severe positive and/or negative symptoms of schizophrenia nonetheless. Patients began taking 1 mg of risperidone b.i.d., increased to 3 mg b.i.d. The dose was raised for nonresponding patients, usually over 2 to 6 months, to a maximum of 16 mg/day of risperidone. The Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Positive Symptoms (SAPS), and Scale for the Assessment of Negative Symptoms (SANS) were used to obtain psychopathology ratings at baseline and during risperidone treatment. Comparison of endpoint rating scores to baseline scores demonstrated significant decreases in both the BPRS total scores ($p < .05$) and the BPRS psychosis factor scores ($p < .05$). At endpoint, 4 patients not only achieved BPRS scores 20% lower than baseline but also were rated "much improved" on the CGI scale by their primary psychiatrist. The BPRS scores of 9 patients were at least 20% lower than at baseline. The authors found that the percentage of patients in this chronic nonresponding population who improved during risperidone therapy in this study was apparently similar to that of chronic nonresponders who improved during clozapine therapy in other studies.

Bondolfi et al.[29] found that risperidone is as effective as low to medium doses of clozapine in patients with chronic schizophrenia who had been resistant to or intolerant of conventional neuroleptics. They compared the 2 agents in an 8-week study of 86 inpatients with a diagnosis of DSM-III-R schizophrenia. The final mean clozapine dose was 291.2 mg/day, and the final mean risperidone dose was 6.4 mg/day. Both agents significantly reduced the severity of psychotic symptoms. At endpoint, 67% of the risperidone-treated patients and 65% of the clozapine-treated patients had a reduction of 20% or more in the total PANSS score. The onset of action for risperidone appeared to be faster. However, it is not clear whether the patients in this study were as refractory as those usually included in such trials. Findings were similar in a preliminary study.[30] Risperidone was also reported to be more efficacious than haloperidol in improving symptoms in treatment-refractory patients with schizophrenia.[31] Additional controlled comparisons of clozapine and risperidone in neuroleptic-resistant patients are needed.

FIRST-EPISODE PATIENTS WITH SCHIZOPHRENIA

Patients who present with a first episode of schizophrenia must be carefully assessed at baseline for abnormal movements, as these may later be mistaken for drug-induced extrapyramidal side effects (EPS). EPS are a bothersome problem among patients treated with the conventional antipsychotics; EPS can be treated with anticholinergic medications, but these drugs themselves also cause adverse effects that may lead to patients discontinuing the regimen. Kopala[32] reported recent clinical experience in Canada showing risperidone to be effective in treating patients with first-episode psychosis. These patients also experienced a low incidence of extrapyramidal symptoms; fewer than 10% required anticholinergic medication. Kopala[33] pointed out that since EPS can be very uncomfortable, patients who have never taken antipsychotic drugs before should be started on a drug such as risperi-

Figure 2. Algorithm for the Treatment of First-Episode Schizophrenia



done, so that they do not become noncompliant due to the adverse consequences of their treatment. The dosing of risperidone in first-episode patients is usually lower than that in chronic patients,[33] with a mean of about 4 mg/day.[32]

A retrospective study by Zarate and colleagues[34] suggested that olanzapine is more effective in patients with a shorter duration of illness and shorter length of stay prior to treatment with olanzapine. The authors found olanzapine more likely to exert a substantial therapeutic effect, documented as moderate-to-marked response, in younger, less chronically ill patients.

ALGORITHM

Many clinicians have searched for an algorithm, which has been elusive, to guide them in treating first-episode schizophrenia patients. The atypical antipsychotics are much more expensive than conventional neuroleptics. Cost considerations have led some health care agencies to demand that patients be treated first with conventional antipsychotics; patients become candidates for atypical antipsychotics only if they fail to respond to the first-line treatment or if they develop severe side effects. Lieberman, however, suggested that while it may seem more cost-effective to prescribe less expensive conventional antipsychotics over the considerably more expensive atypical antipsychotics, a longitudinal perspective will reveal that, over the course of a patient's lifetime, "the rationale for using atypical antipsychotic drugs as a first-line treatment in patients, from the onset of illness, becomes apparent."[35(p70)]

We recommend that first-episode patients with schizophrenia be treated at onset with an atypical antipsychotic other than clozapine. The atypical antipsychotics offer advantages in negative and affective symptom response rates and in side effect rates. Side effects of the conventional neuroleptics may lead to enduring patient noncompliance, so an atypical antipsychotic should be administered initially. If this first treatment fails after an adequate trial (6–8 weeks), another atypical antipsychotic medication should be the second choice. After 2 failures, clozapine is definitely indicated (Figure 2). Controlled trials are needed to determine the proportion of nonresponders to initial trials with risperidone, olanzapine, or quetiapine who go on to respond to a second trial of another of these 3 agents. If it is not a high proportion, it may be safest and most cost-effective to go to clozapine as the second trial agent.

CONCLUSION

The atypical antipsychotics show great promise for treating the special populations who have illnesses comorbid with schizophrenia or who have certain unrelated illnesses, including affective disorders, and the medical and psychiatric illnesses that too often accompany old age.

Drug names: clozapine (Clozaril), cimetidine (Tagamet), glyburide (Micronase, DiaBeta, and others), haloperidol (Haldol and generic brands), lorazepam (Ativan and generic brands), olanzapine (Zyprexa), prazosin (Minipress), quetiapine (Seroquel), risperidone (Risperdal), theophylline (Pemophyllin).

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DISCLOSURE OF OFF-LABEL USAGE

The following off-label uses of the atypical antipsychotics clozapine, risperidone, olanzapine, and quetiapine were discussed: Parkinson's disease, bipolar disorder, drug-induced psychosis, delusional disorder, organic brain disease, senile dementia, pathologic aggression, substance abuse disorder, obsessive-compulsive disorder, personality disorders, stuttering, pervasive developmental disorders.