

# Clinical research

## *Treatment of the special patient with schizophrenia*

*Robert R. Conley, MD; Deanna L. Kelly, PharmD, BCPP*



*Special patient populations with schizophrenia have received little attention. These populations include adolescents, the elderly, substance abusers, and patients who are considered treatment-resistant. Interest in these populations is rapidly growing, especially with regard to their treatment with second-generation antipsychotics. This article describes the treatment of special patient populations and summarizes the research that has been done in this field.*

**M**any advances have been made in the past decade in the treatment of schizophrenia. There have also been advances in the understanding the etiopathophysiology of schizophrenia, with much work studying neurochemical, neuroanatomical, genetic, and post-mortem domains. New research has focused on early detection of schizophrenia, cognitive impairments, and improving long-term outcomes for patients who suffer from this devastating illness.<sup>1-3</sup> Progress has been particularly due to a new class of medications the second-generation antipsychotics (SGAs), which have become available in the last 7 years. However, despite these research efforts, there is still a great deal that we do not know about schizophrenia. Most studies and clinical tri-

als involve participation of adults (18–65 years) who do not have substance-abuse problems and are free from other concomitant disease states, medications, and other symptom domains. Therefore, although it is a growing area, clinical research and understanding of optimal treatment for special patient populations has received little recognition.

This paper will review the current state of treatment for schizophrenic patients who are considered to be in special patient populations; these include children and adolescents, the elderly, substance abusers, and patients who are considered to be resistant to traditional medications.

### **Treatment of schizophrenia in adolescents**

Epidemiological data show that 10% to 30% of patients with schizophrenia develop their first psychotic symptoms prior to their 18th birthday.<sup>4,6</sup> Onset before the age of 18, but beyond puberty is sometimes classified as early-onset schizophrenia or intermediate-onset schizophrenia and those presenting with symptoms before the ages of 12 to 14 years (prepubertal) are labeled as patients with very-early-onset schizophrenia or as having childhood-onset schizophrenia.<sup>7</sup> More male adolescents (2:1) may develop very-early-onset schizophrenia than females; however, the overall prevalence at this young age is very low: 1/10 000.<sup>8</sup>

The diagnosis of schizophrenia in children and adolescents is often difficult to make and should be differentiated from pervasive developmental disorders, attention-deficit/hyperactivity disorder, and language or communication disorders. If a child has prominent hallucinations or delusions, however, the diagnosis of schizophrenia should be considered. Auditory hallucinations are common and occur in approximately 80% of chil-

**Author affiliations:** University of Maryland School of Medicine, Department of Psychiatry, Maryland Psychiatric Research Center, Baltimore, Md, USA

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**Address for correspondence:** Deanna L. Kelly, PharmD, BCPP, Assistant Professor, University of Maryland School of Medicine, Department of Psychiatry, Maryland Psychiatric Research Center, PO Box 21247, Baltimore, MD 21228, USA (e-mail: dkelly@mprc.umaryland.edu)

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## Selected abbreviations and acronyms

<b>AD</b>	<i>Alzheimer's disease</i>
<b>BPRS</b>	<i>Brief Psychiatric Rating Scale</i>
<b>EPS</b>	<i>extrapyramidal side effect</i>
<b>PANSS</b>	<i>Positive and Negative Syndrome Scale</i>
<b>PD</b>	<i>Parkinson's disease</i>
<b>SGA</b>	<i>second-generation antipsychotic</i>
<b>TD</b>	<i>tardive dyskinesia</i>

dren and adolescents with schizophrenia. Command hallucinations are the most frequently occurring type of hallucination. The content and context of delusions in children and adolescents are varied by age with younger children tending to be less complex and less "fixed."<sup>9-10</sup> Some 54% to 90% of patients developing schizophrenia before age 18 will have premorbid abnormalities such as withdrawal, odd traits, and isolation.<sup>11,12</sup>

Treatment for psychotic children and adolescents ideally involves an intensive and comprehensive program. A highly structured environment with special education and psychoeducation is recommended. Day treatment, hospitalization, or long-term residential treatment may be necessary. Pharmacologic treatment is indicated if positive psychotic symptoms cause significant impairments or interfere with other interventions. Traditional antipsychotics have modest efficacy in children and adolescents at doses between 10 to 200 chlorpromazine equivalents. Few studies with the conventional antipsychotics have been published in this population. Three controlled clinical trials to examine the safety and efficacy in children and adolescents with schizophrenia have been published.<sup>13-16</sup> The low-potency agents should be particularly avoided in this population because of sedation and anticholinergic side effects, which may lead to cognitive dulling and interference with schoolwork. Children and adolescents are also more vulnerable to extrapyramidal side effects (EPS), namely dystonias, than adults.<sup>13,15,16</sup> Due to concerns with EPS and tardive dyskinesia (TD) in this group, many children and adolescents are initiated on SGAs and traditional agents are not generally used as first-line therapy.

Several open trials and case series have reported the use of clozapine in children and adolescents for the treatment of schizophrenia.<sup>17-21</sup> Kumra et al<sup>22</sup> compared clozapine with haloperidol in a double-blind fashion in patients aged 6 to 18 with a poor response to antipsy-

chotics. The dosage of clozapine ranged from 25 to 525 mg/day with a mean dosage of 176 mg/day. Clozapine was found to be superior to haloperidol and particularly beneficial for negative symptoms. Although most young patients have improvement during clozapine therapy, side effects in this population may be more pronounced and frequent than in adults. The most prominent symptoms seen are somnolence, hypersalivation, and weight gain. Children and adolescents tend on average to gain more weight than reported in the adult literature. Mean weight gains are up to 7 kg in 6 weeks.<sup>17</sup> Seizures have been reported and may be more frequent than the 3% to 6% prevalence in adults. The risk for agranulocytosis appears to be similar to adults. Children and adolescents who have been found to be resistant to at least two trials of antipsychotics including another SGA may benefit from a trial of clozapine, but it should be used only as a last resort therapy. Young patients should be treated initially with lower doses than adult patients and be titrated at a slower rate. Side effects should be monitored closely during initiation and throughout maintenance therapy. Enuresis may occur with clozapine and often occurs at higher rates in children and adolescents.

The number of published reports of the use of risperidone in children and adolescents has been growing rapidly in the past couple of years. Several reports of risperidone use for patients with pervasive developmental disorders have been published.<sup>23-26</sup> Additionally, many recent publications cite risperidone use for conduct disorder, aggression, bipolar disorder, developmental disabilities, and obsessive compulsive disorder.<sup>27-34</sup> Studies and reports for the treatment of schizophrenia, however, are rare. Armenteros et al<sup>35</sup> published a short-term, open-label study for 10 adolescents with a diagnosis of schizophrenia. Although responses similar to the adult population were seen, the mean dosage used was very high, 6.6 mg/day (range 4–10 mg/day), and well beyond what is currently used clinically for adolescents and adults alike. All other reports for patients with schizophrenia, to our knowledge, have been case reports and chart reviews. Dosing of risperidone in current reports in diseases other than schizophrenia generally use initial dosages of 0.25 to 0.5 mg/day and stabilize patients on dosages of 1.5 to 3 mg/day. Risperidone is known to cause EPS in adults as dosing increases above 6 mg/day.<sup>36</sup> Because young patients are more susceptible to these effects and optimal efficacy is known to occur at lower

doses,<sup>37</sup> the dosage of risperidone for the treatment of schizophrenia in children and adolescents should be in the range of 0.5 to 4 mg/day.

Children and adolescents more often report tiredness and sedation with risperidone treatment than adults.<sup>32</sup> Also unlike the adult population, there have been a few reports of stereotypies and elevations in liver enzymes occurring.<sup>24,38</sup> Other side effects, apart from weight gain, are usually mild and similar to the adult population. Weight gain has been fairly well documented in the adolescent population and appears more pronounced than in adults. Kelly et al<sup>39</sup> reported mean gains of 8.7 kg over 6 months of treatment with risperidone—significantly more than that of traditional antipsychotics (3.0 kg) or no antipsychotic (-1.0 kg) during the same period. Martin and colleagues<sup>40</sup> reported clinically significant weight gains in 78% of children and adolescents treated with risperidone compared with 24% in a comparison group; the average weight gain was 1.2 kg/month. Risperidone is known to cause the greatest prolactin elevations of the SGAs dependent on both dose and dopamine D<sub>2</sub> receptor occupancy.<sup>41</sup> At higher doses, there have been reports of menstrual irregularities occurring in young patients<sup>42</sup> and galactorrhea has occurred in both sexes during clinical treatment. When side effects occur, lowering the dose of risperidone has often been found to be effective.

Olanzapine, like risperidone, has been widely studied in adult populations,<sup>43</sup> but data for adolescents with schizophrenia are scarce. The only study in the adolescent schizophrenic population<sup>44</sup> reported an open trial of olanzapine in patients aged 10 to 17 years. The mean dosage was 17.5 mg/day and the side effects reported included weight gain, increased appetite, anticholinergic side effects, and sedation. Difficulty concentrating, sustained tachycardia, headache, nausea and vomiting, and transient liver elevations were also reported in this study. Although not comparatively studied, olanzapine treatment in young populations appears to cause greater weight gains than risperidone: Potenza<sup>45</sup> reported over 8 kg in only 12 weeks of treatment. Unlike the transient rise and fall in the adult population, a recent report found sustained prolactin elevation in 70% of children and adolescents treated with olanzapine, but little has been published regarding clinical side effects of this phenomenon.<sup>46</sup> The mean dosages being used in the adolescent population are between 5 and 20 mg/day. It is not yet clear what is the ideal dose range for olanzapine in this group.

There is one open-label trial of quetiapine in adolescents with psychotic disorders reporting an improvement from baseline in both positive and negative symptoms. The most commonly occurring side effects were postural tachycardia and insomnia.<sup>47</sup> Currently, little is known about the most appropriate dosing for this population. Dosages of 200 to 800 mg/day are being reported. More research is needed to ascertain the safety and dosing of quetiapine, especially in the young population.

SGAs show great promise in the treatment of psychotic symptoms in patients who are under the age of 18 for symptom improvement and tolerability. Dosing for clozapine and risperidone in particular should be initiated and maintained at doses lower than the adult population. All of the SGAs appear to cause weight gain in the adolescent population, which is the biggest drawback to their routine use; this appears to occur most often with olanzapine and clozapine. Informed consent, addressing the rationale for treatment and potential risks and benefits of therapy, should be obtained from the parents/guardians prior to treatment with any antipsychotic medication and assent should be obtained from the children. Standardized clinician rating, such as the Positive and Negative Syndrome Scales (PANSSs) derived from the Children's Psychiatric Rating Scale, is sensitive to antipsychotic improvements in children and adolescents, and can be helpful in assessing the effects of antipsychotic therapy.

### Treatment of psychosis in the elderly

Schizophrenic symptoms in late life (>65 years) are generally a result of a chronic illness carrying over from younger life; however, few patients may develop psychotic symptoms *de novo*.<sup>48</sup> Data from the Epidemiological Catchment Area Study<sup>49</sup> showed 6-month prevalence rates of schizophrenia in the elderly to be 0.2% to 0.9%. Other illnesses displaying psychotic symptoms are extremely high in this population: 0.1% to 1.6% for psychotic depression and 16.8% to 23% for organic psychosis.<sup>49</sup> Additionally, approximately one third of patients with Alzheimer's disease (AD), Parkinson's disease (PD), and vascular dementia experience psychotic symptoms and the majority of data for antipsychotic use come from treating these disease states.<sup>50-53</sup>

For institutionalized patients, antipsychotics are the most widely prescribed psychotropic drugs.<sup>54</sup> Because of the

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widespread and unnecessary use of these agents in the US for this population in the past, Congress passed regulations governing use in 1987 with the Omnibus Budget Reconciliation Act of 1987 (OBRA-87) and the Nursing Home Reform Amendments administered by the Health Care Financing Administration (HCFA). These regulations developed specific standards for allowable dosages and indications for psychotropic drugs in regular and as required (PRN) use.<sup>55</sup>

Antipsychotics can be safe and effective for the treatment of psychosis if used at lower doses than commonly used in younger adults. Older adults are particularly vulnerable to the side effects of conventional antipsychotics. PD symptoms reportedly occur in over 50% of all elderly patients receiving these agents and the cumulative annual incidence of TD in middle-aged and elderly patients is over 25%.<sup>56</sup> The likelihood of reversing this potentially debilitating condition diminishes with age. Other adverse effects of these agents that are often intolerable in the older population include orthostatic hypotension and anticholinergic effects. Orthostasis is estimated to occur in 5% to 30% of geriatric patients and is a major contributing factor to the occurrence of falls.<sup>57</sup> The elderly are also more prone to the consequences of falls, such as bone fractures, injuries, and dependency. Low-potency antipsychotics and clozapine are more likely to cause significant drops in orthostatic blood pressure. Anticholinergic effects in the elderly may cause side effects, such as constipation, dry mouth, urinary retention, and cognitive impairment. The elderly are especially sensitive to these effects and the use of laxatives or stool softeners is already particularly high in nursing homes. Cognitive impairments may lead to decreased independence, and a more rapid decline in cognitive functioning may occur in the elderly treated with antipsychotics than in the younger adult population.

Clozapine has been used successfully in the elderly population at lower doses than adult patients. Mean dosages range from 50 to 300 mg/day with a much slower rate of titration. This may be a good choice for treating psychotic elderly patients with preexisting PD, because of its lower affinity for D<sub>2</sub> receptors in the striatum. Clinically, however, it is a poorly tolerated antipsychotic in geriatric patients and should be used with caution. The risk for agranulocytosis appears to be about 4% in the elderly population with older women being at highest risk.<sup>58</sup> The risk for seizure activity is increased in the elderly<sup>59</sup> and

sedation is one of the major reasons for discontinuation.<sup>60</sup> Clozapine therapy should be initiated at 12.5 to 25 mg/day given in two divided doses, titrating by increments of 12.5 mg over 5 to 7 days. Controlled studies examining the efficacy of clozapine in the elderly specifically for patients with schizophrenia are rare. Howanitz and colleagues<sup>61</sup> studied clozapine (maximum 300 mg/day) compared with chlorpromazine (maximum 600 mg/day) in a 12-week, double-blind fashion in patients with chronic schizophrenia. Patients on clozapine tended to do better than the chlorpromazine group, although this did not reach significance, probably due to the sample size.<sup>62</sup> Tachycardia and weight gain were problematic for clozapine-treated patients, while those treated with chlorpromazine were highly sedated. Clozapine should be used as a last resort in geriatric patients with schizophrenia and at least one trial of an SGA should be made first.

Risperidone has been shown to be effective in the elderly with schizophrenia, schizoaffective disorder, major depression with psychotic features, bipolar disorder, and delusional disorder. A dosage range of 0.5 to 3 mg/day is the optimal range for the treatment of psychotic symptoms in the elderly. Initially, patients should receive 0.25 to 0.5 mg taken once daily with titration in increments not greater than 0.5 mg/24 hours. A few recent, large, open-label studies with risperidone for geriatric patients with schizophrenia have been published. A 12-month, multicenter trial included 180 patients with a mean age of 72 years and found that 54% of patients had a 20% reduction in PANSS scores at a mean dosage of 3.7 mg/day.<sup>63</sup> Likewise, Madhusoodanan et al<sup>64</sup> found significant symptom improvements over 12 weeks in 103 elderly patients with schizophrenia or schizoaffective disorder. In these and other open studies, risperidone is well tolerated with the most common side effects being orthostatic hypotension and sedation. The rates of EPS are low if risperidone is used at low doses. Most elderly patients in the studies had decreased use of anticholinergic medications and improvements in EPS from baseline. The risk of TD with risperidone treatment is significantly less than conventional antipsychotic treatment in the geriatric population (4% versus 25%).<sup>63,65</sup>

Very little data exist for the treatment of schizophrenia in the elderly with olanzapine. Very few patients over 65 were included in premarketing trials and no controlled trials are yet available for this population. An open-label study of olanzapine 5 to 20 mg/day found



significant improvements in positive and negative symptoms in schizophrenic patients aged 60 to 85 years. Side effects were minimal and generally well tolerated. Another open trial giving olanzapine as an adjunct (mean dosage 8.4 mg/day) to current therapy found significant improvements in EPS; however, no significant improvements were noted on the Brief Psychiatric Rating Scale (BPRS).<sup>66</sup> Most other data available for olanzapine in the elderly relate to its use in AD and PD. While low-dose olanzapine appears well tolerated and effective for AD patients at dosages of 5 to 10 mg/day,<sup>67</sup> patients with PD suffer from unacceptable aggravation of parkinsonism even at low doses.<sup>68-73</sup> The starting dosage of olanzapine should be 2.5 to 10 mg/day and increased by 5 mg no more frequently than every 7 days to a target range of 5 to 15 mg/day in patients with schizophrenia and lower dosages for those with AD.

There are several reports of the use of quetiapine in the elderly for the treatment of psychosis with PD.<sup>74-78</sup> On the basis of both its receptor-binding affinity and its low liability for EPS clinically, it is a good first-line selection for this disorder and may be a option for patients who have been taking clozapine.<sup>79,80</sup> Dosages for psychosis associated with PD are generally 12.5 to 300 mg/day. No controlled studies are currently available for quetiapine use in patients with the diagnosis of schizophrenia only. Two open-label studies and one case series have been reported consisting of patients with a psychotic disorder associated with a mixture of diagnoses and found significant improvements in psychotic symptoms.<sup>81-83</sup> Somnolence, dizziness, and postural hypotension were the most frequently occurring adverse effects, but the majority of cases were considered mild to moderate. Weight gain and EPS occur at low rates with quetiapine use. Dosing for geriatric patients with schizophrenia is not well studied. Dosages used in reports averaged 100 to 150 mg/day, but these dosages were studied in a population with mixed diagnoses.

SGAs appear to be beneficial in the geriatric population at much lower doses than are used in adults. Because geriatric patients are often on many medications and suffer from numerous disease states, vigilance is needed when prescribing the newer medications. Clozapine and olanzapine are metabolized by the cytochrome P-450 isoenzyme 1A2, which may be inhibited by several medications, therefore leading to higher blood levels. This may be compounded in geriatric patients by their already compromised metabolism and

clearance of medications. Additionally, women may potentially be more prone to side effects, since the blood levels of both these medications are higher in women than men.<sup>84,85</sup> This population is particularly prone to falls and anticholinergic side effects, such as constipation, confusion, blurry vision, urinary retention, and dry mouth. All of these antipsychotics block  $\alpha$ -receptors leading to some orthostasis. Patients should be advised to stand or sit up slowly, especially upon medication initiation. Using lower doses and selecting the least anticholinergic of the medications helps prevent these other adverse effects.

Very little data comparing these medications with conventional agents or among SGAs are available. Quetiapine should be used as a first-line agent for psychosis associated with PD.

### Treatment of schizophrenia in patients with substance abuse

The prevalence of substance abuse among persons with schizophrenia is significantly higher than in the general population. Conservative estimates are that one third to as many as one half of people with schizophrenia abuse alcohol and illicit drugs.<sup>86,87</sup> Dually diagnosed patients are more likely to be noncompliant with treatment and medications particularly because of side effects. These people also have a poorer response rate to traditional antipsychotics and have higher rates of rehospitalization.<sup>88,91</sup> For patients discharged on traditional antipsychotics, substance abuse is one of the most significant reasons for readmission.<sup>92,93</sup> EPS may occur more frequently in patients who are substance abusing, and the use of illicit drugs and alcohol is a risk factor for the development of TD.<sup>94,95</sup>

There is evidence that substance-abusing patients respond differently to conventional antipsychotics than non-substance-abusing patients. A few studies have reported that substance-abusing patients receiving fixed doses of haloperidol and perphenazine had a poorer response and more readmissions than non-substance-abusing patients.<sup>89,91</sup> This is very likely due to the fact that the substance-abusers suffer increased rates of parkinsonian side effects from conventional antipsychotics and are less compliant. Substance-abusing patients usually have more floridly psychotic symptoms and higher relapse rates.<sup>88,90,96-99</sup> Despite the fact that substance-abusing patients do poorly with traditional

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antipsychotic treatment, this group has been found to have better premorbid functioning and less functional impairment than non-substance-abusing schizophrenic patients.<sup>100-102</sup> It is possible that, while this group is difficult to treat, they may paradoxically represent a subgroup with a better potential for recovery and perhaps a better opportunity for successful reintegration into community living.

SGAs may offer effective clinical treatment for schizophrenic patients with comorbid substance abuse. These medications are associated with better compliance rates than traditional agents as well as lower rates of rehospitalization.<sup>103-105</sup> Additionally, they have very little liability for causing TD. Unlike what has been observed during conventional antipsychotic treatment, it has been reported that treatment with clozapine is associated with similar response rates between patients with and without a history of substance abuse.<sup>100,106</sup> There is a rapidly growing body of literature indicating that clozapine treatment may actually be associated with a reduction in the use of illicit drugs and alcohol, but no double-blind, controlled studies are available.<sup>107-111</sup> Furthermore, clozapine has been given to cocaine addicts prior to an intranasal dose of cocaine and was noted to significantly diminish the effects of the cocaine as well as lessen the paranoia and nervousness associated with its use.<sup>112</sup>

There are no controlled data available for dually diagnosed schizophrenic patients treated with risperidone. There is no reason to believe, however, that this agent would not be a good selection in patients with schizophrenia and a current or past history of substance abuse. It possesses the favorable benefits of the SGAs particularly the lower recidivism and the risk for TD, which may be of benefit in these dually diagnosed patients. There are several case reports that risperidone is effective in substance abuse, such as amphetamine-induced psychosis, inhalant abuse, cocaine craving, metamphetamine-associated obsessive-compulsive disorder, and alcohol hallucinosis.<sup>113-119</sup> However, only one double-blind trial exists examining risperidone use for cocaine dependence, which found no reduction in cocaine use and low tolerability even at low doses.<sup>120</sup> Therefore, risperidone may offer benefits for the treatment of schizophrenic symptoms, but there is little evidence that it will curb drug use in this population.

The response to olanzapine in a population of schizophrenic patients with and without a history of substance abuse treated openly for 7 weeks was found to be sim-

ilar to that in a treatment-resistant population.<sup>95</sup> The substance-abusing population had higher rates of TD at baseline, which significantly improved during treatment. Olanzapine has been compared with haloperidol in a double-blind study for the treatment of cannabis-induced psychotic disorder. These patients did not differ in outcomes by drug group; however, those treated with olanzapine had fewer EPS during treatment.<sup>121</sup> Very little additional data are available for dually diagnosed patients treated with olanzapine. Likewise, few data are available for comorbid substance abuse and the treatment of schizophrenia with quetiapine.

Although the clinical reality of substance abuse among patients with schizophrenia is widely known, the relationship of these diagnoses and optimal treatments is neither well understood nor studied. Paradoxically, dually diagnosed patients have a better potential for recovery, but may have more symptomatology and side effects.<sup>122</sup> From the data available, this population of patients with schizophrenia will likely benefit more from an SGA than a conventional treatment, and should be expected to respond in the same way as those who are not abusing. Clozapine is the only antipsychotic among the SGAs that appears to provide additional benefits to this group by actually reducing cravings for and use of both illicit drugs and alcohol, but this needs to be studied in a controlled fashion.

## Treatment-resistant schizophrenia

One fifth to one third of all cases of schizophrenia are resistant to drug treatment. This finding has been consistent over time.<sup>123-125</sup> These patients are highly symptomatic and require extensive periods of hospital care.<sup>126</sup> There was a great deal of excitement following the demonstration of clozapine's efficacy in inpatients with treatment-resistant schizophrenia.<sup>127</sup> However, clozapine treatment carries with it a significant morbidity from serious side effects, the need for continual weekly blood monitoring, and a high cost. Many clinicians and patients hoped that other new antipsychotics would share clozapine's effectiveness without its most serious side effects, but no other antipsychotic in this group has clozapine's efficacy.

Commonly, treatment resistance has been considered to be roughly equivalent to chronic or frequent hospitalization.<sup>128-133</sup> This, by itself, is not an adequate definition.<sup>134,135</sup> Patients should also have current and persistent

positive symptoms of psychosis and at least moderate overall severity of illness in order for nonresponsiveness to apply,<sup>136</sup> as chronic hospitalization can occur despite low levels of symptoms.<sup>126</sup> Many people with schizophrenia who have been chronically hospitalized may not be truly resistant to drug treatment. Inadequate psychosocial programming, poor compliance with prescribed drug therapy, or a history of committing violence are all risk factors for chronic hospitalization.<sup>134</sup> Therefore, an optimized medication and treatment trial should be employed before a patient's illness is considered non-responsive. In addition, the effects of drug noncompliance and EPS can both mimic true treatment resistance.<sup>137,138</sup> At least a 1- to 2-year course of persistent symptoms should also be considered as one of the criteria for treatment resistance in schizophrenia, because of the waxing and waning course of this illness.

The most widely accepted current criteria for treatment resistance in schizophrenia were first used by Kane et al.<sup>127</sup> These criteria, modified for clinical use, are as follows:

- Persistent positive psychotic symptoms (item score  $\geq 4$ ) on at least two of four positive symptom items on the BPRS: hallucinatory behavior, suspiciousness, unusual thought content, or conceptual disorganization.
- Current presence of at least a moderately severe illness as rated by the total BPRS (score  $\geq 45$  on the 18-item scale) and a score of  $\geq 4$  on the Clinical Global Impression (CGI) scale.
- Persistence of illness: no period of good social and/or occupational functioning within the last 5 years.
- Drug-refractory condition defined as at least two periods of treatment in the preceding 5 years with appropriate doses of conventional or SGAs, each without clinically significant symptom relief.

The rates for two retrospective drug trial failures have been found to be similar to the rates for three when screening for treatment resistance; this fact is now widely accepted.<sup>138</sup> People not responsive to two adequate antipsychotic trials (one retrospective and one prospective) have less than a 7% chance of responding to another trial.<sup>139</sup> The Food and Drug Administration (FDA) guidelines for clozapine, as reflected in the product labeling for clozapine,<sup>140</sup> also states that people should fail to respond to two separate trials of antipsychotics, before being treated with clozapine.

It is generally recognized that a 4- to 6-week period (rather than strictly a 6-week one) is adequate for a treatment trial of an antipsychotic.<sup>141</sup> Dosages of  $>400$

mg/day of chlorpromazine have been shown to be adequate to block 80% to 90% of dopamine receptors (thought to be the target of this drug action).<sup>142</sup> Higher doses produce no direct therapeutic benefit, even in patients not responsive to therapy, and do not have greater efficacy in acute treatment than lower doses.<sup>143-145</sup> Therefore, two 4- to 6-week trials of 400 to 600 mg/day chlorpromazine or a chlorpromazine equivalent are now accepted as a standard for an adequate trial.<sup>138,146</sup>

Until the arrival of standardized criteria for defining treatment resistance, research into the neurobiological nature of the problem had been scant.<sup>147</sup> Recently, however, with the use of more objective criteria, some consistent findings have been seen. There is a relative paucity of data in this area and more research needs to be done. People with treatment-resistant schizophrenia appear to have increased cortical atrophy on magnetic resonance imaging (MRI) compared with those with responsive illness.<sup>148,149</sup> This was particularly true if they had predominant negative symptoms.<sup>150</sup> Lack of response to early treatment is also predictive of non-response.<sup>148</sup> The most intriguing finding about predicting which new drugs may be effective in treatment-resistant schizophrenia has been the fact that these people appear to have lower catecholamine levels in the cerebrospinal fluid (CSF).<sup>151</sup> Clozapine response has been associated with low ratios of CSF homovanillic acid to 5-hydroxyindoleacetic acid.<sup>152</sup> These findings suggest that drugs with low dopamine antagonism and high serotonergic antagonism may be particularly useful in treatment-resistant schizophrenia. Also, cognitive disorganization has recently been reported to be higher in patients with treatment-resistance than in those who are partial or full responders.<sup>153</sup>

Historically, drug therapy for treatment-resistant schizophrenia centered on the use of either different dose strategies of conventional antipsychotics or adjunct agents, such as lithium,  $\beta$ -blocking drugs, anticonvulsants, and benzodiazepines. Since the arrival of clozapine, attention in the field has shifted to a greater focus on the use of new antipsychotics for treatment resistance in schizophrenia. This interest occurred because of the demonstration of the superior efficacy of clozapine and the fact that new antipsychotics have been shown to have either significantly fewer side effects or improved efficacy compared with a conventional antipsychotic in order to be marketed in the USA. Conventional antipsychotic medications have worked poorly in this population and in

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controlled trials in people with drug-resistant symptoms, fewer than 5% responded after having their drug therapy changed from one conventional antipsychotic to another.<sup>127,154</sup> SGAs should be the first consideration after the failure of conventional drug therapy. These drugs are also effective as first-line therapy (with the exception of clozapine, because of its serious side effects).

Clozapine remains the only drug with proven efficacy in rigorously defined treatment-resistant schizophrenia and approximately 30% to 50% of treatment-refractory patients will respond to this medication.<sup>155</sup> However, fewer than 8% of new antipsychotic prescriptions are written for this medication in the USA. This phenomenon of relative underusage of clozapine probably relates to the costs and complexities of clozapine therapy. These arise from the need for long-term hematologic monitoring for agranulocytosis and persistent serious side effects present with clozapine, such as weight gain, sialorrhea, and sedation. The optimal dose strategy for clozapine is a slow dose escalation. Patients should be evaluated for response at dosage plateaus of 200 to 400 mg/day and 500 to 600 mg/day. Only patients with few side effects to clozapine should be titrated to dosages higher than 600 mg/day. Patients should not be titrated to a higher dose of clozapine if myoclonus is present, as this side effect may precede the development of seizures.<sup>156</sup>

Risperidone has been found to be more effective than conventional antipsychotics for positive and affective symptoms in patients with acute schizophrenia.<sup>36</sup> For patients with treatment resistance, the most rigorously defined double-blind trial found a 24% response rate to risperidone, compared with 11% for haloperidol after 4 weeks.<sup>157</sup> A few other double-blind studies have compared risperidone with clozapine and found similar response rates between drugs, but concerns about the inclusion criteria have been raised.<sup>158,159</sup> Another open study by Flynn et al<sup>160</sup> reported response rates to clozapine of 44%, compared with 28% to risperidone. It appears from the data available that risperidone is not associated with a clozapine-like response, but is associated with response rates of approximately 25%, higher than those of conventional antipsychotic treatments.

A few studies have reported favorable response rates to olanzapine in patients with treatment-resistant schizophrenia of 36% to 47%.<sup>161-163</sup> However, there is some controversy regarding these findings. These studies included patients who were considered treatment-resistant and those who were intolerant to clozapine. A study

by Conley et al<sup>164</sup> in well-characterized, treatment-resistant patients with schizophrenia found only a 7% response rate to olanzapine in this population and 41% of these treatment failures went on to respond to clozapine.<sup>165</sup> Likewise, an open trial of olanzapine in treatment-refractory patients reported no significant improvements in patients treated for at least 6 weeks on 10 to 20 mg/day.<sup>166</sup> Therefore, olanzapine does not have a pattern of response similar to clozapine in a well-characterized sample, but may offer a slightly better rate of response than traditional antipsychotic therapy.

Very little data on quetiapine use in treatment-resistant schizophrenia are available. A few brief reports suggest it may be beneficial to chronic or partial conventional responders<sup>167-169</sup>; however, no controlled trials for treatment resistance have been published.

If patients remain refractory to treatment after trials of SGAs, alternative therapies should be considered. Most of the data for adjunctive treatment are, however, limited and come from case reports and open trials.

Adjunct lithium therapy has been seen to be beneficial in some patients with treatment-resistant schizophrenia; however, these patients were often not defined by the rigorous criteria of later studies.<sup>123,129,170</sup> The published trials of adjunct lithium that are positive were conducted with small numbers of patients, and the criteria for defining treatment resistance were often not clear, or were overinclusive.<sup>171</sup> More recent reports have found no benefits with adjunct lithium therapy and fluphenazine decanoate.<sup>172</sup> A recent report of 5 male patients with schizophrenia treated with olanzapine showed significant improvements with the addition of lithium.<sup>173</sup> Lithium should be used with caution in combination with conventional antipsychotics or clozapine because of the recognized dangers of delirium, encephalopathy, and neurotoxicity that have been reported with these combinations.<sup>138,174,175</sup>

Carbamazepine and valproic acid have been observed to be effective in bipolar disorder<sup>176,177</sup> and are often considered as an adjunctive therapy in patients with schizophrenia. However, these trials included relatively few subjects. Positive effects seen with carbamazepine and valproate have been modest and usually involved non-specific improvement in areas such as behavior and social adjustment. Carbamazepine should be used with caution because it is a potent enzyme inducer and can also reduce the blood level of haloperidol by as much as 50%.<sup>178</sup> Carbamazepine should not be used in combination with



clozapine. There are few data for newer anticonvulsants; however, a few positive results were seen with lamotrigine adjunctive treatment with clozapine.<sup>179</sup>

Electroconvulsive therapy (ECT) for treatment-refractory schizophrenia has had favorable response in short-term trials when added to antipsychotic medications. However, in spite of more than five decades of widespread clinical use, the administration of ECT lacks a strong research base. A recent literature review<sup>180</sup> reports that about 20% patients will have improvement with this combination. Several recent case reports have noted improvements and controlled trials are currently underway.<sup>181-185</sup> The combined treatment with clozapine appears to be well tolerated and associated with few adverse effects. However, the issues of persistence of effect and long-term maintenance of these patients have not yet been adequately addressed.

Combined antipsychotic therapy has recently drawn some attention, as many patients (approximately 15%) currently are treated in this way.<sup>186</sup> While this use is growing, little research is available to support this treatment approach.<sup>187</sup> The most consistent data thus far come from a few case reports suggesting added improvements to clozapine treatment by the addition of risperidone.<sup>188-192</sup> Two cases of olanzapine addition to clozapine have reported favorable results.<sup>193</sup> There is report of the combined use of risperidone and olanzapine with success.<sup>194</sup> Other reports include the addition of pimozide, sulpiride,

and loxapine to treatment-resistant patients treated with clozapine.<sup>195-198</sup> The addition of an antipsychotic with D<sub>2</sub>-blocking abilities may enhance clozapine treatment in partial responders, but large-scale studies are needed.

Other adjunctive therapies reported are associated with very little data or have not been clearly found to be useful for treating symptoms of schizophrenia. There have been some reports of benzodiazepines,<sup>130,199</sup> but no clear benefits in symptoms other than associated anxiety have been found.<sup>128,131,200,201</sup> There are historical studies suggesting that  $\beta$ -blockers may be useful in refractory schizophrenia.<sup>135</sup> However, there are no available controlled studies using current diagnostic criteria. There is very limited evidence that long-term therapy with  $\beta$ -blockers is beneficial.<sup>202</sup>

A defined approach to patients with treatment-resistant schizophrenia is critical. As the antipsychotics being introduced today may have different mechanisms of action from conventional antipsychotics and from each other, clinicians will need to explore the possibility of response with each of these new agents in turn with their patients who suffer from persistently refractory symptoms. To date, clozapine is the only medication with demonstrated efficacy in treatment resistance. The differential efficacy of new drugs in treatment-resistant schizophrenia will only be clear when well-designed, double-blind studies using rigorous entry criteria are completed. □

### **Tratamiento del paciente especial con esquizofrenia**

*Las poblaciones de pacientes especiales con esquizofrenia han recibido poca atención. Estas poblaciones incluyen a los adolescentes, los viejos, los abusadores de sustancias y a los pacientes que se consideran resistentes al tratamiento. El interés en estas poblaciones ha sido de una rapidez creciente especialmente en relación con el tratamiento con antipsicóticos de segunda generación. Este artículo describe el tratamiento de las poblaciones de pacientes especiales y resume la investigación que se ha realizado en este campo.*

### **Traitement des populations particulières de patients atteints de schizophrénie**

*Les populations particulières de patients présentant une schizophrénie ont jusqu'ici reçu peu d'attention. Ces populations comprennent les adolescents, les patients âgés, les toxicomanes et les patients qui sont considérés comme résistants au traitement. L'intérêt que l'on porte à ces populations est en pleine expansion, en particulier pour ce qui est de leur traitement par les antipsychotiques de deuxième génération. Cet article décrit le traitement de populations particulières de patients et fait le point sur la recherche dans ce domaine.*

# Clinical research

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