

# Evaluation of Treatment-Resistant Schizophrenia

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## Abstract

A systematic approach to the evaluation and characterization of treatment resistance in schizophrenia has become increasingly important since the introduction of clozapine, risperidone, and olanzapine. The need for accurate evaluation will increase with the introduction of the next generation of antipsychotic medications. People with schizophrenia may manifest a poor response to therapy secondary to intolerance of medication, poor compliance, or inappropriate dosing, as well as true resistance of their illness to antipsychotic drug therapy. Clinicians facing the decision of when to change from one antipsychotic to another must clearly understand the appropriate length of a trial and what target symptoms respond to antipsychotics in order to maximize the response in patients with treatment-resistant schizophrenia.

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Between one-fifth and one-third of all patients with schizophrenia do not respond adequately to drug treatment. Reports of the proportion of patients with drug-resistant schizophrenia have been consistent over time (Prien and Cole 1968; Davis and Casper 1977; Essock et al. 1996), and treatment of these patients has remained a persistent public health problem. Treatment-resistant patients are often highly symptomatic and may require extensive periods of hospital care (McGlashan 1988). Their care requires a disproportionately high amount of the total cost of treating schizophrenia (Revicki et al. 1990). These facts were the basis for the enthusiasm of clinicians following demonstration of clozapine's efficacy in inpatients with treatment-resistant schizophrenia (Kane et al. 1988). However, clozapine treatment is associated with substantial morbidity from side effects, the need for continual weekly blood monitoring, and a high cost. Many clinicians and patients hoped that other new antipsychotics would have clozapine's effectiveness, but not its most

serious side effects. Now that a variety of new antipsychotics are becoming available, it is important to reevaluate the problem of treatment resistance in schizophrenia.

## Chronicity Versus Treatment Resistance

Studies of treatment resistance in schizophrenia have long been hampered by a lack of consistency in definition. Commonly, treatment resistance was considered to be roughly equivalent to chronic or frequent hospitalization (Holden et al. 1968; Small et al. 1975; Lingjaerde et al. 1979; Ruskin et al. 1979; Carman et al. 1981; Wolkowitz et al. 1986). However, chronic hospitalization can occur despite low levels of symptoms (McGlashan 1988). Current and persistent positive symptoms of psychosis and at least moderate overall severity of current illness should also be used to define nonresponsiveness (Meltzer et al. 1990). Chronicity alone cannot accurately predict the likelihood of response to an antipsychotic trial (Brenner et al. 1990; Christison et al. 1991).

The difficulty with using chronicity as a proxy for treatment resistance was recently illustrated in trials of risperidone in schizophrenia. In the U.S. multicenter trial of risperidone, the fact that this medication was more effective than haloperidol in reducing positive symptoms and total Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) score in patients hospitalized for longer than 6 months led Marder and Meibach (1994) to a tentative conclusion that risperidone might be useful for treatment-resistant schizophrenia. Other published trials to date, however, conclude that no firm evidence supports this suggestion (Cohen and Underwood 1994; Cardoni 1995; Shore 1995). Recently, Altman described a study in which 40 percent of patients who were nonresponsive to risperidone responded to a later clozapine trial (see Buckley and Buchanan 1996). Only 15 percent of patients

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nonresponsive to clozapine responded to a subsequent risperidone trial, suggesting that risperidone may be less effective than clozapine in treatment-resistant schizophrenia.

People with schizophrenia may be chronically hospitalized for reasons other than true resistance to drug treatment. Inadequate psychosocial treatment, poor compliance with prescribed drug therapy, and a prior history of violence (Brenner et al. 1990) are all risk factors for chronic hospitalization. Therefore, an optimized medication and psychosocial treatment trial should be employed before a patient's illness is considered nonresponsive. In addition, both the effects of drug noncompliance and extrapyramidal side effects (EPS) can mimic true treatment resistance (Kinon et al. 1993; Shalev et al. 1993). Because of the waxing and waning course of schizophrenia, at least a 1- to 2-year course of persistent symptoms should also be required as a criterion for true treatment resistance.

## Defining Treatment Resistance

The most widely accepted current criteria for treatment resistance in schizophrenia were first used by Kane et al. (1988) and collaborators in the Multicenter Clozapine Trial (MCT). Originally, these criteria were as follows:

1. Persistent positive psychotic symptoms: Item score  $\geq 4$  (moderate) on at least two of four positive symptom items (rated on a 1–7 scale) on the BPRS—hallucinatory behavior, suspiciousness, unusual thought content, and conceptual disorganization.
2. Current presence of at least moderately severe illness: Total BPRS score  $\geq 45$  on the 18-item scale and a score  $\geq 4$  (moderate) on Clinical Global Impressions (CGI; Guy 1976).
3. Persistence of illness: No period of good social or occupational functioning within the last 5 years.
4. Drug-refractory condition: At least three periods in the preceding 5 years of treatment with conventional antipsychotics from at least two chemical classes at doses  $\geq 1,000$  mg per day of chlorpromazine for 6 weeks, each without significant symptom relief, and failure to improve by at least 20 percent in total BPRS score or intolerance to a 6-week prospective trial of haloperidol at 10 to 60 mg per day.

These criteria require both persistent illness and continuing positive symptoms despite adequate current treatment. Subjects in the MCT who met these criteria showed only a 4 percent rate of response and no significant changes on total BPRS score or positive symptoms when randomized to chlorpromazine treatment. Clozapine's superior effi-

cacy has now been replicated using similar criteria (Pickar et al. 1992; Breier et al. 1994).

## Defining Adequate Drug Trials

The fourth criterion for treatment resistance (three drug trials) has been modified somewhat since it was first proposed. The fact that there was only a 3 percent response rate to prospective haloperidol treatment and a 4 percent response rate to double-blind chlorpromazine treatment in the MCT led investigators to conclude that two retrospective drug trial failures would be as effective as three in screening for treatment resistance. Kane's group recently showed that subjects not responsive to two adequate antipsychotic trials (one retrospective and one prospective) have less than a 7 percent chance of responding to another trial (Kinon et al. 1992). The same investigators now use two prospective drug trials to determine treatment resistance (Kinon et al. 1993). The Food and Drug Administration (FDA) guidelines for clozapine's use, as reflected in the product labeling for Clozaril (*Physicians' Desk Reference* 1996), state that people should fail two separate trials of antipsychotics before treatment with clozapine. Thus, failing two drug trials is now generally accepted (Barnes and McEvedy 1996) as a criterion for treatment resistance.

The medication dosages and treatment duration that define an adequate drug trial have also undergone revisions. It is now recognized that a 4- to 6-week period (rather than strictly a 6-week one) is adequate for a treatment trial of an antipsychotic (Kane and Marder 1993). The dose used during conventional antipsychotic trials was first proposed to be at least 1,000 mg per day of chlorpromazine, or its equivalent. However, doses of at least 400 mg per day of chlorpromazine have been proved adequate for blocking 80 to 90 percent of dopamine preceptors (thought to be the target of this drug's action) (Farde et al. 1992). Higher doses produce no direct therapeutic benefit, even in patients not responsive to therapy (Wolkin et al. 1989; Kinon et al. 1992), and they have no greater efficacy in acute treatment than lower doses (Rifkin et al. 1977; Baldessarini et al. 1988; Van Putten et al. 1990). Therefore, 4- to 6-week trials of 400 to 600 mg of chlorpromazine are now accepted as a standard for an adequate trial (Dixon et al. 1995; Barnes and McEvedy 1996). These modified criteria have been used to define treatment resistance in recent clinical trials (Kinon et al. 1993; Shalev et al. 1993). They are also the basis for a recently proposed treatment strategy that allows a clear progression of drug therapy in any patient with schizophrenia to optimize the likelihood of response throughout the course of drug treatment (Dixon et al. 1995; Frances

et al. 1996). This strategy is outlined in table 1 and will be discussed more fully below.

## Negative Symptoms

While most definitions of treatment resistance have focused on the persistence of positive symptoms of psy-

**Table 1. Strategy for treatment of inadequate response to conventional antipsychotic drug therapy**

1. Optimize trial of antipsychotic medication.
  - a. Use 300–600 mg chlorpromazine equivalents for 6–8 weeks.
  - b. Consider a trial of depot neuroleptic, if not yet done.
  - c. Treat any underlying extrapyramidal symptoms (EPS).
    - i. Consider dose reduction if EPS is present.
    - ii. Add adjunct anticholinergic medication, if needed.
2. If no response to above, switch medication to novel antipsychotic. Cross-taper off conventional antipsychotics for 2–4 weeks. Continue anticholinergic medication until conventional antipsychotics have been discontinued at least 2 weeks. Choices include the following:
  - a. Risperidone, 2–6 mg per day for 6–8 weeks.
  - b. Olanzapine, 15–25 mg per day for 6–8 weeks.
  - c. Sertindole, 20–24 mg per day for 6–8 weeks (when available).
  - d. Quetiapine, 300–450 mg per day for 6–8 weeks (when available).
3. If no response to above, switch to clozapine.
  - a. Increase gradually to 200–400 mg for 4–6 weeks.
  - b. If no response, increase gradually to 500–600 mg for 6 weeks.
  - c. If no response, increase gradually to 700–900 mg for 6 weeks.
    - i. Carefully monitor for side effects.
    - ii. Do not increase dose if myoclonus is present.
4. If no response to clozapine, discontinue.
  - a. Re-institute best prior drug therapy.
  - b. Consider adjunct medication.
    - i. Lithium.
    - ii. Anticonvulsants.
      - (a). Valproic acid.
      - (b). Carbamazepine
    - iii. Benzodiazepines.
    - iv. Propranolol.
    - v. Antidepressants.
    - vi. Higher doses of conventional antipsychotics.
5. If no response to best prior drug therapy or adjunct medications, consider third-line strategies.
  - a. Electroconvulsive treatment.
  - b. Reserpine.

Source.—Adapted from Frances et al. 1996.

chosis, there has been a growing awareness of the problem of persistent negative symptoms. Clozapine and the novel antipsychotics risperidone, olanzapine, and sertindole have each shown superior efficacy in reducing negative symptom ratings in double-blind clinical trials (Kane et al. 1988; Marder and Meibach 1994; Beasley et al. 1996; Zimbroff et al. 1997). There is some controversy as to whether these drugs treat primary negative symptoms or only negative symptoms such as those due to depression, EPS, or psychosis (Meltzer 1994; Carpenter et al. 1995). In either case, the illness of patients who have persistent negative symptoms might be considered refractory, as these patients may also respond to treatment with a novel antipsychotic.

## Prevalence of Treatment Resistance in Schizophrenia

Two independent groups have recently estimated the prevalence of treatment resistance in current treatment populations. Juarez-Reyes et al. (1995) used a broad interpretation of a FDA-approved clozapine package insert to determine treatment-resistance rates in a county mental health system in California. They sampled a random, stratified group of people with schizophrenia ( $n = 293$ ), consisting of all those served by a county mental health system in 1991 (both inpatients and outpatients). Patients were considered treatment resistant if they were older than 16, had a diagnosis of schizophrenia or schizoaffective disorder, had failed two drug trials 4 weeks in length at 600 mg per day or greater, or had tardive dyskinesia and a Global Assessment of Functioning score (American Psychiatric Association 1980) of less than 61. The estimate of treatment resistance based on these broad criteria was  $42.9 \pm 5.9$  percent. (This estimate was lowered to  $12.9 \pm 2.7$  percent when the criteria of Kane et al. [1988] were used, primarily because three drug trial failures could not be documented.) Essock et al. (1996) used the failure criteria of two 6-week drug trials of 1,000 mg per day chlorpromazine equivalents, inpatient status of at least 4 months, and at least 24 months total hospitalization in the preceding 5 years. They estimated that 48 percent of all Connecticut State hospital inpatients with a diagnosis of schizophrenia or schizoaffective disorder were treatment resistant (from a total sample of 803 inpatients). These estimates of the prevalence of treatment resistance are similar to those made when clozapine was first marketed (Terkelsen and Grosser 1990), extrapolating to a total of 200,000 to 500,000 people with treatment-resistant schizophrenia currently living in the United States.

## Neurobiology of Treatment Resistance in Schizophrenia

Until standardized defining criteria became available, research into the neurobiological substrate of treatment resistance was scant (Dencker and Kulhanet 1988). Recently, however, some consistent findings have been seen with the use of more objective criteria. People with treatment-resistant schizophrenia appear to have increased cortical atrophy on magnetic resonance imaging when compared to those with responsive illness (Stern et al. 1993; Bilder et al. 1994), particularly if they have predominant negative symptoms (Ota et al. 1987). Lack of response to early treatment is also predictive of nonresponse (Lieberman 1993; Stern et al. 1993). More research into the neurological correlates of treatment resistance is required.

An intriguing finding bearing on drug development is the observation that patients with treatment-resistant schizophrenia appear to have lower catecholamine levels in their cerebrospinal fluid (CSF) (van Kammen and Schooler 1990). Clozapine response has been associated with low ratios of CSF homovanillic acid to 5-hydroxyindoleacetic acid (Pickar et al. 1988). These findings suggest that drugs with low dopamine antagonism and high serotonergic antagonism may be useful in treatment-resistant schizophrenia.

## Violence Associated With Treatment Resistance in Schizophrenia

Violence in schizophrenia has long been considered a problem (Herrera et al. 1988). People with symptoms of schizophrenia have an increased rate of perpetrating violence toward others (Eronen et al. 1996) as well as being the victims of violence themselves (Malone et al. 1993). Novel antipsychotics may be valuable in reducing violence. Several groups have noted that clozapine is more effective in reducing violent behavior and hostility than standard antipsychotic therapy (Wilson 1992; Ratey et al. 1993; Volavka et al. 1993; Breier et al. 1994; Cohen and Underwood 1994; Bellus et al. 1995). Risperidone treatment has also been seen to decrease hostility (Czobor et al. 1995), which raises the question of whether effectiveness against hostility, rather than being a particular property of clozapine, may reflect reduced EPS liability or other effects shared by clozapine and risperidone. Compared to haloperidol therapy, treatment with low-potency antipsychotics with reduced EPS liability is associated with improvement in violent behavior rates (Herrera et al. 1988). However, this improvement may be

due to the increased sedation associated with low-potency antipsychotics. From both a practical and theoretical standpoint, it will be important to determine the extent to which novel antipsychotics demonstrate differential efficacy in treating violence and aggression in patients with treatment-resistant schizophrenia.

## Drug Therapy for Treatment Resistance

In the past, pharmacological approaches to treatment-resistant schizophrenia centered on either modifying doses of conventional antipsychotics or using adjunctive agents, such as lithium, beta-blocking drugs, anticonvulsants, and benzodiazepines. These strategies have been reviewed in detail elsewhere (Christison et al. 1991; Barnes and McEvedy 1996; Kane 1996) and will be only summarized here. Since the demonstration of clozapine's superior efficacy, attention has shifted to the use of new antipsychotics for treatment-resistant schizophrenia. To obtain approval for marketing in the United States, new antipsychotics must demonstrate a safety or efficacy profile superior to conventional neuroleptics (usually haloperidol).

**Conventional Antipsychotic Drugs.** Conventional antipsychotic drugs have long been the first line of drug therapy for treating schizophrenia. In more than 100 studies that compared two or more conventional antipsychotics, only one study found any of these agents to be more effective than another (Klein and Davis 1969; Janicak et al. 1993). As a result, in terms of efficacy, conventional antipsychotics are considered interchangeable. In controlled trials in people with drug-resistant symptoms, fewer than 5 percent responded after a drug therapy change from one conventional antipsychotic to another (Kane et al. 1988; Breier et al. 1994). The primary reason for choosing between these drugs has been to reduce side effects, provide different dosing strategies, or offer different routes of administration. High-potency drugs like haloperidol and fluphenazine have high EPS profiles, but they cause less sedation and postural hypertension than low-potency drugs such as chlorpromazine or thioridazine. Haloperidol and fluphenazine are the only two conventional antipsychotics available in the United States as injectable depot medication, a formulation that can ensure drug delivery and sometimes optimize response.

The choice of a conventional antipsychotic should be influenced by a patient's past response and proneness to side effects. If no clinical improvement is seen after 2 weeks of therapy, compliance with medication should be evaluated. If the patient is compliant, a different drug trial should be considered after 4 to 6 weeks of minimal response.

**New Generation Drugs.** Novel antipsychotics should be the first consideration after the failure of conventional drug therapy. With the exception of clozapine (because of its serious side effects), these drugs are also indicated as first-line therapy. Five drugs—clozapine, risperidone, olanzapine, sertindole, and quetiapine—will be briefly reviewed here. These drugs were chosen because they either are currently available for the treatment of schizophrenia or are likely to be approved within the next year.

**Clozapine.** In 1990 the FDA approved clozapine for treating patients whose symptoms do not adequately respond to conventional antipsychotic therapy, either because therapy is not effective or because it cannot be continued due to intolerable side effects. Clozapine is still the only drug with proven efficacy in rigorously defined treatment-resistant schizophrenia (Christison et al. 1991; Barnes and McEvedy 1996). It has also been useful in reducing violent behavior (Mallya et al. 1992; Breier et al. 1994), tardive dyskinesia (Tamminga et al. 1994), and the risk of suicide (Wilson 1992; Meltzer and Okayli 1995). Despite this efficacy profile, clozapine had been used in only slightly more than 100,000 people (including all diagnoses) as of January 1996.

The relative underutilization of clozapine probably relates to the cost and complexities of clozapine therapy. In addition to the need for long-term hematologic monitoring for agranulocytosis, persistent serious side effects—weight gain, sialorrhea, and sedation—are barriers to more widespread clozapine use. Despite the robust clinical effects of clozapine in long-term use (Meltzer 1990; Wilson 1992; Breier et al. 1993), benefits that translate into improved living situations and decreased cost of care have not always been shown in large public health sector populations (Zito et al. 1993), particularly in the first year of use (Essock et al. 1996). This lack of benefit is partly because clozapine is often reserved for the most difficult to treat (and discharge) segment of the population with schizophrenia (Safferman et al. 1991) or is prescribed by only a subset of clinicians who are comfortable with its use.

A gradual escalation of dosage is the optimal strategy for clozapine initiation. Patients should be evaluated for response at dose plateaus of 200 to 400 mg per day and 500 to 600 mg per day. Only patients with few side effects from clozapine should be titrated to doses higher than 600 mg per 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 (Bak et al. 1995). We have recently seen that patients who respond to clozapine will begin to respond within 8 weeks of reaching their response dose (Conley et al. 1997). However, the total time course of clozapine response is

still controversial (Carpenter et al. 1995; Meltzer and Okayli 1995).

**Risperidone.** Risperidone was approved for use in schizophrenia in 1994, and clinical trials show that it is an effective treatment for both positive and negative symptoms (Chouinard et al. 1993; Marder and Meibach 1994). In these trials, risperidone has also been shown to be equivalent to placebo in the production of EPS at doses at or below 6 mg per day. Doses of 10 mg per day or higher, however, produce EPS in a dose-dependent fashion. Thus, risperidone typically has a different clinical effect in low doses and high doses.

Although there is some indication from the severely ill patients treated in the U.S. multicenter trial that risperidone demonstrates greater efficacy than haloperidol (Marder and Meibach 1994), to date there are no reports of superior efficacy in patients with rigorously defined treatment-resistant schizophrenia. Chouinard et al. (1994) and Keck et al. (1995) describe patients with poorly responsive schizophrenia who showed some improvement with risperidone, but these studies were open-labeled, retrospective, or not controlled. Klierer et al. (1995) report comparable efficacy between risperidone and clozapine in chronic schizophrenia patients; however, the subjects were not categorized by treatment resistance, and there were too few subjects to adequately test for a differential effect between the drugs.

Risperidone treatment is usually not effective in clozapine responders (Lacey et al. 1995; Shore 1995), and evidence of the efficacy of risperidone in people with drug-resistant symptoms is inadequate (Cohen and Underwood 1994; Cardoni 1995; Klierer et al. 1995). An outpatient trial of risperidone versus clozapine in treatment-resistant schizophrenia currently being conducted by John Kane, Steven Marder, and Nina Schooler should provide more definitive information about the usefulness of risperidone. Its effectiveness in improving the quality of life and reducing hospital stays for drug-responsive schizophrenia patients (Cohen and Underwood 1994; Lindstrom et al. 1995) has been reported, but such studies have yet to be done in patients with refractory symptoms.

**Olanzapine.** Olanzapine was approved for the treatment of schizophrenia in 1996. It has a receptor-binding profile that is very similar to clozapine, and it has been reported to have high affinity at dopamine D<sub>2</sub> receptors (Beasley et al. 1996), which may be a critical determinant of clozapine's superior efficacy (Lahti et al. 1993; Seeman and Van Tol 1993). Effective for both positive and negative symptoms in treatment-responsive schizophrenia in several large multicenter trials, olanzapine has a low incidence of EPS and does not differ from placebo in its incidence of akathisia. Conley et al. (1996) reported

that some well-characterized patients with treatment-resistant schizophrenia improved in an open trial of olanzapine. The most effective doses in this trial were between 15 and 25 mg per day. A trial of olanzapine versus chlorpromazine in rigorously defined therapy-refractory schizophrenia is near completion (Conley et al. 1996).

**Sertindole.** Sertindole received FDA approval for the treatment of schizophrenia in 1996 and should be approved for marketing in 1997. Because of its combination dopaminergic and serotonergic receptor affinity and its relative limbic selectivity, it fits the predictive models of drug efficacy in treatment-resistant schizophrenia. Sertindole was an effective antipsychotic in conventional antipsychotic-responsive or drug-naïve schizophrenia patients in several multicenter studies (Borison 1995; Tamminga et al., in press). In studies published to date, sertindole was equivalent to placebo in its likelihood of producing EPS or akathisia. Its most effective doses are 20 to 24 mg per day. No completed studies have examined sertindole in treatment-resistant schizophrenia or the long-term effectiveness of the drug. One study is now being conducted to compare the efficacy of sertindole with risperidone in patients with poorly responsive schizophrenia.

**Quetiapine.** Quetiapine has been shown to be effective in treatment-responsive schizophrenia (Arvanitis et al. 1996). Its pharmacological profile includes high serotonin (5HT<sub>1a</sub>) receptor affinity compared to dopamine receptor affinity. It is also a low-potency compound. The most effective doses in clinical studies are 300 to 450 mg per day, dose potency similar to clozapine's (Arvanitis et al. 1996). No differences between placebo and quetiapine in the levels of EPS or akathisia are seen in published trials to date. There is one ongoing study of quetiapine versus chlorpromazine in treatment-resistant schizophrenia.

**Alternative Therapies.** If patients remain refractory to treatment after trials of novel agents, alternative therapies should be considered. These include adjunctive medications, reserpine, and electroconvulsive therapy (ECT). The data concerning the efficacy of these therapies are limited, but they may be of use in some patients.

**Lithium.** Adjunct lithium therapy has been beneficial in some patients with treatment-resistant schizophrenia (Small et al. 1975; Growe et al. 1979; Carman et al. 1981), although these patients were often not defined by the rigorous criteria of later studies. A 4-week trial of medication appears adequate to determine response. The response seen may be more prominent in those patients with affective symptoms, but patients who do respond do so in many areas of functioning (Delva and Letemendia 1986). There are reports that lithium has been helpful in reducing hostility in patients with treatment-resistant schizophrenia and may thus be valuable for some violent patients (Christison et al. 1991).

The published trials of adjunct lithium, while positive, were conducted with small numbers of patients and often used ill-defined criteria for treatment resistance. The size of the clinical effect in these trials was limited (Kane 1996), and definitive evidence of the benefit from lithium is not yet present (Johns and Thompson 1995). Lithium in combination with conventional antipsychotics or clozapine should be used with caution because of the recognized dangers of delirium, encephalopathy, and neurotoxicity that have been reported with these combinations (Cohen and Cohen 1974; Miller and Menninger 1987; Barnes and McEvedy 1996).

**Anticonvulsants.** Carbamazepine and valproic acid are effective in bipolar affective disorder (Post 1990; Freeman et al. 1992) and are often considered as an adjunct therapy in patients with schizophrenia. Only carbamazepine has been evaluated in controlled trials. Although these trials have been consistently positive (Schulz et al. 1990; Simhandl and Meszaros 1992; Meltzer and Okayli 1995), they had relatively few subjects and the recorded efficacy was modest, usually involving nonspecific improvement in such areas as behavior and social adjustment.

Carbamazepine must be used with caution because of reports of disorientation and ataxia (Kanter et al. 1984; Yerevanian and Hodgman 1985). It can also reduce the blood level of haloperidol by as much as 50 percent (Kahn et al. 1990). Valproic acid should be used with caution because of the possibility of hepatic toxicity (*Physicians' Desk Reference* 1996).

**Benzodiazepines.** There have been several reports on the use of adjunct benzodiazepines in treatment-resistant schizophrenia. Results are mixed, with some double-blind studies (Lingjaerde et al. 1979; Wolkowitz et al. 1992), but not all (Holden et al. 1968; Hanlon et al. 1970; Ruskin et al. 1979; Pato et al. 1989), showing a treatment effect. Given that patients with schizophrenia often exhibit anxiety and irritability, it is not surprising that benzodiazepines are useful agents in treating this disorder. There is no firm evidence for a specific adjunct antipsychotic effect with these agents, however. Benzodiazepines should be used with an awareness of the risks of chronic sedation, fatigue, ataxia, and dependence. In addition, there are reports of behavioral disinhibition with these drugs (Pato et al. 1989) and the possibility of synergistic toxicity with clozapine (Meltzer 1993). While these reports have not been systematically confirmed, they still suggest caution with this drug combination.

**Other Therapies.** Although some studies suggest that beta-blockers and reserpine may be useful in refractory schizophrenia (Christison et al. 1991), no available controlled studies use current diagnostic criteria. There is

very limited evidence that long-term therapy with either of these agents is beneficial.

To date, there have been no controlled studies of ECT in treatment-resistant schizophrenia patients. Before the use of clozapine, there was some evidence from uncontrolled trials that ECT was beneficial for treatment-resistant patients (Friedel 1986), but the effect of ECT has been the most robust in patients with a short duration of illness (Small 1985). There were two open trials of added ECT in patients who had an inadequate clozapine response (Benatov et al. 1996; Remington et al. 1996); both trials showed some benefit from ECT. However, issues of persistence of effect and long-term maintenance of these patients have not yet been addressed.

## Summary

A defined approach to patients with treatment-resistant schizophrenia is critical. The following practices should maximize the likelihood of successful outcome in an antipsychotic drug trial.

1. Identify clearly defined target symptoms. Antipsychotics are most helpful for the positive symptoms of psychosis: hallucinations, delusions, and thought disorder. Newer medications may also be helpful in reducing negative symptoms, such as social withdrawal, alogia, and affective blunting—particularly if they are secondary to EPS of conventional antipsychotics. Clozapine has been shown effective in hostile, aggressive psychotic patients. Specification of the target symptoms for a drug trial will allow greater clarity in defining the parameters of success and failure.

2. Use medications at sufficient doses and for a sufficient duration to determine efficacy, especially before adjunct drugs are used; these drugs may complicate the therapeutic situation and make it impossible to define the optimal drug treatment for a patient.

3. Consider the role of medication intolerance, non-compliance, inadequate social support, and inadequate psychosocial treatment in the differential diagnoses of treatment resistance before declaring any drug therapy to be a failure. Although therapeutic ranges of most antipsychotics are not well established, measuring blood levels may be useful for establishing compliance and ruling out the unlikely event of poor medication absorption.

4. Maximize therapy with single agents before using multiple agents. There is tremendous pressure for the clinician to find a drug to rapidly treat every psychological problem manifest in a patient. It is important to remember that no adjunct agent has ever been shown to robustly improve antipsychotic response. Hostility, irritability,

insomnia, and social withdrawal can all be secondary to psychosis and may resolve only after a patient has had a good antipsychotic drug effect.

5. Aggressively prevent EPS through appropriate choice of primary therapy. With the availability of antipsychotic agents that are clearly effective at doses that do not produce EPS in the vast majority of patients, it should be possible to almost eliminate persistent side effects as a reason for therapeutic failure.

6. Maintain a positive therapeutic attitude. The range of choices for antipsychotic therapy is greater than ever, and new drugs will continue to appear. Even patients with a history of severe illness might be encouraged to be optimistic that some therapy will be found that will benefit them.

An attempt to generalize these guidelines is presented in table 1, which was adapted from the work of Frances et al. (1996). These guidelines were developed by expert consensus, based on the recommendations of 87 psychiatrists in the United States who were identified as experts in the treatment of schizophrenia. Since no algorithm for the pharmacotherapy of treatment-resistant schizophrenia has been empirically tested and found to be superior to any other, table 1 is an example of a systematic approach to the psychopharmacology of treatment-resistant patients. Without empirical validation, clinical judgment and experience informed by available anecdotal data will have to guide treatment planning.

The novel antipsychotics may have different mechanisms of action than conventional antipsychotics (and than one another), so clinicians should explore the response of patients with persistently refractory symptoms to each of these new agents. We do not yet know whether nonresponsiveness to one novel agent predicts nonresponsiveness to another. To date, clozapine is the only medication with demonstrated efficacy in treatment resistance. The differential efficacy of new drugs in treatment-resistant schizophrenia will become clearer when well-designed double-blind studies using rigorous definitions of treatment resistance are completed.

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## Schizophrenia: Questions and Answers

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