Since the introduction of chlorpromazine, the first antipsychotic drug, it has been evident that a large number of patients have schizophrenia that is treatment resistant. It is estimated that between 20% and 60% of patients have schizophrenia that is resistant to treatment.\(^1,2\)

The relationship between treatment-resistant and treatment-responsive schizophrenia is not strictly black and white. No particular psychopathology of schizophrenia specifically suggests treatment-resistant disease. Brenner and Merlo\(^3\) proposed that treatment-resistant schizophrenia be considered at one end of a spectrum of antipsychotic drug response rather than being clearly differentiated from treatment-responsive schizophrenia. However, patients with treatment-resistant schizophrenia do tend to have prominent negative and cognitive symptoms and more severe psychopathology than patients whose condition responds to antipsychotic drugs.

Chronicity has often been confused with treatment-resistant schizophrenia. Schizophrenia is a chronic disorder that progresses to various levels of clinical deterioration without sustained remission or full recovery. In contrast with treatment-resistant schizophrenia, chronicity is associated with a favorable response to drug treatment, in which schizophrenic features are largely under control for 6 months or longer or there is partial recovery to the premorbid level of functioning.\(^4,5\)
Identifying treatment resistance

Although there are no universally accepted criteria, a common convention is that adequate drug treatment requires a duration of 4 to 10 weeks, a dosage equivalent to 1000 mg/d of chlorpromazine, and trials of 2 to 3 different classes of antipsychotic drugs. Table 1 presents suggested doses of atypical antipsychotics based on recent comparisons of efficacy. The guidelines of the American Psychiatric Association, the Schizophrenia Patient Outcomes Research Team, and the Texas Medication Algorithm Project have suggested that management of treatment-resistant schizophrenia is relevant to clinical practice. The current treatment guidelines recommend 2 or more treatment trials of atypical antipsychotics at adequate dosages. Typical antipsychotics can be used for 4 to 6 weeks to screen for treatment-resistant schizophrenia, after which treatment with clozapine may be considered.

The International Psychopharmacology Algorithm Project (IPAP; http://www.ipap.org) proposes a practical clinical assessment-based screen for treatment-resistant schizophrenia (Table 2). Adequate response to treatment has been defined as at least a 20% reduction in symptoms as measured by rating scales. Kane and colleagues narrowly defined treatment-resistant schizophrenia to identify more homogeneous clusters of patients (Table 3). Their study showed that clozapine is most effective for treatment-resistant schizophrenia. Variations on the Kane criteria have been used in research and practice for the past 2 decades. All include 3 common elements:
• A history of treatment resistance
• Severe current symptoms
• Treatment resistance to current antipsychotic drugs

Various factors are responsible for “apparent” treatment resistance, which can be confused with true treatment resistance. A large number of patients have schizophrenia that does not respond because pharmacological, psychological, and psychosocial treatments are inadequate. Factors that cause “apparent” treatment resistance—most of which are treatable—need to be aggressively identified and actively corrected to enhance therapeutic effectiveness. Poor treatment adherence is the most critical factor. Poor adherence is consistently associated with adverse effects, poor insight, and a poor therapeutic alliance. Comorbid psychiatric and physical disorders and inadequate social support are also crucial factors that can lead to inadequate treatment.

Clinical analyses show that patients with treatment-resistant schizophrenia are more likely to be male, have earlier onset of illness (younger than 20 years of age), more psychiatric hospitalizations and psychotic episodes, fewer remission periods, a longer duration of untreated psychosis, and a history of substance abuse. Because cognitive and negative symptoms do not respond adequately to antipsychotic drugs, the overall response to these agents is heavily weighted to changes in positive symptoms. However, patients with treatment-resistant schizophrenia often have persistent negative symptoms and prominent cognitive impairment. Therefore, IPAP suggests 2 forms of treatment-resistant schizophrenia:
• Kraepelinian schizophrenia with severe, persistent cognitive deterioration
• Deficit schizophrenia with prominent primary negative symptoms
Among neurobiological findings in treatment-resistant schizophrenia, those from brain imaging studies have been the most prominent. These suggest a relationship between ventricular and sulcal enlargements. No particular structural abnormalities of the brain are closely correlated with poor response to antipsychotic drugs.

**Pharmacological treatment**

The effective management of treatment-resistant schizophrenia has been a longstanding challenge. In 1988, Kane and colleagues demonstrated that clozapine was effective in treatment-resistant schizophrenia. Since then, atypical antipsychotics have virtually replaced typical antipsychotics. Reviews, meta-analyses, and practical long-term trials clearly indicate that clozapine is the most effective drug in treatment-resistant schizophrenia (Table 4). Recently, IPAP proposed an algorithm as a practical guideline for treatment-resistant schizophrenia (Figure).

Findings from double-blind, open-label trials and practical studies suggest that clozapine is more efficacious than atypical antipsychotics for treatment-resistant schizophrenia. Meta-analyses and comprehensive reviews conclude that clozapine is more effective than typical antipsychotics for the treatment of positive and negative symptoms. Although not all studies unequivocally confirm the superior efficacy of clozapine, practical, long-term trials have reported that this agent diminishes psychopathology, improves quality of life, and is associated with lower rates of discontinuation.
On the basis of meta-analyses, the Cochrane Center (http://www.cochrane.org) has concluded that clozapine is clearly more effective at improving active positive psychotic symptoms than either atypical or typical antipsychotics. It is not clear, however, whether clozapine is more effective in treating negative symptoms and improving long-term outcomes.

A number of double-blind trials have found that atypical antipsychotics are superior to typical antipsychotics, particularly for the treatment of positive symptoms. The studies also indicate that efficacy varies among the atypical antipsychotics. For example, olanzapine and risperidone are superior to other atypical antipsychotics in clinical efficacy against positive symptoms. These data suggest that atypical antipsychotics are a heterogeneous group, and their efficacy and adverse effects may vary. Interestingly, a recent meta-analysis reported that only some atypical antipsychotics—such as clozapine, amisulpride, olanzapine, and risperidone—were more efficacious than typical antipsychotics.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) showed that perphenazine was nearly as effective as olanzapine in terms of time to discontinuation, and that perphenazine was associated with fewer metabolic adverse effects. A recent follow-up study also reported that while perphenazine does not differ from atypical antipsychotics in quality of life, efficacy, and adverse effects, it had lower associated overall health care costs.

It is generally agreed that atypical antipsychotics may be superior to typical antipsychotics with less risk of extrapyramidal syndrome or tardive dyskinesia. Note, however, that most trials have compared atypical antipsychotics with haloperidol under the assumptions that high and low potency...
typical antipsychotics have similar efficacy and that atypical antipsychotics are definitely more effective than typical antipsychotics. However, an increasing number of studies suggest that atypical antipsychotics may not differ categorically from typical antipsychotics, and that failure to appreciate this can lead to suboptimal clinical decisions. An accumulating body of evidence suggests that both atypical antipsychotics and typical antipsychotics are heterogeneous with respect to efficacy, adverse effects, and pharmacological profiles.

Treatment of clozapine-resistant schizophrenia

Although clozapine is considered the standard pharmacotherapy and the last resort in the management of treatment-resistant schizophrenia, 40% to 70% of patients with treatment-resistant schizophrenia fail to respond to clozapine treatment.3,24 Clozapine-resistant schizophrenia characteristics include persistent active psychotic features despite daily doses of 300 to 900 mg for 8 weeks to 6 months, with plasma drug levels of 350 ng/mL or higher.25 Affected patients have long been problematic in clinical care because no other therapeutic strategies have proved effective. Since the emergence of clozapine as the prototype of atypical antipsychotics, there have been numerous efforts to delineate clinical and biological predictors of response to this agent. Among conflicting results, several factors have been identified as potential predictors of response. These include severe clinical symptoms, higher levels of functioning before the onset of schizophrenia, low levels of homovanillic acid and 5-hydroxyindoleacetic acid in cerebrospinal fluid, reduced metabolism in the prefrontal cortex, reduced volume of the caudate, and the improvement of P50 gating at the 500-ms prepulse interval.26 However, none of these factors is consistent or specific as a predictor of clozapine response.

Plasma clozapine levels of 350 to 500 ng/mL are correlated with a favorable therapeutic response.26,27 These plasma levels correspond to dosages of 150 to 800 mg/d.27 Although it is not clear whether clozapine has a therapeutic window, higher plasma drug levels may reduce clinical improvement and increase the risk of adverse effects.27

The addition of an atypical antipsychotic to clozapine has been used widely in the treatment of clozapine-resistant schizophrenia. Double-blind and open-label studies have shown that augmenting clozapine with risperidone or sulpiride may diminish clinical symptoms of schizophrenia.28-30 Combination trials, case reports, and natural follow-up studies on augmenting clozapine with olanzapine, ziprasidone, or quetiapine are limited and preliminary.

The true effectiveness of augmentation therapy remains inconclusive. Thus the augmentation of clozapine and an antipsychotic drug needs careful assessment for tolerability, adverse effects, potential benefits, and a history of response to the antipsychotic.

The strategy of switching from clozapine to another antipsychotic drug may need to be considered when augmentation fails, when the adverse effects of clozapine are intolerable, or when treatment is an economic burden. Open-label studies and case reports have reported that in some patients, clozapine-resistant schizophrenia responds favorably to olanzapine.1,31,32 Follow-up case studies have shown partial responses to risperidone in patients who had been taking clozapine. Thus, switching from clozapine to an atypical antipsychotic including olanzapine or risperidone could be a beneficial option.

The results of a study by Kho and colleagues33 show that electroconvulsive therapy (ECT) added to clozapine improved positive and negative symptoms of schizophrenia. Although some studies included schizophrenic patients whose condition was not resistant to clozapine therapy, in general the studies suggest that ECT may be a useful augmentation strategy.

Psychotherapy

Pharmacological treatment alone is not adequate for patients with treatment-resistant schizophrenia. Up to 60% of patients have persistent psychotic and cognitive symptoms and are at high risk for suicide despite active pharmacological therapy.1,2 Comprehensive treatment strategies that integrate pharmacological, psychological, and psychosocial approaches should be used (Table 4).

Among various models (including personal therapy, psychodynamic psychotherapy, and family treatment), cognitive-behavioral therapy (CBT) is considered most effective.34,35 The primary aim of CBT is to improve understanding and insight of schizophrenia and enhance coping mechanisms for psychotic and depressive symptoms. Furthermore, CBT is used to reinforce psychosocial skills and thereby alleviate psychological and physical distress. CBT can also help with illness-associated compromised psychosocial behavior. CBT in conjunction with antipsychotic drugs is particularly effective in reducing the intensity of delusions and depressive symptoms and the risk of suicide. CBT also alleviates hallucinations, improves quality of life, and reduces the risk of suicide attempts and
other violent behaviors. Long-term CBT is much more effective than the short-term therapy and provides long-lasting and cost-effective results. CBT has not been shown to be significantly effective in the treatment of acute psychotic relapse and severe impairment in cognitive insight. Several psychosocial treatment models—including social skill improvement, stress reduction, cognitive reframing, and vocational rehabilitation—have also been used in conjunction with pharmacological treatment. Psychosocial treatment should be fully integrated into the care of patients with treatment-resistant schizophrenia to maximize the effects of therapeutic strategies. A variety of psychosocial interventions have been shown to enhance treatment adherence, improve medication management, reduce chances of relapse, provide for faster and longer-lasting recovery, and improve social coping skills. A 10-year follow-up study clearly demonstrated the effectiveness of integrated psychosocial strategies in treatment-resistant schizophrenia. That study used need-adapted treatment—a comprehensive psychosocial strategy that integrates pharmacological, psychological, and psychosocial models. The study showed that the number of psychiatric hospitalizations and the duration of hospital stay were reduced more than 50% in patients who received need-adapted treatment for 10 years. The long-term outcome of these patients was very favorable, their quality of life was improved, and the overall cost was reduced. Thus, multidisciplinary care systems that integrate diverse clinical expertise are essential not only in treating schizophrenic symptoms but also in helping patients achieve an independent psychosocial life.

Conclusion
The clinical management of patients with treatment-resistant schizophrenia is still challenging despite years of extensive research. As shown in the Figure, at least 2 antipsychotic drugs should be tried at adequate dosage and for an adequate period, and various factors that interfere with adherence should be ruled out before making a diagnosis of treatment-resistant schizophrenia. Clozapine should be used only when it is confirmed that patients have treatment-resistant schizophrenia and their condition fails to respond to atypical antipsychotics or typical antipsychotics. The same rule applies in identifying clozapine-resistant schizophrenia. Pharmacological augmentation strategies for managing clozapine-resistant schizophrenia are widely used in clinical practice. However, there is no strong evidence that supports augmentation as an effective treatment option. ECT may be an effective augmentation strategy in the treatment of clozapine-resistant schizophrenia. It should be emphasized that psychological and psychosocial care combined with medication treatment are the key factors in maximizing the effectiveness in the treatment of patients with treatment-resistant schizophrenia.

References:
10. Miller AL, Hall CS, Buchanan RW, et al. The Texas Medication Algorithm Project antipsychotic
15. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry. 2003;60:553-564.


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