Several objective rating scales are available for monitoring positive and negative symptoms as well as EPS. They include the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962; Ventura et al. 1993) and the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987) for monitoring psychopathology and the Drug-Induced Extrapyramidal Symptoms Scales (DIEPSS; Inada 2009) and Abnormal Involuntary Movement Scale (AIMS; Guy 1976) for monitoring EPS. However, most of these scales are time-consuming to administer and are more frequently used in the research field than in clinical settings. The Clinical Global Impressions (CGI) Scale is another tool that is widely accepted for its ease of administration and established correspondence to PANSS total scores (Leucht et al. 2005; Levine et al. 2008) (Table 9–5).

To address functional outcome, which may well be involved in the concept of treatment-resistant schizophrenia, cognitive functioning should be assessed. A variety of neuropsychological test batteries are used for the measurement of cognitive functioning, leading to some difficulty in directly comparing findings across studies. One candidate for a globally standardized test battery to assess outcomes of cognitive changes in clinical trials is the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB), developed by the U.S. National Institute of Mental Health (NIMH) and FDA. MCCB focuses on key cognitive domains relevant to schizophrenia and related disorders and takes approximately 70 minutes to administer. A less time-consuming test battery is the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al. 2004), which takes only 30 minutes to administer, can much more feasibly be used in everyday clinical practice, and demonstrates sound reliability and validity. Unfortunately, BACS does not measure social cognition, which is another key determinant of functional outcome.

Although neuropsychological test batteries have been widely accepted for the assessment of cognitive functioning in psychiatric populations, a tool that can assess cognitive skills directly associated with a patient's daily functioning is also warranted. To address this need, interview-based measures of cognition, such as Clinical Global Impression of Cognition in Schizophrenia (Ventura et al. 2008) and Schizophrenia Cognition Rating Scale (Keefe et al. 2006), have been designed. These measures also may help avoid practical limitations associated with neuropsychological tests, including differences in the amount of prior training of the testers, administration and scoring time, prac-

Table 9–5. Linkage of Clinical Global Impressions–Severity (CGI-S) Scale score and Positive and Negative Syndrome Scale (PANSS) total score

CGI-S	PANSS (Levine et al. 2008)	PANSS (Leucht et al. 2005)
Not ill	31–32	
Mild	55–62	58
Moderate	71–77	75
Marked	88–94	95
Severe	105–110	116
Extreme	126–134	—

tice effects, and validity issues associated with interpretation. These measures assess cognitive deficits and the degree to which they affect daily functioning by obtaining the patient's report, a caregiver's report, and a clinical evaluation of both sources of information by the clinician. Both measures fulfilled the criteria for psychometric property, including sound test-retest reliability, associations with cognitive performance measures, and associations with real-world functioning. It may require further studies to determine whether a combination of both neuropsychological tests and interview-based measures is necessary for the assessment of cognitive functioning or whether administering either of these measures is sufficient.

Several functional outcome measures have been used for the assessment of social and occupational functioning (Bryson et al. 1997; McGurk et al. 2003), activities of daily living, and ability to live independently (Buchanan et al. 2005; Matza et al. 2006). It has been pointed out that the measures do not tap into the cognitive abilities underlying these functions. For example, the Independent Living Scale was primarily designed to help clinicians make decisions regarding treatment choice (Loeb 1996) and not to evaluate the changes in cognitive deficits and functioning by intervention.

Functional outcome measures that are more sensitive to identifying changes in functioning and underlying cognitive abilities are now being introduced. The University of California, San Diego, Performance-Based Skills Assessment (UPSA) is a performance-based measure of the functional capacity, which was developed to assess the capacity of persons with schizophrenia

Table 9–6. Assessment of treatment-resistant schizophrenia

- Patients with schizophrenia should be assessed on various aspects of the illness, particularly those related to functional outcome.
- Assessment tools with adequate feasibility and validity are needed for measuring cognitive skills and functional outcome.
- Interview-based measures that can assess cognitive skills directly associated with daily functioning may well be widely accepted in clinical settings.
- Use of functional outcome measures that are sensitive to changes in function and underlying cognitive abilities are warranted for assessing treatment response.

to adequately perform skills necessary for daily functioning (Patterson et al. 2001). The UPSA has shown high correlations with measures of cognitive function, activities of daily living, interpersonal skills, community activities, and level of independence in living (Bowie et al. 2006; Mausbach et al. 2008; Twamley et al. 2002). A short version, the UPSA-Brief, has been developed that requires only 10–15 minutes to administer (Mausbach et al. 2007). The UPSA-Brief was found to have adequate psychometric properties, predict residential independence, and be sensitive to the changes by intervention.

Some may argue that performance-based functional outcome measures do not fully capture the activities and level of real-life functioning in the community. An interview-based scale such as the Schizophrenia Outcomes Functioning Interview (SOFI) may address this concern by measuring community functioning related to cognitive impairment and psychopathology (Kleinman et al. 2008). The SOFI consists of two versions, one to be completed by the patient (SOFI-P) and the other to be completed by a caregiver informant (SOFI-I). The SOFI has demonstrated strong reliability and validity and is expected to be a useful measure of functional outcomes in schizophrenia. Further studies, particularly longitudinal research tracking the effects of interventions, are necessary to make definitive recommendations for interview-based measures that evaluate a broader range of functional domains (Table 9–6).

Standard Treatment for Schizophrenia

Standard Pharmacological Treatment

Determining what constitutes standard pharmacological treatment for schizophrenia is mandatory before defining the criteria for treatment resistance. It is

critical to note that deterioration of psychiatric symptoms, cognitive abilities, and functioning may emerge secondary to inappropriate pharmacological interventions.

Several existing guidelines for schizophrenia share commonalities in their recommendations for pharmacological treatment. Compared with older FGAs, SGAs are considered to have a lower risk for EPS and to be more effective, as evidenced by a broader spectrum of efficacy—namely, negative, cognitive, and mood symptoms. As a result, many guidelines recommended the use of SGAs in preference to FGAs (Table 9–7). However, data from two large government-sponsored trials, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) in schizophrenia and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS), overturned the view that SGAs were vastly superior to FGAs (Jones et al. 2006; Lieberman et al. 2005). It should, however, be noted that both studies were criticized for their sampling methods and overall methodology, suggesting the need for caution in interpreting their findings (Naber and Lambert 2009).

To clarify the confusing findings, the World Psychiatric Association Pharmacopsychiatry Section reviewed literature on the comparative effectiveness of different antipsychotic treatments for schizophrenia (Tandon et al. 2008). The researchers concluded that SGAs and FGAs were similarly effective in terms of positive symptoms, but that SGAs were consistently more effective than FGAs in alleviating negative, cognitive, and depressive symptoms and had a lower risk for tardive dyskinesia. Although FGAs and SGAs appeared similar in their efficacy in treating psychotic symptoms, substantial differences were seen in terms of side effects. For instance, SGAs generally have a lower risk for EPS and a higher risk for metabolic side effects. In treating schizophrenia, it may be more clinically meaningful to focus on selecting drugs to minimize side effects in a customized manner rather than selecting drugs based on equivocal findings regarding superiority hypotheses for SGAs.

Because the subjects participating in the CUtLASS and CATIE studies were mostly chronically ill patients, great caution is warranted in extrapolating effectiveness findings from these studies to first-episode patients. Results of the European First Episode Schizophrenia Trial h ave recently been published (Kahn et al. 2008). This pragmatic open randomized controlled trial (RCT) was conducted at multiple sites and included 498 patients. The investigators examined the clinical effectiveness of SGAs and FGAs in a broad

Table 9–7. Standard pharmacological treatment of schizophrenia

- Second-generation antipsychotics (SGAs) are generally recommended rather than first-generation antipsychotics (FGAs) for the treatment of first-episode schizophrenia.
- SGAs are more effective than FGAs in alleviating negative, cognitive, and depressive symptoms, whereas SGAs and FGAs are similarly effective in terms of positive symptoms.
- SGAs have a lower risk for extrapyramidal side effects and tardive dyskinesia but a higher risk for metabolic side effects.
- The dosage level should be expeditiously titrated to the target therapeutic dose (approximately 300–1,000 mg/day in chlorpromazine equivalents) while monitoring for intolerance.
- Nonadherence should be continuously monitored; patients with recurrent relapse as a result of nonadherence are candidates for depot medication.

range of patients in the early stages of schizophrenia. Most SGAs were found to be superior to haloperidol in low doses in terms of the proportion of patients who achieved treatment response and remission within 12 months. In addition, the discontinuation rate within 12 months was greater in the patients receiving haloperidol than in those receiving SGAs (Kahn et al. 2008). Although these findings may generally support the use of SGAs rather than FGAs for patients with first-episode schizophrenia, the history of sensitivity to side effects such as weight gain, hyperglycemia, or hyperlipidemia should be taken into consideration. Cost-effectiveness also should be weighed, because it varies according to the resources available in different countries.

Clinical guidelines for the treatment of schizophrenia in developed countries include those developed by the National Institute for Health and Clinical Excellence (2009) in England, the Texas Medication Algorithm Project (TMAP; Miller et al. 1999; Moore et al. 2007) and the American Psychiatric Association (Lehman et al. 2004) in the United States, and the Royal Australian and New Zealand College of Psychiatrists (RANZCP) Clinical Practice Guidelines Team for the Treatment of Schizophrenia and Related Disorders (2005) in Australia. All of these guidelines recommend SGAs rather than FGAs for the treatment of first-episode schizophrenia on the basis of the SGAs' better tolerability and reduced risk of tardive dyskinesia. It is important to select the antipsychotic drug and a dose level that is effective and unlikely to cause side

effects that are subjectively distressful. Optimal antipsychotic dosage ranges recommended for first-episode patients are relatively lower than those recommended for patients with multiepisode illness, because first-episode patients are more sensitive to the therapeutic effects and medication side effects.

Determining the optimal dosage level for antipsychotic medication in the acute phase, regardless of whether in the first episode, is complicated because therapeutic response is usually delayed from the time of treatment initiation. It may take approximately 2–4 weeks before initial response can be seen and up to 6 months for full response to be observed. Therefore, the dosage level should be expeditiously titrated to the target therapeutic range (considered to be approximately 300–1,000 mg/day in chlorpromazine equivalents, depending on the patient's previous experience with antipsychotic medication), while monitoring for intolerance. Unless the patient has uncomfortable side effects, the patient's clinical status then should be monitored for 2–4 weeks before increasing the dose or changing medication. During these weeks, it is important for the clinician to avoid the temptation to prematurely elevate the dose of patients who may be showing improvement at only a limited rate.

If the patient shows no improvement, the clinician first must consider whether the lack of response can be explained by medication nonadherence. If nonadherence is the problem, then the patient's symptoms should not be considered treatment resistant, and behavioral tailoring (i.e., incorporating medication into daily routine), motivational interviewing, and other cognitive-behavioral techniques may be introduced to improve the patient's understanding of the potential benefits of medication (Kemp et al. 1998). Although many patients prefer oral medication, patients with recurrent relapses because of nonadherence are candidates for a long-acting injectable (depot) antipsychotic medication, which has the practical clinical advantage of avoiding covert nonadherence. Plasma concentration is clinically relevant when clozapine and haloperidol are used to confirm the adherence level. Depot preparations guarantee consistent drug delivery and overcome the bioavailability problems that occur with oral preparations. Despite these advantages, some patients may experience depot injection as controlling, limiting of their autonomy, and painful. Nevertheless, more than a few patients receiving depot medication prefer depot to oral medication because of the convenience (Heres et al. 2007; Walburn et al. 2001). If the patient is adhering to treatment but still is not responding to treatment within 2–4 weeks of attaining the target thera-

peutic dose, another medication—preferably one from a different chemical class—should be considered.

In the acute phase of schizophrenia, other psychoactive medications are commonly added to antipsychotic medications to treat comorbid conditions or associated symptoms such as agitation, aggression, affective symptoms, sleep disturbances, and drug side effects. For example, benzodiazepines are commonly used to manage anxiety and agitation. Mood stabilizers and β-blockers are considered effective in reducing the severity of hostility and aggression. Major depression and obsessive-compulsive disorder are common comorbid conditions in patients with schizophrenia and may respond to antidepressants. Sleep disturbances are also very common in the acute phase, and benzodiazepines and sedating antidepressants are reported to be helpful. The decision to use antiparkinsonian medications to treat EPS is driven by the severity and by whether other potential strategies are available, including reducing the dosage of the antipsychotic medication or switching to a different antipsychotic drug. The propensity of the antipsychotic drug to induce EPS, the patient's preferences, the patient's history of EPS, other risk factors for EPS, and potential consequences of anticholinergic side effects must be considered in the decision. Careful attention must be paid to potential drug interactions, especially those related to the cytochrome P450 enzymes, in using these adjunctive medications.

Standard Psychosocial Treatment

It seems reasonable to state that standard psychosocial treatments have not yet been established, gauging from variability among psychosocial treatments recommended in the guidelines. Some basic psychosocial approaches are available that are feasible and essential for the treatment of schizophrenia (Table 9–8). Schizophrenia should not be defined as treatment resistant until these approaches have been administered, even if the patient failed to attain an adequate level of functioning. We briefly refer to these approaches in this subsection.

Above all, establishing a good therapeutic alliance helps the patient to participate actively in treatment in partnership with the clinician. Identifying the patient's goals and relating them to treatment outcomes fosters the patient's motivation for treatment, which ultimately improves treatment adherence. The clinician also may identify factors that could hamper the patient's ability to participate in treatment, such as cognitive deficits, disorganization, lack of

Table 9–8. Standard psychosocial treatment of schizophrenia

- Basic psychosocial approaches should be appropriately administered before the patient is labeled treatment resistant due to suboptimal treatment response.
- Establishing and maintaining a good therapeutic alliance throughout the treatment course is essential for good outcomes.
- Psychoeducation, family intervention, and social skills training are recommended as standard psychosocial approaches, considering their feasibility and effectiveness across broad clinical domains.

insight, and inadequate social resources. Engagement of the family and other significant caregivers is recommended to further strengthen the patient's adherence to treatment. The social circumstances, including living situation, family involvement, relationships with significant others, and available social services, are all areas that may be periodically explored by clinicians. The psychiatrist should work with team members, the patient, and the family to ensure that such concerns are attended to.

At the very least, all patients with schizophrenia should receive education that provides reliable and accurate information about their illness. In mental health care, the delivery of information to clarify the goals of treatment and to help patients or their caregivers change their behavior, skills, and attitudes, with the aim of improving their cognitive, affective, and psychomotor processes, has been termed *psychoeducation.* Psychoeducation has been developed as an aspect of treatment in schizophrenia with a variety of goals beyond the provision of accurate information.

Another standard psychosocial approach is family intervention, which has several aims, including developing an alliance with caregivers, reducing emotional distress, creating or re-creating a positive home atmosphere, recovering a healthy family relationship, problem solving, maintaining realistic expectations of patient performance, and helping to set limits and appropriate relationship boundaries. Family interventions have evolved from studies of the family environment and its possible role in the course of schizophrenia (Bebbington and Kuipers 1994; Brown et al. 1962, 1972). Family interventions usually have three components: 1) alliance formation, 2) didactic instruction, and 3) more specialized family therapy, such as problem solving and crisis management. A given family's needs are assessed, followed by didactics on a range of topics, such

as community resources; clinical features, treatment, and etiology of schizophrenia; and the family's role in promoting recovery. The intended goal is to prevent relapse when the treatment program is provided over 6 months or longer or for more than 10 sessions, especially when the patient is included in the sessions. Families, especially those with high expressed emotion, have been known to benefit from the approach, as indicated by reduced relapse rates. Favorable effects on patient employment and independent living skills also have been reported. Effects of the intervention on families have included lower burden of illness, increased knowledge, and decreased expressed emotion.

Social skills training (SST) was developed as a more sophisticated treatment strategy derived from behavioral and social learning traditions (Wallace et al. 1980), given the complex and debilitating behavioral and social effects of schizophrenia. SST was designed to help people with schizophrenia regain their social skills and confidence, improve their ability to cope in social situations, reduce social distress, improve their quality of life, and aid symptom reduction and relapse prevention.

SST has been thoroughly disseminated in many countries. For example, the modules of the UCLA Social and Independent Living Skills Program have been translated into 23 languages and are used on six continents (Kopelowicz et al. 2006). However, the review used for the National Institute for Health and Clinical Excellence (2009) guidelines found insufficient evidence to determine whether SST as a discrete intervention improved outcomes in schizophrenia. A Cochrane review also failed to find conclusive evidence of benefit (Tungpunkom and Nicol 2008). Nonetheless, the APA guidelines (Lehman et al. 2004) noted the benefit of SST in improving knowledge, social skills, and symptom and medication management when offered with adequate pharmacological treatments. More research is needed to determine whether patients transfer the skills learned in these programs to real-world settings. To enhance generalization of skills to everyday life, social skills training must be tailored to the patient's specific circumstances and integrated with other therapies and treatments, and must also seek to foster supportive relationships with nonprofessional helpers in the patient's environment (Kopelowicz et al. 2006).

Other effective psychosocial treatments, including CBT, supported employment, Assertive Community Treatment (ACT), and intensive case management, are available but may not be the best fit in certain settings because of impracticality and may not be considered standard treatment. Therefore,

these treatments are best regarded as optional according to the patients' needs and social context.

Definitions of Treatment Resistance Beyond the Concept of Clozapine Eligibility

The appropriate definition of *treatment resistance* depends on the circumstances in which the definition is to be applied. For example, a narrow definition is suitable for research purposes relating to an antipsychotic drug for which the indication will be treatment-resistant schizophrenia, whereas a broader definition that incorporates assessment of psychosocial functioning, cognitive deficits, affective symptoms, and behavior problems may be appropriate for clinical practice (Table 9–9).

Narrower definitions primarily focused on suboptimal response of positive symptoms to medication treatment. Persistent psychotic symptomatology gained much interest, largely as a result of lack of valid outcome assessment or standard treatment in other domains such as psychosocial functioning, cognitive deficits, affective symptoms, and behavior problems. A trend in the field has been a movement away from the rigorous criteria of Kane et al. (1988) and toward a broader definition of treatment resistance from the viewpoint of expanding the group of patients who were considered to be clinically eligible for treatment with clozapine. For example, the historical criteria of Kane et al. (1988) required suboptimal response in at least three trials of antipsychotic medication at dosages equivalent to or greater than 1,000 mg/day in chlorpromazine equivalents in order to be categorized as treatment resistant; however, more recent guidelines suggest that two adequate trials at dosages equivalent to 300–1,000 mg/day of chlorpromazine are sufficient.

Additional domains to be used in the broader definition are particularly important for systems of care worldwide, with their growing emphasis on community-based treatment and recovery-oriented practice, although standard criteria for assessment of outcome measures are not yet available. As early as 1990, Brenner et al. clearly stated that "treatment refractoriness is defined as continuing psychotic symptoms with substantial functional disability and/or behavioral deviances that persist in well-diagnosed persons with schizophrenia despite reasonable and customary pharmacological and psychosocial treatment

Table 9–9. Definitions of treatment resistance

- At least two definitions of treatment resistance are proposed: a narrow definition suitable for research purposes and a broader definition appropriate for clinical practice.
- Narrower definitions primarily focused on suboptimal response of positive symptoms to medication treatment.
- A broader definition includes not only medication effects but also psychosocial treatment effects and assessment of psychosocial functioning, cognitive deficits, affective symptoms, and behavior problems.
- A broader definition is appropriate for clinical practice, although standard criteria for assessment of outcome measures are not yet available.
- Both definitions of treatment resistance using a continuum and those using dichotomous cutoff thresholds are of practical use, according to the circumstances.

that has been provided continuously for an adequate time period" (pp. 552–553). Brenner and colleagues noted that it would be premature to label suboptimal response as treatment resistance before providing adequate exposure to well-administered psychosocial treatment. Moreover, they included functional disability and/or behavioral deviances as outcome measures in their definition of treatment resistance (Brenner et al. 1990). It was recognized that accuracy of the clinical history of a patient's exposure to adequate drug and psychosocial treatments might be limited because such information often relies on self-report. With all other complexities, such as the patient's adherence level and side effects that obviate use of appropriate dose levels, further screening for treatment responsiveness under a well-controlled trial may be required before the schizophrenia is categorized as treatment resistant.

The criteria proposed by Brenner et al. (1990) incorporated a construct reflecting a multidimensional continuum of treatment resistance–treatment response (Table 9–10). This method of depicting treatment resistance arose from the view that most patients with schizophrenia who are considered unresponsive to treatment are, in fact, suboptimal responders of various degrees. Meanwhile, dichotomous cutoff thresholds along the continuum also might be relevant in determining "treatment resistance" for referring patients to intensive treatment programs, including psychosocial and pharmacological interventions.

Table 9–10. Global Rating Scale of Treatment Response and Resistance in Schizophrenia

Level 1—Clinical remission	Rapid and substantial response when antipsychotic medication given in recommended dosage, but the patient might manifest some anhedonic traits and other negative symptoms. CGI: normal, not mentally ill. Any of the BPRS psychotic scale items score ≤2. Able to function without supervision.
Level 2—Partial remission	Rapid reduction of schizophrenic symptoms with mild signs of residual psychotic symptomatology. CGI: score of 2 = borderline mentally ill. None of the BPRS psychotic scale items score ≥3. Able to function with only occasional supervision in one domain of social and vocational activities.
Level 3—Slight resistance	Slow and incomplete symptom reduction and residual positive and negative symptoms have adverse effects on two or more areas of personal and social adjustment requiring occasional supervision. CGI: score of 3 = mildly ill. Not more than one BPRS psychotic scale item score ≥4.
Level 4—Moderate resistance	Some symptom reduction, but persistent and obvious symptoms adversely affect four or more areas of personal and social adjustment requiring frequent supervision. CGI: score of 4 = moderately ill. Two of the BPRS psychotic scale items scores = 4. Total BPRS score is at least 45 on the 18-item version and at least 60 on the 24-item expanded BPRS.
Level 5—Severe resistance	Some symptom reduction, but persistent symptoms adversely affect six or more areas of personal and social adjustment requiring frequent supervision. CGI: score of 5 = markedly ill. One BPRS psychotic scale item score = 5, or at least three of the items = 4. Total BPRS score of at least 50 on the 18-item version and at least 67 on the 24-item expanded version.

Table 9–10. Global Rating Scale of Treatment Response and Resistance in Schizophrenia *(continued)*

Level 6—Refractory	Slight or no obvious symptom reduction, and persistent positive and negative symptoms markedly disrupt all areas of personal and social adjustment. CGI: score of 6=severely ill. At least one BPRS psychotic scale item score =6, or two items score ≥5. Total BPRS scores are at least as high as in level 5.
Level 7—Severely refractory	No symptom reduction, with high levels of positive and negative psychotic symptoms associated with behavior observed to be helpless, disturbing, or dangerous. All areas of personal and social adjustment are seriously impaired and require constant supervision. CGI: score of 7=among the most extremely ill patients. At least one BPRS psychotic scale item score =7. Total BPRS scores are at least as high as in level 5.

Note. The scale levels consist of an index of values from the Clinical Global Impressions (CGI) Scale, the psychotic items from the Brief Psychiatric Rating Scale (BPRS), and a determination of independent functioning from a scale such as the Independent Living Skills Survey. "Rapid" reduction of symptoms is defined by relief in the first 6 weeks of treatment. To permit initial treatments to have their effect, no patient should be classified as level 5 or higher before 2 years of persisting symptoms and disability have elapsed following the first admission to hospital. For convenience, the Global Rating Scale can be collapsed into three levels: 1 and 2 reflect "remission"; 3 and 4 reflect "suboptimal response"; and 5, 6, and 7 reflect "treatment refractory."

Source. Reprinted from Brenner HD, Dencker SJ, Goldstein MJ, et al: "Defining Treatment Refractoriness in Schizophrenia." *Schizophrenia Bulletin* 16(4):558, 1990. Used by permission of Oxford University Press.

The Japanese Society of Psychiatry and Neurology is currently in the process of developing clinical guidelines for the treatment of schizophrenia. In the preliminary guidelines, tentative definition criteria for treatment-resistant schizophrenia were developed by combining responses to the survey of expert opinions and the proposals in other previously reported international guidelines (Table 9–11). Although most experts in Japan recognized the need to include domains other than positive and negative symptomatology, such as cognitive and psychosocial functioning, in the criteria, they decided against

Table 9–11. Proposed criteria for treatment resistance in schizophrenia: Japanese Society of Psychiatry and Neurology

Moderate level

1. With appropriate psychoeducation providing information about the illness and monitoring medication adherence, at least two trials of different antipsychotic medications with adequate daily dosage levels (≥600 mg/day of chlorpromazine equivalents) for a period of at least 6 weeks should be administered, along with other appropriate psychosocial approaches.
2. With appropriate psychoeducation providing information about the illness and monitoring medication adherence, and if adequate daily dosage levels (≥600 mg/day of chlorpromazine equivalents) could not be attained because of severe side effects, the eligible upper limit of dosage levels should be administered, along with other appropriate psychosocial approaches.
3. Positive or negative symptoms that may adversely affect the patient's activities of daily living (score of at least 3 in at least two items of Positive and Negative Syndrome Scale [PANSS] positive or negative symptom scales and PANSS total scores of at least 80) should last for at least 1 year.

Severe level

1. With appropriate psychoeducation providing information about the illness and monitoring medication adherence, at least two trials of different antipsychotic medications with adequate daily dosage levels (≥1,000 mg/day of chlorpromazine equivalents) for a period of at least 6 weeks should be administered, along with other appropriate psychosocial approaches.
2. With appropriate psychoeducation providing information about the illness and monitoring medication adherence, and if adequate daily dosage levels (≥1,000 mg/day of chlorpromazine equivalents) could not be attained because of severe side effects, the eligible upper limit of dosage levels should be administered, along with other appropriate psychosocial approaches.
3. Prominent positive or negative symptoms that may seriously affect the patient's activities of daily living (score of at least 4 in at least two items of PANSS positive or negative symptom scales and PANSS total scores of at least 100) should last for at least 1 year.

Source. Reprinted from Nakagome K: "Treatment refractory, treatment resistant?" in *Treatment Strategies for Treatment-Refractory Psychiatric Disorders* ("Lumière" Series for Specialists of Clinical Psychiatry no. 15). Edited by Nakagome K. Tokyo, Japan, Nakayama Shoten Co., Ltd., 2010, pp. 2–11. Used with permission.

including them at this time because they were unable to reach a consensus on the standard cutoff thresholds for defining "treatment resistant" in these domains. They also refrained from rigorously defining the standard psychosocial treatments for a similar reason, considering the great variance in the range and level of available treatments. Finally, they agreed that the definition of treatment resistance should reflect a continuum of responsiveness-unresponsiveness, and thus, two-stage models—including both a moderate level and a severe level—were adopted. The proposed guidelines have many limitations that must be overcome in the future. For example, what are the appropriate psychosocial treatments? We need more evidence to support which psychosocial approach is most effective for a particular patient and more clinicians in the field who could implement the psychosocial treatment optimally by promoting a process of dissemination.

Before moving to the topic of methods to treat schizophrenia that is labeled as treatment resistant, we need to explore other confounding factors relevant in forming a clinical picture as observed in a treatment-resistant patient. The patient factors include illicit substance misuse, physical comorbidity, and poor quality of the social environment, and the treatment factors include noncompliance, drug-drug interactions, delay in initiating treatment, drug bioavailability problems, and poor therapeutic alliance between physician and patient, all of which should be addressed before undergoing various interventions noted in the next section.

Treatment of Resistant Schizophrenia

Recommendations for Physical Treatment

Clozapine

Strong evidence suggests that clozapine is more efficacious than other antipsychotic drugs in treatment-resistant schizophrenia (Table 9–12). However, clozapine's potential for agranulocytosis and other serious side effects has generally limited its use to patients with treatment-resistant schizophrenia (Tandon et al. 2008). Clozapine has shown benefits over other antipsychotic drugs not only for positive symptoms but also for suicidality (Meltzer et al. 2003), violent behaviors (Krakowski et al. 2006), and comorbid substance misuse (Green 2006). Clozapine also was found to be associated with a remarkably

Table 9–12. Physical intervention strategies for treatment-resistant schizophrenia

- Clozapine shows superiority in treatment-unresponsive and -intolerant schizophrenia.
- Clozapine shows benefits not only in terms of positive symptoms but also suicidality, violent behaviors, or comorbid substance misuse.
- Clozapine is associated with low incidence of tardive dyskinesia and plasma prolactin elevation.
- Clozapine has been underused for various reasons, including occurrence of agranulocytosis, restriction of the providers, costs, and complexities of clozapine treatment.
- Besides clozapine, limited treatment options with scarce evidence are often used in a trial-and-error process, including augmentation or adjunctive strategies with various types of drugs.
- Efficacy of electroconvulsive therapy (ECT), maintenance ECT, and repetitive transcranial magnetic stimulation (rTMS) adjunctive to antipsychotic medications is supported by several studies.
- Recently, development of novel drugs that target unmet treatment needs, including cognitive deficits, has been in progress with the hope that they may show efficacy against treatment-resistant schizophrenia of broader definition.

low incidence of tardive dyskinesia and plasma prolactin elevation, which may be the result of its weak dopamine type 2 (D_2) receptor blockade. In contrast to clozapine's superiority in treatment-unresponsive and -intolerant schizophrenia, no such evidence of its greater efficacy is found in first-episode schizophrenia (Lieberman et al. 2003) or among other patient populations, raising the question of exactly when in the course of the illness clozapine's benefits for treatment-resistant schizophrenia begin to appear.

Several studies suggested that clozapine serum concentrations can be useful to help guide dosing (Perry et al. 1991; VanderZwaag et al. 1996). Dosage levels of 300–600 mg/day are generally needed to achieve the plasma concentrations for good response (≥350 ng/mL), although care is needed because nicotine lowers the concentrations (Chung and Remington 2005). The dosage levels should be increased gradually—not exceeding 600 mg/day—to avoid serious side effects (e.g., the risk of seizures is dose-dependent).

Although many researchers strongly recommend clozapine as the agent of choice for treatment-resistant schizophrenia, and progression to clozapine use in the treatment course is explicitly encouraged, reluctance to use clozapine in the clinical field is apparent. For example, Phase II results of CATIE showed that many participants chose the tolerability pathway (n=444) over the efficacy pathway (n=99) (Swartz et al. 2008), presumably to avoid being assigned to clozapine treatment (clozapine was an option in the efficacy pathway of Phase II but not in the tolerability pathway). The provider restrictions, high costs, and complexities of clozapine treatment are necessary for treatment safety and efficiency but may have had the unintended consequence of reducing training opportunities for many residents and leading to underuse of clozapine for patients who might otherwise gain benefit from the drug.

Augmentation and Adjunctive Strategies

Besides clozapine, options are limited for the many patients with treatment-resistant schizophrenia, and none has been supported by systematic evidence. Various augmentation strategies that have limited or no evidence supporting their efficacy are often used. Overall effectiveness in a certain patient group does not always translate into effectiveness in each individual patient. No best drug or best dose of any drug exists for all patients. Predicting which antipsychotic medication might be optimal for a given patient is impossible. Decisions about antipsychotic therapy consequently entail a trial-and-error process with careful monitoring of clinical response and side effects and an ongoing risk-benefit assessment. Therefore, clinicians may consider a time-limited trial of a drug to determine whether it may offer any benefit exceeding risk to an individual patient.

It is recommended that patients with treatment-resistant schizophrenia be given a trial of clozapine monotherapy for up to 6 months insofar as no serious side effects occur. If optimal response is not attained after an adequate trial of clozapine, adjunctive agents such as mood stabilizers (e.g., lithium, valproate, lamotrigine), benzodiazepines (e.g., clonazepam), propranolol, antidepressants, or antipsychotic drugs may be tried, depending on the residual symptom profile. It should be noted that these augmentation strategies for clozapine are not supported by evidence. For example, the TMAP algorithm recommends clozapine augmentation with an SGA or FGA for patients whose symptoms do

not respond to clozapine alone, although a review of the TMAP documentation suggests that the evidence favoring either risperidone or lamotrigine is weak (Moore et al. 2007). In one study, the placebo group actually showed greater improvement than the risperidone group on PANSS positive syndrome scale scores (Anil Yaciolu et al. 2005). RANZCP guidelines, by contrast, recommend the use of the most effective prior drug and an appropriate adjunctive therapy, such as lithium (Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for the Treatment of Schizophrenia and Related Disorders 2005). Such adjunctive strategies should be considered on an individual basis, with goals of treatment carefully defined and subsequently monitored so that ineffective polypharmacy is not sustained.

Adjunctive Brain Stimulation Therapies

Patients with schizophrenia who are not eligible for clozapine treatment because of intolerable side effects or physical comorbidity may respond to electroconvulsive therapy (ECT) in combination with different antipsychotic medications (Tharyan and Adams 2005). Even though this initial beneficial effect may not last long, several studies suggest the sustained effectiveness of maintenance ECT adjunctive to antipsychotic medications (Chanpattana et al. 1999; Shimizu et al. 2007). Efficacy of adjunctive ECT with clozapine also was supported by several case series and open studies, which did not present any serious side effects of coadministration (Braga and Petrides 2005).

Several studies indicated the efficacy of slow repetitive transcranial magnetic stimulation (rTMS) adjunctive to antipsychotic medications, targeting the left temporoparietal cortex at a frequency of 1 Hz, for treatment-resistant auditory hallucinations. In a meta-analytic review of 10 sham-controlled trials (involving 212 patients), a significant mean weighted effect size for rTMS versus sham—d=0.76 (95% confidence interval=0.36–1.17)—was observed for treatment gain on hallucination ratings across the studies, but no significant effect was seen on a composite index of general psychotic symptoms (Aleman et al. 2007). Although more studies are needed to confirm its efficacy, slow rTMS may well be a treatment option for resistant auditory hallucinations. Only one small controlled study compared the efficacy of active rTMS with sham for clozapine nonresponders; it concluded that rTMS could be administered safely to patients taking clozapine, although no significant benefit was found for rTMS in this population (Rosa et al. 2007).

Novel Pharmacological Approaches

Although scarcely any evidence favors antipsychotic combination therapy, which also increases the side-effect burden, an alternative paradigm has been proposed (Carpenter 2004; Webber and Marder 2008). In this paradigm, the relative independence of reality distortion, disorganization, negative pathology, and cognition deficits is stressed. Monotherapy with antipsychotic drugs does not address all of these problems. These unmet treatment needs are clinical targets for drug discovery involving novel therapeutic strategies including combination therapy. Considering the unique properties of clozapine's mechanism of action, clozapine's major active metabolite *N*-desmethylclozapine (NDMC), which has glycine reuptake inhibition properties and cholinergic muscarinic-1 receptor agonistic function, is a candidate for an adjunct to existing antipsychotic medications for patients with treatment-resistant positive symptoms (Natesan et al. 2007). In regard to persistent negative symptoms, the effectiveness of adjunctive antidepressants has been reported in several studies, although findings remain inconsistent. Augmentation of antipsychotic medications with mirtazapine, paroxetine, fluvoxamine, or the selective monoamine oxidase type B inhibitor selegiline has shown benefit in respective controlled studies that have isolated the effect on negative symptoms from the effect on secondary factors, including positive symptoms, depression, and EPS (Webber and Marder 2008). The MATRICS project identified nine promising molecular targets for cognition-enhancing agents with a potential for pronounced efficacy in cognitive deficits in schizophrenia, which has been unfulfilled by atypical antipsychotic drugs (Green 2007; Webber and Marder 2008):

1. α_7-Nicotinic receptor agonists
   - Partial α_7-nicotinic cholinergic agonist (3-[(2,4-dimethoxy)benzylidene]-anabaseine, DMXB-A)
   - Acetylcholinesterase inhibitor (galantamine)
2. D_1 receptor agonists
   - Full D_1 agonist (dihydrexidine, DAR-0100)
3. AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) glutamatergic receptor agonists
   - Positive allosteric modulators of AMPA receptors, AMPAkines (CX-516)

4. α_2-Adrenergic receptor agonists
   - α_2 Receptor stimulators, antihypertensive drugs (clonidine, guanfacine)
5. *N*-methyl-D-aspartate glutamatergic receptor agonists
   - D-Cycloserine, glycine, D-serine
6. Metabotropic glutamate receptor agonists
   - mGlu2/3 agonist (LY2140023)
7. Glycine reuptake inhibitors
   - Sarcosine
8. M_1 muscarinic receptor agonists
   - NDMC (ACP-104)
9. γ-Aminobutyric $acid_A$ receptor subtype selective agonists
   - α_2-Subunit specific stimulator, positive allosteric modulators

Recommendations for Psychosocial Treatment

Psychosocial treatments may play an important role in improving outcomes in treatment-resistant schizophrenia. In the same way that pharmacological treatment must be individually tailored to the needs and preferences of the patient, so, too, must psychosocial treatment (Table 9–13). The selection of appropriate and effective psychosocial interventions for patients with treatment-resistant schizophrenia must be driven by the individual patient's needs and his or her social circumstances. Most patients will benefit from at least some of the recommended psychosocial interventions. However, because patients' health and social needs may vary at different points in their illness course, it would be rare for all of these psychosocial interventions to be used during any one phase of illness for an individual patient.

The contribution of pharmacological treatment in enabling patients to fully benefit from participation in psychosocial treatment programs is noteworthy. Rosenheck et al. (1998) monitored the use of different levels of psychosocial treatments and rehabilitation in patients assigned to a comparison of clozapine and haloperidol. Patients receiving clozapine were more likely to use higher levels of psychosocial treatment. Moreover, the use of these higher