New Developments in the Treatment of Schizophrenia

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the planning teleconferences "New Developments in the Treatment of Schizophrenia," which were held in September 2006. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Janssen, L.P. administered by Ortho-McNeil Janssen Scientific Affairs, LLC.*

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Schizophrenia is a disease that ranks in the top 5 causes of disability for young adults in developed countries.[1] In addition to the delusions, hallucinations, and disturbances in affect that are characteristics of schizophrenia, the illness is also associated with impairments in the high-level functions of planning, learning, and social activity. The impairments of schizophrenia impact every aspect of a patient's life and thereby have a debilitating effect on the patient's ability to function in society.

Evidence shows that while the psychotic symptoms of schizophrenia can be adequately treated with medication, relatively less improvement is usually seen in the areas of occupational, social, and independent functioning.[2,3] The cognitive deficits of schizophrenia have been shown to be directly linked to functional ability[4,5]; therefore, successful medical treatment of cognitive impairment should improve a patient's functional outcome.[6]

Another reason for poor functional outcome may be the high rate of medication noncompliance. Studies[7–9] have shown that as many as 50% to 80% of patients are unwilling or unable to take medication as directed. Clinicians need to be aware of the potential for increasing medical adherence through the use of long-term drug delivery systems.

The purpose of this ACADEMIC HIGHLIGHTS is to provide clinicians with the necessary information to help in the formulation of individualized treatment plans for patients with schizophrenia. Topics such as the efficacy and safety profiles of available treatments, the improvement of cognitive function, compliance with medication, and the functional outcome of treatment were presented by experts in the treatment of patients with schizophrenia.

Treatment Compliance and Outcome With Atypical Antipsychotics

John M. Kane, M.D., began his presentation by briefly outlining the goals of schizophrenia treatment. On first presenting to a hospital or emergency department, a patient may be agitated, aggressive, or violent. Controlling this behavior should be the physician's first concern. Focus should then be turned to the patient's positive symptoms, for example, disorganized behavior, thought disturbances, suspiciousness, delusions, or hallucinations. Next, a treatment strategy should be considered for the patient's negative symptoms such as impaired cognition, motivation, affect, and mood, which can affect the outcome of the treatment as a whole. Dr. Kane described the ultimate goal of treatment—and probably the best test of its success—as the ability of the patient to reenter the community and function socially and in the workplace.

Understanding and Preventing Relapse

Dr. Kane noted that a clinician may face several challenges during the course of treating schizophrenia, including the risks of patient suicide or violence, nonadherence to the treatment regimen, relapse of symptoms, and deterioration over time. Dr. Kane explained that relapse can be extremely costly to patients' self-esteem, social and family relationships, educational

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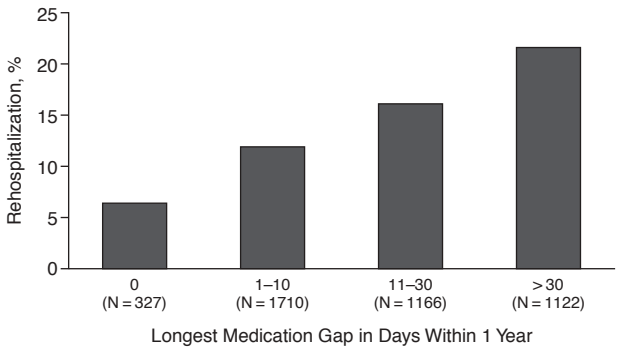
Table 1. First-Episode Relapse Rates for Patients With Schizophrenia (N = 104)[a]

Year Since Last Episode	Relapse Rate, %
1	16.2
2	53.7
3	63.1
4	74.7
5	81.9

[a]Adapted with permission from Robinson et al.[10]

Figure 1. Patients With Schizophrenia Rehospitalized Because of Partial Compliance With Medication[a]



[a]Adapted with permission from Weiden et al.[11]
All pairwise comparisons were significant at $p < .005$.

goals, and career, especially for patients in the early phase of the illness. Patients can feel devastated at losing their hard-won progress.

One study[10] found that patients with first-episode schizophrenia or schizoaffective disorder had a relapse rate of about 82% after the first 5 years of treatment (Table 1). The most likely contributors to relapse were discontinuation of medication or partial compliance with the prescribed medication regimen. In fact, patients who discontinued medication were almost 5 times more likely to relapse than those patients who continued their medication.

In a study of partial compliance, Weiden and colleagues[11] reviewed the prescription records of several hundred patients with schizophrenia to identify the occurrence and duration of medication gaps. The study found a direct correlation between the length of the medication gap and the likelihood of rehospitalization (Figure 1). Even the shortest gap, 1 to 10 days, resulted in a significant ($p < .005$) increase in the rate of relapse and rehospitalization in comparison to those patients with no medication gap. Dr. Kane stressed that, although managing partial compliance or nonadherence is challenging for clinicians, encouraging patients to continue medication is critical for preventing relapse.

Dr. Kane related that adverse events associated with a prescribed medication can negatively affect medication adherence. Research[12] has shown that of those side effects attributable to antipsychotic medication, akinesia, weight gain, anticholinergic side effects, and sexual problems were most distressing to patients. If patients are distressed by medication, and clinicians are not successful in managing the source of that distress, the risk of nonadherence is increased, according to Dr. Kane. Selecting the appropriate antipsychotic medication for the patient is one of the strategies that may help prevent nonadherence due to intolerable side effects.

Choosing an Antipsychotic

Dr. Kane named 3 considerations when choosing an antipsychotic medication for the treatment of schizophrenia: the illness profile, the patient profile, and the medication profile. First, the clinician needs to have a thorough understanding of the onset and course of the illness and its presenting signs and symptoms. Second, patient variables should be considered, including vulnerability to adverse effects and tolerance of them, degree of insight and attitude toward the illness, previous response to treatment and treatment preferences, any comorbid medical or psychiatric conditions, comorbid substance abuse, and network of social support. Last, the medication profile should be considered, taking into account short- and long-term efficacy and tolerability, available formulations and delivery methods, any required patient monitoring, the cost of the medication, and any possible pharmacokinetic considerations.

Comparing Conventional Antipsychotics With Atypical Antipsychotics

Dr. Kane summarized data examining the possible superiority of atypical (or second-generation) antipsychotics over conventional (or first-generation) medications by comparing the relative efficacy, safety, and rates of adherence and relapse of each class of drugs.

Efficacy. Citing a meta-analysis by Davis et al.,[13] Dr. Kane stated that research has suggested that, when it comes to the efficacy of atypical antipsychotics, clozapine, amisulpride, risperidone, and olanzapine have demonstrated the greatest separation from the conventional medications. Dr. Kane stressed that the other atypical drugs are not necessarily less effective than those previously mentioned, but that fewer data supporting their superiority are available.

Safety. Besides efficacy, another important consideration with medication selection is safety and tolerability. Dr. Kane recounted the results of a review[14] in which he and his colleagues compared first- and second-generation antipsychotics in regard to the incidence of tardive dyskinesia, a major long-term adverse effect associated with first-generation antipsychotics.

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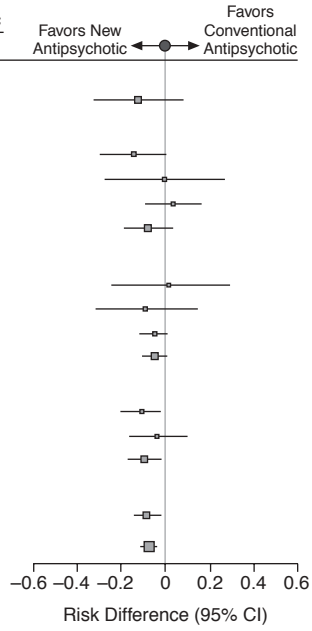
Figure 2. Difference in Risk of Relapse Rates in Patients With Schizophrenia: New Versus Conventional Antipsychotics[a]



[a]Adapted with permission from Leucht et al.[17]
[b]Heterogeneity: $\chi^2 = 4.24$, df = 2, p = .12; risk difference = –0.08, 95% CI = –0.19 to 0.04, z = –1.35, p = .18.
[c]Heterogeneity: $\chi^2 = 0.38$, df = 2, p = .83; risk difference = –0.05, 95% CI = –0.11 to 0.01, z = –1.59, p = .11.
[d]Heterogeneity: $\chi^2 = 0.91$, df = 1, p = .34; risk difference = –0.10, 95% CI = –0.18 to –0.02; z = –2.49, p = .01.

Despite variability in the data, compelling evidence suggested that treatment with atypical antipsychotics reduced the risk of tardive dyskinesia to about 20% of what it was with conventional agents.

Nonadherence and discontinuation. Patient adherence to antipsychotic treatment can be problematic. A study[15] analyzing pharmacy refill records found that, over the course of 1 year, patients who were prescribed conventional antipsychotics went without their drugs for an average of 7 days per month, while those prescribed atypical antipsychotics went without for an average of 4 days per month. Compliant fill rates were about 55% for atypical agents and about 50% for conventional agents. Dr. Kane observed that while adherence was higher with the newer agents, the results were still disappointing.

In his discussion of patient-driven discontinuation of treatment, Dr. Kane reviewed the results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE),[16] a large study funded by the National Institute of Mental Health (NIMH) that compared the effectiveness of a series of atypical antipsychotics with a single first-generation antipsychotic. Subjects with tardive dyskinesia were not allowed to be assigned to the first-generation agent. One outcome of the first phase CATIE was that about 75% of patients discontinued their assigned medication owing to lack of efficacy, intolerability, or both. Olanzapine showed a slight advantage over the other medications, with an average discontinuation rate of 64%, but even this rate is less than satisfactory. An important message from the CATIE study was that patients and clinicians were not sufficiently satisfied with either the response or the tolerability of the conventional or atypical antipsychotics and often felt that it was necessary to change medications.

Relapse. Another finding of the CATIE trial was that the mean duration of successful treatment, which was defined as a relatively stable and asymptomatic phase, for each of the studied drugs except olanzapine was about 1 month.[16] Olanzapine again showed a slight advantage with a mean duration of successful treatment of approximately 3 months.[16] Even when using the second-generation medications, most patients achieved the level of successful treatment for a very brief period.

However, a meta-analysis[17] of studies that randomly assigned patients to either first- or second-generation antipsychotics and followed their progress for a year found a significant difference in favor of the atypical antipsychotics in reducing the rate of relapse (Figure 2). At the end of 1 year, the average relapse rate with the conventional drug haloperidol was 23%, compared with an average relapse rate of 15% with second-generation medications. Dr. Kane interpreted this study's results as showing that if 1000 patients are treated for 1 year with an atypical antipsychotic instead of a conventional drug such as haloperidol, an additional 80 relapses would be avoided.

Nonpharmacologic Treatment

Dr. Kane stated that psychosocial strategies can play an important role in increasing the efficacy of medication treatment and decreasing the rate of patient relapse. Such approaches include psychoeducational interventions involving the patient and the patient's family or caregiver, assertive community treatment, social skills training, cognitive remediation/therapy, and vocational rehabilitation.[27] These strategies can be very effective when combined with medication in improving overall outcome and functioning in a variety of psychiatric illnesses. One study[28] of bipolar disorder, for ex-

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ample, showed that group psychoeducation combined with medication was more effective than medication alone in preventing relapse. Likewise, schizophrenia treatment guidelines[29] state that although medication is necessary, education and psychosocial support are usually also necessary to help patients learn about the disorder and manage their feelings and decisions associated with it.

Conclusion

Dr. Kane reiterated that the newer antipsychotic medications have shown better results in efficacy and tolerability than conventional drugs and that these drugs used in combination with psychosocial treatment strategies have contributed to clinicians' making positive progress in the management of schizophrenia, but many obstacles to successful treatment still exist. Dr. Kane stressed the need for clinicians to be especially sensitive to the following considerations: how efficacious a particular drug is for the individual patient; the occurrence, management, and prevention of adverse events; and what type of psychosocial or disease management strategy might most decrease the chance of relapse and increase the likelihood of a positive overall outcome for the patient.

Measurement-Based Clinical Care in Schizophrenia

In his presentation, Stefan Leucht, M.D., examined the interpretation of response and remission rates in antipsychotic drug trials. He began by describing the development of rating scales used to evaluate symptoms and severity in schizophrenia.

Advantages and Disadvantages of Existing Rating Scales

When the first antipsychotic drug trials were conducted in the 1950s, patients were often described simply as "responders" or "nonresponders" and "improved" or "not improved." An improvement of subjective clinical judgments was the development of the Clinical Global Impressions scale (CGI),[30] a 7-point scale that was published in 1976. The version of the CGI scale that measures severity (CGI-S) assigns scores ranging from 1, "not at all ill," to 7, "among the most extremely ill patients." The version of the CGI that rates improvement (CGI-I) assigns scores ranging from 1, "very much improved" to 7, "very much worse." The scale is intuitive, such that, using his or her total experience of patients with schizophrenia, a clinician can quickly and easily rate the patient's overall clinical state. However, the scale has never been validated; no anchors define what a score of 1 or 5 means, and little research has been undertaken on the psychometric properties of the CGI.[31] But the general problem remains that clinicians have different interpretations of terms such as "much improved," which vary depending on the psychiatrist's personal experience, the ward he or she works in, and so on. Standard definitions are needed.

Rating scales such as the Brief Psychiatric Rating Scale (BPRS)[32,33] and the Positive and Negative Syndrome Scale (PANSS)[34] published in 1962 and 1987, respectively, overcome the problem of the subjective nature of clinical global impressions. The psychometric properties of these scales have been well examined, and the scales have anchors, i.e., clear descriptions, for all their scores. Theoretically, all clinicians trained to use the BPRS or the PANSS should produce the same scores for the same patients. Currently, the PANSS is used more often than the BPRS because the PANSS scores are better anchored. Also, the PANSS covers positive, negative, and general symptoms.

Dr. Leucht pointed out, however, that several problems occur when using the BPRS and PANSS.[35] First, these scales are not intuitive, and it is difficult to say how a particular numerical score on the BPRS or on the PANSS relates to how ill the patient is. Second, understanding the meaning of the cutoff scores used to define response in antipsychotic drug trials is an even more difficult problem. In recent trials,[36,37] a reduction of at least 20% in these scores has often been used as a cutoff in measuring whether patients were responders or nonresponders to medication. Score reductions of 30%,[38,39] 40%,[40] or 50% have also been used, but there is no consensus about which is the most appropriate one. If the cutoff were chosen post-hoc, even manipulations of the data could occur. Dr. Leucht cited a study by Moncrieff and Kirsch[41] that suggested that, if data are normally distributed, taking the mean response rate as the cutoff score would result in the highest sensitivity in finding the superiority of the trial medication against the comparator. By using an artificial boundary between subjects just over or just under the cutoff point, this method resulted in a situation in which a change in score of 1 point could move a large percentage of participants from one category to another.

To compare the clinical meaning of the CGI, BPRS, and PANSS rating scale scores, Dr. Leucht and colleagues undertook an equipercentile linking analysis,[35,42,43] from which it is possible to compare the results of 2 scales that are correlated. To do this type of analysis, the scales should be similar, but they do not need to measure exactly the same constructs; corresponding points on the scales can be found.

Using this analysis method, Dr. Leucht and colleagues first compared the BPRS[35] and then the PANSS[42] total scores and percentage reduction from baseline scores with the CGI-S and CGI-I scores. Anchor points were found for total scores at endpoint of the BPRS and the PANSS compared

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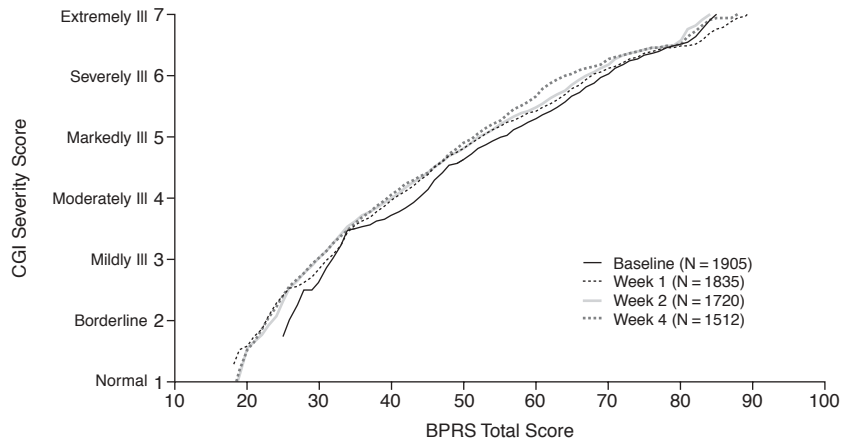
Figure 3. Linking of Clinical Global Impressions (CGI) Severity Score With Brief Psychiatric Rating Scale (BPRS) Total Score[a]



[a]Reprinted with permission from Leucht et al.[35]

with the CGI-S scale rating and the percentage reduction in BPRS and PANSS scores from baseline versus CGI-I scale ratings. These analyses showed that, for example, if the patient scores about 40 on the BPRS or 75 on the PANSS he or she is, on average, moderately ill on the CGI-S scale (Figure 3[35]).[42]

These comparisons have implications for percentage cutoffs used in clinical trials to measure response to treatment, because a 25% reduction in BPRS or PANSS scores means "minimally improved" according to the CGI-I, whereas a 50% reduction in BPRS or PANSS scores means "much improved" on the CGI-I scale.[35,42] These results led to the conclusion that the 20% cutoff frequently used in trials is not a useful cutoff because the patient has not even minimally improved. In acutely ill patients with schizophrenia, a 50% cutoff meaning "much improved" is more clinically useful.

Dr. Leucht commented that a time effect was noted; at week 1, patients needed a smaller percentage of BPRS improvement in order to be rated "much improved" on the CGI-I scale than they needed at weeks 4 or 6 to receive the same CGI-I rating.[35] This result was also observed with the PANSS percentage reduction scores.[42] Dr. Leucht ascribed this effect to problems with CGI ratings, which are not based on anchors, and the fact that physicians feel that any change for the better is important early in treatment. Although methodologically interesting, these effects were not so pronounced as to challenge the conclusions.

Dr. Leucht reported that in the next stage of the research, he and his colleagues examined the clinical meaning of the absolute (not percentage) BPRS and PANSS changes (often used to measure the primary outcome in antipsychotic drug trials).[43] This comparison showed that, on average, a 10-point absolute reduction of the BPRS score and a 15-point absolute reduction of the PANSS score mean clinically "minimally improved" according to the CGI-I scale and also correspond to a reduction of the CGI-S score of at least 1 point.

Dr. Leucht commented that a severity effect was found when the results were divided into 2 groups of patients according to their median BPRS or PANSS total score at baseline; one group had less than the median level of symptoms and the other had more than the median level of symptoms.[43] A relatively smaller absolute reduction of the PANSS or the BPRS scores was associated with a specific degree of change according to the CGI in patients with relatively few symptoms at baseline compared with more severely ill patients. Thus, in severely ill patients, an absolute reduction of the PANSS or the BPRS meant less CGI change than in the less severely ill patients. Dr. Leucht's explanation for this effect was that when a patient has few symptoms at baseline and improves by 5 points on the BPRS or PANSS score, clinicians tend to judge the patient as being "much better." However, when a patient has many symptoms at baseline and then improves by 5 points, he or she still has many symptoms, and the clinician tends to use the rating "minimally improved" or not even judge the patient to be "minimally improved." Dr. Leucht noted that this dependence on baseline severity was not so apparent when the percentage change BPRS or PANSS scores were used.

Interpreting Clinical Trial Results

Dr. Leucht observed that these linking analysis results[35,42,43] are important for interpreting clinical trial results, and people who are familiar with the findings will be able to conclude, for example, that patients with a PANSS score of 60 at endpoint are "mildly ill" according to the CGI-S scale or that a 25% reduction of the BPRS or PANSS score means that clinically the patients are "minimally" better.

Understanding the nuances of interpretation can also help clinicians understand the results of meta-analyses, which may have implications for clinical practice. For example, a meta-analysis by Agid and colleagues[44] showed no delay in onset of action of antipsychotic drugs. The greatest reduction of symptoms in antipsychotic drug trials was found after 1 week, with a 13.8% reduction in total scores on the BPRS and the PANSS scales. However, many clinicians think that there is a delay in onset of action. The reason for this discrepancy between trial results and clinical beliefs is that, whereas the 13.8% reduction in scores was statistically significant, it repre-

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Table 2. Suggestion for a Simple Table to Display Response Rates[a]

Group	Total N	≤ 0% PANSS/BPRS Reduction	> 0% < 25% PANSS/BPRS Reduction	25% to 49% PANSS/BPRS Reduction	50% to 74% PANSS/BPRS Reduction	75% to 100% PANSS/BPRS Reduction
Intervention Group	N	N (%)	N (%)	N (%)	N (%)	N (%)
Control Group	N	N (%)	N (%)	N (%)	N (%)	N (%)

[a]Adapted from Leucht et al.[45]
Abbreviations: BPRS = Brief Psychiatric Rating Scale; PANSS = Positive and Negative Syndrome Scale.

sents less than "minimal improvement" clinically.

Another problem in interpreting clinical trial results is cutoff points. In antipsychotic drug trials for schizophrenia, a variety of percentage reductions in BPRS or PANSS scores are used, and p values and other effect size measures can fluctuate depending on the cutoff. For instance, a statistically significant difference could be found using a 50% cutoff but not using a 30% cutoff. Dr. Leucht recommended clinical usefulness as the best guide in setting cutoffs. A 50% reduction in BPRS and PANSS scores makes sense in acutely ill patients who are not treatment-resistant, whereas in treatment-resistant patients, a 25% cutoff could be useful because even a small change is clinically meaningful.

Dr. Leucht reflected that even when based on clinical meaningfulness, the choice of cutoff points is somewhat arbitrary. He recommended that it might be clearer to present results in a table organized into columns that each show 25% greater reductions in score (Table 2).[45] In this way, it would be possible to show the numbers of patients who achieved less than a 25% reduction from baseline, a 25% to 49% reduction, 50% to 74% reduction, and 75% to 100% reduction. Tables like this can be used to display the overall distribution of results rather than only one arbitrary cutoff, but a statistical test can also be applied using one cutoff that was defined a priori.

Remission Criteria

Dr. Leucht pointed out that new remission criteria for schizophrenia have been developed recently.[46] In contrast to the response measures already discussed, which describe change expressed as a percentage of improvement relative to baseline such as a 50% reduction in symptoms, the intent of remission criteria is to measure presence or severity of symptoms. The term *remission* usually means that symptoms are not present; however, according to the new criteria, remission occurs when 8 symptoms (that reflect diagnostic criteria according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition [DSM-IV][47] and that are included in the PANSS) are mild or nonexistent, and sustained remission occurs when symptoms are mild or nonexistent for at least 6 months. This threshold for remission has been debated because patients can still have mild symptoms, but it was set because mild symptoms were considered to not interfere with patients' functioning. Dr. Leucht stated that patients who are severely ill at baseline may show a reduction of symptoms by 50% at the end of a study but will still be very ill, whereas if patients in a study are mildly ill at baseline, the number of patients who achieve remission at endpoint may be high using these remission criteria, even if the reduction in symptoms was small. Dr. Leucht concluded by stating that often the indication of both response and remission rates is warranted as it is current practice in depression trials.

Implications for Clinically Meaningful Trials

Dr. Leucht remarked that the pharmaceutical industry is involved in most of the clinical trials, which on one hand is appropriate because industry has the financial and logistical resources to conduct multinational, multicenter double-blind trials. On the other hand, the problem of conflict of interest remains. A recent article[48] found that the sponsor's drug was found to be superior in 90% of published studies, resulting in conflicting findings. Dr. Leucht next explored the new field of pragmatic, or large and simple, effectiveness trials that offer clinically meaningful data and response measures appropriate for that type of study.

Alternative Response Measures for Pragmatic Effectiveness Trials

Dr. Leucht stated that alternatives to using the BPRS or the PANSS are available. Outcomes of clinical trials are sometimes measured for registration purposes, but it is debatable whether these results are always clinically meaningful. One of the properties that people are looking for in pragmatic trials is that outcome measures should be clinically intuitive and meaningful to the clinician. Several outcome measures have been tried. Dropout, or study discontinuation, for example, has been used as a primary outcome of interest, but this measure can be problematic because it has not been validated and clinicians' reasons for which they permit participants to discontinue may vary. In addition, the reasons why patients drop out may be poorly documented in the literature. In the CATIE study,[16] for instance, between 24% and 34% of participants dropped out on the grounds of unspecified "patient decision." Dr. Leucht's opinion was that dropout rates can be useful in pragmatic studies, but that in typical double-blind efficacy studies, they are not a reliable outcome measure because clinicians typically try to keep patients in these studies for as long as possible, thus leading to underestimation of clinical dropout rates.

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Similarly, length of stay in the hospital and rates of rehospitalization have been considered as outcome measures, but these too are dependent on factors such as individual clinicians' judgments and differences in systems regulating the length of time a patient remains in the hospital before he or she is discharged.

Dr. Leucht stated that in order to carry out studies with large numbers of patients but without funding from industry and possibly even without government funding, as well as in real clinical settings where doctors have little time to fill out rating scales, short questionnaires would have to be used. Dr. Leucht described an example of an intuitive, inexpensive, clinically meaningful, and validated outcome measure from the Cochrane collaboration studies of rapid tranquilization of aggressive or agitated patients.[49] In this randomized clinical trial, 301 agitated patients were rated by how many were tranquil or asleep 20 minutes after treatment initiation. The ratings were in part validated by a second person who also rated the patients.

Dr. Leucht suggested that another possibility might be to return to using the CGI because it is simple and clinically intuitive. Research[50] has shown that the original CGI may be as sensitive as the BPRS in detecting differences between drugs and that the CGI took less time to complete; however, more study is needed because both scales were completed by the physicians, so information gathered for the BPRS may have informed physicians who then completed the CGI.

A new CGI version has been developed specifically for schizophrenia.[51] Unlike the original CGI, the schizophrenia CGI is composed of 5 subscales: global impressions, positive symptoms, negative symptoms, depressive symptoms, and composite symptoms. Because these subscales all use the same rating scale from 1 to 7, the schizophrenia CGI questionnaire can be completed quickly, and it still provides information separately on the positive and negative symptoms. The schizophrenia CGI scale has been validated and has been shown to have sufficient psychometric properties.[51]

Dr. Leucht stressed that, in his opinion, the CGI deserves further investigation in which the scoring is completed independently from the BPRS and in which knowledge of the anchors and use of time and resources are scrutinized. Although in many clinical trials, rating scale anchors are used carefully, the CGI could have advantages in pragmatic trials and in clinical practice where scores may have to be completed quickly. For example, although the PANSS is useful in experimental studies and situations in which detailed information about symptoms is needed, it comprises 30 items, and each item has 7 different descriptions for each degree of severity, making 210 different definitions that clinicians need to know thoroughly and use frequently to fill in the PANSS well and quickly.

Dr. Leucht went on to describe telemedicine, which is another attempt to improve the use of rating scales in trials and in the clinical setting. The goal of telemedicine is to make the ratings more objective and consistent. Patient interviews are conducted not by the physician who is treating the patient but by a person or persons assigned to conduct all the interviews. This system helps avoid problems such as rating patients as having more residual symptoms in order to ensure that they fall within the inclusion criteria for a study.

Treatment Strategies to Improve Functional Outcome in Patients With Schizophrenia: Translating the Evidence Into Practice

Researchers have documented the possibility for patients with schizophrenia to achieve sustained recovery from symptoms and adequate social/vocational functioning through the combination of a variety of treatment strategies. Unfortunately, these methods are not being implemented by many clinicians in the practice setting yet, despite their potential for increasing the likelihood of patient remission. These strategies and the importance of moving them from the laboratory to the clinic were the subject of a presentation given by Delbert G. Robinson, M.D.

Treatment Strategies Known to Improve Functional Outcome

The second edition of the American Psychiatric Association's (APA) treatment guidelines for schizophrenia[52] suggests a multipoint treatment course consisting of a variety of strategies known to improve functional outcome. The initial step is the selection and application of an antipsychotic medication to treat and control acute psychotic symptoms. This first step should include strategies for maintaining medication adherence, since noncompliance with a prescribed drug regimen is a leading factor contributing to patient relapse. Next, the clinician should identify and treat any comorbid conditions such as major depressive disorder or substance use disorders. Once the acute phase has been effectively treated and the patient has stabilized, several psychosocial treatment approaches with demonstrated effectiveness in improving outcome are available to the clinician (Table 3). These approaches play a dual role of being helpful in improving the symptoms of schizophrenia and also improving a patient's ability to function socially and vocationally.

Aside from the first steps of medicating a patient and treating his/her comorbidities, few of the treatments mentioned are used often in practice even though their use could mean sustained control of symptoms, adequate func-

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Table 3. Psychosocial Treatment Strategies Known to Improve Functional Outcome[a]

Family interventions/psychoeducation
Supported employment
Assertive community treatment
Social skills training
Cognitive-behaviorally oriented treatment

[a]Based on American Psychiatric Association.[52]

Table 4. Long-Term Recovery Rates in Patients With Schizophrenia[a]

Study	N	Time to Follow-Up, Years	Recovered/Mild Impairment at Follow-Up, %
Bleuler[54]	208	23	66
Ciompi and Muller[55]	289	37	50
Harding et al[56]	269	32	62

[a]Data from Harding.[53]

tional outcome, and even clinical recovery for many patients with schizophrenia. According to Dr. Robinson, that such potentially beneficial tools are used infrequently in the practice setting is a serious problem and highlights the need for clinicians to recognize that many patients can achieve a better functional outcome than what is generally expected.

Clinical Attitudes and Research Data Regarding Long-Term Treatment Outcome

Clinicians tend to focus on patients that do not respond well to treatment, and, because this group of patients is large, it may be commonly perceived that poor treatment response is the norm. This viewpoint can be understood by looking at the characteristics of subjects who participated in registration trials for some of the early second-generation antipsychotic agents approved for use in the United States. For instance, in one of the registration trials[37] for risperidone, the 388 subjects had a mean 9.1 prior hospitalizations and had been ill for approximately 15 years. Because patient profiles like these are so common, clinicians tend to assume that patients are unable to achieve a better outcome and that some basic level of symptom management is probably the best that can be hoped for.

However, the long-term course of schizophrenia may not be so bleak. One review[53] of the results of 3 long-term studies[54–56] that followed patients for decades after the onset of illness found that 50% to 66% of the patients achieved recovery or a state of only mild impairment (Table 4). These results suggest that it is possible for patients to attain a minimal symptom level even without the benefit of the additional treatments. Dr. Robinson stated that by using treatment strategies outlined in Table 3, patients may achieve similar outcomes within the first few years after schizophrenic onset instead of several decades later.

Recovery Rates Within 5 Years of Schizophrenic Onset

Dr. Robinson described a study[57] that attempted to ascertain whether patients could attain a sustained treatment response with adequate social/vocational functioning in the short term, and if they could, whether there were predictors that could help clinicians identify which patients might or might not respond favorably to treatment. The study included 118 patients with first-episode schizophrenia or schizoaffective disorder. Because the study began in 1986, patients were treated with first-generation antipsychotics, with clozapine given to those who were treatment-resistant. Patients were treated at Zucker Hillside Hospital, a large psychiatric hospital with a full range of social/vocational programs, by a research team that treated and monitored them for 5 years and research social workers who instituted psychoeducation.

Recovery criteria. To properly assess the results of their study,[57] Dr. Robinson and associates used measures derived from recovery criteria[58] developed by researchers at the University of California at Los Angeles that identified specific levels of symptomatic remission and social/vocational functioning.

To be considered recovered from symptoms, patients had to have a rating of mild (3) or less on the Schedule for Affective Disorders and Schizophrenia–Change Version (SADS-C) with psychosis and disorganization items and a global rating of moderate (3) or less on the Scale for the Assessment of Negative Symptoms (SANS). To explain the severity of symptoms specified by the symptom remission criteria, Dr. Robinson used an example of a patient who had paranoid delusions about his neighbors. A patient who firmly believes that his neighbors were trying to harm him in the past but are no longer trying to harm him would receive a rating of 4 on the SADS-C delusion item and not meet remission criteria. If the patient improved to the point that he questioned whether his neighbors ever had been trying to harm him, he would be rated a 3 on the SADS-C. Functional outcome recovery required patients to fulfill appropriate role function, be able to perform day-to-day living tasks without supervision, and have regular social interactions.

The patient would be considered to have an appropriate role function if he or she either had paid employment in the competitive sector or was attending school at least half-time or, if the patient was a homemaker, he or she was performing that role adequately.

The day-to-day living criteria required patients to have reasonably neat and appropriate grooming habits and hygiene. Patients also had to perform the appropriate household functions associated with their personal demographics. For instance, a 16-year-old patient was required to do the sort of household chores generally expected of adolescents.

In terms of social interactions, the patient would need to have regular contact with someone outside of his or her family, whether friendly or romantic, at least once a week.

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Table 5. Prospective Cumulative Recovery Rates (%) of Patients After Their First Episode of Schizophrenia or Schizoaffective Disorder[a]

Follow-Up Year	Symptom Remission for ≥ 2 Years	Adequate Social/Vocational Functioning for ≥ 2 Years	Full Recovery for ≥ 2 Years
3	24.8	16.3	9.7
4	32.3	21.3	12.3
5	47.2	25.5	13.7

[a]Data from Robinson et al.[57]

To be rated as being clinically recovered, patients had to meet all the criteria for both symptom remission and functional outcome continuously for a minimum of 2 years.

Results. Dr. Robinson reported that, during a 5-year period, almost half of patients had symptom remission for 2 or more years (Table 5).[57] Approximately one fourth of patients achieved adequate social/vocational functioning for 2 or more years over the course of 5 years. Almost 14% of patients achieved full recovery for at least 2 years.

Although the functional outcome category of the study yielded results showing that current treatments are less effective than those used to control symptoms, it should be encouraging for clinicians to know that at least a quarter of their patients could achieve adequate social/vocational functioning. For this reason, clinicians should consider implementing the previously mentioned treatment strategies outlined by the APA Practice Guideline.[52] Also, the overall recovery rate of 13.7% was encouraging considering that few clinicians believe that recovery from schizophrenia is even possible; however, the recovery rate obviously shows the need to use more effective treatments than conventional antipsychotics and/or clozapine.

Predictors of recovery. The next step in the study[57] was identifying predictors of symptom remission, functional recovery, and full recovery that could be used to develop treatment strategies for improving overall outcome.

In the area of symptom remission, patients who had experienced psychotic symptoms for long periods of time before entering the study were less likely to respond to treatment than those who were treated soon after their acute episode. Likewise, the poorer a patient's cognitive functioning was, the less likely that a favorable response to treatment would occur. The study[57] also found that patients with schizoaffective disorder had better chances of symptom remission than those with schizophrenia.

Patients with better cognitive abilities at study entry were more likely to achieve adequate functional outcome than patients with more severe cognitive deficits. A second predictor of functional outcome was an MRI measure called torque, a measurement of the symmetry of the 2 sides of the brain. Healthy people have asymmetrical brains, and patients with schizophrenia tend to have brains with less asymmetry than those of healthy control subjects. Patients whose brains more closely resembled the healthy control pattern of asymmetry were more likely to achieve adequate social/vocational functioning.[57]

The predictors of overall recovery were found to be healthier torque measurements, better cognitive ability, and shorter duration of psychotic symptoms before entry into the study.

In thinking about these predictors from the clinical perspective, Dr. Robinson concluded that some are poor targets for the development of clinical treatment strategies. Brain asymmetry, for instance, begins to develop in utero and would therefore be difficult to treat or change. Similarly, duration of symptoms before treatment initiation is impossible for the clinician to change. Cognition appears to be the only predictor of successful outcome that is potentially amenable to clinical intervention. An important consideration for clinicians and researchers is whether cognitive deficits can be improved, and if so, whether that improvement will translate into better long-term outcomes and higher rates of recovery.

Conclusion

Dr. Robinson explained that, because psychiatrists in the field are generally pessimistic about the potential for a positive outcome from schizophrenia, if they do encounter a patient who has achieved recovery, they often assume that the patient must not actually have the disease. In fact, when some of the patients from the Zucker Hillside Hospital study[57] who had achieved recovery left the study and entered maintenance treatment in their communities, they were told by their new clinicians that they did not have schizophrenia. They were then taken off their antipsychotics, which, of course, produced relapse. This turn of events demonstrates the extreme importance of clinicians' understanding that current data suggest that clinical recovery from schizophrenia is possible for a significant portion of patients and that the implementation of treatment approaches such as psychoeducation and psychosocial interventions is instrumental in increasing the chances of patient recovery.

Improving Cognitive Function in Schizophrenia

In his discussion of cognitive function in schizophrenia, Stephen R. Marder, M.D., reviewed the targets of schizophrenia treatment, examined the role of cognitive impairment in schizophrenia, suggested the inadequacy of traditional treatment strategies, and detailed the development of new approaches to the management of this debilitating disease.

Schizophrenia: Treatment Targets

Dr. Marder explained that schizophrenia has 5 core symptom clusters.[59]

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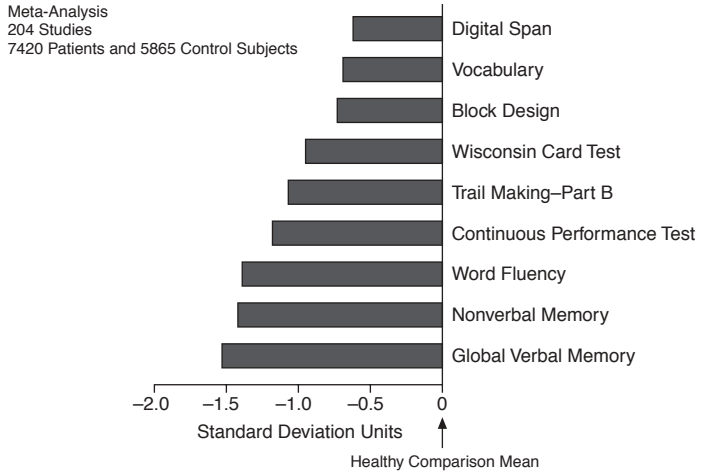
Figure 4. Magnitude of Cognitive Deficits in Schizophrenia[a]



[a]Data from Heinrichs and Zakzanis.[65]

First is the positive symptom cluster, including delusions, hallucinations, and thought disorganization. Negative symptoms, such as affective blunting, alogia, avolition, and anhedonia, comprise the second cluster. The third cluster consists of neurocognitive symptoms, including deficits in attention and memory, and problems with executive functions such as abstraction. Finally, the fourth and fifth clusters include hostility/excitement and anxiety/depression.

Historically, treatment for schizophrenia has focused on controlling the positive symptoms of patients, usually through the use of antipsychotics, a class of drugs that has been available for more than 50 years. The positive symptom burden on patients has been reduced over the 5-decade course of antipsychotic pharmacotherapy, but the ability of patients to function in the community has not significantly increased. In fact, only up to 20% of patients with schizophrenia are able to work independently,[60] showing that the focus on controlling hallucinations and delusions, while important, does little to enable patients to hold a job or return to their premorbid levels of functional adjustment. Because improvement of the patient's quality of life and ability to function normally in work and social situations are the ultimate goals of treatment, some patients and their families have proposed that clinicians may need to shift their focus from the positive symptom cluster to overall recovery. Dr. Marder stated that many clinicians and researchers in the field agree that there should be greater focus on the negative and cognitive symptoms, as they are more highly associated with a patient's social and occupational functioning than either the positive or affective symptom clusters.[61]

Cognitive Impairment in Schizophrenia

According to Dr. Marder, many psychiatrists have begun to focus on cognitive impairments in schizophrenia for a number of reasons. In the early 1900s, Swiss psychiatrist Eugen Bleuler hypothesized that the associational disturbance in schizophrenia is the fundamental part of the illness; i.e., he believed that symptoms such as hallucinations and delusions are only secondary phenomena and that the impairment of basic thought processes is central to the disease. Bleuler's ideas were reformulated by Andreasen et al.,[62] who developed a concept claiming that schizophrenia can be explained as a fundamental disruption of mental processing. They explained that the phenomenon of cognitive dysmetria, a condition of relatively poor coordination of mental activity, can lead not only to cognitive impairments but also to hallucinations and delusions.

Dr. Marder went on to explain that the cognitive impairments in schizophrenia are severe and widespread, with patients generally having deficits in more than one area of cognitive functioning. Cognitive impairments can often be detected in children who later develop schizophrenia, and they can be detected as early as the first grade.[63,64] Moreover, these impairments are usually present during the initial schizophrenic episode and tend to remain relatively stable throughout the patient's life.

A meta-analysis by Heinrichs and Zakzanis[65] compared the degree of impairment severity in different areas of cognitive function in schizophrenia with the normal, or healthy, level of cognition. The study found that impairments were greatest in the areas of memory, attention, and executive function (Figure 4). For example, in the area of verbal memory, impairment was 1.5 standard deviations below the mean. Despite some preservation of old learning and visual perceptual skills, impairments were found to be severe in all cognitive areas and present in almost every patient suffering from this illness.

Dr. Marder noted an observation made by Goldberg and colleagues[66] after evaluating patients with schizophrenia who were members of a monozygotic twin set and who performed within the normal range on neuropsychological tests. The patients' healthy siblings tended to perform well above average on the same tests, suggesting that the patients' normal results indicated impairment relative to the results they probably would have achieved were they not hampered by the disorder. This finding underscores the data from Heinrichs and Zakzanis[65] that cognitive impairment is found to some degree in nearly every person who develops schizophrenia.

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Dr. Marder explained that while an association exists between the positive symptoms of schizophrenia and the functional outcome of treatment, this association is weaker than the relationship between the presence of cognitive deficits and functional outcome.[61] The associations between specific cognitive constructs and functional outcome are not great, but the effect is cumulative such that the association of their summary score with functional outcome is significant. Therefore, cognitive deficits are reliable predictors and correlates of functional outcome. Moreover, the severity of these deficits is strongly associated with the success of psychiatric rehabilitation.

Development of Cognition-Enhancing Drugs

According to Dr. Marder, these observations concerning the role of cognition in schizophrenia have led researchers to suggest that developing drugs that improve cognition would in turn improve the overall functional outcome of patients with the disorder.[6] Unfortunately, no drugs are currently approved by the U.S. Food and Drug Administration (FDA) for improving cognition in schizophrenia, and until recently, there was little activity in the pharmaceutical industry in researching and developing such a drug.

To facilitate drug development in this area, the NIMH established the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) program. The goal of this program was to pursue the development of new treatments for schizophrenia, define and gain consensus on the guidelines for such developments, and address obstacles to the process. Such obstacles included a lack of consensus on cognitive measures, uncertainty about relevant neuropharmacologic targets, and concerns regarding the likelihood of FDA acceptance of an indication in this area. The NIMH-MATRICS approach to dealing with these obstacles was to use a consensus-building process among experts and scientists from the pharmaceutical industry, government, and academia, as well as consumer representatives, to resolve issues in each key area. A path to consensus development was agreed upon in order to include each of the involved parties at all stages of the process, and for the sake of transparency, every meeting was open, and all decisions were posted at www.matrics.ucla.edu. The initial goals were to define the basic elements, or separable domains, of cognition; to develop methods for measuring each element as a potential endpoint in clinical trials; to develop a clinical trials methodology; and to prioritize molecular targets.

The separate domains of cognition. The first issue addressed was identifying and defining the separable cognitive domains in schizophrenia. To accomplish this goal, a number of experts were interviewed, factor analysis was conducted, and the resulting information was gathered and discussed at a large meeting. As a result, it was agreed that 7 separate cognitive domains exist[67]: speed of processing, attention or vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition. The most controversial of these was social cognition, or the ability to recognize faces and affect in other people. This domain was felt to be of singular importance despite the relative lack of research in this area.

Dr. Marder described a biosocial pathway analysis[68] that found a strong relationship between social cognition—in this case, the perception of emotion—and neurocognitive ability. This relationship appears to have a large role in social competence, which in turn is closely related to functional outcome. In other words, the way that neurocognition affects functional outcome is through this vital area of social cognition.

Measurement of cognitive domains and methodology of clinical trials. After the determination of the 7 cognitive domains, a battery of tests for measuring severity of impairment in each area was developed by consensus over a period of almost 2 years. The development of this battery was somewhat hindered by controversy over the fact that many of the tests being considered were relatively old. Some academic investigators had proposed newer, more specific measures that were rejected on the basis of an inadequate understanding of their psychometric properties.

An unanticipated problem in the development of the testing battery arose when the MATRICS panel learned that simply demonstrating a change in a neuropsychological test would be insufficient to garner FDA approval for a drug.[69] It would also be necessary for the sponsor to demonstrate that the patient showed improvement in something more closely aligned with functional outcome. However, this did not mean that patients should improve to the point that they could get a job or change their living circumstances while participating in clinical trials, but rather that they show the ability to perform some of the tasks that are clearly associated with functional improvement.

To meet this criterion, it was necessary to develop new measures[69] that would be added to the cognitive battery for drug trials. The first new measure would address functional capacity by simulating daily activities and demonstrating whether the patient was capable of performing functional tasks in testing, but not in the community. The second measure would be interview-based assessments of cognition used to determine if either the patients themselves or someone living with the patient could recognize an improvement in functioning. After completion, the entire cognitive battery was put into a single package, which has been made available to clinicians and investigators through a number of distributors of psychological tests.

The standards for clinical trials were defined at a joint NIMH-FDA conference.[70] First, studies should include subjects who are clinically stable, and the only patients who should be excluded are those whose impairment somehow compromises test validity. In

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Table 6. Ranking of Selected Molecular Targets for Antipsychotics[a]

Target	Nominations
α_7 Nicotinic receptor agonists	31
D_1 dopamine receptor agonists	30
AMPA glutamatergic receptor agonists	14
α_2 Adrenergic receptor agonists	14
NMDA glutamatergic receptor agonists	12
Metabotropic glutamate receptor agonists	12
Glycine reuptake inhibitors	8
M_1 muscarinic receptor agonists	7
$GABA_A$ receptor subtype selective agonists	5

[a]Based on Measurement and Treatment Research to Improve Cognition in Schizophrenia[71]
Abbreviations: AMPA = α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid, GABA = γ-aminobutyric acid, NMDA = *N*-methyl-D-aspartate.

testing any comedication, the augmenting drug added to antipsychotic treatment should be compared with placebo added to the current antipsychotic. Any broad-spectrum antipsychotic considered to have cognition-improvement properties would need to be compared with an antipsychotic that was at least neutral with regard to cognition, that is, comparing the drug with an antipsychotic that impaired cognition would not be sufficient. Last, the outcome of these tests would be monitored with the MATRICS consensus battery and a coprimary measure of functional outcome.

Molecular targets. Finally, molecular targets for antipsychotics were selected and ranked. This process involved interviewing experts in the field about possible targets and then including those experts and others in a meeting to narrow the list and vote on potential targets. This meeting resulted in a consensus on a range of 9 molecular targets, with alpha-7 nicotinic agonists receiving the highest ranking (Table 6).[71] It appears that the MATRICS process has been successful so far, since there are currently a substantial number of drugs at different stages of development directed at each of the 9 targets selected.

Alternative Cognitive Treatments

Dr. Marder emphasized that although no effective drug has been approved for treating impaired cognition, other tools are available to clinicians interested in addressing cognitive deficits. Several psychosocial approaches have proved effective in improving cognition in patients with schizophrenia. One study[72] has shown that a patient's ability to recognize facial affect in others can be improved through training. Specialized cognitive training can improve working memory[73] and attention.[74] Another approach, called cognitive enhancement therapy,[75] has successfully improved cognition and processing speed.

Conclusion

In closing, Dr. Marder reiterated that current treatments for schizophrenia are limited in their ability to improve functional outcome. To improve functional outcome, it will be necessary to focus on the pathology domains of cognition and negative symptoms. Innovations in treatment are likely to emerge through a better understanding of the neurobiology of basic cognitive and motivational processes.

Evidence Regarding New and Future Treatments and Drug Delivery Systems for Schizophrenia

Steven Siegel, M.D., Ph.D., stated that one of the most important factors driving the current investigation of new delivery systems for drugs in the treatment of schizophrenia is the level of evidence suggesting that patients have a difficult time taking medication as indicated. Although nonadherence is a problem with most disorders that require chronic treatment,[76] many studies[10,77–79] have demonstrated that poor adherence to medication is one of the leading causes of relapse and rehospitalization in schizophrenia.

Rates of Adherence to Treatment

A wide range of estimates has been calculated for rates of adherence to treatment in schizophrenia, with some studies[7–9] finding that up to 50% or even as high as 80% of patients are unable to take medication as directed. The reason for such a large variation may be due to the various definitions of adherence; for example, if adherence is defined as taking every pill exactly as prescribed, almost no one can comply. However, if a looser definition of adherence is used, for example, taking most pills most of the time, then perhaps 20% to 50% of patients are able to comply.

Reasons for Nonadherence

One of the more commonly mentioned reasons for poor adherence to medication in schizophrenia is patients' poor insight into the disease, which is one of the more prevalent symptoms of the disorder. However, many patients with psychiatric disorders, including schizophrenia, are aware that they need to take their medication as directed but still have difficulty doing so for a variety of reasons, including logistic problems of accessing prescriptions and getting refills,[80] as well as forgetfulness.[81] Forgetfulness could potentially be a result of the cognitive limitations of schizophrenia but is also present in nonpsychiatric conditions and thus may be more attributable to the burden of taking medication every day than to a symptom of the disorder.[82]

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Table 7. Advantages of Current Injectable Formulations Over Daily Oral Administration

Increased adherence[82]
Decreased risk of relapse following discharge from hospital[83]
Better steady-state delivery and lower peak serum levels[82]
Avoidance of first-pass metabolism[82]
Decreased risk for some forms of adverse events[82,83]

Relapse

When people are unable to take their medications properly, the risk of relapse is high. Even intermittent compliance is suboptimal compared with strict adherence. Nonadherent patients with schizophrenia are 5 times more likely to relapse than those who conform to a prescribed antipsychotic regimen.[10] Dr. Siegel contended that the rate of relapse for partially compliant or nonadherent patients rises to 90% to 100% over the course of 2 years.

Current Injectable Formulations

A variety of long-term medications have been developed to meet the need for continuous medication treatment throughout a patient's life. Historically, these have included decanoate formulations, and because these long-term delivery systems have been around for some time, the body of literature suggests a dramatically improved outcome for patients who use them. Some of the potential benefits include increased adherence and decreased relapse following hospitalization.[83] Pharmacokinetic advantages also exist with long-term delivery systems, such as lower peak serum levels and better steady-state delivery. In addition, because the drug is delivered outside the enteric system, a first-pass metabolism is avoided, which means there is less liver toxicity and a potential decrease in adverse effects (Table 7).[84]

Decanoate formulations. Until recently, the strategy for long-term delivery of antipsychotic medication has been decanoate formulations. These formulations involve making a pro-drug, or molecule that precedes the active moiety, that is sequestered in the periphery of the body until the process of hydrolysis slowly degrades the molecule into the active agent, freeing it to circulate and go to the brain.[85,86] The main limitation has been that this approach requires the active drug to have a free functional group, usually a hydroxyl, to enable formation of an ester linkage to a carbon chain or other molecule to form the pro-drug.[87] Few antipsychotics approved in the United States have this required chemistry, limiting this highly effective formulation to 2 agents, haloperidol decanoate and fluphenazine decanoate. Each of these agents is administered monthly.

Microsphere preparations. The first alternative approach to creating long-term injectable preparations involves the use of the biodegradable polymer poly-lactide-co-glycolide (PLGA) to sequester drugs in microspheres,[88] explained Dr. Siegel.[89] This approach opens the door to the development of long-term delivery systems that are not limited to drugs that have the ability to form an ester bond to a long carbon chain. An additional advantage to using PLGA is that it is nontoxic and has been used safely in humans as sutures, pins, plates, and other biodegradable devices for over 20 years.[90] The material is metabolized into carbon dioxide and water and excreted from the body through normal respiration. The polymer is safe, goes away over time, and releases the drug in a controlled fashion so that it can be utilized by the patient.

Currently, risperidone is the only atypical antipsychotic agent being used with PLGA microspheres, although this technology has been used in medications for other psychiatric illnesses and medical conditions.[91,92] Long-acting risperidone is dosed at 25 mg to 50 mg intramuscularly every 2 weeks.

Microsphere technology does have limitations, including lower drug loads and the lesser degree of convenience associated with bimonthly as opposed to monthly injections, although perhaps after being studied in monthly use, this option will become available. Additionally, microsphere preparations have certain logistic requirements that make them less convenient than other treatments. First, they have to be shipped directly to the physician's office and refrigerated on site, and then they have to be prepared using the supplied needle and a special kit during the patient's visit. The older formulations can be picked up at a pharmacy, brought to the physician's office, and injected using whatever type of needle the doctor prefers to use.

Future Injectable Formulations

Dr. Siegel reported that a new approach is being developed that may address the limitations of microspheres. It is possible to make a long acting pro-drug using an ester linkage to the main active metabolites of risperidone, called 9-OH risperidone. Because 9-OH risperidone has a functional group to form ester bonds, it is amenable to creating monthly pro-drugs without the limitations of lower drug loads, shorter duration, and special preparation requirements of the microsphere formulation. A new formulation called paliperidone palmitate has the potential to provide the advantages of earlier decanoates, again expanding the repertoire of long-term injectable agents that can be applied in the treatment of schizophrenia.[93] Additionally, because hundreds of thousands of patients have been exposed to risperidone and, by default, also exposed to its metabolites, there is reason to believe that paliperidone palmitate is nontoxic and will be effective.[94]

Potential Long-Term Formulations

While long-term injectable treatments have shown potential for improving outcomes in the treatment of schizophrenia by changing adherence requirements from daily to monthly or bimonthly injections, preclinical studies are investigating the use of implantable formulations that could provide several months of uninterrupted treatment.[83,95] Such implants would use PLGA material and contain drug loads

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high enough to allow for 1 procedure every 3 to 6 months. The requirements for an implantable drug are similar to those for microsphere technology: the drug should be low-dose and high-potency to keep the implant small enough to be manageable while retaining its effectiveness. As such, the medications that have been used in decanoates, palmitates, and microspheres may also be ideal for implants.

Community Reaction to Long-Term Implants

When considering the use of implants, the acceptance of such a novel approach by patients and their families and members of the psychiatric community is of primary importance. Patient attitudes toward implantable formulations of antipsychotic medications have been studied. According to Irani et al.,[81] approximately half of the 206 psychiatric patients surveyed said that they would be willing to get their medication through an implant. Unpublished observations have shown high levels of enthusiasm for this sort of treatment from patients' family members and health care providers.

Conclusion

Dr. Siegel concluded his presentation by stressing that long-term delivery formulations, including injections and implants, represent one of the most important and previously untapped approaches to improving the treatment of schizophrenia. These systems not only provide a better pharmacokinetic profile, but they also have the potential to dramatically increase adherence to medication, thereby providing the possibility of much better functional outcome for patients suffering from schizophrenia.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), fluphenazine decanoate (Prolixin decanoate), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal Consta, Risperdal).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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