Cognitive Functioning in Schizophrenia: A Consensus Statement on Its Role in the Definition and Evaluation of Effective Treatments for the Illness

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Background: Truly effective treatments for schizophrenia require much more than clinical efficacy. Symptom improvement is all that is required to demonstrate clinical efficacy. However, for a treatment to be effective in a wide-ranging manner, improvement in various life domains, such as social functioning, independent living, and employment, should also be found. Thus, a much wider range of improvements, not widely produced by previous treatments, is required to take treatment for schizophrenia to a new level of effectiveness.

Consensus Process: A teleconference consensus meeting was held with the bylined authors on December 10, 2002, to explore the factors that hinder the most effective treatments for schizophrenia. We argue that a possible unifying factor underlying these apparently disparate domains of effective treatment is cognitive functioning, which is impaired in people with schizophrenia. Treatment of cognitive dysfunction may have a central role in increasing the breadth of effective treatment for schizophrenia.

Conclusions: Novel antipsychotics and specific cognitive-enhancing medications have preliminarily been shown to have cognitive benefits that might lead to broader effectiveness of treatments, eventually reflected in improvements in the daily lives of patients. These treatments may have their greatest impact when combined with focused psychological interventions. While the research to date does not provide a large number of successes, this area will be one of considerable research interest for the next decade, with developments likely to be very important to clinicians treating patients with schizophrenia.

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Remarkable strides have been made in the treatment of schizophrenia, and antipsychotic agents have contributed to these advances by reducing the severity of psychotic symptoms. Drug approval by regulatory agencies is based upon demonstration of efficacy against a subset of schizophrenic symptoms. Yet, there is considerable evidence that medication treatments for schizophrenia can demonstrate efficacy but fail to improve many of the important features of schizophrenia.[1] Specifically, patients with schizophrenia who experience reductions in psychotic symptoms when receiving treatments with demonstrated efficacy may still have marked impairments in multiple aspects of life functioning, including occupational, social, and independent living domains.[2] Even after successful treatment of psychotic symptoms, these patients typically experience reduced quality of life, manifest multiple medical comorbidities, and are at high risk for relapse. Thus, treatments with demonstrated efficacy can lead to only transient improvement in limited aspects of patient functioning.

Historically, the major distinction between efficacy and effectiveness was based on clinical trial design.[3] An efficacy study is conducted with predetermined entry criteria and takes place over a limited period of time. Patients with comorbidities such as substance abuse or medical illness are often excluded, even when the comor-

bidity, such as substance abuse, is present in most patients with the disorder. Effectiveness studies take place in more naturalistic settings, with more flexibility in treatment strategies, and are often longer in duration.[4] As a result, outcome measures can also be different in effectiveness studies and could include broader assessments such as indices of functional outcome, medical status, and quality of life. Since effectiveness studies attempt to study real-world outcomes in naturalistic settings, the definition of a clinically effective treatment would be an intervention that yielded positive results in such a study design. While effectiveness studies can have a narrow range of outcome variables such as sustained remission and medication adherence, there is no intrinsic reason that effectiveness studies need to be limited in terms of outcomes.

Psychotic symptoms are only one of a set of features of schizophrenia, and their severity is not strongly correlated with many of the other important dimensions of life functioning noted above.[5] These other features of the illness are not consequences of psychotic symptoms or their treatment, yet they all contribute to reductions in functioning on the part of patients with schizophrenia (see Elvevag and Goldberg[6] for a review). Improvement in these other domains of life functioning would be required to meet the goal of providing treatments that improve patients' overall well-being. Therefore, more broadly effective treatments would appear to be those treatments that reduce multiple symptoms of disease, reduce treatment burden, and promote wide-ranging functional improvement. While this definition of clinical treatment goals is broader than those usually employed in efficacy studies, for any treatment to make a real difference in schizophrenia it must impact these other domains of functioning.

In our consensus meeting December 10, 2002, we reviewed evidence that cognitive functioning is a consistent correlate of the multiple aspects of functioning that are impaired in schizophrenia. We suggest in this article that cognitive enhancement could be the key to improving the breadth of treatment effects in schizophrenia, as defined above, suggesting that there are multiple potential strategies for cognitive enhancement. We then critically evaluate the current status of cognitive enhancement in schizophrenia, examining current treatments that have demonstrated efficacy and evaluate whether these treatments could also enhance cognitive functioning and meet the criteria for having wider benefits for patients.

NONPSYCHOTIC DOMAINS OF SCHIZOPHRENIA

Cognitive Functioning

Cognitive functioning is severely impaired in patients with schizophrenia, and performance on important components of cognition can reach 2 standard deviations below the mean of healthy control subjects.[7–9] The most severe impairments are found in verbal memory, executive functions, vigilance, verbal fluency, and motor speed. These impairments have been shown not to be a consequence of other symptoms of the illness (such as negative or positive symptoms) or treatments for schizophrenia. They are also not completely accounted for by motivational deficits or unwillingness to meaningfully participate in the cognitive assessment process. Cognitive impairments have been recognized for years, but the clinical implications of these impairments are only now becoming widely appreciated.

When considering cognitive impairments in schizophrenia, it is important to understand that these impairments occur very early in the course of the illness. Individuals who are genetically vulnerable to schizophrenia have notable cognitive impairments,[10] while individuals who receive cognitive assessments before they develop schizophrenia are found to have impairments in a variety of areas.[11] First-episode patients with schizophrenia have a profile of cognitive impairments that is fully developed when compared with more chronic patients,[12,13] indicating that cognitive impairments, while not progressive throughout most of the illness, are present very early on. Although some patients with schizophrenia may not appear to have cognitive impairments relative to normative standards,[14] they are in the minority and may be the patients with the highest level of premorbid cognitive functioning.[15] Thus, it is plausible that every schizophrenic patient manifests cognitive functioning below the level that would be expected in the absence of the illness.

Adherence and Relapse

A high percentage of schizophrenic patients demonstrate poor adherence to medication regimens.[16] Poor adherence to medication treatments is not specific to schizophrenia, being present across a wide range of physical and psychiatric disorders.[16–18] Nonadherence may be exaggerated in certain subgroups of patients, including those with antisocial tendencies,[19] and is associated with an increased risk of symptom exacerbation, rehospitalization, emergency department visits, and homelessness.[20] Average annualized rates of relapse for medicated and nonmedicated patients across studies with variable lengths of follow-up have been found to be approximately 20% and 55%, respectively,[19] and approximately 50% of patients who discontinue antipsychotics will relapse within 3 to 10 months.[21] It has been reported that as many as 74% of patients with schizophrenia become noncompliant with conventional antipsychotic medication within 2 years after hospital discharge.[16]

Even for patients who are compliant with maintenance conventional antipsychotics, rates of relapse have been reported to be as high as 40% within 1 year after hospital discharge.[22] The high rate of relapse despite adherence to conventional medication treatment is present even in

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compliant patients.[23] Irregular medication use and partial compliance are also strong predictors of hospitalization and increased costs for patients with severe mental illness.[24] Among the predictors of poor compliance is the experience of extrapyramidal side effects, which increases the likelihood that patients will discontinue their medications.[25] Thus, in the presence or absence of full compliance, conventional treatments are associated with a substantial risk of relapse. Furthermore, many of the side effects of older medications promote partial compliance or noncompliance, which accelerates the time course of relapse in patients with schizophrenia.

Relapse in schizophrenia is associated with multiple detrimental consequences in personal, legal, and symptomatic domains. Patients who experience relapse are more likely to engage in unstable behavior and come in contact with the legal system, often while alienating family members. Furthermore, it has been argued that partial compliance and relapse are primary factors that lead to the development of treatment resistance.[26] Thus, improvement of adherence to treatment is important to consider in the development of clinically effective treatments for schizophrenia.

Functional Impairments

Deficits in adaptive life skills are a feature of schizophrenia that is of major importance. Reduction in social or occupational functioning is one of the criteria for a diagnosis of schizophrenia according to DSM-IV,[27] and a worsening in functional status must be present for a diagnosis to be assigned. Multiple functional domains are adversely affected by schizophrenia. Independent living is rare and there are major deficits in employability. Social deficits are reflected by the low frequency of marriage and having children, particularly among male patients, as well as by the fact that many patients with schizophrenia live essentially solitary lives.

Schizophrenia ranks in the top 5 causes of disability for young adult men and women in developed countries.[28] The course of functional status is variable, with some patients improving, some declining, and others remaining stable.[29] It has been estimated that approximately 50% of schizophrenic patients are employed at any time in any capacity.[30] The proportion of patients who are employed in a competitive environment is much smaller, ranging from about 10% to 20%,[31] with only about 10% of patients with a diagnosis of schizophrenia able to sustain full-time competitive employment. This underemployment occurs despite the understanding that employment has a number of benefits for patients with schizophrenia, including increases in quality of life, reduced symptom burden, and reductions in hospital time.[32]

Independent living is another domain that is impacted by schizophrenia. Ho et al.[33] showed that disability began fairly rapidly after the onset of schizophrenia. In this study, it was determined that approximately 50% of first-episode patients with schizophrenia were receiving disability payments and living in supported living arrangements within 6 months of their first episode of illness. It is difficult to fully estimate how many patients with schizophrenia are living independently, but most estimates indicate that fewer than 20% of patients with schizophrenia are living in unsupported housing arrangements. Many patients who live in supported housing have been discharged from long-stay psychiatric hospitals, indicating that they have been determined to have experienced improvement in the psychotic symptoms, which does not translate into independent residential status.[34]

Quality of Life

A patient's subjective perception of quality of life (QoL) is multidimensional,[35] with domains including emotional, financial, and health-related features, as well as the impact of these subjective reactions on future expectations.[36] Subjective assessments involve self-reported happiness, contentment, and satisfaction with current life status. Most patients with schizophrenia experience substantial reductions in their subjective quality of life, with these effects being present very early in the course of the disorder and persisting over the entire course of illness.

The impact of reduced QoL on patients with schizophrenia is substantial. The rate of suicide in schizophrenia is substantially elevated, while evidence regarding the timing of the suicides suggests that they occur, like in major depression, after partial treatment response.[37] Such timing suggests that suicide may be related to increased awareness of the poor quality of the current life situation, as it has been shown that depression is associated with suicidal ideation, but not necessarily suicide attempts, in schizophrenia.[38] As a reduction in symptoms leads to decreased subjective focus on psychotic (i.e., delusional or hallucinatory) experiences, increased focus on realistic aspects of the typical life situation (e.g., unemployment, poverty) may lead to distress, which could promote suicidal ideation. Thus, reductions in quality of life and serious adverse consequences can arise even after treatments with demonstrated efficacy are employed to treat patients with schizophrenia.

Medical Status

Life expectancy is reduced in patients with schizophrenia, partially because of the increased incidence of suicide,[39] particularly in younger male patients as described above. Patients with schizophrenia are likely to have more medical problems, including poorly treated congenital anomalies and diseases of the digestive and musculoskeletal systems, than the general population.[40] Many of these health-related problems are related to substandard medical care that appears to be provided to persons with schizophrenia.[41] In addition, patients with schizo-

phrenia fail to spontaneously seek medical care for many of their illnesses.[42] Other medical problems can be related to medication adverse effects, such as weight gain.[43] In fact, weight gain with treatment may be more of a problem with some of the newer treatments than with older ones, as discussed below.

Much of the medical comorbidity in schizophrenia is, theoretically, preventable. Premature death may be associated with lifestyle choices such as smoking.[44] Weight gain and diabetic complications may be related to schizophrenia in general[45] but can be caused by pharmacologic treatments. Failure to spontaneously seek medical care until problems are very severe is also a feature of patients with schizophrenia. Thus, a number of aspects of medical comorbidity are potentially modifiable in schizophrenia, in which more effective treatments could have a beneficial effect.

EFFICACY DOES NOT ALWAYS TRANSLATE INTO EFFECTIVENESS

Conventional antipsychotic medications that are approved for the treatment of schizophrenia are, by definition, superior to placebo for reducing psychotic symptoms. Up to 90% of first-episode patients have evidence of good response to treatment with conventional antipsychotics,[46] in that they experience a period of remission in the first year of their illness. This initially good treatment response is reduced somewhat over time, in that 65% of patients with an established course of illness have a similarly good clinical response following symptomatic exacerbation, with evidence of the development of treatment resistance in the rest of the patients.[47]

These rates of good response, in terms of reduction of targeted clinical symptoms, are still higher than for other medical procedures such as angioplasty and antihypertensive treatment.[48] As a result, conventional antipsychotic medications have efficacy that is comparable or superior to other widely accepted medical procedures. However, as evidenced above by the review of the other features of schizophrenia, largely studied in patients receiving conventional antipsychotic medications, conventional medications have limitations in wide-ranging effectiveness. Despite demonstrated clinical efficacy, the overall outcome for schizophrenia, as indexed by stable remission and community residence, has changed little during the course of the past century.[49]

Social and functional deficits do not appear to be markedly improved by conventional treatments. In a follow-up study in Iceland,[50] many of the patients receiving conventional treatments experienced symptomatic remission, but approximately half of the study group had never married and almost the entire sample (95%) had impaired social relationships. In a long-term study of patients who were discharged from long-stay psychiatric care while treated with conventional antipsychotic medications, most reported having one or no friends after their community placement.[51]

Despite high rates of success in the treatment of psychotic symptoms with conventional antipsychotic medications, reduced QoL also persists in patients with schizophrenia. When queried about the major sources of their reduced quality of life, few patients cite the symptoms of illness that are used to define clinical efficacy.[52] Tellingly, the presence of psychotic symptoms, particularly delusions and hallucinations, is not often cited by patients with schizophrenia as a factor in their reduced QoL. Thus, the types of symptoms most effectively targeted by conventional antipsychotic treatments are not among the aspects of the individual's personal situation that they see as reducing their quality of life. Some of the reduction in QoL may be caused by treatment-related (medication) adverse effects, such as extrapyramidal symptoms (EPS).[53] Thus, conventional treatments for schizophrenia have a complex relationship to QoL: reductions in QoL may be associated with side effects, but increases in QoL are not necessarily produced by treatments with demonstrated efficacy.

THE COGNITION CONNECTION: THE ASSOCIATION OF COGNITIVE FUNCTIONING AND OTHER FEATURES OF SCHIZOPHRENIA

One aspect of schizophrenia that has received increasing recognition is the connection between cognitive impairments and other features of the illness. This connection applies, to a variable extent, to all aspects of the illness reviewed above, including relapse prevention, functional impairments, QoL, and medical status. In addition, negative symptoms and the presence of the deficit syndrome are also related on a correlational basis to cognitive impairments. In meta-analyses, neurocognitive skills have been found to be related to several global and specific functional outcomes.[54] Cognitive impairments appear to be potential determinants of adaptive functioning deficit, with correlations found between the severity of cognitive deficits and social dysfunction, impairments in independent living, occupational limitations, and self-care impairments. Cognitive functioning is one of the major correlates of level of care,[55,56] in that patients who live in full-care settings such as nursing homes or chronic psychiatric hospitals are likely to have more substantial cognitive impairments than outpatients with schizophrenia or lifelong community dwellers who are currently experiencing an acute episode. Deficits in the performance of specific skills that are critical for independent living (paying bills, shopping, and emergency communications) are correlated with the severity of cognitive impairments,[57,58] and multiple different aspects of cognitive dysfunction correlate with these various functional limitations.[59]

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Relapse may be partially related to cognitive impairment. The cognitive deficits described above can contribute to the typical patterns of medication mismanagement that are associated with poor adherence and subsequent risk of relapse: forgetting to take doses of medication, failing to refill prescriptions, misplacing medications, misunderstanding the instructions given by treating physicians, and failing to establish routines that promote the regular administration of medication.[60,61] Poor performance on tests of attention and visual memory has been found to be related to decreased medication compliance in patients with schizophrenia.[61] In a study by Donohoe et al.,[62] memory impairment was the best predictor of partial compliance in patients with schizophrenia. Patients with more severe cognitive limitations, indexed by poorer global scores on a cognitive assessment battery, also perform more poorly on analogue medication management tests.[63]

Some evidence suggests that reductions in QoL are associated with cognitive impairment as well as with other features of the illness. Specifically, it has been shown that executive functioning moderates the relationship between subjective experience and social functioning,[64] with patients who experience more severe executive deficits having less realistic impressions of their social functioning. In addition, anticholinergic treatment is also associated with reductions in quality of life. While the principal relationship between reductions in QoL and anticholinergic medications may be related to the EPS that trigger anticholinergic medication prescriptions, it has been known for years that anticholinergic medications impair attentional and memory functions in patients with schizophrenia.[65] Patients with treatment-related reductions in their memory performance were also found to have reductions in their global quality of life scores.[66] Thus, interventions that reduce cognitive functioning lead to disturbances in quality of life.

Medical comorbidities in schizophrenia are correlated with the severity of cognitive impairments. The medication compliance issues described above, which are correlated with cognitive disturbances, apply as well to compliance with treatments for medical conditions, which can impact outcomes of medical treatments. Furthermore, the reduced ability of patients with schizophrenia to curtail potentially damaging habits such as smoking[67] has also been shown to be correlated with deficits in attention and memory functions.[68] One recent longitudinal study[69] demonstrated that in elderly patients with schizophrenia, cognitive and functional impairments predict the later incidence of new-onset medical problems, whereas newly incident medical problems did not predict the subsequent worsening of cognitive and self-care deficits. Thus, cognitive impairments have been shown to have a direct relationship to medical comorbidities in schizophrenia. At the same time, some of the most promising treatments for cognitive impairments may also have the potential to affect medical status, as described below.

Negative and Deficit Symptoms

Negative and deficit symptoms are also correlated with poor functional outcomes and reduced quality of life. Multiple studies have consistently demonstrated a relationship between the severity of cognitive impairments and negative symptoms (see Addington[70] for a detailed review). In addition, patients with the deficit syndrome appear to have a fairly specific signature of cognitive impairments, with more substantial impairments in tests of parietal lobe and frontal lobe functions than nondeficit patients.[71,72] The course of negative and cognitive symptoms appears similar, in that both have greater stability within patients over time than positive symptoms.[73] When the correlations between negative and cognitive symptoms are examined over time, there is evidence that these symptom dimensions are correlated but discriminable.[74] In terms of the differential relationship between functional skills performance and cognitive and negative symptoms, the results of several studies have suggested that cognitive deficits are more strongly correlated with functional outcomes than are negative symptoms.[56,69,75] In both the Harvey et al.[56] and Velligan et al.[75] studies, the correlations between negative symptoms and functional skills were reduced when the severity of cognitive impairment was considered.

The nature of the relationship between deficit symptoms and cognitive impairment is still being investigated. These 2 domains of schizophrenia have an intrinsic relationship, based on the findings of the studies above that identified differential patterns of cognitive impairment in deficit and nondeficit patients.[71,72] Patients with the deficit syndrome appear to have a number of distinctive features that have led to the conclusion that these patients may constitute a biologically distinct subtype of schizophrenia.[76] More research is required in order to determine the differential contributions of these 2 aspects of illness to outcome in schizophrenia.

FAILURE TO IMPROVE COGNITION MAY CONTRIBUTE TO POOR LONG-TERM OUTCOME

Conventional treatments for schizophrenia have led to consistent improvements in the short-term reduction of psychotic symptoms but arguably have not led to improvements in overall outcome. It is theoretically possible that this failure to improve outcome is due to the modest impact of these treatments on cognitive functioning. The effect of conventional treatments on cognition has been addressed by numerous studies conducted over the past 40 years, and many reviews of the literature have arrived at the same conclusion: although acute and chronic treatment with conventional antipsychotic medications meets

criteria for clinical efficacy, these agents appear to have limited cognitive benefits,[77] despite few detectable cognitive costs.[78] Granted, for years, patients with schizophrenia were treated with excessive doses of conventional antipsychotic medication, which may have had direct adverse cognitive effects and also led clinicians to use anticholinergic medications to control side effects. There is some evidence that lowering dosages of conventional antipsychotic medications has some modest cognitive benefit,[79] which suggests that some of the failures of conventional medications to improve cognition may be due to use of excessive doses. Some recent evidence has suggested that very low doses of conventional medications may have cognitive benefits,[80,81] but it is not clear that low doses of conventional medications would also lead to symptomatic remission at the same rate as higher doses. Thus, there may be an efficacy cost in using the doses of conventional medications that are most likely to lead to modest improvements in cognitive functioning.

Higher doses of conventional medications, in the ranges that are often used to obtain clinical efficacy, are associated with greater potential for EPS, impaired motor performance, and increased use of anticholinergic medications.[82] While most conventional treatments have minimal intrinsic anticholinergic effects, the need to use anticholinergic medications to control EPS means that total cholinergic burden must be considered when evaluating their effects. Since many cognitive tests require some kind of timed motor response, motor impairments secondary to EPS may result in decrements in performance on cognitive tests.

A more subtle liability of conventional medications may be in the domains of interference with practice-related learning. When cognitive tests are administered repeatedly, patients taking conventional antipsychotics do not demonstrate the expected "practice effect" (see Harvey et al.[83] for an example and Blyler and Gold[77] for a detailed discussion). Although cognitive performance does not decline on retesting following conventional antipsychotic treatment, failure to demonstrate significantly enhanced performance on the second or third exposure to the testing procedure may be due to a variety of potential interfering effects, including interference with procedural learning. Even low doses of conventional medications have the potential to interfere with practice-related learning,[84] although this effect may be attenuated with longer-term follow-up of the patients.[80]

We suggest that the failures of older antipsychotic medications, including failures to improve functional skills, quality of life, and health status, as well as failures at relapse prevention, could, theoretically, have a similar underlying cause: limited potential to enhance cognition. While this point is difficult to prove in a single study, multiple lines of evidence are consistent with this hypothesis. Each area of functioning that is poorly treated by conventional medications is multiply determined, and cognitive impairments are clearly not the sole factor that leads to the limited success of previous treatments. While there is evidence that conventional antipsychotics have modestly beneficial effects on cognition under some circumstances, their low level of benefit and the overall level of severity of impairment in cognition in schizophrenia result in "successfully treated" patients typically having considerable remaining cognitive impairments. These remaining cognitive impairments are correlated with remaining impairments in other functional domains.

WHY NEWER TREATMENTS MAY HAVE MORE PROMISE

Atypical Antipsychotics

There has been a surge of interest in the treatment of cognitive functioning in schizophrenia. This interest has been spurred by the evidence that second-generation antipsychotic medications appear to have modest cognitive-enhancing effects and by the development of several medications for other conditions whose primary effect is cognitive enhancement. These 2 developments have the potential to improve other features of schizophrenia.

Atypical antipsychotic medications appear to have greater cognitive benefits compared with conventional medications.[84,85] This issue is still controversial, and many of the studies that support cognitive enhancement with these medications are methodologically limited in a variety of ways. The improvements have been reported in cognitive domains that have functional relevance, which is encouraging. For example, across a number of studies, treatment with the atypical medications risperidone,[86–90] olanzapine,[81,88–91] quetiapine,[92–94] and ziprasidone[95] has shown improvements in episodic memory performance compared with either baseline performance or parallel treatment with conventional antipsychotics. Episodic memory is a consistent correlate of multiple dimensions of functional outcome in schizophrenia. For instance, Harvey et al.[89] found that patients treated with either risperidone or olanzapine had an approximately 40% chance of improving by more than half a standard deviation in episodic memory performance. In 2 separate studies[92,94] with a longer duration, quetiapine treatment also improved episodic memory by amounts even greater than this when compared with haloperidol treatment. This level of improvement appears consistent across stages of illness and in special subpopulations. Bilder et al.[88] reported memory improvements of similar magnitudes in treatment-refractory patients, and Harvey et al.[90] reported that elderly patients with over 35 years of illness also improved in their memory performance by similar amounts. First-episode patients treated with either olanzapine[81] or risperidone[87] improved more than first-episode patients randomly assigned to treatment with very low

doses of haloperidol. Thus, there is evidence that second-generation antipsychotic medications are superior to conventional treatments in terms of enhancement of some aspects of cognitive performance.

There are a number of caveats to these findings and they cannot, at this time, be considered definitive. The differences between conventional and atypical medications may be partly dosage dependent, because the cognitive differences between conventional and atypical medications in similar clinical populations are larger when large doses of a first-generation medication are prescribed.[80,86] The magnitude of cognitive enhancement with atypical medications is moderate at most across cognitive domains, with some domains showing very little improvement, while the level of impairment seen in schizophrenia is, on average, very large to extreme. Most patients are not returned to normal functioning in these studies. There are also variations in the extent of improvement across patients, in which those patients with the lowest levels of baseline impairment improve the most with pharmacologic cognitive enhancement treatment.[89,90] Some patients, therefore, would be expected to experience reasonably large improvements (1.0 SD or more), whereas others will be essentially unchanged. Finally, the efficacy-study length of many clinical trials examining atypical antipsychotic medications has generally precluded assessment of the types of outcome measures needed to prove that these compounds are actually more broadly effective than older medications.

Trials of atypical antipsychotic agents have begun to include assessments of QoL, which could be impacted by all of the other functional outcome domains discussed in this article. In a trial of olanzapine and haloperidol,[53] there was a statistically significant change from baseline to endpoint in the Positive and Negative Syndrome Scale negative syndrome scores, Montgomery-Asberg Depression Rating Scale scores ($p < .0001$), and the Simpson-Angus Scale scores ($p = .015$). Reductions in negative and depressive symptoms and extrapyramidal side effects were associated with improvements in QoL scores. In a study[94] comparing quetiapine and conventional antipsychotic treatment, QoL was improved with quetiapine treatment but not with conventional treatments. Thus, improvement in QoL can be found in short-term periods when patients are treated with atypical antipsychotic medications.

Much more work needs to be done to understand the cognitive effects of atypical antipsychotic treatments. One of the troubling issues yet to be resolved is whether the benefits of newer medications are indirect rather than being caused by some unique pharmacologic properties. Are these improvements the result of atypical antipsychotics simply being less toxic to cognition than conventional medication? This perspective is consistent with the findings of Green et al.,[80] who found no relative benefit of risperidone treatment compared to low-dose treatment with haloperidol. These findings may suggest that previous reports of benefits of newer medications are simply due to their lower propensity for causing movement disorders or the need for reduced levels of anticholinergic treatment. Although low-dose treatment studies of first-episode patients have still yielded consistent cognitive benefits compared with conventional medications, this issue is not resolved and will require more attention.

Does the Metabolic Syndrome Associated With Atypical Antipsychotics Counteract Other Aspects of Their Usefulness?

This area is rapidly emerging and highly controversial. Metabolic syndrome refers to a constellation of related features including abdominal adiposity, glucose dysregulation, dyslipidemia, and increases in blood pressure. It appears that, despite the benefits of newer medications in areas such as general tolerability, relapse prevention, and moderate cognitive enhancement, some newer medications cause a new class of side effects. While patients with schizophrenia are at risk for metabolic syndrome independent of treatment,[96] recent reports have found weight gain, increased prevalence of newly incident diabetes, changes in lipid levels, and occasional cases of potentially lethal diabetic ketoacidosis associated with treatment with some of the newer antipsychotic medications.[97,98] While there is an ongoing debate about the extent to which these medications are directly responsible for these metabolic changes, compared with being related to schizophrenia, this issue clearly needs to be considered when treating patients with newer medications. The correlates of the metabolic syndrome have the potential to reduce quality of life and aspects of medical status that need to be considered in the overall cost-benefit ratio of these treatments. Potential stand-alone cognitive-enhancing treatments described below will also have to be evaluated for their medical side effects as part of a realistic cost-benefit assessment.

Pharmacologic cognitive enhancers without antipsychotic effects. Although atypical antipsychotic medications appear to have greater cognitive benefits compared with conventional medications, most patients do not consistently reach levels of performance consistent with either normal functioning or their own levels of premorbid functioning. Therefore, the possibility of using additional cognitive enhancers has received recent attention. While several different pharmacologic directions could be considered (see Friedman[99] for a comprehensive review), there are few successes to date and no long-term effectiveness studies. Previous studies have examined the effects of cholinergic, noradrenergic, and glutamatergic interventions. While the results of these studies have been somewhat mixed, particularly for cholinergic agents (see Friedman et al.[100] in contrast to Buchanan et al.[101] for an example), this area is very important for future studies. In

fact, this area has just received priority status from the National Institute of Mental Health, which has instituted a systematic initiative aimed at the evaluation of potential cognitive-enhancing compounds for the treatment of cognitive impairment in schizophrenia (see Hyman and Fenton[102] for a position paper). This research project, based at the University of California, Los Angeles, will develop a program aimed at evaluating the efficacy of potential cognitive enhancers and also formulate a plan through which these compounds can be evaluated for wide-ranging clinical effectiveness.

Although this area of research is in its infancy, some interesting issues have already arisen. Medications will not necessarily have to have antipsychotic effects in order to be considered by the U.S. Food and Drug Administration for approval as cognitive enhancers. At the same time, medications that worsen other features of schizophrenia (e.g., psychotic symptoms) will not be suitable as cognitive enhancers. Medications that improve only one aspect of cognitive functioning may not be as useful as those with broader effects. It is clear that control of psychotic symptoms must continue when additional cognitive enhancers are added to the treatment regimen. Some research has already tentatively suggested that potential cognitive enhancers may also work best in conjunction with atypical antipsychotic medications. An intriguing preliminary finding generated by Friedman et al.[103] is that patients treated with guanfacine, an alpha-2 adrenergic agonist, manifested improvement in working memory if they received concurrent treatment with atypical antipsychotics, but not if treated with conventional medications. While the reasons for this interaction are complex, it is possible that some characteristics of atypical medications may make them a more suitable platform for supplemental cognitive enhancement than conventional medications. This finding, and this aspect of the treatment of schizophrenia in general, will be the focus of considerable attention in the coming few years.

Although there are no major success stories to date in terms of cognitive enhancement in schizophrenia with agents that are not antipsychotics, this area is receiving intensive research attention. There will be constant attempts to develop medications to enhance cognition in patients with schizophrenia, with the results of these efforts having a potential impact on cognitive functioning and subsequently on functional outcome. Keeping track of these developments will be critical for clinicians treating patients with schizophrenia.

Behavioral interventions. Nonpharmacologic interventions have also been investigated for the treatment of cognitive impairment in schizophrenia. Cognitive remediation seeks to directly improve cognitive functioning, using computerized or pen-and-paper tests that require patients to focus and sustain attention, plan, or use memory techniques. A number of controlled trials have yielded mixed results.[104–107] Some findings suggest that cognitive task performance can be improved with training, but that the benefits of the training may not always generalize to similar tasks or to improvements in adaptive function.[108–110] A recent review of literature[111] suggests that there is not enough evidence to conclude that remediation will be successful in clinical treatment, but there are a number of studies demonstrating wide-ranging effects of these treatments. Medalia et al.[112] found that remediation of problem-solving deficits with behavioral strategies may improve everyday functioning. Spaulding et al.[113] found that Integrated Psychological Therapy, a combination of cognitive remediation and social skills training, improved a variety of measures of cognitive functioning and social competence. Wykes et al.[108] demonstrated that cognitive remediation improved cognition and led to changes in social functioning and self-esteem. Compensatory strategies and environmental supports have also been designed to bypass cognitive deficits in an effort to improve community functioning[114] rather than attempting to alter cognitive functioning per se. Research has demonstrated that errorless learning, a training method designed to minimize errors during skills acquisition, facilitates training of individuals whose cognitive deficits would otherwise limit their ability to benefit from training programs.[115,116] Establishing environmental supports such as alarms, signs, and checklists to cue and sequence adaptive behavior in the home environment has been shown to improve community functioning and decrease symptomatology and rates of rehospitalization.[114–117]

Interactions of behavioral and pharmacologic interventions. Because cognitive performance is improved for some patients receiving atypical antipsychotics, patients taking these atypical medications may derive greater benefit from rehabilitation programs that require cognitive skill development.[118–120] There is evidence to suggest that patients receiving atypical antipsychotic medications such as clozapine, quetiapine, olanzapine, and risperidone may benefit more from cognitive remediation than patients treated with conventional antipsychotics.[119] For example, patients in long-term psychiatric rehabilitation who were taking atypical antipsychotics had less severe negative and hostile/excitement symptoms and better cognitive functioning than those taking conventional antipsychotics.[121] McGurk and Meltzer[122] found that subjects participating in vocational rehabilitation who were taking an atypical antipsychotic medication were more likely to be working full time than those treated with conventional antipsychotics. Harvey et al.[83] found that patients treated with atypical antipsychotic medications learned simple skills with practice to the extent that their performance was normalized after 3 to 4 weeks of daily practice, whereas patients treated with haloperidol or fluphenazine at low doses (5 mg or less per day) failed to improve at all with the same amount of practice. These data suggest that

for patients to experience improvement in comprehensive rehabilitation programs, atypical antipsychotic medication treatment may be required. Similar to the findings of the Friedman et al.[103] study of adjunctive pharmacologic treatments, low doses of conventional medications were not a suitable platform for behavioral cognitive rehabilitation.

In the domain of direct pharmacologic enhancement of cognition, there are more promises than success stories. The lack of previous success does not necessarily mean that there is no potential for the future. Again, a number of ongoing studies are examining the interaction of pharmacologic (including both atypical antipsychotics and other cognitive enhancers) and behavioral cognitive enhancement strategies. The results of these studies may have the potential to inform clinical treatment decisions in the near future.

What Can Clinicians Do to Increase the Breadth of Treatment Response?

Employ assessment strategies. Clinicians treating patients with schizophrenia should consider patients' cognitive functioning as well as the other aspects of illness described in this article. Many clinicians have previously focused nearly exclusively on the domains of illness associated with efficacy, even during longer-term treatment. It would also be helpful to consider quality of life, functional skills, relapse prevention, and medical status while engaging in the long-term treatment of patients with schizophrenia. Making treatment decisions that consider these other dimensions of the illness is likely to lead to better treatment outcomes.

An efficient tool for measuring cognition in patients with schizophrenia could be a useful guide for clinicians who are making decisions about rehabilitation potential. In the past, however, there has been a clear shortage of psychologists to perform assessments at the typical clinical sites where schizophrenia patients are seen. Many abbreviated assessments, such as the Mini-Mental State Examination,[123] are not sensitive to the cognitive impairments in schizophrenia. Other abbreviated assessments are not yet validated or are not relevant for the assessment of patients with schizophrenia. There are, however, some tests available. For example, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[124] is one test that is commercially available and that has been investigated for its repeatability and validity in schizophrenia populations. It is a standardized screening instrument with alternate forms designed to evaluate global neuropsychological functioning in a brief assessment and is sensitive to some of the impairments typically found in schizophrenia.[125] RBANS scores have been reported to have weak associations with some components of cognition in schizophrenia, including executive function, motor performance, and vigilance.[126]

The Brief Assessment of Cognition in Schizophrenia (BACS)[127] has been developed to assess cognitive change in clinical trials. It assesses the domains of cognition found to be consistently related to outcome in schizophrenia, verbal memory, working memory, motor speed, attention, executive function, and verbal fluency. It yields a high completion rate in schizophrenic patients and has high reliability. The BACS was found to be as sensitive to cognitive impairment in patients with schizophrenia as the standard battery of tests that requires more than 2 hours to administer. Composite scores developed from the BACS were highly correlated with the standard battery composite scores in patients ($r = 0.76$) and healthy controls ($r = 0.90$). However, the BACS has not received wide enough usage to date to ensure that it is sensitive to all of the cognitive impairments related to the other important features of illness described in this article.

Consider cognition when selecting treatments. Some treatments for schizophrenia, such as anticholinergic medications, have been demonstrated to have detrimental cognitive effects. As reviewed above, there is some evidence that atypical medications are preferable for cognitive enhancement in most populations and at most doses. As medications that enhance cognition become available, clinicians should consider them for essentially all patients with schizophrenia, in that there is evidence that even after treatment with atypical medications there would be room for additional cognitive enhancement.

Support comprehensive treatment. Even with cognitive-enhancing medications, patients with schizophrenia may not spontaneously execute functional skills appropriately. Nonpharmacologic interventions that provide social skills training, assist in the development of functional skills, encourage medication management, and provide cognitive enhancement will increase the chances that functional skills will be more effectively deployed. In times of shrinking budgets, this approach may seem unrealistic. It should be kept in mind, however, that even in academic medical centers, many patients do not receive available programs simply because the referral is never suggested.

CONCLUSIONS

Treatments with demonstrated clinical efficacy can have limitations in many other important aspects of the illness, as evidenced by high rates of relapse, poor functional outcomes, poor treatment compliance, and medical comorbidities in patients who experience reductions in their psychotic symptoms. Cognitive deficits contribute to an extent to all of these domains: poor medication adherence, inadequate social functioning, reductions in health and wellness, and decreases in quality of life. Reduced quality of life can also be attributed to medication side effects or failures in other daily activities, such as

finances, independent living, and medical status. Improvements in cognition can have a positive impact on many domains such as social functioning, employment, independence, health, and financial aspects of daily living, although the impact of improved cognition on these domains is yet to be fully elucidated.

While cognitive impairment is a consistent predictor of many domains of functional limitations, the fact that little success in cognitive enhancement has previously occurred limits our ability to claim that reducing cognitive deficits would reduce correlated impairments. Some reports have suggested that treatments with medications that enhance cognition are associated with greater improvements in response to various behavioral treatments, but these responses have not been shown in rigorous clinical trials to be associated with community adjustment. Not enough data are available to suggest that in short-term studies notable improvements in functional outcome are associated with newer antipsychotic treatments. Developments in these areas will be of substantial importance for treatment of schizophrenia in the future. The results of studies aimed at reducing cognitive impairment will be a critical part of the development of new treatments for schizophrenia in the near future.

Drug names: clozapine (Clozaril), fluphenazine (Permitil and others), guanfacine (Tenex), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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