Cognitive Dysfunction in Schizophrenia and Its Importance to Outcome: The Place of Atypical Antipsychotics in Treatment

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The neurocognitive impairment associated with schizophrenia has been well established. Such impairment may be present prior to the onset of the positive symptoms of schizophrenia and persist during periods of remission. Neurocognitive deficits predict multiple domains of outcome; treating such deficits is therefore regarded as highly important. Conventional antipsychotic agents do not appear to favorably affect cognitive function in schizophrenia. Indeed, their propensity to induce adverse effects such as extrapyramidal symptoms may further impair cognitive function. A growing body of evidence suggests that patients taking atypical antipsychotics perform better on some tests of neurocognitive ability than patients receiving conventional agents, with implications for adaptive functioning. The neurocognitive benefits of the atypical antipsychotic agents discussed in this article support their use as a first-line therapy for schizophrenia.

Research has consistently demonstrated that patients with schizophrenia perform more poorly on a wide range of tests of neurocognitive function than age-matched control subjects. As illustrated in Figure 1, the mean performance rating of schizophrenia patients is between 1 and 2 standard deviations below that of controls. In addition to this generalized cognitive impairment, specific deficits have been identified in the areas of attention, memory, information-processing speed, and executive functions (the ability to plan and carry out goal-directed activity). Neurocognitive deficits have been found to be present prior to the onset of the positive symptoms of schizophrenia and during periods of relative remission of positive symptoms in a majority of patients.

NEUROCOGNITIVE DEFICITS AND FUNCTIONING IN SCHIZOPHRENIA PATIENTS

Neurocognitive deficits are important because they predict multiple domains of outcome for patients with schizophrenia, including performance of basic activities of daily living, social functioning, occupational functioning, and level of independent living in the community. In fact, in recent studies, our research team and others found that neurocognitive deficits accounted for as much as 50% of the variance in adaptive functioning. In addition, results of path analysis revealed that neurocognitive deficits were much stronger predictors of community functioning than levels of either positive or negative symptomatology (Figure 2).

The results of these studies suggest that cognitive dysfunction is a central part of schizophrenic illness and that it should be viewed as another domain of pathology along with positive and negative symptoms. Given the centrality of neurocognitive functioning to community adjustment, cognition has been increasingly regarded as an important outcome in the assessment of treatment efficacy in this population.

Unfortunately, traditional antipsychotic medications, which primarily block D₂ receptors, do not favorably affect cognitive function in schizophrenia. In addition, the extrapyramidal side effects (EPS) of traditional antipsychotic medications significantly impair neurocognitive function, particularly on tests requiring motor output, speed, and readiness to respond. Furthermore, the anticholinergic medications used to treat EPS impair cognition, most notably memory function. Traditional approaches to treatment can therefore worsen the cognitive impairments that characterize schizophrenia.

Atypical Antipsychotic Agents and Cognitive Function

In general, atypical antipsychotics are characterized by a more favorable side effect profile than traditional antipsychotics in that they are much less likely to cause EPS at...
doses that are effective in treating psychotic symptoms. However, when doses at the upper range are needed, atypical antipsychotics appear to differ in their likelihood of causing EPS. Furthermore, lower rates of EPS decrease or eliminate the need for anticholinergic medications such as benztropine. Thus atypical antipsychotics, when given in doses that do not produce EPS, do not cause the cognitive problems associated with EPS and their treatment.

A growing body of evidence suggests that patients taking novel or atypical antipsychotic medications perform better on some tests of neurocognitive ability than patients taking standard neuroleptics. For example, studies in patients receiving clozapine have shown that these patients perform better on tests of reaction time, verbal fluency, and attention compared with patients receiving standard neuroleptics. There is some evidence, however, that patients receiving clozapine may perform more poorly on tests of memory function than patients receiving haloperidol, likely due to the anticholinergic properties of clozapine.

Quetiapine and Cognitive Function

In a recent multisite clinical efficacy study, we examined the neurocognitive effects of quetiapine versus haloperidol in 58 stable outpatients with a diagnosis of schizophrenia. Like clozapine, quetiapine has a higher affinity for 5-HT₂ receptors compared with D₂ receptors. Unlike clozapine, quetiapine has minimal intrinsic anticholinergic properties.

Results of the study indicated that patients receiving quetiapine, 600 mg/day, improved to a greater extent than patients in the haloperidol, 12 mg/day, group as measured by the overall level of neurocognitive function over a 6-month period. Overall cognitive function scores over time for patients in the quetiapine and haloperidol groups are shown in Figure 3. A clinically relevant difference of more than 1 standard deviation in cognitive performance between the 2 patient groups after 6 months of treatment.
was found. With respect to individual neurocognitive domains, tests of both executive functions (verbal fluency) and verbal memory (paragraph recall) improved significantly ($p < .03$) for patients receiving quetiapine compared with those receiving haloperidol. Differences of neurocognition between groups were not attributable solely to changes in symptomatology or side effects or to anticholinergic use. Quetiapine appeared to have a direct beneficial effect on cognitive performance independent of these factors.

This research illustrates the important place of atypicals in the treatment of patients with cognitive dysfunction. In addition, treatment with these newer agents raises the possibility that we may be able to avoid or reverse the process of cognitive impairment in schizophrenia.

Improvements in neurocognitive function over time with quetiapine are also illustrated in a case study from Stip and coworkers$^{22}$ (reprinted above). This case describes the improvement in both neurocognition and community functioning that can occur with atypical antipsychotic medications. These new agents may greatly improve community adjustment and quality of life for patients with schizophrenia.

Case Study

Cognitive improvement following treatment with quetiapine, as discussed above, is clearly illustrated by the case of a 31-year-old man who had been admitted to hospital with an exacerbation of psychotic symptoms.$^{22}$ His case is summarized in this supplement; however, in brief, this patient had experienced persistent negative symptoms that had not been relieved by conventional antipsychotic therapy. Following initiation of quetiapine treatment, his hallucinations ceased and he felt generally more energetic and sociable. In terms of cognitive function, all aspects of cognition that were examined improved during quetiapine treatment.
treatment, including short-term and explicit memory. In fact, 6 months after the start of quetiapine treatment, his cognitive functioning was similar to that of normal controls.

Atypical antipsychotics such as quetiapine offer patients effective control of positive and negative symptoms. In addition, their apparent beneficial effects on cognitive function have implications for adaptive functioning, including the possibilities of improved community outcomes and quality of life. Such far-reaching benefits support the use of atypical antipsychotics as a first line therapy for the treatment of schizophrenia.

**ASSESSING COGNITIVE FUNCTION IN THE CLINIC**

A practical issue raised by this discussion of the neurocognitive benefits of atypical antipsychotics is that of assessing cognitive deficits. If treatment of neurocognitive deficits is to be integrated into routine clinical care, it will be important to develop test batteries that are practical to administer and score in clinical settings. A number of research groups—including ours—are working to validate brief neurocognitive batteries for use as clinical tools in this population.

*Drug names:* benzotropine (Cogentin and others), clozapine (Clozaril and others), haloperidol (Haldol and others), quetiapine (Seroquel).

**REFERENCES**