

# 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.

*(J Clin Psychiatry 1999;60[suppl 23]:25–28)*

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.<sup>1–3</sup> As illustrated in Figure 1, the mean performance rating of schizophrenia patients is between 1 and 2 standard deviations below that of controls.<sup>3</sup> 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).<sup>1</sup> 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.<sup>1,4–6</sup>

## 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.<sup>7,8</sup> In fact, in recent studies, our research team<sup>8</sup> and others<sup>9</sup> 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).<sup>8</sup>

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.<sup>7,10</sup>

Unfortunately, traditional antipsychotic medications, which primarily block D<sub>2</sub> receptors, do not favorably affect cognitive function in schizophrenia.<sup>10,11</sup> 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.<sup>12</sup> Furthermore, the anticholinergic medications used to treat EPS impair cognition, most notably memory function.<sup>12</sup> 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

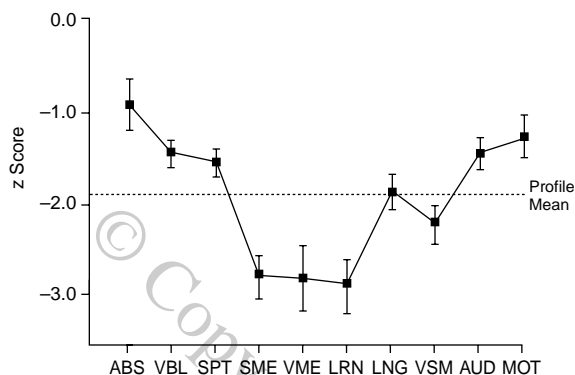
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*Supported by an unrestricted educational grant from  
AstraZeneca.*

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**Figure 1. Neuropsychological Profile (± SD) for Patients With Schizophrenia (N = 36) Relative to Controls (N = 36) Whose Performance Is Set at Zero (= 1 SD)<sup>a</sup>**



<sup>a</sup>Reprinted from Saykin et al.,<sup>3</sup> with permission. Abbreviations: ABS = abstraction, AUD = auditory processing and attention, LNG = language, LRN = verbal learning, MOT = motor speed, SME = semantic memory, SPT = spatial organization, VBL = verbal cognitive, VME = visual memory, VSM = visual-motor processing and attention. The mean and SDs of the normal control groups were used to transform the raw data into z scores to ensure comparability across tests.

doses that are effective in treating psychotic symptoms.<sup>13</sup> However, when doses at the upper range are needed, atypical antipsychotics appear to differ in their likelihood of causing EPS.<sup>14,15</sup> 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.

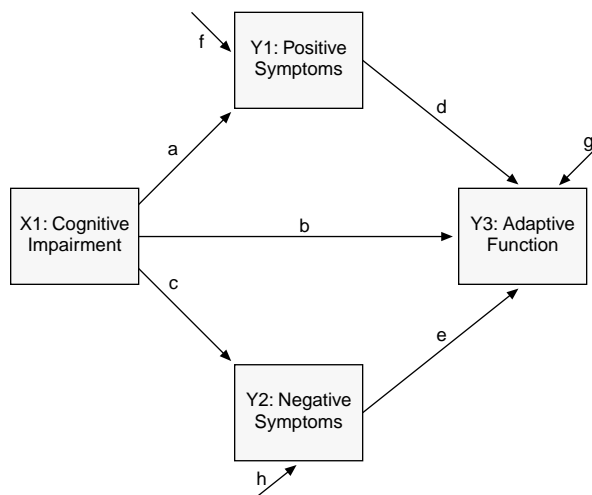
A growing body of evidence suggests that patients taking novel or atypical antipsychotic medications perform better on some tests of neurocognitive ability than patients taking standard neuroleptics.<sup>7,16,17</sup> For example, studies in patients receiving clozapine have shown that these patients perform better on tests of reaction time, verbal fluency, and attention compared with patients receiving standard neuroleptics.<sup>16-18</sup> There is some evidence, however, that patients receiving clozapine may perform more poorly on tests of memory function than patients receiving haloperidol,<sup>19</sup> 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.<sup>20</sup> Like clozapine, quetiapine has a higher affinity for 5-HT<sub>2</sub> receptors compared with D<sub>2</sub> receptors. Unlike clozapine, quetiapine has minimal intrinsic anticholinergic properties.<sup>21</sup>

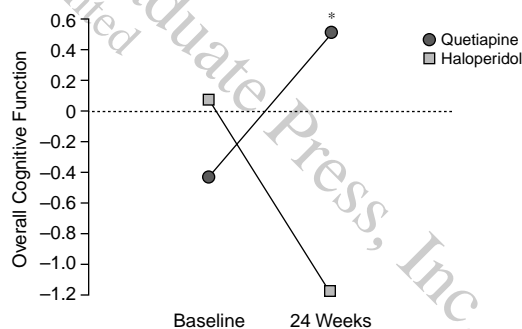
Results of the study indicated that patients receiving quetiapine, 600 mg/day, improved to a greater extent than

**Figure 2. Illustration of Hypothetical Relationships Between Symptomatology, Cognitive Function, and Adaptive Function From Both Inpatient and Outpatient Samples of Schizophrenia Patients<sup>a</sup>**



<sup>a</sup>Reprinted from Velligan et al.,<sup>8</sup> with permission. Abbreviations: X1 = cognitive impairment (Negative Symptom Assessment [NSA] cognition factor score/neuropsychological test battery summary score), Y1 = positive symptoms (Brief Psychiatric Rating Scale psychosis factor), Y2 = negative symptoms (NSA global score [without cognition factor]/NSA motivation factor score), Y3 = adaptive function (Functional Needs Assessment mean score). According to this model, cognitive function contributes to both positive and negative symptoms as well as to adaptive function (a, b, and c). The relationship between symptoms and adaptive function (d and e) arises from deficits in cognitive function. Additional variables that may lead directly to symptoms and impaired adaptive functioning are represented by lines f, g, and h.

**Figure 3. Overall Cognitive Performance Over 24 Weeks in Schizophrenic Patients Receiving Either Quetiapine, 600 mg/day, or Haloperidol, 12 mg/day<sup>a</sup>**



<sup>a</sup>Data from Velligan et al.<sup>20</sup>  
\*p < .03.

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

## Quetiapine and Cognitive Improvement in a Patient With Schizophrenia

Emmanuel Stip, M.D.

### Case history: diagnosis and treatment<sup>a</sup>

Personal details	31-year-old, single man Poor social life, living in a staffed group home
Psychiatric history	Hospitalized on several occasions with diagnosis of paranoid schizophrenia
Previous treatments and outcomes	Haloperidol, flupenthixol, trifluoperazine, pipotiazine No significant improvement of his mostly negative symptoms
Symptoms present at current admission	Mild dyskinetic movements localized in right arm Bradykinesia without tremor Paranoid delusions Auditory hallucinations Poor self-care and speech Blunted affect Constant childlike smile without reason
Present treatment and outcomes	Quetiapine initiated at 450 mg/day and titrated up to 700 mg/day Auditory hallucinations and paranoid delusions ceased Improvement in social communication, including disappearance of childlike smile Patient felt more energetic, able to complete projects and increase social activities
Cognitive improvements	Significant improvement in cognitive function, including all studied components of attention: Short-term memory returned to normal (comparable to the mean of normal controls) by 6 months Explicit memory improved dramatically (46% over 6 months)
Commentary	In conclusion, as well as relieving both the positive and negative symptomatology of schizophrenia in this patient, quetiapine, 700 mg/day, had a marked effect on his cognitive impairment, facilitating his rehabilitation and eventual discharge from hospital.

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<sup>a</sup>Adapted from Stip et al. Seroquel and cognitive improvement in patients with schizophrenia. *Biol Psychiatry* 1996;40:434–435

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<sup>22</sup> (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.<sup>22</sup> 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, 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:* benztropine (Cogentin and others), clozapine (Clozaril and others), haloperidol (Haldol and others), quetiapine (Seroquel).

### REFERENCES

1. Gold JM, Harvey PD. Cognitive deficits in schizophrenia. *Psychiatr Clin North Am* 1993;16:295–312
2. Nuechterlein KH, Dawson ME. Information processing and attentional functioning in the developmental course of schizophrenic disorders. *Schizophr Bull* 1984;10:160–203
3. Saykin AJ, Gur RC, Gur RE, et al. Neuropsychological function in schizophrenia: selective impairment in memory and learning. *Arch Gen Psychiatry* 1991;48:618–624
4. Jager J, Douglas E. Neuropsychiatric rehabilitation for persistent mental illness. *Psychiatr Q* 1992;63:71–94
5. Morice R, Delahunty A. Frontal/executive impairments in schizophrenia. *Schizophr Bull* 1996;22:125–137
6. Velligan DI, Bow-Thomas CC. Executive function in schizophrenia. *Sem Clin Neuropsychiatry* 1999;4:24–33
7. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 1996;153:321–330
8. Velligan DI, Mahurin RK, Diamond PL. The functional significance of symptomatology and cognitive function in schizophrenia. *Schizophr Res* 1997;25:21–31
9. Harvey PD, Howanitz E, Parrella M, et al. Symptoms, cognitive functioning, and adaptive skills in geriatric patients with lifelong schizophrenia: a comparison across treatment sites. *Am J Psychiatry* 1998;155:1080–1086
10. Sharma T, Mockler D. The cognitive efficacy of atypical antipsychotics in schizophrenia. *J Clin Psychopharmacol* 1998;18:12S–19S
11. Cassens G, Inglis AK, Appelbaum PS, et al. Effects on neuropsychological function in chronic schizophrenic patients. *Schizophr Bull* 1990;16:477–499
12. Mortimer AM. Cognitive function in schizophrenia: do neuroleptics make a difference? *Pharmacol Biochem Behav* 1996;56:789–795
13. Thomas CS, Lewis S. Which atypical antipsychotic? *Br J Psychiatry* 1997;172:106–109
14. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. *Am J Psychiatry* 1994;151:825–835
15. Hellewell JSE. A review of tolerability of Seroquel (quetiapine) in the treatment of schizophrenia. In: *Advances in Preclinical and Clinical Psychiatry*. Excerpta Medica. In press
16. Hoff AL, Riordan H, O'Donnell DW, et al. Neuropsychological functioning of first-episode schizophreniform patients. *Am J Psychiatry* 1992;149:898–902
17. Meltzer H. Dimensions of outcome with clozapine. *Br J Psychiatry* 1992;160(suppl 17):46–53
18. Goldberg TE, Weinberger DR. The effects of clozapine on neurocognition: an overview. *J Clin Psychiatry* 1994;55:88–90
19. Green MF, Marshall BD Jr, Wirshing WC. Does risperidone improve verbal working memory in treatment-resistant schizophrenia? *Am J Psychiatry* 1997;154:799–804
20. Velligan DI, Newcomer JW, Pultz J, et al. Changes in cognitive functioning with quetiapine fumarate versus haloperidol. In: *New Research Program and Abstracts of the 152nd Annual Meeting of the American Psychiatric Association*; May 20, 1999; Washington, DC. Abstract NR633:247
21. Arvanitis LA, Rak IW. Efficacy, safety and tolerability of Seroquel (quetiapine) in elderly subjects with psychotic disorders. Presented at the 151st Annual Meeting of the American Psychiatric Association; May 30–June 5, 1998; Toronto, Ontario, Canada
22. Stip E, Lussier I, Babai M, et al. Seroquel and cognitive improvement in patients with schizophrenia. *Biol Psychiatry* 1996;40:434–435