CME

Do Novel Antipsychotics Improve Cognition? A Report of a Meta-Analysis

Richard S. E. Keefe, PhD; Anna M. Bollini, BA; and Susan G. Silva, PhD

Sebastian is 28 years old and has chronic schizophrenia. Five years ago he moved from Chile to New York City, where he became a taxi driver. After a few months, he began to experience anxiety as a result of the chaotic traffic, rude passengers, and his demanding boss. He tried to schedule his shifts so that he could avoid working during the rush hours, but he still found himself overcome with stress. In addition to his growing anxiety, Sebastian was having problems remembering the passengers' destinations and planning which route was the most time and distance efficient. Twice he ran through red lights because he was not paying attention to his driving. Many passengers felt endangered and bothered by his circuitous routes. Several complained to his employer or refused to pay the fare. After 6 months, Sebastian was fired. He sought employment at other taxi companies, but found that he had the same difficulties driving for them and eventually gave up driving a taxi altogether.

Like many patients with schizophrenia, Sebastian has significant cognitive deficits. A neuropsychological testing battery suggests that his working memory, which refers to his ability to keep information in mind during brief periods of time, is poor, falling in the bottom 25%, compared with non-schizophrenic individuals his age. In addition, his ability to categorize information, make decisions, and construct plans is poor, with scores in the bottom 10%, compared with normal individuals. Tests show that his attention and verbal memory are also substandard, with scores in the bottom 10% to 15%, compared with normal individuals. Anyone involved in Sebastian's treatment would be concerned about these cognitive deficits and would be inclined to ask the following questions: To what degree do these cognitive deficits affect Sebastian's life? Are they a result of his other symptoms of schizophrenia, such as his negative symptoms, or are they independent, warranting a treatment regimen aimed specifically at ameliorating them? Are medications available to treat these cognitive deficits? Will the improvements caused by these medications be clinically meaningful? What changes can Sebastian and his physician expect?

It is important to consider these questions because they concern areas that are central to the quality of life of individuals with schizophrenia. As reviewed by Green et al.,[1] cognitive impairment in schizophrenia is strongly related to poor outcome and poor everyday functioning. Employment status is strongly related to performance on cognitive tests (S. McGurk and H. Meltzer, unpublished data, April 16, 1999). Many studies conducted during the past 40 years have addressed the question of whether typical

All of the authors are from the Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina. Address reprint requests to Richard Keefe, PhD, Box 3270, Duke University Medical Center, Durham, NC 27710.

Dr. Keefe's research activities are sponsored by Eli Lilly and Company and Janssen. He is a paid consultant to Janssen, Eli Lilly and Company, and Wyeth–Ayerst.

TABLE 1

Methodologies of 15 Studies of the Effect of Novel Antipsychotic Medication on Cognitive Functions in Patients With Schizophrenia

	Diagnosis of Subjects	Baseline Neuro-cognitive Assessment (Medication Status)	Multiple Arms With Random Assignment	Study Duration	Daily Medication Doses	Neuro-cognitive Test Batteries	Sample Size	Assessment of Neuro-cognitive/ Clinical Relationships
Double-blind studies (N = 3)								
Meyer-Lindenberg et al.,[7] 1997	Treatment-resistant schizophrenia	Yes (4-day washout)	Yes	Testing at day 2, then weekly for 6 weeks	Clozapine: 150–450 mg; zotepine: 150–450 mg	Maze tests only	26	No
Buchanan et al.,[8] 1994 (phase I)	Treatment-responsive schizophrenia	Yes (fluphenazine hydrochloride)	Yes	10 weeks	Clozapine: 400 mg (200–600); haloperidol: 20 mg (10–30)	4 cognitive domains	9 subjects in each group	Yes
Green et al.,[1] 1997; McGurk et al.,[9] 1997; and Kern et al.,[10] 1999	Treatment-resistant schizophrenia	Yes (3- to 7-day washout following 3-week haloperidol stabilization)	Yes	4 weeks	Risperidone: 6 mg; haloperidol: 15 mg	4 domains overall; 2 measures per publication	59	Yes
Open-label studies (N = 12)								
Goldberg et al.,[11] 1993	Psychotic disorders	Yes (conventional antipsychotic)	No	3–24 months; mean = 15 months	Clozapine; many adjunctive medications	9 domains	15	No
Hagger et al.,[12] 1993	Treatment-resistant schizophrenia	Yes (27 drug free; 5 typicals; 4 1–3 days of clozapine)	No	6 weeks; 6 months; 1 year	Clozapine: 363 ± 11 mg for 6 weeks, 403 ± 208 mg for 6 months	6 domains	36	Yes
Buchanan et al.,[8] 1994 (phase II)	Treatment-responsive schizophrenia	Yes (fluphenazine hydrochloride)	No	1 year	Clozapine: 200–600 mg	3 domains	33	Yes
Lee et al.,[13] 1994	Treatment-responsive schizophrenia	Yes	Yes	6 weeks; 6 months; 1 year	Not available	6 domains	Conventional = 23; clozapine = 24	Yes

Zahn et al.,[14] 1994	Schizophrenia	Yes (fluphenazine hydrochloride or placebo)	No	6 weeks each phase	Fluphenazine hydrochloride: mean = 23 ± 14.8 mg; clozapine: mean = 444 ± 189 mg	2 tests	25	No, hallucinations only
Gallhofer et al.,[15] 1996	Schizophrenia	No	No	7 days	Clozapine: 200–400 mg; risperidone: 4–8 mg; haloperidol: 3–15 mg; fluphenazine hydrochloride: 6–24 mg	Maze tests only	16	No
Hoff et al.,[16] 1996	Treatment-resistant schizophrenia	Yes (conventional neuroleptic)	No	12 weeks	Baseline CPZ equivalents: 1,418 ± 809; clozapine: 425–900 mg, mean = 668 ± 164	10 domains	20	Yes
Stip and Lussier,[17] 1996	Schizophrenia	Yes (conventional neuroleptic)	No	8 weeks; 20–30 weeks	Haloperidol: 1 patient—40 mg; risperidone: 1 patient—11 mg, 2 patients—10 mg	3 domains	13	Minimal; correlations with BPRS and PANSS total scores
Rossi et al.,[18] 1997	Schizophrenia	Yes (1 week placebo)	No	4 weeks	Risperidone: 2 mg	3 tests	30	Yes
Serper and Chou,[19] 1997	Schizophrenia	Yes (medication free; time period unknown)	No	4 weeks	CPZ equivalents: 827 ± 528 mg; ziprazidone: N/A; aripiprazole: N/A	3 measures	Atypical = 9; typical = 12	No
Galletly et al.,[20] 1997	Schizophrenia	Yes (1 medication free; 4 risperidone; 14 conventionals)	No	6.5 ± 2.0 months	Clozapine: mean = 393 ± 182 mg	7 domains	19	Yes
Fujii et al.,[21] 1997	Treatment-resistant schizophrenia	Yes (conventional neuroleptics)	No	12–16 months	Clozapine: 250–900 mg, mean = 643	7 domains	10	No

CPZ = chlorpromazine; BPRS = Brief Psychiatric Rating Scale; PANSS = Positive and Negative Syndrome Scale; N/A = not available.

Long-term treatment with conventional antipsychotic medications improves symptoms, but appears to have limited cognitive benefits.

antipsychotics improve cognitive function in patients with schizophrenia. Numerous literature reviews, including a recent review of data collected during the past 9 years,[2] have arrived at the same basic conclusions: long-term treatment with conventional antipsychotic medications improves symptoms, but appears to have limited cognitive benefits. In fact, the literature examining the cognitive effects of typical antipsychotics provides some of the clearest demonstrations of the recalcitrant nature of cognitive impairment despite symptom change. The results of several studies may be interpreted to suggest that typical antipsychotic medications actually prevent adequate learning effects and worsen motor skills,[3] memory function,[4] and executive abilities, such as problem solving and performance assessment.[5]

META-ANALYSIS METHODS

The advent of novel antipsychotics has motivated researchers to examine how these medications affect cognitive impairments compared with conventional medications. To address this question empirically, a meta-analysis was conducted including the 15 studies that, as of June 30, 1998, had investigated the impact of novel antipsychotic medication on cognitive dysfunction in patients with schizophrenia.[6] The methodology used in each of the 15 studies is listed in Table 1. The analysis was not restricted to studies investigating a particular novel antipsychotic medication. Three of the studies were randomized and double-blind, and 11 were open-label studies. In 1 study,[19] the patients who received novel antipsychotics and a portion of the patients who received haloperidol were assessed in a double-blind manner; however, several of the patients who received haloperidol were not. One of the open-label studies[13] used multiple study arms with random assignment. The numbers of studies that included the various novel antipsychotics are as follows: clozapine, 11; risperidone, 4; zotepine, 1; ziprazidone, 1; and aripiprazole, 1.

The 15 studies used a wide range of test measures. Some studies examined only a few neurocognitive measures, whereas others conducted a more comprehensive neuropsychological assessment. The number of different neurocognitive tests given to subjects ranged from 1 to 13. Because of the variability in the type and the number of measures used to assess neurocognitive effects, test results were grouped into the following categories: (1) attention subprocesses; (2) executive function; (3) working memory; (4) learning and memory; (5) visuospatial analysis; (6) verbal fluency; (7) digit symbol substitution; and (8) fine motor function.

Each study was examined to determine improvement in performance on a single test after treatment with novel antipsychotic medication compared with after conventional antipsychotic treatment (atypical vs typical) or a significant positive change in performance after treatment with novel antipsychotic medication relative to baseline. Our definition of improvement was conservative. We corrected for multiple comparisons in each study using an experimentwise P value of less than .05, even if the study authors did not complete this statistical procedure. For instance, if 10 measures were reported in a study, we assigned a significance criterion of $.05/10 = .005$ for each measure.

The cognitive domains in which each investigator reported improvement with novel antipsychotic treatment are displayed in Table 2, along with the improved cognitive domains resulting from our multiple comparison analysis. After we corrected for multiple comparisons, 9 of the 15 studies demonstrated significant neurocognitive improvement on at least 1 test measure following treatment with novel antipsychotic medication compared with conventional antipsychotics.

TABLE 2

Meta-Analysis Results of Impaired Cognitive Functions in 15 Studies

Study	Attention Subprocesses	Executive Function	Working Memory	Learning and Memory	Visuospatial Analysis	Verbal Fluency	Digital Symbol Substitution	Fine Motor Function	Total IQ
Meyer-Lindenberg et al.,[7] 1997		X						X	
Buchanan et al.,[8] 1994 (phase I)					X*	X*			
Green et al.,[1] 1997; McGurk et al.,[9] 1997; and Kern et al.,[10] 1999	X*	X						X	
Goldberg et al.,[11] 1993									
Hagger et al.,[12] 1993	X	X				X*	X*		
Buchanan et al.,[8] 1994 (phase II)		X			X	X*			
Lee et al.,[13] 1994		X*		X		X*	X*		
Zahn et al.,[14] 1994	X								
Gallhofer et al.,[15] 1996		X*						X*	
Hoff et al.,[16] 1996						X	X		
Stip and Lussier,[17] 1996	X*								
Rossi et al.,[18] 1997		X	X				X*		
Serper and Chou,[19] 1997	X								
Galletly et al.,[20] 1997			X		X	X	X		
Fujii et al.,[21] 1997							X		X*

X = investigator reported neurocognitive improvements.
**Neurocognitive improvements after correction for multiple comparisons.*

STATISTICAL PROCEDURE

The statistical meta-analytic procedures used to examine the results of these studies are described in detail by Keefe et al.[6] Briefly, Fisher's method for combining *P* values was used. It provides a summary of the statistical significance of the results and a test of the null hypothesis that there is no difference between the effects of novel antipsychotics and conventional antipsychotics. When a given study included multiple test measures, the average *P* value for that study was used in the statistical procedure. If multiple test measures were included in a single domain of cognitive functioning, the average *P* value for that domain was used in the statistical procedure. When *P* values were not available, we calculated them using the published means and standard deviations. In one case, we contacted the authors to obtain unpublished means and standard deviations.

RESULTS OF THE META-ANALYSIS

The meta-analysis of the 15 studies indicated that there was a significant effect of novel antipsychotics compared with typical antipsychotics in their ability to improve cognitive functioning (chi-square = 62.41, $P = .0004$). The effect of novel antipsychotic medication on specific domains of cognitive function was also examined by combining all studies that reported data for each domain. Corrections were not made for multiple comparisons because this would have

required setting a variable P value for each domain. Meta-analyses indicated significant improvement with novel antipsychotics in each of the aforementioned categories: attention, executive functions, working memory, visuospatial analysis, verbal fluency, digit symbol substitution, and fine motor functions.[6]

Despite a conservative statistical approach of correcting the results of each study for the number of statistical comparisons made, the meta-analysis strongly suggests that novel antipsychotics, when compared with conventional antipsychotics, improve cognitive functions in patients with schizophrenia. The measures that responded the most strongly to novel antipsychotics were verbal fluency, digit symbol substitution, fine motor functions, and executive functions. Attention subprocesses were also responsive. Learning and memory functions were the least responsive.

CONCLUSION

Because of the limited number of studies included in the meta-analysis, it is difficult to conclusively determine the pattern of cognitive improvements that can be expected with any specific novel antipsychotic treatment. There is, however, preliminary support for the notion that verbal fluency, attention, and motor speed improve with clozapine. It has been shown that risperidone has beneficial effects on verbal working memory, selective attention and alertness,[1] and executive functions.[15] A study conducted by Rossi et al.[18] suggests that negative symptoms correlate with performance on the Wisconsin Card Sorting Test before and after treatment with risperidone, implying that cognitive deficits and negative symptoms have a common substrate targeted by risperidone. Data published since our meta-analysis was completed suggest that quetiapine may have beneficial effects on attention,[22] short-term memory, and explicit memory.[23] As reviewed by Meltzer and McGurk,[24] preliminary data suggest that olanzapine also has beneficial effects on a variety of cognitive functions.

None of the 15 studies met all of the recently developed standards for the assessment of cognitive change in schizophrenia.[6] Only 3 of the 15 studies used double-blind methodology and the impact of the various rater biases inherent to open-label studies of patients with schizophrenia, described recently in the Veterans' Administration collaborative study of clozapine,[25] may be strong. However, these 15 studies serve an important function—they support the relatively recent notion that cognitive deficits can be improved in patients with schizophrenia. As a result of these initial studies, several large-scale comprehensive investigations of the effect of novel antipsychotics on cognitive impairment in schizophrenia are currently under way. The results of these studies will be of great interest because the possibility of improved cognitive functions in individuals with schizophrenia will help to further enhance their quality of life.

REFERENCES

1. Green MF, Marshall BD, Wirshing WC Jr, et al. Does risperidone improve working memory in treatment-resistant schizophrenia? *Am J Psychiatry*. 1997;154:799-804.
2. Blyler CR, Gold JM. Cognitive effects of typical antipsychotic treatment: another look. In: Sharma T, Harvey PD, eds. *Cognitive Deficits in Schizophrenia*. Oxford: Oxford University Press. In press.
3. Keefe RSE, Gold JM. Comparing pharmacologic strategies of improving cognition. In: Keefe RSE, ed. *Improving Cognitive Function in Schizophrenia*. London: Science Press. In press.
4. Stip E. Memory impairment in schizophrenia: perspectives from psychopathology and pharmacotherapy. *Can J Psychiatry*. 1996;41(suppl 2):27S-34S.
5. Peretti CS, Danion JM, Kauffmann-Muller F, Grange D, Patat A, Rosenzweig P. Effects of haloperidol and amisulpride on motor and cognitive skill learning in healthy volunteers. *Psychopharmacology (Berl)*. 1997;131:329-338.
6. Keefe RSE, Silva SG, Perkins DO, Lieberman JA. The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. *Schizophr Bull*. 1999;25:201-222..
7. Meyer-Lindenberg A, Gruppe H, Bauer U, Lis S, Krieger S, Gallhofer B. Improvement of cognitive function in schizophrenic patients receiving clozapine or zotepine: results from a double-blind study. *Pharmacopsychiatry*. 1997;30:35-42.
8. Buchanan RW, Holstein C, Brier A. The comparative efficacy and long-term effect of clozapine treatment on neuropsychological test performance. *Biol Psychiatry*. 1994;6:717-725.
9. McGurk SR, Green MF, Wirshing WC, et al. The effects of risperidone vs haloperidol on cognitive functioning in treatment-resistant schizophrenia: the trial making test. *CNS Spectrums*. 1997;2:60-64.
10. Kern RS, Green MF, Marshall BD Jr, et al. Risperidone vs. haloperidol on reaction time, manual dexterity, and motor learning in treatment-resistant schizophrenic patients. *Biol Psychiatry*. 1999;44:726-732.
11. Goldberg TE, Greenberg RD, Griffin SJ, et al. The effect of clozapine on cognition and psychiatric symptoms in

patients with schizophrenia. *Br J Psychiatry*. 1993;162:43-48.
12. Hagger C, Buckley P, Kenny JT, Friedman L, Ubogy D, Meltzer HY. Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. *Biol Psychiatry*. 1993;34:702-712.
13. Lee MA, Thompson PA, Meltzer HY. Effects of clozapine on cognitive function in schizophrenia. *J Clin Psychiatry*. 1994;55(suppl B):82-87.
14. Zahn TP, Pickar D, Haier RJ. Effects of clozapine, fluphenazine, and placebo on reaction time measures of attention and sensory dominance in schizophrenia. *Schizophr Res*. 1994;13:133-144.
15. Gallhofer B, Bauer U, Lis S, Krieger S, Gruppe H. Cognitive dysfunction in schizophrenia: comparison of treatment with atypical antipsychotic agents and conventional neuroleptic drugs. *Eur Neuropsychopharmacol*. 1996;6(suppl 2):13-20.
16. Hoff AL, Faustman WO, Wieneke M, et al. The effects of clozapine on symptom reduction, neurocognitive function, and clinical management in treatment-refractory state hospital schizophrenic inpatients. *Neuropsychopharmacology*. 1996;15:361-369.
17. Stip E, Lussier I. The effect of risperidone on cognition in patients with schizophrenia. *Can J Psychiatry*. 1996; 41(suppl 2):35-40.
18. Rossi A, Mancini F, Stratta P, et al. Risperidone, negative symptoms and cognitive deficit in schizophrenia: an open study. *Acta Psychiatr Scand*. 1997;95:40-43.
19. Serper MR, Chou JCY. Novel neuroleptics improve attentional functioning in schizophrenic patients: ziprazidone and aripiprazole. *CNS Spectrums*. 1997;2:56-59.
20. Galletly CA, Clark RC, McFarlane AC, Weber DL. The relationship between changes in symptom ratings, neuropsychological test performance, and quality of life in schizophrenic patients treated with clozapine. *Psychiatry Res*. 1997;72:161-166.
21. Fujii DEM, Ahmed I, Jokumsen M, Compton JM. The effects of clozapine on cognitive functioning in treatment-resistant schizophrenic patients. *J Neuropsychiatry Clin Neurosci*. 1997;9:240-245.
22. Sax KW, Strakowski SM, Keck PE Jr. Attentional improvement following quetiapine fumarate treatment in schizophrenia. *Schizophr Res*. 1998;33:151-155.
23. Stip E, Lussier I, Babai M, Fabian JL, Link C. Seroquel and cognitive improvement in patients with schizophrenia. *Biol Psychiatry*. 1996;40:434-435. Letter.
24. Meltzer HY, McGurk SR. The effect of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophr Bull*. 1999;25:233-255.
25. Rosenheck R, Cramer J, Xu W, et al. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia: Department of Veterans' Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. *N Engl J Med*. 1997;337:809-815.