Evaluating the Effects of Antipsychotics on Cognition in Schizophrenia

Collaborative Working Group on Clinical Trial Evaluations

Cognitive deficits are an integral feature of schizophrenia and have a deleterious effect on the ability of schizophrenic patients to work and function in a social environment. Drugs that bring about substantial cognitive improvement represent a major contribution in improving the quality of life in schizophrenia. Recent studies have suggested that the atypical antipsychotics may be more useful than conventional agents for improving cognition. There is evidence that scores on neuropsychological assessments have improved after treatment with clozapine, risperidone, and quetiapine. Future research is needed to characterize and quantify the cognitive effects of the atypical antipsychotics.

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Cognitive deficits are core features of the kraepelinian description of schizophrenia. Abnormalities in attention, executive function, and memory—episodic, verbal, and visual—are among the major problem areas. These abnormalities have not been explained by symptomatology, motivation, or institutionalization. Cognitive deficit has a tremendous impact on the vocational and social function of people with schizophrenia, independent of positive and negative symptoms. In fact, predicting which patients will have a successful outcome from treatment is possible on the basis of their level of cognition but not on the basis of severity of symptoms.

There has been some debate about whether schizophrenia causes a static cognitive deficit (that remains stable after the initial losses) or a progressive decline.[1,2] Regardless of the stability or progression of the cognitive deficit, some antipsychotics affect cognition. While the conventional neuroleptics cause marginal improvement in some areas of cognition, other areas such as fine motor function may worsen. The atypical neuroleptics may result in better cognitive outcomes than the conventional antipsychotics, as recent studies have suggested (see below). Evaluating the cognitive effects of the antipsychotics is important, as doing so can assist in choosing among the drugs. The ability of the atypical drugs to improve cognition may help to return the lives of some patients with schizophrenia to greater normalcy through improvement of social and vocational function. Drugs that bring about substantial cognitive improvement contribute to improving the quality of life of patients and reducing the human and financial costs of schizophrenia.

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A complete list of the collaborators in the Collaborative Working Group on Clinical Trial Evaluations appears at the end of this article.

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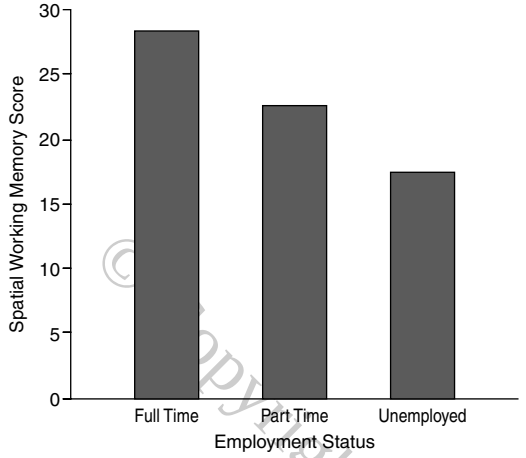
COGNITION AS A PREDICTOR OF REHABILITATION

Neuropsychological deficits are prevalent in patients with schizophrenia and, more so than psychopathology, are predictive of occupational and social dysfunction.[3] Occupational and social dysfunction are very costly aspects of schizophrenia in financial and human terms. The cognitive difficulties of patients with schizophrenia make it impossible for many of them to function socially, which includes maintaining jobs as well as interpersonal relationships. There is a strong correlation, shown in Figures 1 and 2, between scores on cognitive tests and ability to hold a job. Key problem areas affected by schizophrenia are attention, verbal fluency, memory, and executive function.[4] Poor verbal fluency makes functioning in society difficult for people with schizophrenia. Patients with schizophrenia have trouble summoning adequate words from their lexicon. Working memory is critical also; it reflects the ability to remember phone numbers or what happened a few minutes ago. For example, college students who develop schizophrenia may report trouble with reading because by the time they get to the end of a paragraph, they have forgotten what they read at the beginning. Another key problem patients with schizophrenia face is problem-solving, an executive function that is necessary for job tasks and interpersonal relationships.

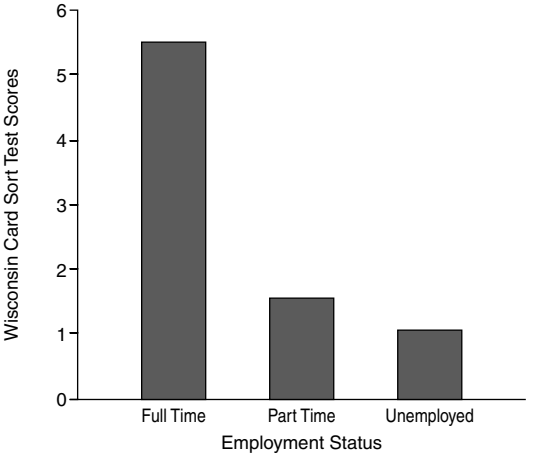
Data showing unique advantages of different neuroleptics with regard to cognition, which are discussed later, suggest that the association between certain drugs and spe-

Figure 1. Employment Status and Spatial Working Memory Test Results in Schizophrenic Patients*



*S. McGurk and H.Y. Meltzer, unpublished data, 1997. Fifteen-second delay in Spatial Working Memory Test.

Figure 2. Employment Status and the Results on the Wisconsin Card Sort Test (WCST) in Schizophrenic Patients*



*S. McGurk and H.Y. Meltzer, unpublished data, 1997.

cific cognitive deficits could be the basis for choosing among the antipsychotics when the clinician makes risk-benefit and safety analyses. Cognitive effects of the neuroleptics are now targets of antipsychotic drug treatment and are becoming considered as part of the efficacy of the drugs; additional study of these deficits is needed to refine both theory and clinical practice in the treatment of schizophrenia. The critical task for clinicians and researchers is to show that improvements in memory are meaningful in terms of rehabilitating patients so that they may enter or reenter the work force.

ETIOLOGY

It appears that instead of cognitive decline progressing gradually in patients with schizophrenia, static encephalopathy—a stable deficit—takes place; young patients with schizophrenia may have no better cognition than older patients who have had the disorder longer, once the normal effects of aging are taken into account.[1,5] One study tested patients with schizophrenia using various cognitive measures and retested them after 12 months, and most measures were stable over time.[2] Scully et al.[6] suggest that cognitive deficit may be determined by gender. Among men, deficits may become "locked in" earlier in the course of the illness than in women, whose deficits may not seem evident early but worsen as the illness progresses.

Cognitive improvement may be related to rapidity in initiating treatment of the illness, since the best improvements have been seen in patients who have been ill for the shortest periods of time.[7] If decline is assumed to be rapid at onset but then to remain stable, then treating the decline early could prevent it from reaching the nadir that it normally would.[8] Scully et al.[9] studied 48 patients who developed schizophrenia before the development of antipsychotic drugs in the 1950s. The investigators controlled for age and for duration and continuity of subsequent antipyschotic treatment. Current severity of both negative symptoms and cognitive deficit were strongly predicted by increasing duration of initially untreated psychosis; duration of illness after the start of antipsychotic treatment did not predict severity. Neither of these indices predicted severity of positive symptoms or executive dysfunction. It is possible that executive dyscontrol is "locked in" at an early phase of the illness. These findings point to the necessity of starting a first-episode patient on an antipsychotic quickly.

Although the improvement and decline in cognition caused by the antipsychotics are clinically meaningful, the etiology of these changes is still a matter of question. Properties of the drugs themselves probably cause effects on cognition. Mortimer[10] points out that ample evidence exists that neuroleptics can cause cognitive modification and notes that any modification would depend on the receptor blockade pattern of the drug. Therefore, prediction of cognitive effects is simpler with relatively pure blockers of 1 system than with nonspecific drugs like chlorpromazine. Furthermore, different tasks may require arousal of different systems, and 1 drug may improve 1 system and impair another while a different drug has the opposite effects. For example, cognitive dysfunction in planning and organizing sequences of behavior may be related to a reduction in dopamine activity in the prefrontal cortex, in which case drugs that block dopamine D_1 receptors would impair function further. Some cognitive improvements during treatment with atypical antipsychotics may be due to fewer extrapyramidal symptoms (EPS). Drugs with anticholinergic activity used to treat EPS, e.g., benztropine,

may impair cognitive functions, such as memory and motor paradigms; thus, the atypical agents, which cause fewer EPS and do not require addition of an anticholinergic drug, are likely to lead to less cognitive decline.[7,8,10,11]

Some cognitive improvement caused by the antipsychotics may result from alleviation of the positive and negative symptoms. For example, attention may improve as psychosis is controlled. Some studies[7,12] suggest that certain cognitive deficits are relatively dependent on the negative symptoms of the disorder. If cognitive deficits were merely secondary to the positive symptoms of schizophrenia, then cognition should improve with neuroleptic treatment. This has not been the case with neuroleptics; cognition has usually remained stable as symptoms improved with some treatments.[8] When cognition does improve, specific areas of cognition respond with different drugs. This is consistent with evidence that cognitive improvement is not simply the result of improving symptoms.

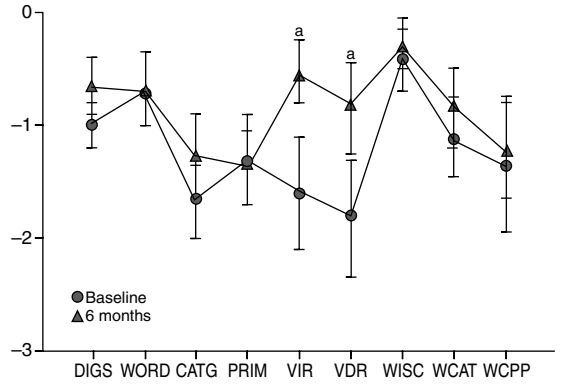
Another theory is that patients who are receiving neuroleptic medication are more cooperative and more willing to undergo testing procedures and thus generally produce better scores on rating scales.[13] Patients taking neuroleptic medication may also be more responsive to cognitive retraining, whether or not the drug itself improves cognitive function.[8] In addition, trial participants who are tested at baseline and then at various treatment intervals may improve on certain tests due to practice,[13,14] although this would not be the case for those whose memory is dysfunctional. No evidence was found for practice effects in a study of clozapine effects by Hagger and colleagues.[15]

Further research is needed to determine whether the cognitive improvements are a primary effect of antipsychotic therapy or secondary to other aspects of treatment. Also, more systematic studies are needed to explain some of the conflicting data regarding specific cognitive effects of the antipsychotics, which are described below.

TYPICAL NEUROLEPTICS

Conventional neuroleptics do not, in general, create consistent, significant positive effects on cognition.[10,16,17] Conventional antipsychotics with anticholinergic effects, such as thioridazine, chlorpromazine, and mesoridazine, may actually worsen primary working memory and have no impact on verbal working memory (Figure 3). Small positive effects that were clinically significant were found in attention, the digit symbol test, the semantic memory category generation, and immediate recall, which showed the most improvement. Results from a study[18] of patients taking antipsychotics for traumatic brain injury support the hypothesis that cholinergic activity regulates cognitive processes; cognition improved more in the patients who were discontinued from thioridazine than from haloperidol. Stip[11] notes that haloperidol may exacerbate memory dysfunction.

Figure 3. Scores on Cognitive Tests in Schizophrenic Patients (N = 17) Taking Typical Neuroleptics*



*Data from reference 21.
[a]p < .05. Abbreviations: DIGS = WAIS-R Digit Symbol Substitution Test; Word = Controlled Word Association Test; CATG = Category Instance Generation; PRIM = Primary Working Memory Test; VIR = Verbal List Learning–Immediate Recall; VDR = Verbal List Learning–Delayed Recall; WISC = Wechsler Intelligence Scale for Children; WCAT = Wisconsin Card Sort Test–Categories; WCPP = Wisconsin Card Sort Test–Percent Preservation.

In a study[19] of cognitive and motor skills in patients treated with haloperidol versus an atypical neuroleptic (amisulpride) or placebo, the haloperidol-treated subjects needed significantly more moves to solve a puzzle and acquire a problem-solving routine—some of the patients had routinized a nonoptimal solution. Haloperidol seemed to impair higher cognitive functions such as ability to assess one's performance and/or to shift from one strategy to another. Mortimer[10] remarks that, given the extrapyramidal effects of the conventional drugs, there is little point in assessing motor tasks where speed and accuracy are required because the motor impairments caused by the drugs will offset any therapeutic effects that the drugs may have on cognition.

Sorting data from conflicting studies is difficult; Stip[11] offers a summary of the effects of conventional neuroleptics on cognition. These neuroleptics can affect any of the major cognitive spheres: attention-vigilance; motor dexterity; abstract thought and problem solving; memory and learning; and verbal behavior. After acute treatment, the negative effects of neuroleptics are mainly in attention-vigilance and motor skills, and, with prolonged treatment, only motor skills remain affected. The beneficial effects of the neuroleptics appear after prolonged treatment and are mainly in sustained-attention and visuomotor tasks.

ATYPICAL ANTIPSYCHOTICS

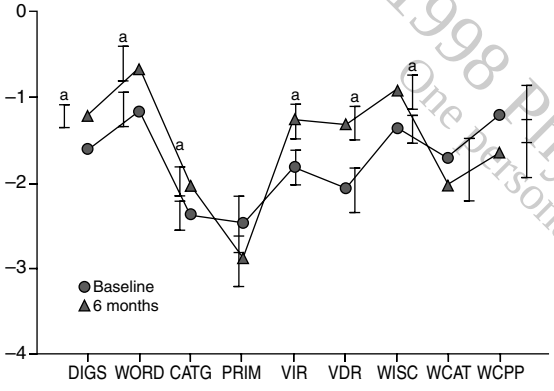
Several recent studies have examined the effects of atypical antipsychotics on cognition, and most reports involve clozapine (Table 1). Although many studies have addressed the effects of clozapine on cognition, they have

Table 1. Significance (p Values) of Effects of Clozapine and Typical Neuroleptics on Neuropsychological Performance in Non–Treatment-Resistant Schizophrenia*

	Typical Neuroleptics[a]			Clozapine[a]		
Test	6 Wk (N = 21)	6 Mo (N = 20)	12 Mo (N = 18)	6 Wk (N = 22)	6 Mo (N = 21)	12 Mo (N = 22)
Digit Symbol	. . .	. . .	. . .	0.005	0.001	0.0001
Consonant Trigram	. . .	. . .	. . .	0.05	. . .	. . .
Category Instance Generation	. . .	. . .	. . .	. . .	0.007	0.03
Controlled Word Association	. . .	. . .	. . .	0.0003	0.0003	0.0002
VLL-IR	0.04	0.005	. . .	. . .	0.03	. . .
VLL-DR	0.02	. . .	0.03	. . .	0.03	. . .
WCST-Category	. . .	. . .	0.05	. . .	. . .	. . .
WCST-Perseveration	0.04	. . .	. . .	. . .	0.04	0.04
WISC-R Maze	. . .	. . .	. . .	. . .	0.007	. . .

*Data from reference 21. Abbreviations: VIR = Verbal List Learning–Immediate Recall; VDR = Verbal List Learning–Delayed Recall; WCST = Wisconsin Card Sort Test; WISC-R = Wechsler Intelligence Scale for Children–Revised.
[a]N may be less than Baseline because some patients were lost to follow-up, missed evaluations, or had not yet reached all evaluation phases.

Figure 4. Scores on Cognitive Tests in Schizophrenic Patients Taking Clozapine (N = 42)*



*Data from reference 21 and H. Y. Meltzer and M. Lee, unpublished data, 1998.
[a]p < .05. Abbreviations: DIGS = WAIS-R Digit Symbol Substitution Test; Word = Controlled Word Association Test; CATG = Category Instance Generation; PRIM = Primary Working Memory Test; VIR = Verbal List Learning–Immediate Recall; VDR = Verbal List Learning–Delayed Recall; WISC = Wechsler Intelligence Scale for Children; WCAT = Wisconsin Card Sort Test–Categories; WCPP = Wisconsin Card Sort Test–Percent Preservation.

not conclusively answered the questions regarding the effects, due to methodological problems such as small sample sizes, lack of control groups, no baseline measurements, or short drug trial periods.[10,11]

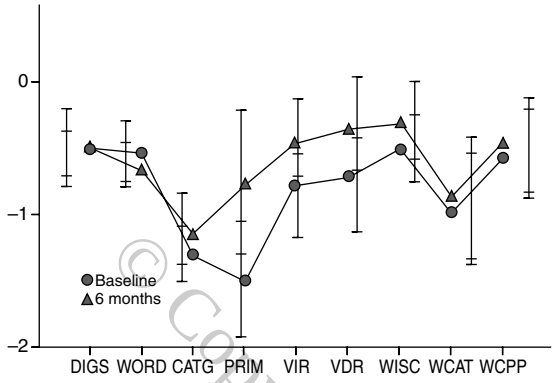
Clozapine, the atypical agent approved only for treatment-resistant schizophrenia, has shown some benefit on verbal fluency, semantic memory, attention, and some types of executive functioning, as shown in Figure 4. Clozapine took patients to within the normal range for verbal fluency and improved immediate and delayed recall on various cognitive tests and on the Wisconsin Card Sort Test, results of which are related to ability to hold full-time employment.[17,20] However, even with the improvements, clozapine-treated patients were still significantly impaired, compared with normal controls, except in verbal fluency.[21] One study[15] reported that clozapine improved semantic memory and attention, although it worsened verbal working memory at 6 weeks; at the 6-month assessment, memory was almost back to baseline level. However, Mortimer[10] discussed a study in which clozapine produced amnestic results in patients due to its antimuscarinic activity.

The negative results concerning working memory may be due to the D_1 antagonist properties of clozapine.[13] Although clozapine[12] and olanzapine[22] both have substantial in vitro potential for anticholinergic effects, they produce much less blockade of cholinergic receptors in vivo.[23] Olanzapine appears to cause no improvement in verbal working memory (H. Y. Meltzer and S. McGurk, unpublished data, 1998).

Clozapine may speed up reaction time in patients undergoing cognitive testing. Zahn and colleagues[24] used 2 reaction time paradigms to examine the effects of clozapine on sustained and selective attention compared with fluphenazine and placebo in 25 patients with chronic schizophrenia. Patients on all 3 treatments showed visual dominance, reacting faster to lights than to tones, but clozapine reduced failure to respond to tones, an effect apparently due to reduction of hallucinations and thus improvement of attention. However, several other studies have demonstrated a decrease in visual memory with clozapine, reports Mortimer.[10]

Risperidone seems to produce different results than clozapine; patients with schizophrenia who take risperidone show an improvement in working memory (Figure 5). Green et al.[16] measured verbal working memory under both distracting and nondistracting conditions at baseline and after 4 weeks of both fixed- and flexible-dose pharmacotherapy with risperidone. They found that risperidone had a more beneficial effect on verbal working memory than haloperidol across testing conditions and study phases. This effect is possibly due to the 5-HT_{2A} receptor

Figure 5. Scores on Cognitive Tests in Schizophrenic Patients Taking Risperidone (N = 14)*



*Data from H. Y. Meltzer, S. McGurk and M. Lee, unpublished data, 1998, Abbreviations: DIGS = WAIS-R Digit Symbol Substitution Test; Word = Controlled Word Association Test; CATG = Category Instance Generation; PRIM = Primary Working Memory Test; VIR = Verbal List Learning–Immediate Recall; VDR = Verbal List Learning–Delayed Recall; WISC = Wechsler Intelligence Scale for Children; WCAT = Wisconsin Card Sort Test–Categories; WCPP = Wisconsin Card Sort Test–Percent Preservation.

antagonism. Risperidone also seems to improve selective attention and alertness, which in turn improves performance on tests with explicit memory and attentional components.[4] Moreover, memory was not impaired, as may happen with clozapine. These improvements are important for patient success in rehabilitation programs and everyday lives. The efficacy of risperidone in reducing cognitive abnormalities was demonstrated in a study by Rossi and colleagues.[12] This study suggests that negative symptoms and cognitive deficits have a common underlying substrate that risperidone targets; the authors state that the negative symptoms but not the positive symptoms correlated with the WCST before and after treatment with risperidone. The positive symptom reduction of risperidone would be due to a different action of the drug.

Another study, by Gallhofer et al.,[25] compared performance on maze tasks in patients taking conventional neuroleptics (haloperidol or fluphenazine) or atypical agents (risperidone and clozapine). Patients taking the atypicals were better able to maintain motor coordination while planning and sequencing other tasks.

The possible interaction of serotonin and dopamine in the antipsychotic activity of risperidone and the lower affinity for cholinergic receptors may be responsible for the greater efficacy of this drug in the treatment of negative symptoms and the lower incidence of EPS, which may cause less cognitive decline than the conventional agents do.[12]

A case report on quetiapine noted cognitive improvement in a patient taking high doses (700 mg/day) of the new atypical drug.[26] Quetiapine has high affinity for serotonin S_2 receptors and lower affinity for D_2 and D_1 receptors compared with conventional neuroleptics, as well as less muscarinic cholinergic receptor antagonist activity. The patient's short-term memory, while always in the normal range, improved to the level of normal control subjects, and explicit memory also improved. The patient's implicit memory was never impaired. Sustained and selective attention were impaired at baseline, but performance improved to that of the controls. The question that the authors ask is, did the patient improve on cognition directly because of the quetiapine, or did the improvement of positive and negative symptoms of schizophrenia cause the cognitive effects secondarily? They advocate future research with this drug.

CONCLUSION

Since EPS-causing drugs or drugs with anticholinergic or dopamine-blocking activity are likely to lead to more cognitive decline, the atypical agents, which have less anticholinergic and antidopaminergic activity and have been shown to cause fewer EPS than the conventional antipsychotics, are probably the better choice of drug for a first-episode patient with schizophrenia. If it is the case that treating a first-episode patient early staves off some of the initial decline, then selecting an atypical agent would be better than selecting a conventional neuroleptic, since the conventional antipsychotics themselves may cause cognitive decline and the atypicals have been shown to produce positive effects on cognition.

Not only should the class of atypical antipsychotics be used instead of the class of conventional agents in view of the lack of anticholinergic effects and dopamine antagonism, but also, since the atypical antipsychotics have different effects on cognition, this should be a consideration when selecting among the atypicals. If the most severe cognitive problem a schizophrenia patient has is, for example, a working-memory deficit, the best drug choice may be risperidone. Characterizing these drugs according to cognitive effects will be useful for the field and could even have pharmacoeconomic impacts because patients who were untreated and unable to work before may now hold a job and need less disability assistance.

Further research is needed in the etiology of cognitive deficits in schizophrenia and the relationship between them and symptoms.

Drug names: benztropine (Cogentin and generic brands), chlorpromazine (Thorazine and generic brands), clozapine (Clozaril), fluphenazine (Prolixin and generic brands), haloperidol (Haldol and generic brands), mesoridazine (Serentil), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and generic brands).

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