The Effects of Clozapine on Cognitive Functioning in Schizophrenia

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Cognitive function may be markedly impaired in patients with schizophrenia; however, it has only recently been recognized as an important factor in determining patient outcome. Research has shown that improvements in cognitive functioning occur independently of improvements in positive or negative clinical symptoms, and whereas typical antipsychotics may improve clinical symptoms, they have little or no efficacy in improving cognitive dysfunction. However, there is evidence that the atypical antipsychotic clozapine may improve this core deficit of schizophrenia. This review summarizes 12 published studies that assessed the effect of clozapine on cognitive functioning. As a group, these studies suggest that psychomotor speed, verbal fluency, and verbal learning and memory may be improved by treatment with clozapine. Such cognitive improvements with clozapine treatment may offer an advantage to patients with schizophrenia by enhancing the possibility of better vocational functioning and quality of life. *(J Clin Psychiatry 1999;60[suppl 12]:24–29)*

Cognitive functioning is impaired in most patients with schizophrenia, with many patients exhibiting marked deficits. The level of impairment seen in schizophrenia is more profound than in other psychiatric disorders that may also have associated psychotic symptoms, including bipolar disorder and depression. Patients with schizophrenia demonstrate significant dysfunction in a variety of cognitive processes including attention, executive functioning, verbal fluency, working memory, secondary verbal and spatial memory, and motor functioning.[1] Although aspects of cognitive dysfunction can be detected in groups of children who later develop schizophrenia,[2] they are not usually evident in individual patients until the first episode of illness. However, at first episode, cognitive dysfunction is largely fully developed and remains stable in most patients,[3] with modest to severe deterioration observed in some patients with severe chronic schizophrenia.[4,5]

Evidence that impaired cognition may be of equal or greater importance than positive or negative symptoms in predicting poor functional outcome, such as chronic unemployment and impaired adaptive life skills, has led to increasing awareness of its importance.[6] Nevertheless, there is no conclusive evidence of efficacy for typical antipsychotics in improving cognitive function.[7] This review explores the extent of cognitive dysfunction in schizophrenia and the implications for outcome in work status, and provides a critique of the clinical trials that have assessed the effect of the atypical antipsychotic clozapine on cognitive functioning in patients with schizophrenia.

THE EXTENT OF COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

Saykin et al. demonstrated the extent of cognitive dysfunction in schizophrenia by comparing patients with first-episode schizophrenia (N = 37), chronic previously treated schizophrenia patients (N = 65), and healthy controls (N = 131) (Figure 1).[1] The most significant cognitive deficits of schizophrenia were in attention, particularly focused sustained attention, and verbal and visuospatial memory. Verbal learning and memory accounted for most of the variance between patients and controls and was significantly impaired relative to the control group after controlling for all other functional measures. The magnitude of these deficits is not likely to be explained by a global worsening in cognitive capacity, because cross-sectional studies have demonstrated that in patients with schizophrenia, IQ is often only about 1 standard deviation below average.[3,8] Additionally, Goldberg et al. demonstrated that 70% of schizophrenia patients in their sample obtained a relatively lower score on the Wechsler Memory Scale-Revised than on the Wechsler Adult Intelligence Scale-Revised (WAIS-R), suggesting a differential memory impairment in the majority of patients.[9]

Cognitive Dysfunction and Unemployment

In addition to cognitive deficits, schizophrenic patients display long-term disability in a variety of outcomes, such as the ability to live independently in the community. The

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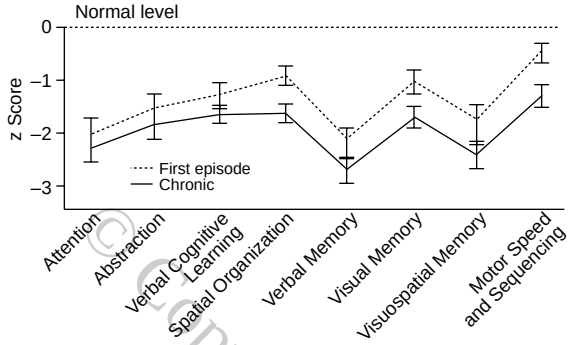
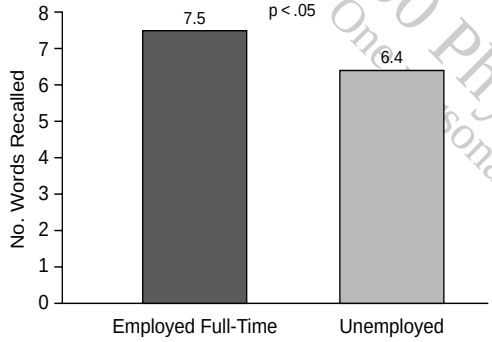
Figure 1. Level of Cognitive Functioning of Normal Controls, First-Episode Schizophrenic Patients, and Those With Chronic Pretreated Schizophrenia[a]



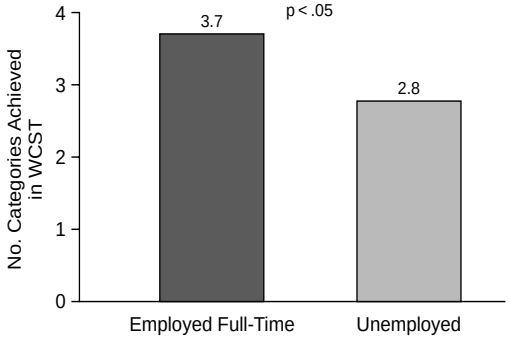
[a]Data from reference 1. Raw test scores were transformed to standard equivalents (z scores) using the means and standard deviations of the normal control subjects.

Figure 2. Verbal Learning and Memory Test Scores of Patients With Schizophrenia Employed Full-Time or Unemployed[a]



[a]Adapted from reference 12, with permission.

Figure 3. Number of Categories Achieved in the Wisconsin Card Sorting Test of Patients With Schizophrenia Employed Full-Time or Unemployed[a]



[a]Adapted from reference 12, with permission.

most prominent disability is in vocational functioning. Up to 85% of schizophrenic patients are not engaged in competitive gainful employment.[10] Even among patients who are considered to be "employed," many are working only part-time or in sheltered environments. In the United States, public assistance to unemployed (or "underemployed") patients accounts for a large part of the indirect costs associated with this disorder.[11] Therefore, in addition to the human burden in quality of life, improvement of vocational functioning is a worthy goal for economic reasons.

Studies that have evaluated the relationship of cognitive dysfunction and unemployment in schizophrenic patients strongly suggest a link between specific areas of cognitive dysfunction and unemployment.[12–15] For example, 39 patients who had been employed full-time for at least 1 year performed significantly better on a range of cognitive tasks compared with 243 unemployed patients.[12] There were no significant differences between the groups for age, age at illness onset, and illness chronicity. However, the unemployed group had significantly more positive symptoms as measured by the Brief Psychiatric Rating Scale. Performance on verbal learning and memory (Figure 2) and the Wisconsin Card Sorting Test (WCST), a measure of executive functioning (Figure 3), effectively discriminated work status in these patients.

THE EFFECTS OF CLOZAPINE ON COGNITIVE FUNCTION

Several studies have demonstrated the lack of efficacy of typical antipsychotics for the cognitive impairments inherent in schizophrenia.[7] However, atypical antipsychotics such as clozapine may improve this aspect of schizophrenia. To date, 12 published studies[16–27] have addressed the effects of clozapine on cognitive functioning (Table 1). These studies differ widely in their methodology, such as the baseline medication, number of patients, treatment-resistant status of the patients, concomitant medication, and dose of clozapine. Baseline assessments occurred while patients were treated with a typical antipsychotic (9 studies) or while unmedicated during a washout period (2 studies).[17,19] The remaining study was of a crossover design with patients receiving either clozapine or risperidone at baseline.[21] All of these studies were small, including between 13 and 36 patients, and 11 of the studies were of an open-label design; the study by Buchanan et al. was blinded with an open-label extension.[18] Six of the studies included a comparison group of patients who received typical antipsychotics, risperidone, zotepine, or normal controls. The study patients were generally treatment-resistant (10 studies) and were administered an average dose of 350 mg/day of clozapine, although a wide range of doses were used (range, 150–600 mg/day). The average duration of the trials was 10 weeks, although some studies continued for several years (range, 6 weeks–3 years). The domains of cognitive function assessed in these studies included verbal fluency, attention/psychomotor speed, verbal learning and memory, executive functioning, verbal

Table 1. Clinical Trial Results on the Efficacy of Clozapine on Cognitive Functioning[a]

Study	Patient Population (no. patients entered)	Study Design, Length, and Treatment	Cognitive Function Test	Significant Improvement?
Goldberg et al, 1993[16]	13 patients with schizophrenia, 1 patient with schizoaffective disorder, 1 patient with psychosis	Open; 15 mo (average); clozapine	Verbal fluency: category test	No
			Attention: WAIS-R digit symbol substitution test	No
			Verbal learning and memory: WMS-R paired associates	No
			Executive function: WCST	
			categories	No
			% perseveration	No
			Category test	No
			Visual learning and memory: WMS-R	Worsening
Hagger et al, 1993[17]	36 treatment-resistant schizophrenic patients	Open; 6 mo; clozapine	Verbal fluency: controlled word association test	Yes at 6 wk or 6 mo
			Attention: WAIS-R digit symbol substitution test	Yes
			Verbal learning and memory: list learning, IR	Yes
			list learning, DR	Yes
			Executive function: WCST	
			categories	Not at 6 wk or 6 mo
			% perseveration	Not at 6 wk or 6 mo
			Verbal working memory: auditory consonant trigrams	No
Buchanan et al, 1994[18]	41 outpatients with partially responsive schizophrenia	Randomized, double-blind; 10 wk; clozapine or haloperidol and following open, 1 y with clozapine	Verbal fluency: category fluency	Yes
			Executive function: WCST	
			categories	Not at 10 wk
			% perseveration	Not at 10 wk
			Stroop color-word interference trial	Worsening at 12 mo
			Trails B	Yes[b]
			Visual learning and memory: Mooney faces	Yes at 12 mo
Lee et al, 1994[19]	47 patients with non–treatment-resistant schizophrenia	Open, randomized; 1 y; clozapine or typical neuroleptic	Verbal fluency: controlled word association test	Yes at 6 wk and 6 mo
			Attention: WAIS digit symbol substitution test	Yes
			Verbal learning and memory: list learning, IR	Yes
			list learning, DR	Yes
			Executive function: WISC-R mazes	Yes at 6 mo
			WCST	
			categories	No
			% perseveration	Yes
			Verbal working memory: auditory consonant trigrams	No
Zahn et al, 1994[20]	25 chronic schizophrenic patients	Open; at least 6 wk; clozapine plus fluphenazine or placebo	Attention: reaction time	Yes
Daniel et al, 1996[21]	20 outpatients with schizophrenia or schizoaffective disorder, stable on clozapine at the time of screening	Randomized, crossover; 12 wk; clozapine or risperidone	Attention: continuous performance test	No
			Verbal learning and memory: WMS-R logical memory	No
			Executive function: WCST	
			categories	No
			WAIS-R similarities	Yes
			Visual learning and memory: Rey complex figure	No
Grace et al, 1996[22]	31 patients with treatment-resistant schizophrenia	Open; 3 y; clozapine and psychosocial treatment program	Verbal fluency: controlled word association test	Yes
			Attention: WAIS-R digit symbol substitution test	Yes
			WAIS-R digit span	Yes
			Verbal learning and memory: 5-word list, IR	No
			5-word list, DR	Yes
			Executive function: Trails B	Yes
			Verbal working memory: WAIS-R digit span backwards	Yes
			Visual learning and memory: complex figure test	Yes
Hoff et al, 1996[23]	30 chronic, treatment-resistant inpatients with schizophrenia	Open; 12 wk; clozapine	Verbal fluency: controlled word association test	Yes
			Attention: digit symbol modalities	Yes
			Verbal learning and memory: associative learning	No
			California verbal learning and memory test	Yes
			Executive function: WCST	
			categories	Worsening
			perseverative errors	No
			total errors	No
			Visual learning and memory: Benton visual retention	Worsening
			WMS-R visual reproduction	No

Continued on next page.

Table 1 (Continued). Clinical Trial Results on the Efficacy of Clozapine on Cognitive Functioning[a]

Study	Patient Population (no. patients entered)	Study Design, Length, and Treatment	Cognitive Function Test	Significant Improvement?
Fujii et al, 1997[24]	22 treatment-resistant patients with schizophrenia	Open; 1 y; clozapine	Attention: WAIS-R digit symbol substitution test	Yes
			Executive function: Trails B	No
			WAIS-R similarities	Yes
			WCST	
			categories	Yes[b]
			perseverative errors	Yes[b]
			WAIS-R picture arrangement	No
Galletly et al, 1997[25]	19 schizophrenic outpatients	Open; 6.5 mo (mean); clozapine	Verbal fluency: controlled word association test	Yes
			Attention: WAIS-R digit symbol substitution test	Yes
			Verbal learning and memory: list learning	Yes
			Verbal working memory: auditory consonant trigrams	Yes
Meyer-Lindenberg et al, 1997[26]	50 patients with treatment-resistant schizophrenia	Randomized, double-blind; 6 wk; clozapine or zotepine	Executive function: computer mazes	Yes
Lindenmayer et al, 1998[27]	21 treatment-resistant patients	Open trial; 12 wk; clozapine or risperidone	Attention: WAIS-R digit symbol substitution test	No
			Verbal learning and memory: paragraph memory test	No
			Executive function: Trails B	Yes[b]
			Stroop color-word	No
			Visual learning and memory: pattern memory test	No

[a]Abbreviations: DR = delayed recall; IR = immediate recall; Trails B = Trail-Making Test, part B; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WCST = Wisconsin Card Sorting Test; WISC-R = Wechsler Intelligence Scale for Children-Revised; WMS-R = Wechsler Memory Scale-Revised.
[b]Trend ($p < .10$).

working memory, and visual learning and memory. These intertrial differences need to be considered when comparing the results.

An additional complication in the evaluation of the effects of primary treatment on cognitive functioning is the use of concomitant medications. For example, anticholinergic drugs used in the treatment of parkinsonian side effects may affect cognitive functioning.[28] Overall, use of concomitant medication was minimal in these studies, except for one in which medications used in addition to clozapine included lithium, valproate, fluoxetine, clonazepam, lorazepam, and primidone.[16]

Verbal Fluency

Verbal fluency is the ability to generate words on command, for example, "Tell me all the words you can think of that begin with the letter *g* or all the animals you can name." Of 7[16–19,22,23,25] studies evaluating this domain, 6[17–19,22,23,25] found a significant improvement in verbal fluency with clozapine treatment. In some of the studies, verbal fluency improved substantially to within 1 standard deviation of baseline for the control group, such that the patients' performance was statistically indistinguishable from that of the controls.

Attention/Psychomotor Speed

Attention/psychomotor speed was also improved by clozapine treatment. Of 10[16,17,19–25,27] evaluated studies, 7[17,19,20,22–25] found a significant improvement following clozapine treatment. Eight[16,17,19,22–25,27] of these studies used the digit symbol substitution test, a subset of the WAIS-R. However, clozapine may have improved motor functioning, which is an important component of this test, rather than attentional ability itself. This would likely be a function of clozapine's low propensity to induce extrapyramidal symptoms. Further studies are required to resolve this issue. Again, in some of these studies, patient performance was normalized, becoming indistinguishable from control groups.

Verbal Learning and Memory

Verbal learning and memory is the ability to acquire and retain verbal information and, as has been described above, is important for success in the workplace. This cognitive domain was one of the areas of cognitive dysfunction that distinguished those patients who were employed full-time from those who were unemployed, as described earlier. Verbal learning and memory was assessed in 8[16,17,19,21–23,25,27] of the studies, 5[17,19,22,23,25] of which demonstrated improvements in immediate and/or delayed recall using list learning tests. However, the degree of improvement—approximately 0.5 standard deviation in some of the studies—was insufficient to normalize performance. Results of more complicated measures of verbal learning and memory, paragraph learning and paired associates, which were used in 2[16,27] studies, were not improved compared with performance at baseline.

Executive Functioning

Executive functioning was assessed in 7[16–19,21,23,24] of the studies using the WCST. In the studies reviewed here, clozapine treatment showed little impact on the ability to

perform adequately on the WCST. Only 2[21,24] of the 7 studies found significant improvements on the WCST following clozapine treatment. Clozapine had mixed results on other measures of executive functioning. Tests of executive functioning that showed an improvement following clozapine treatment tended to have a psychomotor component, such as the Trail-Making Test, part B and maze tests, that involves psychomotor speed.[18,19,22,26,27]

Verbal Working Memory

Verbal working memory, the ability to hold verbal information in the mind when it is no longer present in the environment, has only recently been assessed in schizophrenia. An example of verbal working memory is recall of a phone number over a short delay. Verbal working memory is thought to involve prefrontal cortical functioning, which has been shown to be impaired in many patients with schizophrenia. The effects of clozapine on this particular cognitive domain are equivocal. Of 4[17,19,22,25] studies that assessed verbal working memory, 2[22,25] found significant improvements following clozapine treatment. Both of these studies had a long treatment duration, 6 months to 3 years, suggesting that long-term treatment with clozapine is required to improve this domain. Hagger et al. also found a time-dependent effect of clozapine on this function with an impairment after 6 weeks' treatment, but a return to baseline levels after 6 months' treatment.[17] This illustrates an additional point to consider when analyzing these studies, that there may be time-dependent effects of clozapine treatment not only on clinical symptoms but also on cognitive functioning. Nevertheless, it remains unclear why there should be short-term impairment in a cognitive domain followed by a longer term return to baseline.

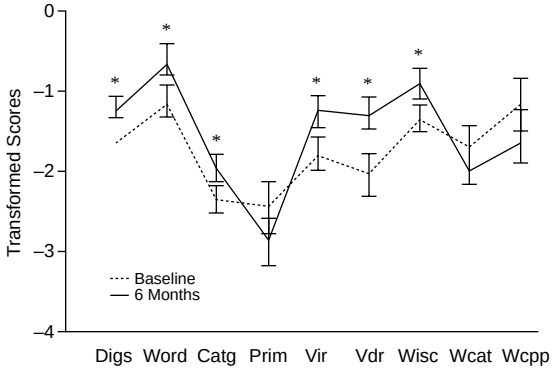
Visual Learning and Memory

Visual learning and memory is the ability to acquire and retain visually presented stimuli and is considered to be a form of nonverbal memory. Animal studies have demonstrated the importance of cholinergic transmission in this type of memory. Some studies have shown an impairment in visual learning and memory that has been attributed to the antimuscarinic activity of clozapine.[16] Two[16,23] of the 6[16,18,21–23,27] studies reviewed here that assessed visual learning and memory found significant worsening, 2[18,22] found improvement, and the remaining 2[21,27] found no effect. This would suggest a lack of effect, either beneficial or deleterious, of clozapine on visual learning and memory.

Summary of Clozapine's Effects on Cognitive Functioning in Schizophrenia

The majority of studies that evaluated attention and verbal fluency found significant improvements with clozapine treatment, in some cases to the point that performance was normalized. A limited beneficial effect was also demonstrated in verbal learning and memory and some measures of executive functioning. There was minimal or no effect of clozapine demonstrated in visual learning and memory and verbal working memory.

Figure 4. The Effect of Clozapine on Cognitive Functioning of Patients With Treatment-Resistant Schizophrenia (N = 42)[a]



[a]Data from reference 17. Abbreviations: Digs = digit symbol substitution, Word = phonological fluency, Catg = category fluency, Prim = verbal working memory, Vir = immediate recall, Vdr = delayed recall, Wisc = Wechsler Intelligence Scale for Children-Revised Maze test; Wcat = Wisconsin Card Sorting number of categories, Wcpp = Wisconsin Card Sorting percent perseverative errors. *$p < .05$.

The study by Hagger et al. exemplifies the improvements demonstrated by these studies following clozapine treatment.[17] After 6 months' treatment of refractory patients, improvements were observed in digit symbol substitution test, phonological and categorical measures of verbal fluency, immediate and delayed verbal memory, and the Wechsler Intelligence Scale for Children-Revised (WISC-R) Maze test (Figure 4). Primary memory or verbal working memory was significantly impaired after 6 weeks' treatment and impaired, but not significantly so, after 6 months' treatment. Clozapine had no effect on performance on the WCST.

Two of the 12 assessed studies failed to find a significant effect of clozapine on any cognitive test,[16,27] and a third study[21] found a significant improvement in only 1 measure of executive functioning. Two of these studies included the frequent use of concomitant medication, suggesting that the interaction of these drugs with clozapine affected cognitive performance.[16,21] Furthermore, the study of Daniel et al. was a crossover design such that half of the patients had been treated with clozapine for an undetermined amount of time before they were again assessed on clozapine treatment.[21] However, if clozapine does improve cognitive functioning, improvement may have occurred before patients were assessed.

Although not discussed in detail above, improvements in cognitive performance in the studies reviewed were unrelated to improvements in either positive or negative

clinical symptoms. The independent nature of improvements in cognitive functioning and clinical symptoms has been demonstrated for both novel and typical antipsychotics in patients with schizophrenia. For example, improvement in clinical symptoms may occur without improvement in cognitive symptoms and vice versa.

CONCLUSIONS

Although cognitive impairment may be the most rate-limiting factor for outcome in schizophrenia,[16] over 40 years of treatment with conventional antipsychotics have demonstrated little or no ability to improve this very important core aspect of schizophrenia. Clozapine was the first medication for schizophrenia with a demonstrated ability to improve cognitive functioning. Recent studies have demonstrated that clozapine may have efficacy, not only in improving clinical symptoms in treatment-resistant patients, but also in improving cognitive dysfunction in both treatment-resistant and treatment-responsive patients. Furthermore, clozapine improves cognitive functioning in those areas that are known to be important in determining the patient's ability to work. Indeed, some studies have suggested that clozapine may enhance a patient's ability to return to work.[29,30] The improvement that clozapine treatment has on the quality of life of some patients with schizophrenia is well demonstrated, as is the accompanying reduction in hospitalization.[31] However, the differential contributions to improved outcomes of enhancement in cognitive functioning, decreased psychopathology, and fewer extrapyramidal side effects produced by treatment with clozapine have yet to be determined. Nevertheless, the ability of clozapine to improve attention/psychomotor speed, verbal fluency, and verbal learning and memory may indicate a significant potential for improving vocational functioning, the ability to live independently, and benefits derived from psychiatric rehabilitation.

Drug names: clonazepam (Klonopin), clozapine (Clozaril, Leponex), haloperidol (Haldol and others), fluoxetine (Prozac), fluphenazine (Prolixin and others), lorazepam (Ativan and others), primidone (Mysoline), risperidone (Risperdal).

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