HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol. Clin. Exp. **15**, 513–519 (2000)

A Preliminary Study of the Comparative Effects of Olanzapine and Fluphenazine on Cognition in Schizophrenic Patients

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The aim of the study was to compare the effect of olanzapine versus fluphenazine treatment on cognitive functioning. Eighteen schizophrenic outpatients, aged 25–61 (average 37 years), all meeting DSM-IV diagnostic criteria for schizophrenia, were included in the study. They were randomly assigned to 22 weeks of either olanzapine or fluphenazine treatment. Certain subscales of the Wechsler Adult Intelligence Scale, the Stroop Neuropsychological Screening Test and the Wisconsin Card Sorting Test were performed. Olanzapine treatment proved to have a beneficial effect on digit-symbol performance and some aspects of executive function. In comparison to the fluphenazine treatment, the olanzapine treatment only showed a beneficial effect in increased percentage of conceptual level responses. Although the results are preliminary, they could implicate that the benefit of olanzapine treatment is primarily related to certain aspects of executive function, i.e. frontal lobe functioning. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS — schizophrenia; cognition; olanzapine; fluphenazine; antipsychotic agents; therapeutic use; comparative study

INTRODUCTION

Neurocognitive deficit has been recognized as an important feature, or even a core deficit, of schizophrenia (Bilder and Szeszko, 1996; Gourovitch and Goldberg, 1996; Bilder, 1997; Green and Nuechterlein, 1999; Sharma, 1999). Neurocognitive dysfunction in schizophrenic patients seems to be associated with impaired temporal and prefrontal cortical systems, as suggested by neuroimaging and neuropsychological studies (Weinberger *et al*., 1992; Gold *et al*., 1992; Tompkins *et al*., 1995; Lawrie and Abukmeil, 1998).

Patients with schizophrenia display general intellectual impairment (Aylward *et al*., 1984; Barber *et al*., 1996) as well as disproportionate deficits of attention, executive functions, aspects of memory and language (reviewed in Gourovitch and Goldberg, 1996). Deficits in schizophrenic patients are especially noticeable in executive functions, i.e. abstraction, problem solving, and other prefrontal functions (Goldberg *et al*., 1987; Green *et al*., 1992), in comparison both to normal controls and other psychotics (Taylor and Abrams, 1984; Hoff *et al*., 1992; Beatty *et al*., 1994).

Conventional neuroleptics have shown effects in reducing psychiatric symptomatology in schizophrenic patients, but variable and relatively weak effects on neurocognition. Conventional antipsychotics may demonstrate no effect on cognitive functioning (Berman *et al*., 1986), or minimal beneficial effects on cognitive functioning (Goldberg *et al*., 1991), or can even further impair cognitive functioning (Sweeney *et al*., 1991). In summary, according to numerous studies (reviewed in Cassens *et al*., 1990; Green and King, 1996; King and Green,

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1996; Mortimer, 1997; Sharma, 1999), there is evidence to suggest that the effects of conventional antipsychotics on cognition are minor.

Atypical neuroleptics may have the capacity to remediate neurocognitive impairment in schizophrenia, owing to their novel mechanism of action. There is indeed an increase in data suggesting that novel antipsychotic drugs may cause not only better improvement in psychiatric symptomatology and less impairments of cognitive functions, but also an increased efficacy for cognitive deficits compared with conventional neuroleptics (reviewed in Mortimer, 1997; Keefe *et al*., 1999; Meltzer and McGurk, 1999; Sharma, 1999). More recently, evidence has emerged demonstrating significantly enhanced frontal function in schizophrenic patients in relation to atypical drug (e.g. risperidone) administration (Honey *et al*., 1999).

A novel atypical antipsychotic agent, olanzapine, a potent multi-receptor antagonist (Buymaster *et al*., 1996), demonstrated the greater improvement in the general psychiatric state and a diminishment of positive as well as negative symptoms of schizophrenia (Baseley *et al*., 1997; Fulton and Goa, 1997), compared to conventional antipsychotics. At the same time, it showed lower extrapyramidal symptoms (Tran *et al*., 1997) and fewer discontinuations of treatment due to a lack of drug efficacy or adverse events (Tollefson and Sanger, 1997), compared to conventional antipsychotics. Olanzapine proved to be superior in the efficacy as well as in the safety profile compared to fluphenazine (Jakovljević *et al*., 1999), a conventional antipsychotic being highly efficacious in acute productive psychotic symptomatology (Levinson *et al*., 1995).

Preliminary evidence in one study suggests that olanzapine improves verbal learning and memory, verbal fluency and executive function, but does not improve attention, working memory, or visual learning and memory (Meltzer and McGurk, 1999). On the other hand, another preliminary study found that olanzapine produced no significant improvement in verbal memory and simple motor speed (Žakić-Milas *et al*., 1999). However, to our knowledge, no studies on the cognitive effects of olanzapine compared with those of conventional antipsychotics in the cognitive domain of multifactorial cognitive functions and executive functions have yet been published.

The aim of this study was to compare the psychometric effects of olanzapine and fluphenazine treatments on general cognitive performance, multifactorial cognitive measures, and executive function in schizophrenic patients.

MATERIALS AND METHODS

Subjects

Twelve male and six female outpatients, aged 25–61 (average 37 years), all meeting diagnostic criteria for schizophrenia according to the DSM-IV criteria (APA, 1994) were included in the study. The diagnosis was based on a structured clinical interview and chart review, performed by experienced psychiatrists. Patients were required to have a Clinical Global Impression-Severity of Illness (CGI-S) score (Guy, 1976) of at least four. Patients with a diagnosis of a DSM-IV organic mental disorder or substance-use disorder active within 3 months of entering the study were excluded, as were patients at serious suicidal risk.

Patients also met all additional inclusion and exclusion criteria. The additional inclusion criteria were: female patients must be using a medically accepted means of contraception; each patient must have a level of understanding sufficient to communicate intelligently with the investigators and nurses, must be reliable and understand the nature of the study. Exclusion criteria were: female patients who were either pregnant or lactating; serious unstable illnesses including hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, neurologic, immunology or haematological disease such that hospitalization for the disease was anticipated within 3 months or death was anticipated within 3 years; uncorrected hypothyroidism or hyperthyroidism; myasthenia gravis; narrow angle glaucoma; chronic urinary retention; one or more seizures without a clear and resolved aetiology; leucopenia, previous exposure to olanzapine or fluoxetine within 4 weeks prior to the start of active treatment; remoxipride within 6 months prior to the start; treatment with non-reversible monoamine oxidase inhibitor within 2 weeks prior to the start, and treatment with lithium, anticonvulsants, benzodiazepines, antidepressants, psychostimulants, reversible monoamine oxidase inhibitor, reserpine, guanethidine, or guanadrel within 1 week prior to the start of active treatment. All patients were right handed. Most (61%) had finished secondary school.

After being randomly selected to receive either fluphenazine or olanzapine, the groups showed no statistical differences in baseline performance intel-

ligence quotient of Wechsler Adult Intelligence Scale, WAIS (Wechsler, 1992), or in clinical global impression assessed by Clinical Global Impression Severity Scale (Guy, 1976). All patients signed the informed consent.

Assessment of cognitive functions

First, certain subscales of WAIS (Wechsler, 1992) were performed. The subscales are designed to be multifactorial: object assembly measuring visuo-spatial organization ability, speed of visual organization and motor response and ability for visuo-spatial conceptualization; two-dimensional construction test measuring two-dimensional construction ability; digital symbol task measuring psychomotor speed, visuo-motor coordination, sustained attention; task of picture completion measuring general ability and visual recognition; similarities measuring verbal concept formation.

Additionally, neuropsychological tests related to frontal lobe functioning were performed. Tasks included executive functions measured by the Stroop Neuropsychological Screening Test, SNST (Trenerry *et al*., 1994) and the Wisconsin Card Sorting Test, WCST (Heaton *et al*., 1993).

Procedure

Schizophrenic patients completed a 22-week double-blind study within the study Efficacy and Safety of Olanzapine versus Fluphenazine (F1D-VI-HGCH) (Mimica *et al*., 1998). Before entering the study, all patients were on a low dose of conventional antipsychotics. After a placebo lead-in phase of 2–9 days, they were randomized to receive either olanzapine (5–20 mg/day) or fluphenazine (6–21 mg/day) treatment. Due to a drop out of some patients, the final olanzapine group had 10 patients and the final fluphenazine group eight patients. The study design was double-blind so neither the psychiatrists, nor the clinical psychologists who performed psychological assessment were aware of patients' treatment group.

Neuropsychological measurement of cognitive functions was performed at baseline and at the endpoint of treatment, during the last treatment week. Alternative versions of the tests were administered whenever possible to minimize improvement from having repeatedly taken the same set of tests.

Statistical analyses

In order to evaluate the effect of olanzapine treatment, the patients receiving olanzapine treatment were compared in cognitive measures, at baseline and at endpoint of treatment by means of a *t*-test for dependent samples. The same analysis was also done for the fluphenazine treatment group, in order to evaluate the effect of fluphenazine treatment.

In order to compare the effect of olanzapine treatment versus fluphenazine treatment, the differences between baseline scores and end-point testing scores were calculated. Then olanzapine and fluphenazine groups were compared across cognitive measures by means of *t*-test for small independent samples, with *t*-ratio for unequal variances used where previous Levene's test for equality of variances showed a significant *F*-ratio at level $p < 0{\cdot}05$.

Due to multiple comparison between the groups, the risk of type I error was thereby increased. However, because of the explanatory nature of this study and the importance of not prematurely discarding a finding that might not be due to chance, we decided to use only *t*-tests without the Bonferonni correction for multiple comparisons.

RESULTS

Schizophrenic patients treated with olanzapine showed treatment related improvement in digit-symbol task of WAIS, the number of words on Stroop color task, percentage of nonperseverative errors, and percentage of conceptual level responses on Wisconsin Card Sorting Test (Table 1). Although there were no significant improvements in other cognitive measures, most differences pointed in the same direction. Schizophrenic patients treated with fluphenazine did not demonstrate statistically significant treatment related improvement in any of the cognitive measures ($p > 0{\cdot}05$). Nonetheless, the majority of cognitive variables showed a treatment related tendency of improvement.

The second analysis was done in order to compare the effect of olanzapine treatment versus fluphenazine treatment. Therefore, only cognitive measures in which an olanzapine effect was shown were used in this analysis. The differences between baseline scores and end-point testing scores were calculated for the digit symbol task of the WAIS, number of words in the Stroop color task, percentage of nonperseverative errors of WCST and the percentage of conceptual level response of WCST. Olanzapine showed a statistically sig-

Table 1. Mean baseline and post-treatment scores (M), standard deviations (SD), and *t*-values comparing baseline and end-point scores for cognitive measures in olanzapine treatment group ($n = 10$)

Neuropsychological tests and measures	Baseline M ± SD	End-point M ± SD	*t*-values
WAIS			
Overall performance functioning (PIQ)	77·4 ± 19·74	80·9 ± 22·71	1·81
Object assembly	5·2 ± 4·05	6·9 ± 4·71	2·05
Two-dimensional construction test	6·2 ± 4·19	6·4 ± 4·58	0·18
Digit symbol	4·3 ± 3·62	5·2 ± 3·55	2·59*
Picture completion	5·9 ± 3·00	6·0 ± 3·62	0·17
Similarities	6·9 ± 2·48	8·9 ± 3·44	2·10
Stroop color task			
Number of words	181·9 ± 51·80	218·6 ± 48·32	3·22*
Number of errors	2·1 ± 3·17	1·4 ± 3·10	1·77
Stroop color–word task			
Number of words	61·3 ± 35·88	75·3 ± 44·99	1·88
Number of errors	2·9 ± 4·20	3·7 ± 4·69	0·80
Wisconsin card sorting test			
Total number correct	48·2 ± 22·22	57·9 ± 29·68	1·24
% Perseverative errors	11·1 ± 6·14	11·8 ± 7·35	0·29
% Nonperseverative errors	29·5 ± 13·94	20·4 ± 14·65	4·54**
% Conceptual level responses	40·3 ± 22·68	52·2 ± 26·02	2·27*

* $p < 0{\cdot}05$; ** $p < 0{\cdot}01$.

nificant benefit in comparison to fluphenazine treatment but only in increased conceptual level responses ($t = 2{\cdot}37$, $p = 0{\cdot}031$).

DISCUSSION

Neurocognitive impairments and underlying cortical network dysfunction are seen to be a relatively independent, cardinal feature of schizophrenia (Gourovitch and Goldberg, 1996; Keefe *et al*., 1999; Sharma, 1999), and the temporal and prefrontal cortical systems are implicated (Weinberger *et al*., 1992; Lawrie and Abukmeil, 1998). Additionally, the extent of cognitive impairment, but not psychotic symptoms, appear to be predictive of a functional outcome (Green, 1996). Based on this, cognitive function has been proposed to become a target for drug (Davidson and Keefe, 1995) and rehabilitation treatment (Green and Nuechterlein, 1999).

For these reasons, evaluations of antipsychotic medication should include their effects on cognition. On the other hand, as noted by Green and King (1996), if antipsychotic drugs have an effect on the cognitive processes of schizophrenic patients, this may provide a better understanding of the mechanism of action of these drugs. In our opinion, this in turn may lead to further insights into the cognitive pathology of schizophrenia.

In this study statistically significant improvements in some cognitive functions were observed in schizophrenic patients treated with olanzapine. Schizophrenic patients treated with olanzapine showed an increase in psychomotor performance and an improvement in certain aspects of executive function, i.e. an increase in the number of words in the Stroop color task, a decrease in percentage of nonperseverative errors on WCST and an increase in percentage of conceptual level response on WCST.

The psychomotor performance in the digital-symbol task of WAIS is considered a multifactorial neurocognitive function and therefore did not implicate particular brain regions. The other three cognitive measures which showed improvement are considered to represent frontal processing, i.e. are tasks on the Stroop Neuropsychological Screening Test, SNST (Trenerry *et al*., 1994) and Wisconsin Card Sorting Test, WCST (Heaton *et al*., 1993).

It seems therefore that the effect of olanzapine

Table 2. Mean baseline and post-treatment scores (M), standard deviations (SD), and *t*-values comparing baseline and end-point scores for cognitive measures in fluphenazine treatment group ($n = 8$)

Neuropsychological tests and measures	Baseline M ± SD	End-point M ± SD	*t*-values
WAIS			
Overall performance functioning (PIQ)	75·0 ± 10·65	81·6 ± 13·18	2·12
Object assembly	5·9 ± 4·41	6·3 ± 4·83	0·32
Two-dimensional construction test	6·6 ± 2·97	7·9 ± 3·00	1·23
Digit symbol	4·4 ± 1·85	5·5 ± 2·56	1·94
Picture completion	4·4 ± 1·51	5·8 ± 3·15	1·72
Similarities	7·8 ± 4·76	8·4 ± 4·83	1·50
Stroop color task			
Number of words	206·1 ± 52·00	214·1 ± 50·58	0·41
Number of errors	0·8 ± 1·04	1·0 ± 2·14	0·28
Stroop color–word task			
Number of words	83·5 ± 19·41	82·1 ± 19·10	0·20
Number of errors	2·6 ± 2·56	1·9 ± 1·81	1·00
Wisconsin card sorting test			
Total number correct	49·8 ± 10·78	57·4 ± 28·64	0·83
% Perseverative errors	7·6 ± 3·58	10·3 ± 5·39	1·38
% Nonperseverative errors	20·9 ± 8·77	17·1 ± 12·40	0·82
% Conceptual level responses	59·3 ± 16·37	48·5 ± 25·03	1·27

* $p < 0{\cdot}05$; ** $p < 0{\cdot}01$.

treatment is primarily related to improvement of neurocognitive functions associated to frontal processing. However, as noted by Keefe *et al.* (1999), the mechanisms of this improvement are far from clear, and the knowledge about pharmacology of cognitive functions is quite limited.

Studies by Meltzer and McGurk (1999) reported that olanzapine produced significant improvement on one measure of executive function, i.e. the Stroop Color–Word Interference Test, but not on cognitive measures on WCST. The results of our study also showed that olanzapine had no effect on the WCST-Percent Perseveration, consistent with the results of Meltzer and McGurk's (1999), but did have an effect on the WCST-Percent Nonperseveration, a cognitive measure which was not used in the Meltzer and McGurk study.

In the fluphenazine group, there was no treatment effect in any of the cognitive and neurocognitive measures. However, after the fluphenazine treatment, the majority of measures were in the direction of improvement, although they did not reach a level of statistical significance. The failure to detect differences in the fluphenazine group was almost certainly due to lack of power, since there were only eight patients in the fluphenazine group and 10 in the olanzapine group.

It should be also noted that in both the olanzapine and the fluphenazine group, treatment related impairments in some cognitive measures were detected, although they were not statistically significant. Conclusively, both improvements and impairments were detected in both groups.

When the effect of olanzapine treatment was evaluated in comparison to the effect of fluphenazine treatment, olanzapine showed a statistically significant benefit only in the increase of conceptual level response on the WCST. Olanzapine treatment resulted in the increase of conceptual level response, while fluphenazine treatment produced a decreasing tendency of conceptual level response. However, this can be accounted for by the differences in baseline between the two groups, while the scores at end point were very similar between the groups.

It is possible that the period of 22 weeks may be too short for an improvement to take place in other cognitive and neurocognitive measures, no matter what antipsychotic agent is applied. On the other hand, some degree of cognitive impairment may be

relatively independent from schizophrenic symptoms and such impairment may represent part of a residual enduring 'trait' vulnerability (Cantor *et al.*, 1995).

However, the study suffers from several shortcomings. The main limitation of this study lies in the small number of subjects. Therefore, the study suffers from a low power and conclusions are only of a preliminary type. Additionally, an improvement in cognition in such trials using relatively nonsedative new antipsychotics can also be attributed to the reduction in sedation brought about by entry into such a trial. However, the results implicate that a benefit in cognitive functioning related to olanzapine treatment is worth studying further. Further studies to show whether olanzapine facilitates cognitive functioning directly, or indirectly, by reducing schizophrenic symptoms that influence the cognitive functioning level are also of interest.

ACKNOWLEDGEMENT

We would like to thank Eli Lilly and Co. for permission to do this research during the study 'Efficacy and Safety of Olanzapine versus Fluphenazine (F1D-VI-HGCH)'.

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