

Improvement in cognitive functioning in patients with first-episode psychosis during treatment with quetiapine: an interim analysis*

K. P. GOOD, I. KISS, C. BUITEMAN, H. WOODLEY, Q. RUI, D. WHITEHORN and L. KOPALA

Background The efficacies of second-generation antipsychotic medications in reducing symptoms are reasonably well-documented, but their effects on cognition are less clearly understood.

Aims To undertake an interim analysis of an open label, 2-year study examining the effects of quetiapine on cognition in patients with a first episode of schizophrenia and related disorders.

Method Cognitive testing was performed before quetiapine was initiated and repeated after 3, 6 and 12 months of treatment. To date, 13 patients have been fully assessed (mean dose 517.9 mg/day; s.d.=225.8).

Results Statistically significant improvement was noted on measures of attention (Continuous Performance Test; CPT), verbal productivity (Verbal Fluency Test) and executive function (Object Alternation Test) after 6 and 12 months of treatment. For the CPT, improvement was also noted after 3 months of treatment.

Conclusions During treatment for 1 year with quetiapine, cognitive performance was improved in young patients with psychosis. Continued controlled investigations of the effects of quetiapine on cognition are desirable.

Declaration of interest Partial support from AstraZeneca (unrestricted grant) and the Department of Health, Province of Nova Scotia.

This study describes an interim analysis of changes in cognitive function in young patients with a first episode of psychosis during treatment with quetiapine. The symptomatic relief afforded by second-generation antipsychotic medications (clozapine, risperidone, olanzapine and quetiapine) is well-described (Kane *et al*, 1988; Marder & Meibach, 1994). The second generation agents reduce the positive symptoms but in contrast to the older (typical) antipsychotics also improve negative or deficit symptoms (Kane *et al*, 1988; Hagger *et al*, 1993). As well, a distinctive side-effect profile, including fewer extrapyramidal side-effects, is a defining feature of these newer agents (Kopala *et al*, 1997).

Although the efficacies of second-generation antipsychotics in reducing symptoms are reasonably well-documented, their effects on cognition are less clearly understood. Evidence to date, however, indicates that these newer compounds are able to target and improve specific aspects of cognition (Hagger *et al*, 1993; Hoff *et al*, 1996; Purdon *et al*, 2000). Specifically, treatment with clozapine has been linked to possible improvements in verbal fluency and visuomotor tracking (Hagger *et al*, 1993; Lee *et al*, 1994; Hoff *et al*, 1996), whereas risperidone treatment has been associated with probable enhancement of verbal working memory, new learning and attention (Green *et al*, 1997; Purdon *et al*, 2000). A more controversial profile of improvements (which requires replication) has been demonstrated with olanzapine treatment (learning, motor skills, executive abilities and visuospatial functioning; Purdon *et al*, 2000). A recent meta-analysis of the extant literature examining the effects of these medications on cognition indicated a modest effect size (Keefe *et al*, 1999). However, in many reports,

potentially confounding variables were not ruled out. Difficulties ascertaining drug-specific effects persist (Harvey & Keefe, 2001).

The effects of antipsychotic medication on cognitive function depend on accurate characterisation of the nature and magnitude of cognitive impairment in the group of patients to be studied. When examined longitudinally, patients who are in the early phases of a psychotic disorder (first-episode) demonstrate a remarkably consistent pattern of neuropsychological deficits over time, at least in the short-term (Censits *et al*, 1997). Longer-term follow-up studies are required to determine if further deterioration occurs with illness chronicity. In general, patients with non-affective psychotic disorders, such as schizophrenia, schizophreniform disorder and schizoaffective disorder are impaired on measures of memory, both verbal and non-verbal, attention, executive function, fluency and motor speed (Saykin *et al*, 1994).

Few studies have examined changes in cognitive functioning after treatment with quetiapine (Sax *et al*, 1998; Velligan & Miller, 1999; Purdon *et al*, 2001). To date, no study has examined patients with a first-episode of psychosis before and after treatment with quetiapine. Despite the small number of chronically ill patients investigated, two double-blind studies provided complementary results, demonstrating significant improvements in verbal reasoning, fluency, executive function, motor speed and verbal memory (Velligan & Miller, 1999; Purdon *et al*, 2000). These effects are in contrast to those observed in haloperidol-treated patients (Velligan & Miller, 1999; Purdon *et al*, 2001). A further study documented amelioration of attentional capacity after treatment with quetiapine (Sax *et al*, 1998).

Cognitive performance is believed to be the single most important factor contributing to longer-term functional recovery (Green *et al*, 2000). Consequently, the effects of second-generation medications on cognition hold exciting promise for improving functional adaptability, particularly for those in the early stages of illness. The goal of this study was to examine first-episode patients and document the effects of quetiapine on their cognitive abilities. We hypothesised that improvements would be noted on measures of verbal and visuospatial memory, attention and executive functioning. Because of the

*Presented in part at the European First Episode Schizophrenia Network Meeting, Whistler BC, Canada, 27 April 2001.

low potential for extrapyramidal side-effects, no changes in motor/sensory performance were anticipated.

METHOD

Subjects

Preliminary analysis from an ongoing, investigator initiated, 2-year, open label study of first-episode patients with a non-affective psychosis (schizophrenia, schizoaffective disorder, schizophreniform disorder or psychosis not otherwise specified (NOS)) has been completed. In- or out-patients were recruited from the Nova Scotia Early Psychosis Programme (Halifax, Nova Scotia, Canada) who were between the ages of 18 and 65 years. All patients were in the early stages of illness and had no more than 25 weeks of cumulative (lifetime) exposure to antipsychotic medications. Patients were excluded if they had previously been involved in a clinical investigation of quetiapine, or had participated in any clinical trial within the past month. No patients were enrolled who had a history of serious medical illness. All provided written, informed consent before participating in the study.

Study design

Before initiation of quetiapine, baseline assessments were performed. These included the Positive and Negative Syndrome Scale (PANSS; Kay *et al*, 1987) and Global Assessment of Function (GAF; DSM-IV; American Psychiatric Association, 1994). These ratings were repeated weekly for 6 weeks, followed by monthly thereafter, until study completion. Diagnosis was re-evaluated at 6 months.

For all patients, exposure to antipsychotic medications was brief, so a medication wash-out period was not deemed necessary. Antipsychotic medications were crossed over. Quetiapine was initiated at 25 mg daily, then 25 mg twice daily and increased by 50–100 mg approximately every 3 days thereafter until therapeutic dose was reached. The maximum dose employed was 800 mg. (Maximum doses vary among different countries. According to Canadian Guidelines (the country in which this study was completed), 800 mg is the maximum recommended dose.) Therapeutic dose was defined as the level at which psychotic symptoms were adequately controlled in the absence of problematic side-effects.

Cognitive testing was performed before quetiapine was initiated and was repeated at 3 months, 6 months and 1 year. The neuropsychological test battery was chosen to assess cognitive domains that are impaired in patients with psychotic disorders and would have functional significance if performance were ameliorated. The battery included the following tasks (for more information see Lezak, 1995).

- (a) Rey Auditory Verbal Learning Test. This task is thought to measure immediate memory span, learning curves and strategies for verbally presented material.
- (b) Benton Visual Retention Test. This task is used to measure recall of visually presented material.
- (c) Wisconsin Card Sorting Test. This task has been extensively used in research in schizophrenia and appears to examine abstract behaviour and set-shifting ability.
- (d) Continuous Performance Test. This task is thought to measure the capacity to sustain a focus of attention.
- (e) Object Alternation. This is a task that has been borrowed from the non-human primate literature and modified to examine executive functioning, specifically response switching.
- (f) Verbal Fluency. This task assesses verbal productivity by asking the subject to spontaneously generate words that begin with a given letter of the alphabet.
- (g) The Trail Making Test. This is a two-part test of visuomotor and conceptual tracking.
- (h) Grooved Pegboard. This task assesses motor speed and accuracy.

- (i) Finger Tapping. This task measures motor speed.

The list of specific variables examined from each neuropsychological test can be found in Table 1. Alternate versions were employed for those tests for which they are available.

Statistics

Repeated-measures analysis of variance were performed on selected cognitive test scores to examine the effects of quetiapine on cognition. The specific cognitive variables were selected to allow comparison with studies of the effects of quetiapine on cognitive function in patients with chronic psychotic illness. These test variables were thought to be those that are sensitive to: cognitive difficulties of patients with psychotic disorder, and changes with treatment.

RESULTS

A total of 34 patients were enrolled into the study (6 females and 28 males). The sample at study entry was 24.1 (s.d.=6.5) years of age and had been educated, on average, for 12.4 (s.d.=2.3) years. At study entry, patients were mildly to moderately ill according to the positive and negative sub-scales of the PANSS. Symptomatic improvement in the positive and negative sub-scales was noted over time (see Fig. 1). At the time of interim analysis, 27 had completed the 3-month evaluation, 23 finished the 6-month assessment and 13 had reached the 1-year mark. Eight patients' data were excluded from the study. Three patients withdrew because of lack of compliance, three withdrew consent and two were discontinued for lack of efficacy.

Table 1 Neuropsychological test battery and the specific cognitive variables investigated

| Test | Variable examined |
|--|--|
| Auditory Verbal Learning Test ¹ | Total recalled over 5 trials ² |
| Benton Visual Retention Test ¹ | Number of errors |
| Wisconsin Card Sorting Test | Number of perseverative errors |
| Object Alternation | Number of perseverative errors |
| Continuous Performance Test | Ability to discriminate target from non-target items, <i>d'</i> total ² |
| Verbal Fluency ¹ | Total number of words generated ² |
| Trail Making Test | Time for Trails A and B |
| Grooved Pegboard | Time to completion (dominant and non-dominant hands) |
| Finger Tapping | Mean number of taps ² (dominant and non-dominant hands) |

1. Alternative versions were employed.

2. Higher scores indicate better performance.

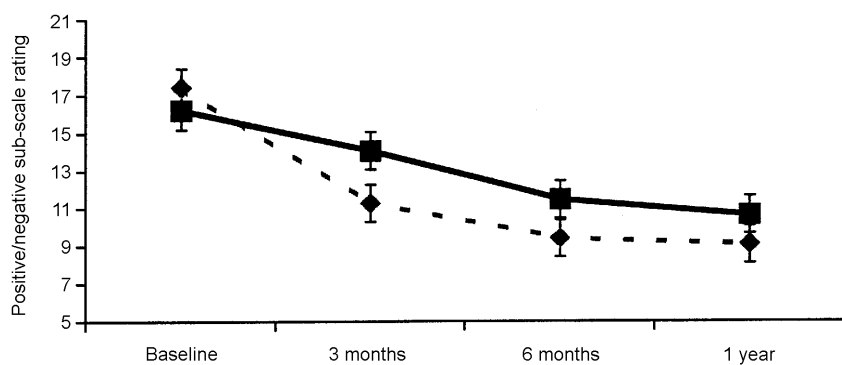


Fig. 1 Positive (—◆—) and negative (—■—) sub-scale ratings from the Positive and Negative Syndrome Scale at baseline, 3 months, 6 months and 1 year.

Table 2 Neuropsychological test scores at study test points (mean, 95% CI)

| Test | Baseline | 3 month | 6 month | 1 year | P |
|-------------------------------|-------------------|-------------------------------|--------------------------------|--------------------------------|-------|
| Auditory Verbal Learning Test | 47.9 41.8–54.0 | 48.6 41.8–55.4 | 48.8 40.8–56.8 | 49.1 38.1–60.1 | NS |
| Benton Visual Retention Test | 2.3 1.32–3.27 | 2.1 1.12–3.08 | 2.2 0.95–3.45 | 1.8 0.77–2.83 | NS |
| Wisconsin Card Sorting Test | 10.3 6.46–14.1 | 21.6 8.42–34.8 | 11.2 4.34–18.1 | 8.2 5.01–11.4 | NS |
| Object Alternation | 4.0 1.88–6.12 | 3.2 0.92–5.48 | 0.38 ¹ 0.03–0.73 | 1.2 ¹ 0.17–2.32 | 0.006 |
| Continuous Performance Test | 1.2 0.77–1.63 | 1.7 ¹ 1.16–2.24 | 1.9 ¹ 1.36–2.44 | 1.8 ¹ 1.47–2.13 | 0.001 |
| Verbal Fluency | 34.3 28.9–39.7 | 37.0 30.4–43.6 | 38.8 ¹ 30.8–46.8 | 41.5 ¹ 33.9–49.1 | 0.02 |
| Trail Making Test | | | | | |
| Trails A | 28.0 21.7–34.3 | 26.2 19.1–33.3 | 22.5 19.0–26.0 | 22.9 18.7–27.1 | NS |
| Trails B | 61.3 49.9–72.7 | 57.4 42.4–72.4 | 52.5 40.6–64.4 | 54.7 45.0–64.4 | NS |
| Grooved Pegboard ² | | | | | |
| Dominant | 65.5 60.1–70.9 | 64.9 61.6–68.2 | 60.2 54.4–66.0 | 64.0 61.0–67.0 | NS |
| Non-dominant | 71.6 65.5–77.7 | 71.2 65.6–76.8 | 67.4 62.7–72.1 | 68.2 64.6–71.8 | |
| Finger Tapping ² | | | | | |
| Dominant | 50.7 47.3–54.1 | 51.9 48.4–55.4 | 51.6 47.5–55.7 | 52.3 48.3–56.3 | NS |
| Non-dominant | 47.5 44.7–50.3 | 46.8 43.5–50.1 | 46.8 43.6–50.0 | 47.7 44.1–51.3 | |

1. Significantly different from baseline.
2. Main effect for hand significant.

Twelve patients (35%) were anti-psychotic medication naïve at the time of study entry. The remainder had been medicated for 7.4 (s.d.=6.2) weeks on average as follows: risperidone (n=11); quetiapine (n=6); haloperidol (n=2); loxapine (n=2); or olanzapine (n=1). Mean chlorpromazine

equivalent dosage for initial medications \bar{x} =288.3 (s.d.=172.4) mg/day.

On average, male patients were treated with higher doses of quetiapine (\bar{x} =520.0 mg/day, s.d.=220.1) than females (\bar{x} =512.5 mg/day, s.d.=275.0). Mean optimal dose for the first-episode

patients studied was 517.9 mg/day (s.d.=225.8).

Mean neuropsychological test scores over the four study visits are shown in Table 2. With the exception of the timed motor tasks (Finger Tapping and Grooved Pegboard), performance was enhanced on all tasks during treatment with quetiapine. Statistically reliable improvements were noted on the Continuous Performance Test (CPT) (*d'* total score, i.e. the ability to discriminate target from non-target items), Object Alternation (number of perseverative errors) and Verbal Fluency Test (total score). Simple contrast *post hoc* tests indicated that CPT performance was improved at all three time points examined (3-month, 6-month and 1-year) relative to baseline, whereas Object Alternation and Verbal Fluency capacity was enhanced at 6 months and 1 year.

DISCUSSION

This study documents the interim analysis of a longer-term study of the effects on cognitive performance in a cohort of young patients with a first episode of schizophrenia and related disorders who were treated with quetiapine. To our knowledge, the data provide the first clear indication that cognitive test performance is improved in young patients with psychosis who were treated with quetiapine. Statistically significant improvements were observed on measures of attention, executive function and verbal fluency at 6 months and 1 year of treatment. Improvements in attention (CPT) were also noted at the 3-month testing session. These findings are consistent with studies of chronically ill, medicated patients.

Memory and attention deficits are common in patients with psychotic disorders (Lussier & Stip, 2001) and could represent the domains of cognition that are most severely disturbed (O'Carroll, 1992; Saykin *et al*, 1994). Our data clearly demonstrated impairment in these cognitive domains at baseline as compared with published normative data. Of these domains, performance on a measure of attention attained normal levels and also underwent statistically significant improvement. Performance on verbal and non-verbal memory measures did not reach significance, although there did appear to be an indication of improved functioning over time.

The number of perseverative errors on Object Alternation (a task used to assess response switching) was reduced to below baseline levels for a sample of healthy controls (details available from author on request). In contrast, the number of perseverative errors from the Wisconsin Card Sorting Test did not reliably decrease. However, an unusual pattern of performance was observed on this measure: better scores were observed at baseline than on subsequent sessions, suggesting a non-representative estimate of baseline functioning. A larger sample could permit better understanding of this finding.

There are several advantages to the study design employed. The open label design ensured that patients were treated optimally and thus, potential symptomatic confounds were minimised. Also, examining patients with a first episode of illness is beneficial as the pre-drug status was known (naïve or short-term prior exposure) and is likely to contribute minimally to the observed effects. Finally, the frequency of cognitive assessments and adequacy of the neuropsychological test battery allowed for the examination of early and longer-term effects on cognition (Keefe *et al*, 1999). At the same time, we were able to diminish the motivational challenges that occur with too frequent or elaborate assessments.

The lack of a control group (or a group of patients treated with another agent) leaves unanswered whether the improvements noted were simply a result of facilitation because of repeated exposure to the tasks. Several factors argue against this interpretation. First, alternate forms were employed for those tasks for which they were available (see Table 1). Although this measure would not mitigate procedural practice effects, content-specific memory would not be affected. The greatest influence of practice may reasonably be expected to occur on initial readministration with inter-test intervals of 3 months or less. Performance in our sample continued to improve beyond the second testing session. Second, patients who are treated with conventional antipsychotic medications do not demonstrate cognitive improvement with repeated administration of neuropsychological tests (Kern *et al*, 1998; Purdon *et al*, 2000). Nevertheless, without a comparator group, the effects of practice cannot be ruled out. Regardless of the basis for improvement, patients in the current study did improve over time

CLINICAL IMPLICATIONS

- In young patients with first-episode psychosis treated with quetiapine, statistically significant improvement was noted on measures of attention (Continuous Performance Test; CPT), verbal productivity (Verbal Fluency Test) and executive function (Object Alternation Test) after 6 months and 1 year of treatment.
- For the CPT, improvement was also noted after 3 months of treatment.
- Positive and negative symptoms, as measured by the Positive and Negative Syndrome Scale, appear to be well-managed by the doses of quetiapine used in this study.

LIMITATIONS

- Without a control group, the effects of practice cannot be ruled out.
- Larger sample sizes are required to confirm the validity of these findings.
- Further study is required to determine whether these putative improvements in cognition translate into enhanced functional adaptability (outcome).

KIMBERLEY P. GOOD, PhD, IVAN KISS, CPsych, Department of Psychiatry, Dalhousie University, Canada; CHRISTINE BUITEMAN, BA, HAZEL WOODLEY, RN, QING RUI, MD, The Nova Scotia Early Psychosis Programme, Canada; DAVID WHITEHORN, PhD, Department of Psychiatry, Dalhousie University and The Nova Scotia Early Psychosis Programme, Canada; LILI KOPALA, FRCPC, Department of Psychiatry, Dalhousie University, Canada

Correspondence: Dr Kimberley Good, Department of Psychiatry, Dalhousie University, Suite 3073-AJLB, 5909 Veterans' Memorial Lane, Halifax, Nova Scotia, Canada B3H 2E2.
E-mail: kimpgood@is.dal.ca

and this observation may be the most meaningful.

Despite modest sample size, statistical improvement over time was observed in a quarter of the cognitive test variables studied. For all other test variables (with the exception of the timed motor/sensory tasks, which were predicted to be unchanged), all mean scores showed trends towards better performance with treatment. These values supported our hypotheses and will be carefully examined in future analyses.

The results of this preliminary study are encouraging but remain tentative. Clearly, larger sample sizes, along with more rigorous study designs (including patients treated with other antipsychotic medications) will allow for better characterisation of the drug-specific effects of quetiapine on various domains of cognition. Nevertheless, this study indicates that, at least, quetiapine is not likely to have adverse effects on cognitive function and

could well have beneficial effects. Given the strong relationship between cognition and functional adaptation, continued intensive study of the effects of quetiapine on cognition is highly desirable. Further data on patients' functional adaptability after treatment with quetiapine and other aspects of the study will be forthcoming.

ACKNOWLEDGEMENTS

We thank Drs H. Milliken, C. Hault, D. Devarajan, U. Wadhwa, T. Ahmed, M. Alexiadis, N. Robertson, L. Campbell, C. Day, J. Gallant, L. Whitehorne and P. Hobin.

REFERENCES

- American Psychiatric Association (1994)** *Diagnostic and Statistical Manual of Mental Disorders (4th edn)* (DSM-IV). Washington, DC: APA.
- Censits, D., Ragland, J., Gur, R., et al (1997)** Neuropsychological evidence supporting a neurodevelopmental model of schizophrenia: a longitudinal study. *Schizophrenia Research*, **24**, 289–298.

- Green, M., Marshall, B., Wirshing, W., et al (1997)** Does risperidone improve verbal working memory in treatment-resistant schizophrenia? *American Journal of Psychiatry*, **154**, 799–804.
- , **Kern, R., Braff, D., et al (2000)** Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the “right stuff”? *Schizophrenia Bulletin*, **26**, 119–136.
- Hagger, C., Buckley, P., Kenny, J., et al (1993)** Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. *Biological Psychiatry*, **34**, 702–712.
- Harvey, P. & Keefe, R. (2001)** Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *American Journal of Psychiatry*, **158**, 176–184.
- Hoff, A., Faustman, W., Wieneke, M., et al (1996)** The effects of clozapine on symptom reduction, neurocognitive function, and clinical management in treatment-refractory state hospital schizophrenic in-patients. *Neuropsychopharmacology*, **15**, 361–369.
- Kane, J., Honigfeld, G., Singer, J., et al (1988)** Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Archives of General Psychiatry*, **45**, 789–796.
- Kay, S. R., Fiszbein, A. & Opler, L. A. (1987)** The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, **13**, 261–276.
- Keefe, R., Silva, S., Perkins, D., et al (1999)** The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. *Schizophrenia Bulletin*, **25**, 201–222.
- Kern, R., Green, M., Barringer, D., et al (1998)** Risperidone vs. haloperidol on reaction time, manual dexterity, and motor learning in treatment-resistant schizophrenia patients. *Biological Psychiatry*, **44**, 726–732.
- Kopala, L., Good, K. & Honer, W. (1997)** Extrapyramidal signs and clinical symptoms in first-episode schizophrenia: response to low-dose risperidone. *Journal of Clinical Psychopharmacology*, **17**, 308–313.
- Lee, M., Thompson, P. & Meltzer, H. (1994)** Effects of clozapine on cognitive function in schizophrenia. *Journal of Clinical Psychiatry*, **55**, 82–87.
- Lezak, M. (1995)** *Neuropsychological Assessment* (3rd edn). New York: Oxford University Press.
- Lussier, I. & Stip, E. (2001)** Memory and attention deficits in drug naive patients with schizophrenia. *Schizophrenia Research*, **48**, 45–55.
- Marder, S. & Meibach, R. (1994)** Risperidone in the treatment of schizophrenia. *American Journal of Psychiatry*, **151**, 825–835.
- O’Carroll, R. (1992)** Neuropsychology of psychosis. *Current Opinion in Psychiatry*, **5**, 38–44.
- Purdon, S., Jones, B., Stip, E., et al (2000)** Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone or haloperidol. *Archives of General Psychiatry*, **57**, 249–258.
- , **Malla, A., Labelle, A., et al (2001)** Neuropsychological change in patients with schizophrenia after treatment with quetiapine or haloperidol. *Journal of Psychiatry and Neuroscience*, **26**, 137–149.
- Sax, K., Strakowski, S. & Keck, P. (1998)** Attentional improvement following quetiapine fumarate treatment in schizophrenia. *Schizophrenia Research*, **33**, 151–155.
- Saykin, A., Shtasel, D., Gur, R., et al (1994)** Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. *Archives of General Psychiatry*, **51**, 124–131.
- Velligan, D. & Miller, A. (1999)** Cognitive dysfunction in schizophrenia and its importance to outcome: the place of atypical antipsychotics in treatment. *Journal of Clinical Psychiatry*, **60**, 25–28.