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# Quetiapine treatment and improved cognitive functioning in borderline personality disorder

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Objective: We aimed to assess whether executive functioning improved over time in a sample of borderline personality disorder (BPD) subjects that took part in a quetiapine treatment trial. Methods: Performance on the following neurocognitive tasks was assessed at enrolment and at the end of the 12 weeks quetiapine treatment: Trail Making Task, Word Fluency Task and Tower of London Task. Forty-one BPD patients were recruited, of whom 32 completed the trial. An intention-to-treat analysis with a mixed linear model was applied. Results: The data show that participants significantly improved on most executive functioning measures. Patients' scores decreased significantly (mean [SD] difference; *p*-value) on the Trail Making Task Part A (11.7 [2.3]; $p < 0.0001$), Part B (51.8 [9.2]; $p < 0.0001$) and 'B minus A' (40.1 [8.2]; $p < 0.0001$), on a Phonological (15.9 [1.6]; $p < 0.0001$) and Semantic (9.8 [1.1]; $p < 0.0001$) Verbal Fluency tasks, and on the Tower of London total correct score (2.5 [0.4]; $p < 0.0001$), total move score (29.5 [4.5]; $p < 0.0001$) and total time (172.9 [35.8]; $p < 0.0001$). Conclusions: In this study we have demonstrated that executive functioning in BPD is improved after treatment with quetiapine. Neurocognitive measures of executive functioning should be considered as valuable outcomes in the study of treatment efficacy in BPD. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS — quetiapine; borderline personality disorder; cognitive functioning; executive functions

## INTRODUCTION

More insight in the psychopathology and treatment of the borderline personality disorder (BPD) is needed. In line with a growing movement that argues that there is insufficient evidence to support the current distinction between DSM-IV axis I and axis II, some propose to shift BPD to axis I (New *et al*., 2008; Siever and Davis, 1991). This novel approach is likely to not only impact on attitudes in clinical practice but also on research into the nature and treatment of this disorder (New *et al*., 2008).

Although psychotherapy remains the treatment of choice, clinical pharmacological studies have provided substantial evidence to recommend symptom-targeted drug treatment in BPD (American Psychiatric Association, 2001; Herpertz *et al*., 2007). Antidepressants, mood stabilisers and antipsychotics have been shown to reduce scores on self-report and interviewer-rated clinical measures of impulsivity and affective symptoms (Nosé *et al*., 2006). These assessment tools have inherent disadvantages, certainly when used in open-label studies. In contrast to BPD, research in other psychiatric disorders has applied neurocognitive performance as a method to evaluate efficacy in treatment studies in schizophrenia (e.g. Harvey *et al*., 2006), obsessive-compulsive disorder (de Geus *et al*., 2007) and anorexia nervosa (Bosanac *et al*., 2007). Although participant characteristics such as motivation may have an effect on task performance, neurocognitive assessment is not subject to the personal interpretation of statements or phrases in questionnaires and interviewer-rated measures. Additionally neurocognitive measures measure a different aspect of functioning than questionnaires and interviews that are mostly focus on presence/absence of symptoms and symptom severity. Therefore, we suggest the use of neurocognitive outcome measures as an alternative and novel strategy to evaluate treatment efficacy in BPD.

Cross-sectional studies in BPD have demonstrated impairments on several neurocognitive domains (van Reekum *et al*., 1993), including executive functioning (Arntz *et al*., 2000; Dinn *et al*., 2004; Fertuck *et al*., 2006;

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Posner *et al*., 2002; van Reekum *et al*., 1996). Some, however, were unable to confirm these executive function findings (Kunert *et al*., 2003; Sprock *et al*., 2000).

The efficacy of atypical antipsychotics, including quetiapine, is being increasingly investigated in BPD (e.g. Binks *et al*., 2006; Herpertz *et al*., 2007). We have conducted a clinical trial with quetiapine in BPD in which we found this intervention to reduce affective symptoms and impulsivity (Van den Eynde *et al*., 2008). We report here on the findings on executive functioning as an additional assessment measure of efficacy in the same sample.

## MATERIALS AND METHODS

### *Subjects*

The study sample and data on the clinical outcomes impulsivity and affective symptoms have been described elsewhere (Van den Eynde *et al*., 2008). Forty-one (7 males and 34 females; mean age ± standard deviation: 27.0 ± 9.0 years) quetiapine-naïve treatment-seeking BPD patients (DSM-IV-TR diagnosis) completed a 12-week clinical trial with quetiapine. Nine subjects, all females, prematurely discontinued the study.

Exclusion criteria consisted of a primary or comorbid diagnosis of schizophrenia, dementia or any other cognitive disorder, or substance dependence; and having taken any antipsychotic, tricyclic antidepressant, mood stabiliser or a norepinephrine and dopamine reuptake inhibitor 8 weeks prior to enrolment in the study. Comorbid ('current') DSM-IV axis I diagnoses were Posttraumatic Stress Disorder ($n = 3$), Eating Disorder Not Otherwise Specified ($n = 3$), Body Dysmorphic Disorder ($n = 2$) and Social Anxiety Disorder ($n = 1$). One participant – who discontinued the study prematurely – used a benzodiazepine in a dose equivalent to 2 mg of lorazepam. Twenty completers (62.5%) and five of those who dropped out the study (55.6%) were on either a selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) for at least 2 weeks prior to the start. The dose remained unchanged for the duration of the study. None of the enrolled patients had a history of electroconvulsive treatment or major brain trauma that required medical attention.

The mean daily dose ± standard deviation of quetiapine at endpoint was 412.5 mg ± 229.6 mg (range: 100–800 mg). Although 22 (66.8%) participants reported sedation at some time during the trial, this adverse event was not present in any subject at either the first or the second assessment.

Participants enrolled either in a dialectical behavioural therapy program, or alternatively were offered psychiatric counselling.

### *Procedure*

The following tasks that assess aspects of executive functioning (set-shifting, fluency, and planning and problem-solving) were performed in the same sequence in every subject.

A. *Trail Making Task* (TMT, Reitan, 1955): This task consists of two main parts in which the time to track a number sequence (TMT A) or a sequence of alternating numbers and letters (TMT B) is measured. TMT A time is considered to measure attention, whereas time to complete the TMT B trial (or subtracted by the time on TMT A) is a measure of set-shifting and mental flexibility.

B. *Verbal Fluency*: We used a word generation task in which subjects were asked to name as many words as possible in 1 min. During three separate trials of 1 min, words needed to start with a specific letter (N, A and K) (phonological task). Then, subjects were requested to name in 1 min as many words as possible of a semantic category (animals, professions) (semantic task). The total number of words on both the phonological and the semantic tasks, and the overall number of words are a measure of verbal fluency.

C. *Tower of London* Task (Shallice, 1982): We used the manual version of this task which assesses planning and problem solving and consists of 10 trials. Participants have two different displays of coloured discs inserted into vertical rods and are asked to rearrange the discs in one display to match the pattern of the top in as few movements as possible. The total number correct of correctly completed trials is a measure of accuracy. The total number of steps needed to complete the 10 trials provides a general measure of performance or efficiency. The total time gives an idea of speed of performance and planning during the solution. Some have split the total time in the 'initiation time' or the time that a subject takes to make the first move, and the 'execution time' or that time from the end of the first move to till the solution has been found. The interpretation of the initiation time is not straightforward. Some believe it reflects thorough and deliberate planning, whereas others have suggested it might reflect ineffective planning. The execution time is though to be an index of problem-solving/planning speed (Berg and Byrd, 2002).

The neuropsychological assessments took place at enrolment in the study and at completion of the trial, and were all performed by the same investigator (FVDE).



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*Statistics*

An intention-to-treat analysis including all patients enrolled in the study was performed. Statistical software R (version 2.4.0) was used for the mixed model analyses, which have been suggested to be the preferable assessment method for repeated measures (Gueorguieva and Krystal, 2004). The mean change from baseline was assessed by a linear mixed model with patient as random effect. The number of weeks of psychotherapeutic (dialectical behavioural therapy) treatment and antidepressant use were included as covariates in the model. The effects of assessment were assessed by means of likelihood ratio tests. The *p*-values for these comparisons were corrected for multiple testing according to Sidak's method. All statistical tests were performed two-sided at the 5% level of significance.

The study protocol was approved by the Ethical Committees of both participating hospitals and subjects gave written informed consent to participate in the study. The study was carried out in accordance with the Declaration of Helsinki.

## RESULTS

The intention-to-treat analysis with the mixed linear model showed that patients significantly improved on most executive functioning measures (Table 1). Firstly, on the TMT participants' performance improved significantly not only on the part that assesses attention (Part A), but also the set-shifting or mental flexibility indices (Part B and B – A). Secondly, compared to enrolment (semantic and phonological) verbal fluency was better after treatment. Thirdly, on the Tower of London Task participants were more accurate (total correct score), more efficient (total move score) and showed better planning (total time) to resolve the trials.

## DISCUSSION

In this research we found that BPD patients, who completed a 12-week treatment trial with quetiapine, improved on neurocognitive tasks that assess aspects of executive functioning. This is the first report on the use neurocognition in the evaluation of treatment efficacy in BPD.

There are ample data indicating that quetiapine has beneficial effects on cognitive functioning in schizophrenia (e.g. Cheer and Wagstaff, 2004; Harvey *et al*., 2006; Keefe *et al*., 1999; Voruganti *et al*. 2007). Preliminary data suggest that quetiapine might improve neurocognition in anorexia nervosa (Bosanac *et al*., 2007) and – as an add-on to an antidepressant – it does not negatively impact on cognition in obsessive compulsive disorder (de Geus *et al*., 2007). In the latter study, only failure to maintain set on the Wisconsin Card Sorting Test was reported to be associated with quetiapine administration. Attention difficulties owing to somnolence were believed to have been the cause. In bipolar disorder type I patients, compared to risperidone, quetiapine appeared to have a somewhat negative effect on neurocognition in the early phases of treatment (Harvey *et al*., 2007). Again, sedative aspects were thought to be responsible. In our sample, sedation was mainly present in the beginning of the treatment. However, sedation was not present at the time of the neurocognitive assessments. At enrolment,

Table 1. Neurocognitive outcome measures

| Measure | Enrolment | Endpoint | Mean difference (enrolment vs. endpoint) ± SD | 95% Confidence interval | *p*-Value for time effect (baseline corrected) |
|---|---|---|---|---|---|
| Trail Making Task | | | | | |
| Part A | 42.0 (16.5) | 31.0 (7.6) | 11.7 ± 2.3 | 10.9–12.5 | <0.0001 |
| Part B | 98.3 (57.3) | 50.6 (16.7) | 51.8 ± 9.2 | 48.6–55.0 | <0.0001 |
| Part B – Part A | 56.3 (48.5) | 19.6 (11.3) | 40.1 ± 8.2 | 37.2–43.0 | <0.0001 |
| Word Fluency Task | | | | | |
| Phonological | 27.8 (9.2) | 43.8 (9.5) | 15.9 ± 1.6 | 15.3–16.5 | <0.0001 |
| Semantic | 35.8 (10.2) | 44.8 (6.0) | 9.8 ± 1.1 | 9.4–10.2 | <0.0001 |
| Tower of London | | | | | |
| Total correct score | 2.5 (2.1) | 5.1 (2.7) | 2.5 ± 0.4 | 2.4–2.6 | <0.0001 |
| Total move score | 50.3 (33.1) | 23.1 (20.5) | 29.5 ± 4.5 | 27.9–31.1 | <0.0001 |
| Total time | 451.9 (246.2) | 285.5 (129.7) | 172.9 ± 35.8 | 160.4–185.4 | 0.002 |
| Total initiation time | 51.3 (26.2) | 57.3 (24.7) | 4.0 ± 3.7 | 2.7–5.3 | <0.612 |
| Total execution time | 403.0 (246.9) | 228.2 (126.3) | 178.9 ± 36.6 | 166.2–191.6 | 0.001 |
| Total time violation | 2.2 (2.7) | 0.44 (0.91) | 1.81 ± 0.4 | 1.7–1.9 | 0.003 |

Data at enrolment ($n = 41$) and end point ($n = 32$) were the mean (SD) of the raw data. The mean (SE) difference was calculated in the linear mixed model.



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the assessment took place before the first quetiapine dose was administered. At endpoint, none of the participants reported sedation. The mean daily dose ± standard deviation of quetiapine at endpoint was 412.5 mg + 229.6 mg (range: 100–800 mg). This is somewhat lower than the dose generally used in bipolar disorders and schizophrenia.

It is hard to establish what underlies the improved performance on the tasks. In schizophrenia research, cognitive benefits of quetiapine have been attributed to its loose binding to and fast dissociation from the dopamine receptors, resulting in less cognitive adverse events (Voruganti *et al*., 2007). The latter combined with an overall recovery of the psychopathology is likely to result in a positive progress in neurocognition (Voruganti *et al*., 2007). Our data suggest a similar mechanism in BPD. In this sample, affective symptoms and impulsivity, which lie at the core of the clinical problem, were significantly reduced. This clinical improvement is also reflected in behavioural outcome measures, i.e. neurocognitive tasks. However, alternative explanations cannot be ruled out, such as a learning effect due to the repetition of tasks. Nevertheless, it is unlikely that this would account entirely for the considerable improvement that we observed. Furthermore participants were not aware that the same tasks would be repeated and were not given feedback after the first assessment.

As our main focus was on the effects of quetiapine, in the analysis we controlled for the weeks in psychotherapy and antidepressant use. These two interventions are known to have a degree of clinical efficacy in BPD (Binks *et al*., 2006).

The limitations of the open-label study design and the lack of control group should of course be taken into account.

In conclusion, neurocognitive measures of executive functioning might serve as relevant outcomes in the study of treatment efficacy in BPD. We have demonstrated in this study that executive functioning in BPD is enhanced after treatment with quetiapine.

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