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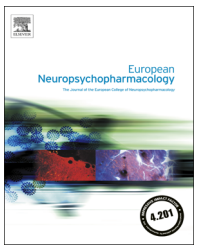

Acute anxiolytic effects of quetiapine during virtual reality exposure—A double-blind placebo-controlled trial in patients with specific phobia

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Abstract
Anxiety disorders are among the most frequent psychiatric disorders. With regard to pharmacological treatment, antidepressants, the calcium modulator pregabalin and benzodiazepines are recommended according to current treatment guidelines. With regard to acute states of anxiety, so far practically only benzodiazepines provide an immediate anxiolytic effect. However, the risk of tolerance and dependency limits the use of this class of medication. Therefore, there is still a need for alternative pharmacologic strategies. Increasing evidence points towards anxiety-reducing properties of atypical antipsychotics, particularly quetiapine. Therefore, we aimed to evaluate the putative acute anxiolytic effects of this compound, choosing the induction of acute anxiety in patients with specific phobia as a model for the evaluation of *ad-hoc* anxiolytic properties in a proof-of-concept approach. In a randomized, double-blind, placebo-controlled study, 58 patients with arachnophobia were treated with a single dose of quetiapine XR or placebo prior to a virtual reality spider challenge procedure. Treatment effects were monitored using rating scales for acute anxiety as well as measurements of heart rate and skin conductance. Overall, quetiapine showed significant anxiolytic effects compared to placebo. However, effects were not seen on the primary outcome measure (VAS Anxiety), but were limited to somatic anxiety symptoms. Additionally, a significant reduction of skin conductance was observed. Further exploratory analyses hint towards a

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mediating role of the (*COMT*) val158met genotype on treatment response. The present results thus suggest a possible suitability of quetiapine in the acute treatment of anxiety, particularly with regard to somatic symptoms.
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1. Introduction

Anxiety disorders are among the most frequent psychiatric disorders (Kessler et al., 2005; Wittchen et al., 2011), conferring a marked economic burden due to their high prevalence and chronicity (Olesen et al., 2012). Treatment options comprise psychotherapeutical — primarily cognitive-behavioural therapy — as well as psychopharmacological interventions (Bandelow et al., 2008; Diemer et al., 2010). With regard to pharmacotherapy, antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors (SNRIs) and the calcium modulator pregabalin represent the first-line therapy for most anxiety disorders according to current treatment guidelines (Bandelow et al., 2008). However, although usually effective and well tolerated, up to 30% of patients do not respond to first treatment or suffer from side effects (Barlow, 2002). Delayed onset of action represents a major disadvantage of this class of medication (Bandelow et al., 2008). On the other hand, fast-acting benzodiazepines, mostly used for the treatment of acute anxiety and severe panic attacks, bear the risk of tolerance and dependency (Lader, 2011). Therefore, there is still a need for alternative pharmacological strategies.

In this context, an increasing number of reports points towards anxiolytic properties of atypical neuroleptics in anxiety disorders (for reviews see Gao et al., 2006; Maher et al., 2011). For example, single or add-on therapy with olanzapine resulted in a significant reduction in anxiety symptoms in patients with GAD and social phobia (Barnett et al., 2002; Pollack et al., 2006), and ziprasidone was equally anxiolytic as diazepam in a study of healthy subjects with dental anxiety (Wilner et al., 2002). Compared to other atypical antipsychotics, quetiapine has shown particular potential as a possible anxiolytic agent (Maher et al., 2011). Quetiapine was reported to be beneficial in reducing anxiety symptoms in patients with social phobia in two small studies over the course of 12 and 8 weeks, respectively (Schutters et al., 2005; Vaishnavi et al., 2007). More recently, a double-blind placebo-controlled trial has shown that a once-daily quetiapine XR monotherapy at 50 and 150 mg/day is effective in improving anxiety symptoms in patients with GAD already after 4 days (Bandelow et al., 2010); similar results for 150 and 300 mg/day of quetiapine XR in GAD confirm these findings (Merideth et al., 2012). Quetiapine XR has also been shown to be an effective maintenance therapy for GAD (Katzman et al., 2011). A recent Cochrane review concludes that the efficacy of quetiapine may be comparable to that of antidepressants for GAD, while the rates of drop-outs and side effects, particularly weight gain and sedation, are higher (Depping et al., 2010).

Beneficial effects of drugs modulating not only the serotonergic and noradrenergic, but also the dopaminergic system might be expected. There is evidence from both a pathobiological/-physiological and a genetic perspective that — partly linked with serotonergic dysfunction — altered dopaminergic neurotransmission might play an important role in the pathogenesis of anxiety disorders (Hettema et al., 2008). In particular, a specific role for the dopamine catabolising enzyme catecholamine-O-methyltransferase (*COMT*), which differentially influences phasic and tonic dopaminergic firing (Bilder et al., 2004), has been suggested for phobic anxiety and panic disorder. Significantly elevated erythrocyte *COMT* activity has been reported in patients with anxiety states (Shulman et al., 1978), and *COMT* inhibitors are effective in the treatment of anxiety symptoms in Parkinson's disease (Richard et al., 1996). Also, molecular studies have suggested association mostly of the more active val allele of the *COMT* val158met polymorphism with panic disorder and phobic anxiety (Domschke et al., 2007; Hamilton et al., 2002; McGrath et al., 2004).

In view of the evidence pointing towards anxiolytic effects of quetiapine and advantages over antidepressants with regard to onset of action (Depping et al., 2010), we conducted a proof-of-concept study to further explore the acute anxiolytic properties of quetiapine. Experimental induction of anxiety in patients with specific phobia was used as a paradigmatic model suited for the investigation of acute anxiety states, which can be readily provoked in phobic patients by an anxiety-relevant challenge. We employed a Virtual Reality (VR) challenge, which offers maximum standardisation. VR challenges have been shown to provoke both intense subjective fear (e.g., Cornwell et al., 2011; Freire et al., 2010; Mühlberger et al., 2005) and typical behavioural avoidance associated with anxiety disorders (Mühlberger et al., 2008). Quetiapine XR was chosen due to its greater tolerability, enabling us to avoid confounds with undesired drug effects. Further, our study design included two challenge procedures on the same day (results of an fMRI experiment not reported here), which required a duration of medication effects of 5–7 h.

We hypothesised subjective and objective anxiety symptoms to be significantly lower following quetiapine vs. placebo treatement. Additionally, a modulating effect of the *COMT* val158met genotype on anxiety levels and treatment outcome was expected.

2. Experimental procedures

This is a double-blind, randomized, placebo-controlled parallel-group study designed to test the acute anxiolytic properties of a single dose of 100 mg quetiapine XR or placebo in patients with arachnophobia. The study was approved by the local ethics committee (Ethikkommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der WWU Münster). Written informed consent was obtained from all participants.

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