Title:	Anxiolytic effects of single-dose quetiapine XR administration on clinical symptoms and amygdala activation during exposure in patients with simple phobia
German title:	Anxiolytische Effekte einer einmaligen Dosis Quetiapin XR auf klinische Symptome und Amygdala-Aktivität während Exposition bei Patienten mit spezifischen Phobien

This is a randomized, double-blind, placebo-controlled monocentric parallel group study investigating the anxiolytic effects of a single dose of 100mg Quetiapin XR in a sample of n=60 patients suffering from specific phobia.

Investigational product:	Quetiapine XR (Seroquel Prolong®)
Indication:	Proof-of-concept study / Specific phobia
Phase:	II
Acronym:	QUISS
Eudra-CT-Nr.:	2008-001371-30
Sponsor's Protocol Code:	D1443L00051
Start date:	29.06.2009
End date:	01.03.2011

This study was conducted in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

Investigator sponsored study (ISS) supported by an unrestricted grant from AstraZeneca Germany.

Final Report

Sponsor of the Clinical Trial:

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2 Synopsis

Sponsor: University Hospital Muenster	
Investigator sponsored study (ISS) supported by an unrestricted grant from AstraZeneca Germany.	
Investigational Product: Seroquel Prolong®	
Active Substance: Quetiapine XR	
Title: Anxiolytic effects of single-dose quetiapine XR administration on clinical symptoms and amygdala activation during exposure in patients with simple phobia	
Study Protocol: Version 03 of 18.08.2008, including Amendment 01 of 02.12.2008	
Principal Investigator: Prof. Dr. P. Zwanzger	
Study Centre: Department of Psychiatry, University Hospital Muenster	
Publication: Diemer J, Domschke K, Mühlberger A, Winter B, Zavorotnyy M, Naunin S, Silling K, Arolt V, Zwanzger P. (2013). Acute anxiolytic effects of quetiapine during virtual reality exposure – a double-blind placebo-controlled trial in patients with specific phobia. European Neuropsychopharmacology 23(11), 1551-1560. Further publication in preparation.	
Study period: 2 years **first patient in:** 29.06.2009 **last patient out:** 01.03.2011	**Phase:** II
Objectives of the study: The study aims to investigate the putative anxiolytic properties of quetiapine XR in patients with anxiety disorders. Therefore, in a proof-of-concept design patients with simple phobia were selected to investigate specific anxiolytic and antipanic activity during acute anxiety. Moreover, in a combined fMRI/visual stimulus presentation paradigm activity of fear-network associated brain structures such as the amygdala were investigated under quetiapine XR or placebo.	
Methods: This is a randomized, double-blind, placebo-controlled monocentric study aimed at investigating the anxiolytic effect of a single dose of quetiapine XR in patients with specific phobia. 60 patients were recruited. For inclusion into the study, every patient had to fulfil inclusion criteria. Patients were randomly assigned to receive either a single dose of 100mg Quetiapine XR or matching placebo. After administration of either Quetiapine XR or placebo, patients were confronted with anxiety-relevant stimuli twice: 1.) Confrontation with anxiety-relevant picture stimuli in 3T fMRI. Fear network (including amygdala) activity was measured. 2.) Challenge in virtual reality (VR). Heart rate and skin conductance levels were registered. Further, subjective anxiety reactions during fMRI exposure and VR challenge were also assessed using a range of fear questionnaires (API, FAS, BAI, POMS, 100mm visual analogue scales for Anxiety, Tension and Avoidance). Finally, common variants in genes potentially directly or indirectly involved in the	

mediation of the anxiolytic effects of quetiapine (e.g. dopamine receptor DRD2, dopamine transporter, serotonin receptor 2A (5-HT2A)) are investigated for association with the anxiolytic effect ("pharmacogenetic approach") as well as with fMRI measured activity in anxiety-related brain regions (e.g. amygdala, prefrontal cortex, cingulum) ("imaging genetics approach").

Sample size (planned and analyzed): 60

Diagnosis and main inclusion criteria:
Diagnosis: Specific Phobia (Arachnophobia)
Main inclusion criteria:

1. Provision of written informed consent
2. A diagnosis of simple phobia by Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV)
3. Females or males aged 18 to 70 years
4. Able to understand and comply with the requirements of the study
5. Females of childbearing potential must have a negative serum pregnancy test within 7 days prior or at enrolment and be willing to use an effective method of birth control for the duration of the study. Effective methods of birth control are defined as those which result in a low failure rate (i.e. pearl-index < 1%) when used consistently and correctly such as:
   - a hormonal oral, transdermal, or injectable contraceptive agent with a double-barrier method
   - an implantable contraceptive device with a failure rate less than 1% for at least 3 months prior to enrolment
   - vasectomized partner

Investigational Product (dose, administration, batch number): Seroquel Prolong®, 100mg, single dose (oral); batch numbers 615DE090073 and 615DE100027

Duration of treatment: single dose

Reference product (dose, administration, batch number): placebo, single dose (oral); batch numbers 615DE090073 and 615DE100027

Unblinding: after „last patient out"

Criteria for evaluation:
Efficacy: The primary outcome variable was VAS-Anxiety. Further efficacy variables are: State-Trait-Anxiety-Inventory (STAI), Beck Anxiety Inventory (BAI), Phobia specific questionnaires (FAS), Acute Panic Inventory (API), Profile of Mood States (POMS), VAS-Avoidance, VAS-Tension, VAS-Sedation, heart rate, and skin conductance. As a secondary outcome measure amygdala reactivity was measured using fMRI at 3T during exposure to visual stimulus material.
Safety: Adverse events were collected throughout the study.

Statistical methods:
All statistical analyses were calculated with PASW Software, Version 19 and IBM SPSS Statistics 20 software. Pearson Correlations, ANOVA and (M)ANCOVA were the main strategies used.
fMRI Study:
fMRI images were analyzed using the general linear model for block designs in SPM5. The individual BOLD-contrasts (first level) were converted into a 2 factorial ANOVA (factors *condition* and *group*) using SPM5 'full factorial' design (second level). To quantitatively assess differences between the placebo and the quetiapine group, left and

right mean signal intensity changes of the fear network during the different conditions were determined.

VR Challenge:

Physiological data were pre-analysed with BrainVision Analyser Software 2.0. Analyses consisted of two steps: First, the anxiogenic effect of the VR challenge was determined using repeated-measure ANOVA for all measures (questionnaires and online measures). Second, group differences (verum vs. placebo) were investigated.

Summary of results and conclusions:

Efficacy Results:

fMRI Exposure:

Imaging Data

Primary fear network: amygdala. The results of the BOLD response analysis clearly indicate that the fMRI challenge paradigm (viewing spider images) is able to activate the primary fear network of the brain. However, no significant group effect was detected between the placebo and quetiapine groups.

Secondary fear network: For the parahippocampus (PHK), a delayed activity response was observed for the quetiapine group, while PHK activity habituated in the placebo group during the course of the experiment. This may indicate that quetiapine may delay the response to phobic challenges.

Questionnaire Data

The fMRI exposure to anxiety-relevant picture stimuli produced a strong anxiety response in the participants. We found an effect of quetiapine on this anxiety response in questionnaires and scales measuring somatic anxiety (BAI, API Physical, VAS Tension), but not on more general and cognitive anxiety measures (API Cognitive, API Fear, FAS).

VR Challenge:

The VR challenge produced a strong anxiety response in our participants (mean SUDS increase: 6.5/10). We found an effect of quetiapine on this anxiety response in questionnaires and scales measuring somatic anxiety (BAI: Δ verum = 7.6, Δ placebo = 12.3; API Physical: Δ verum = 1.7, Δ placebo = 3.1; VAS Tension: Δ verum = 32.0, Δ placebo = .46.4) and in online EDA response, but not on more general and cognitive anxiety measures (VAS Anxiety, API Cognitive, API Fear, FAS) or HR. This dissociation points towards a differential effect of 100mg quetiapine XR on acute somatic symptoms of anxiety.

Genetic Data

We discerned a significant effect of COMT genotype on baseline VAS Anxiety and baseline FSQ with GG(val/val) genotype carriers displaying significantly higher anxiety levels than the carriers of at least one A allele (val/met and met/met genotype carriers). RM-ANOVA of VAS Anxiety revealed a significant main effect of COMT genotype, but no further effects. RM-ANOVA of FSQ indicated a significant three-way interaction implicating the GG (val/val) genotype to confer a better response to quetiapine as compared to the AG/AA (val/met and met/met) genotypes. While FSQ increased from baseline to VR challenge in the placebo group by 15.77 points for the AG/AA (val/met and met/met) genotypes, and 23.33 points for the GG (val/val) genotype, in the quetiapine group, FSQ increased by 18.14 points for the AG/AA (val/met and met/met) genotypes, while the average change for the GG (val/val) genotype was -1.86 points (i.e., a slight decrease).

Safety Results:

There were 14 adverse events, affecting 12 participants. The most frequent adverse event was headache (n=9), followed by nausea (n=2), weakness (n=2), and backache

(n=1). Adverse events were equally frequent in the placebo (8 adverse events, affecting n=6 participants) and the quetiapine group (6 adverse events, affecting n=6 participants). All of these adverse events were reported by participants at the end of the study day and may thus be attributable to quetiapine, placebo, the VR challenge, or fatigue after the long hours spent at the study centre. Of note, the adverse event weakness occurred in the quetiapine group only, while nausea (in both cases with headache) occurred in the placebo group only. There were no serious adverse events.

Conclusions:

Quetiapine appears to reduce acute somatic anxiety symptoms in patients with simple phobia.

Date of this report: 14.03.2014

Signature (Principal Investigator):