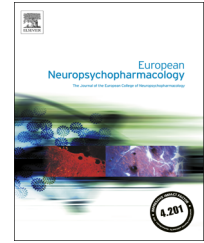




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Subjective well-being in schizophrenia: A randomised controlled open-label 12-month non-inferiority study comparing quetiapine XR with risperidone (RECOVER)



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Abstract

This randomised 12-month open study analysed the effectiveness of quetiapine XR (400–800 mg) versus risperidone (2–6 mg) on subjective well-being in schizophrenia (NCT00600756). Primary objective was to demonstrate non-inferiority of quetiapine XR to risperidone in 6-month responder rate using the Subjective Well-Being under Neuroleptics scale (SWN-K) (per-protocol at Month 6 [PP 6] population). Non-inferiority was defined as the lower limit of the 95% confidence interval (CI) greater than -9.7% for the adjusted difference between quetiapine XR and risperidone. Secondary objectives included non-inferiority of quetiapine XR versus risperidone (lower limit of 95% CI greater than -7.5 points) for SWN-K change from baseline to Month 12 (PP 12). 798 patients were randomised (quetiapine XR, $n=395$; risperidone, $n=403$); at Month 12, 212 (54%) and 227 (56%) patients, respectively, completed the study. At Month 6, SWN-K responder rate in the PP 6 population was 65% (136/210) with quetiapine XR and 68% (158/232) with risperidone (adjusted treatment difference: -5.7% ; 95% CI: $-15.1, 3.7$); thus, non-inferiority could not be established. SWN-K change from baseline to Month 12 was 23.2 points for quetiapine XR and 21.1 points for the risperidone group; treatment difference was 2.1 (95% CI: $-0.8, 5.0$); non-inferiority was established (PP 12). Conclusion: SWN-K response at 6 months was comparable between the two antipsychotics. However, with a lower than expected responder rate and a lower than expected number of evaluable patients in the

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PP 6 population, non-inferiority was not demonstrated. A secondary objective (SWN-K total score) established non-inferiority of quetiapine XR to risperidone at Month 12.
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1. Introduction

It is widely accepted that multidimensional outcome in schizophrenia comprises three different aspects: symptomatic remission (Andreasen et al., 2005; Lambert et al., 2010), functional improvement (Emsley et al., 2011) and adequate subjective well-being/quality of life (Lambert et al., 2008). Concurrent and sustained long-term achievement of each of these objectives, so-called recovery, is a desirable property of present and future antipsychotic agents (Correll, 2011).

The concept of subjective well-being was originally designed to assess subjective experiences under neuroleptic treatment (Naber, 1995; Naber et al., 2001). However, further research has expanded the subjective well-being concept to an overall subjective outcome dimension in schizophrenia (Vothknecht and Schoevers, 2011), which is highly associated with quality of life (Vothknecht and Schoevers, 2011; Wehmeier et al., 2007, 2008). Poor subjective well-being is linked to a diagnosis of schizophrenia more than to other psychotic disorders (Lambert et al., 2009a) and is caused by high levels of psychopathology and, similar to quality of life (Tomotake, 2011), specifically by depression, negative symptoms and anxiety (Karow et al., 2005; Lambert et al., 2009a). Furthermore, adverse subjective well-being is related to high antipsychotic D₂ receptor occupancy above 60-70% (de Haan et al., 2000, 2003; Mizrahi et al., 2007) and antipsychotic side effects, particularly if they cause a high level of subjective distress (Schimmelmann et al., 2005). Subjective well-being at baseline, and especially its early improvement, are predictors of medication adherence (Karow et al., 2007) and of short- (Schennach-Wolff et al., 2011) and long-term (de Haan et al., 2008) symptomatic remission, as well as short- (Lambert et al., 2007, 2009b) and long-term (Lambert et al., 2009c) recovery outcomes.

Given the importance of subjective well-being and quality of life from a patient's point of view and its central position in the patient's recovery definition (Bellack, 2006; Resnick et al., 2005), it is surprising that we know of only three randomised controlled trials with antipsychotics to date that compare different antipsychotics with regard to subjective well-being or quality of life as the primary endpoint. Two of these trials compare the differential effectiveness of first- and second-generation antipsychotics (Jones et al., 2006; Silva de Lima et al., 2005) and one trial compares two second-generation antipsychotics (Naber et al., 2005; olanzapine versus clozapine in mostly treatment-resistant patients). To date, we know of no head-to-head randomised controlled trial comparing quetiapine with risperidone for subjective well-being.

As such, the present study was designed to assess the long-term subjective well-being of outpatients with schizophrenia, treated with either quetiapine XR or oral risperidone at a flexible dose in a naturalistic setting for a period of one year. Risperidone was chosen as the comparator in this study as it is a well-established oral antipsychotic, and it was hypothesised that comparable results in terms of

subjective well-being, quality of life, and effects on depressive symptoms would be observed for quetiapine XR versus risperidone.

2. Experimental procedure

2.1. Study design

The trial was a 12-month, randomised, prospective, parallel-group, open-label study (RECOVER; ClinicalTrials.gov identifier: NCT00600756), which consisted of a 1-day screening and randomisation phase and a 12-month treatment phase. Patients were randomised 1:1 to the treatment groups using an interactive voice response system. The first dose of study drug was to be administered on the day of randomisation.

2.2. Patients

Patients enrolled were male or female outpatients at centres in Europe, Brazil, Mexico or Costa Rica. Inclusion criteria comprised: age 18-65 years, a DSM-IV-TR diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder, and a certain level of reduced subjective well-being, defined by a Subjective Well-being under Neuroleptics treatment scale (SWN), short form (SWN-K; (Naber et al., 2001)) total score ≤ 75 points. Exclusion criteria encompassed a previous change of medication from quetiapine XR or risperidone due to a lack of tolerability or efficacy within the previous three months, receiving antidepressant or mood stabiliser treatment not at a stable dose for at least two weeks, unstable diabetes mellitus, pregnancy or lactation, evidence of clinically relevant disease, or high risk of suicide.

The use of concomitant antipsychotic therapy was not permitted throughout the study. Use of a selective serotonin reuptake inhibitor, serotonin noradrenaline reuptake inhibitor, or a mood stabiliser was permitted if it had been maintained at a stable dose for at least two weeks prior to enrolment; the use of other antidepressants was not allowed.

Patients (or their legally authorised representatives) provided written informed consent prior to initiation of any study-related procedures. The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonisation Good Clinical Practice Guidelines. The final study protocol was approved by an independent ethics committee.

2.3. Antipsychotic treatment

Eligible patients received either quetiapine XR once daily (day 1, 300 mg; day 2, 600 mg; day 3 and onwards, 400-800 mg) or risperidone at the recommended dose for Europe (day 1, 2 mg; day 2, 4 mg; day 3 and onwards, 2-6 mg). From day 3 onwards, the dose of either drug could be adjusted depending on clinical response and tolerability. Patients were offered study treatment from day 1 (baseline) to the end of month 12.

2.4. Assessments and measures

Subjective well-being was assessed using the SWN-K. The SWN was originally constructed as a 38-item self-report scale with 20 positive and 18 negative statements assessed on a six-point Likert scale

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