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Pregabalin for anxiety in patients with schizophrenia — A randomized, double-blind placebo-controlled study

Ole Schjerning [a,b,*], Per Damkier [c,d], Signe Engelhardt Lykkegaard [a], Klaus Damgaard Jakobsen [a,b], Jimmi Nielsen [a,b,e]

[a] Department of Psychiatry, Aalborg University Hospital, Aalborg, Denmark
[b] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[c] Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Denmark
[d] Institute of Clinical Research, University of Southern Denmark, Odense, Denmark
[e] Mental Health Centre Glostrup, University of Copenhagen, Copenhagen, Denmark

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ABSTRACT

Introduction: Anxiety is frequent in patients with schizophrenia and poses a major impact on patients perceived quality of life, daily functioning and risk of suicide. Pregabalin has shown effective in the treatment of generalized anxiety disorder and has been suggested for the treatment of anxiety in patients with schizophrenia. As evidence is sparse regarding treatment of anxiety in this patient group, we aimed to investigate the use of pregabalin for anxiety in patients with schizophrenia.

Methods: A randomized, double-blind placebo controlled study was used. Patients were randomized to either placebo or pregabalin (≤600 mg/d) as add-on treatment. Primary analyses were intention-to-treat based with change in Hamilton Anxiety Scale after 4 and 8 weeks of treatment as primary outcome. Secondary outcomes were change in psychopathology, quality-of-life, cognitive functioning and sleep. The study used centralized raters to increase accuracy and minimize baseline inflation.

Results: A total of 54 patients were included with 46 completing the study. Pregabalin reduced the HAM-A_6 score significantly compared to placebo and with a medium effect size 0.72 ($p = 0.01$). No significant between-group difference was found for the overall HAM-A_{14}. Most common side-effects were weight gain, dizziness, sedation and increased duration of sleep.

Conclusions: Although no effect was found on overall HAM-A_{14}, pregabalin might be effective in the treatment of psychic anxiety symptoms in patients with schizophrenia with a medium effect size.

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1. Introduction

Schizophrenia is a severe chronic mental disorder affecting approximately 0.5% of the population, with up to 10% of patients being institutionalized (Uggerby et al., 2011). Anxiety symptoms have been recognized as a core aspect of the psychopathology of schizophrenia (Kraepelin et al., 1919), but the diagnostic approach is inconsistent. Whether the anxiety symptoms in schizophrenia differ qualitatively from conventional anxiety disorders remains unclear (Bosanac and Castle, 2015), and the severity of anxiety may fluctuate with other symptoms throughout the course of the disease (Braga et al., 2013). Anxiety in schizophrenia is associated with increased risk of suicide, sleeping disturbances and reduced quality of life (Huppert et al., 2001). Benzodiazepines and antidepressants have been used to treat anxiety in patients with schizophrenia, although the evidence remain sparse (Braga et al., 2004). The use of benzodiazepines is controversial as these have been associated with increased mortality in patients with schizophrenia (Tiihonen et al., 2012). Pregabalin has been shown effective in generalized anxiety disorder (GAD) (Bech, 2007; Feltner et al., 2008) with efficacy comparable to lorazepam and venlafaxine, but with a more favorable cognitive profile than that seen with the benzodiazepines (Hindmarch et al., 2005). Pregabalin is not approved for the treatment of anxiety in schizophrenia, but it has been suggested that pregabalin may have a role as an "off label" add-on treatment for anxiety in schizophrenia (Englisch et al., 2010; Schonfeldt-Lecuona et al., 2009). As no randomized studies have been conducted so far, this study aimed to evaluate the efficacy and safety of pregabalin as add-on treatment for anxiety in patients with schizophrenia by using the Hamilton Anxiety Scale (HAM-A) as primary outcome.

2. Materials and methods

This investigator-initiated study was designed as a randomized, double-blind, placebo-controlled study. Patients were recruited from

* Corresponding author at: Aalborg University Hospital, Department of Psychiatry, Mølleparkvej 10, 9000 Aalborg, Denmark.
E-mail address: o.schjerning@rn.dk (O. Schjerning).

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different psychiatric outpatient clinics or psychiatric departments in all five regions of Denmark. Patients were randomized 1:1 to either placebo or pregabalin as add-on treatment. First patient was included at 5th of March 2012 and last patient ended the study at 15th of August 2016. The study was ended before sample size goal was met due to failure in accessing eligible patients. The decision to end the study was made by investigator.

2.1. Participants

Patients aged 18 to 65 years with a diagnosis of schizophrenia (ICD-10 research diagnostic criteria, F20.0 to F20.3 or F20.9) were included. Only patients without changes in primary psychopharmacologic treatment (antipsychotics, antidepressants and sedatives) for at least 4 weeks were included and all treatment other than study intervention were fixed during the study. Severity of anxiety symptoms was measured using the Hamilton Anxiety Scale (Hamilton, 1959) and only patients with a total score above 15 were included. To exclude anxiety secondary to acute psychosis or depression only patients with a Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987) score below 70 and a Calgary Depression Scale Score (CDSS) (Addington et al., 1990) below 10 were included. Exclusion criteria were significant substance abuse or dysregulated diabetes. Females were not included if they were pregnant or breastfeeding. Pregnancy test was performed at screening visit and all sexual active and fertile female patients used contraceptives throughout the study. Legal coercion according to the Danish psychiatric law and suicidal ideation were also cause for exclusion.

2.2. Ethics

All participants provided written informed consent to participation. This study was performed in accordance with the ICH-CGP guidelines and the Declaration of Helsinki. The Local Ethics Committee, the Danish Health Authority and the Danish Data Protection Agency approved the study.

2.3. Interventions

Pregabalin/placebo was initiated at 75 mg/d. After one week, dosage was increased to 150 mg/d and a flexible dosage regiment allowing weekly increments by 150 mg/d, up to a maximum of 600 mg/d — depending on effect and tolerability. Dosages ≥450 mg/d were divided in two doses. Compliance was calculated after 4 and 8 weeks.

2.4. Primary outcome

Primary outcome was change in severity of anxiety symptoms as measured by the HAM-A. The full scale is multidimensional and consists of 14 items measuring severity of anxiety (HAM-A_{14}) (Hamilton, 1969). It can be divided into two subscales covering two different factors; a psychic factor (items 1, 2, 3, 4, 5, 6 and 14) and a somatic factor (items 7, 8, 9, 10, 11, 12 and 13) (Hamilton, 1969). A shorter version of the scale, HAM-A_6 (items 1, 2, 3, 5, 7 and 14), has been found to cover the core items for anxiety state severity (Meoni et al., 2001) and later evaluation of the two scales psychometric validity found better scalability of the HAM-A_6 (Bech, 2007). All interviews were video recorded for deferred centralized rating. Recordings was censored for information that could un-blind raters, i.e. information regarding side-effects, study visit or treatment duration. Outcome assessment was based on the centralized ratings.

2.5. Secondary outcomes

Secondary outcomes were changes in psychopathology assessed by PANSS (Kay et al., 1987) and Clinical Global Impression — Severity Scale (CGI-S) and Improvement Scale (CGI-I) (Busner and Targum, 2007). PANSS data was analyzed as total PANSS score, positive subscale, negative subscale and general symptoms subscales (3-factor model). Ancillary analyses were made on PANSS data using the five-factor model as described by Marder et al (Marder et al., 1997). Quality of life was measured using the short version of the World Health Organization Quality of Life instrument (WHOQOL-BREF) (WHOQOL-Group, 1998). Quality of sleep was measured using the Leeds Sleep Evaluation Questionnaire (LSEQ) (Parrott and Hindmarch, 1980) and functioning by the Personal and Social Performance Scale (PSP) (Morosini et al., 2000). Tolerability was evaluated using the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale (Lingjaerde et al., 1987), sedation by a Visual Analog Scale (VAS) and akathisia using the Barnes Akathisia Rating Scale (BARS) (Barnes, 2003). Changes in cognitive functioning was measured using the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004). Adverse events were registered at any time they were reported by the patients. Patients were actively questioned about adverse events at weekly contacts per telephone and at the follow up visits after 4 weeks and 8 weeks. All participants had ECG and blood samples taken and blood pressure and body weight assessed at all three study visits.

2.6. Centralized rating

None of the three central raters had participated in any of the practical procedures during the study. All raters were trained in the use of the HAM-A scale prior to the rating of the study results. All interviews were rated by all three raters and mean values (integers) were used in the analysis of treatment efficacy.

2.7. Sample size

Power calculation was made using STATA 11 Corp. The assumptions were that mean baseline HAM-A_{14} was 23 ± 9. A clinically relevant change was a 5-point improvement and mean endpoint HAM-A_{14} was 18 ± 6. With these assumptions, a power of 80% would require 25 patients in each treatment group. A sample size of 35 in each treatment group was chosen to keep sufficient power with a drop-out rate of up to 30%.

2.8. Randomization and concealment

Randomization was done in blocks with variable block size (4, 6 and 8) to maintain an equal allocation of patients over time. Randomization sequence was generated by the Hospital Pharmacy, Aalborg University Hospital, Aalborg, Denmark. All research staff and patients were blinded to treatment allocation. Before treatment allocation was revealed, results of site-based HAM-A ratings, PANSS ratings, CGI and any censoring in video recordings were mailed to the Hospital Pharmacy. Treatment allocation was not revealed to central raters at any time during the rating process. Pregabalin capsules and placebo capsules were identical and provided by Pfizer Denmark.

2.9. Statistical methods

Data was entered in EPI-data using double entry by two different persons. Entry-files were compared electronically to avoid typing errors. Statistical analysis was performed using STATA version 14. Primary analysis was intention-to-treat (ITT) and secondarily as per protocol (PP). Missing data in the ITT-analysis was replaced as "Last Observation Carried Forward" (LOCF) and all patients receiving at least one dose of treatment medication was included in the ITT analysis. In the PP analysis, patients with a compliance < 70% were excluded and missing data was not replaced.

Data were assessed for normality using visual inspection. Logarithmic transformation was used when possible for variables not normally distributed. When transformation was not possible or not sufficient, data was tested with the Wilcoxon rank sum test. Effect size was

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