Psychiatry Research 258 (2017) 289–294

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Symptomatic remission in schizophrenia: Results from a risperidone maintenance treatment study

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ARTICLE INFO

Keywords:
Schizophrenia
Maintenance treatment
Antipsychotics
Risperidone
Remission
Relapse
PANSS

ABSTRACT

This study aimed to investigate remission following the treatment of schizophrenia patients with risperidone. Clinically stabilized patients with schizophrenia (n = 374) were randomly assigned to 4-week, 26-week, or no-dose-reduction groups, in which the baseline risperidone dose was continued for 4, 26, or all weeks during 1-year period. The 'Positive and Negative Syndrome Scale' (PANNS) was assessed at baseline and monthly for six months, followed by every two months until the last recruited patient completed 1-year follow-up. Symptomatic remission was defined according to criteria established by the Schizophrenia Working Group. A Generalized Linear Mixed Model indicated significant variation in remission over time, which increased after baseline in the entire group ($F = 49.32$, $df = 1, 3114$, $P < 0.001$). The overall length of risperidone treatment ($F = 4.34$, $df = 1, 416$, $P = 0.038$) and the duration of illness ($F = 8.51$, $df = 1, 359$, $P = 0.004$) had significantly negative effects upon remission. Baseline remission patients were associated with a significantly increased time to relapse compared with the baseline of non-remission patients over a one year follow up period ($F = 5.74$, $df = 1, 367$, $P = 0.017$). One-year risperidone maintenance treatment increased remission rates in schizophrenia. A shorter illness duration, risperidone treatment length, and a lower total PANSS score were clinically useful predictors of remission. Achieving remission may postpone relapse.

1. Introduction

Schizophrenia is characterized by a chronic and disabling disease course which requires long-term treatment for life. Remission is achievable and sustainable for a relatively substantial number of patients (Leucht et al., 2007). In 2005, the Remission in Schizophrenia Working Group (RSWG) recommended specific criteria and a rationale for the consensus of remission in schizophrenia (Andreasen et al., 2005). Symptomatic remission, a more uniform definition, may represent the stage of a treatment course previous to recovery, which can be regarded as a specific treatment goal (Kane and Correll, 2010; Liberman and Kopelowicz, 2002). In addition, symptomatic remission has been strongly associated with functional outcome (De Hert et al., 2007). In a validation study regarding remission criteria for schizophrenia, 145 patients met the symptomatic remission criterion at baseline compared with 172 patients who did not; moreover, the change over time in remission (median follow up: 1132 days) was associated with various functional outcomes (e.g., scores on the Global Assessment of Functioning Scale and the quality of life) (van Os et al., 2006). The remission of patients who met remission criteria was strongly correlated with good function; for example, an odds ratio of 13.2, and the proportions of remitters and non-remitters who exhibited good function at the five-year follow-up were 73% and 17%, respectively (Boden et al., 2009). Thus, remission is a particularly important long-term outcome measure and a specific treatment goal for schizophrenia.

The risperidone maintenance treatment in schizophrenia (RMTS) study was designed to investigate the duration of maintenance treatment required with the initial therapeutic dose compared with a reduced dose (Wang et al., 2010). The RMTS comprised a prospective, multi-center study which compared the 4-week, 26-week, and no-dose-reduction groups. The primary findings were that patients with no-dose-reduction had fewer relapses than those with dose reductions after 4 weeks or 26 weeks during maintenance treatment. The main results of

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http://dx.doi.org/10.1016/j.psychres.2017.08.068
Received 15 August 2016; Received in revised form 31 May 2017; Accepted 23 August 2017
Available online 24 August 2017
0165-1781/

the research were published in 2010 (Wang et al., 2010). However, this previous publication described initial analysis and did not specifically assess remission. The current study was specifically designed to investigate remission during the maintenance treatment of schizophrenia with risperidone. Our first aim was to compare the course of remission over time (i.e., a comparison of differences from baseline) in patient groups and identify potentially related factors. The second aim was to investigate relapse in patients with remission compared to those who were not in remission.

2. Methods

2.1. Design

This study was conducted between December 1st, 2002 and January 31st, 2005 at 19 mental health centers in China. The study was conducted in accordance with the guidelines of the International Conference on Harmonization for Good Clinical Practice, and our protocols were approved by the clinical research ethics committees of the respective study centers. Written informed consent was obtained from each participant prior to enrollment. A detailed description of this trial has been described in a previously published article (Wang et al., 2010). The main results of this trial were that patients who received the full risperidone dosage during an acute episode had fewer relapses than those who received a reduced dosage after 4 or 26 weeks during follow up.

2.2. Patients

We recruited suitable in- or outpatient adults (aged between 18 and 65 years) with a diagnosis of schizophrenia based upon the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) at study entry, who were clinically stable for at least 4 weeks but not more than 8 weeks following an acute episode. 'Clinical stability' was defined as a score of < 36 points on the Brief Psychiatric Rating Scale (BPRS), and patients were treated with risperidone monotherapy at an optimal dose (4–8 mg/day). Patients who fulfilled these inclusion criteria were randomly assigned to three groups using a computer-based central telephone randomization system: 4-week, 26-week, and no-dose-reduction groups. Patients were excluded from the study if they experienced any of the following conditions: relapse, pregnancy, a serious medical condition, or acute and intolerable extrapyramidal (EPS); these patients were subsequently treated as clinically appropriate. The rate of discontinuation of 1-year treatment for any reason, including relapse, was 34.4%, 33.3%, and 24.8% in the 4-week, 26-week, and no-dose-reduction groups, respectively.

2.3. Treatment

Patients were administered with the baseline risperidone dose for 4 weeks and 26 weeks in the 4-week and 26-week groups, respectively; the dose was then gradually reduced by 50% of the baseline dose over the subsequent 8 weeks and were then maintained until the end of the study. The patients in the no-dose-reduction group continued the baseline risperidone dose throughout the entire study. The study continued until the last recruited patient completed one year follow-up. No additional psychosocial interventions were adopted.

2.4. Assessments

All qualified raters were trained in the use of the clinical scales used herein. Relapse was defined according to the criteria of Csernansky et al. (2002) by any one of the following factors: psychiatric hospitalization; an increase in the level of psychiatric care and an increase of 25% from baseline in total score on the Positive and Negative Syndrome Scale (PANSS), 20 points, or an increase of 10 points, if the baseline score was 40 or less; deliberate self-injury; suicidal or homicidal ideation which was clinically significant in the investigator's judgment; violent behavior; or substantial clinical deterioration, defined as a change in score to 6 ("much worse") or 7 ("very much worse") on the Clinical Global Impressions Scale". Basic socio-demographic and clinical data were collected from each patient using a questionnaire which was specifically designed for this study. The BPRS was used as a screening tool at entry. The severity of the disease was evaluated using the Chinese version of PANSS (He and Zhang, 1997). An assessments were conducted at baseline and monthly for 6 months, followed by every two months until the last enrolled patient completed the study or at the time of relapse, discontinuation, or drop out. The pill count method was used to assess compliance (Wang et al., 2010).

2.5. Definition of remission

The RSWG proposed a consensus definition of remission for schizophrenia with operational criteria for its assessment (Andreasen et al., 2005). The RSWG criteria simultaneously require the achievement of a score of 3 (mild), 2 (minimal), or 1 (absent) for at least 6 months for eight items on the PANSS: P1 (delusions), P2 (concept disorganization), P3 (hallucinatory behavior), N1 (blunted affect), N4 (passive/apathetic social withdrawal), N6 (lack of spontaneity and flow of conversation), G5 (mannerisms and posturing) and G9 (unusual thought content). The present study used the RSWG criteria without the duration requirement. In the current study, remission was described by a dichotomous variable which depended on this criteria. Specifically, patients were considered to be in remission if they achieved the RSWG criteria, whereas patients were considered to be not in remission if they did not achieved the RSWG criteria.

2.6. Data analysis

All data were analyzed using SAS 9.2 (SAS Institute, Inc., Cary, N.C., USA) for Windows. Analyses were conducted in per-protocol sets. Data relating to drop outs were included in the analysis before they withdrew from the study. Comparisons of demographic and clinical characteristics between the remission patients who fulfilled the symptomatic remission criterion at baseline and the non-remission patients who did not fulfill the criterion at baseline were performed using Chi-square tests (or Fisher's exact tests) for categorical variables, and by analysis of variance (ANOVA) for continuous variables, as appropriate. To investigate the evolution of remission in the three study groups, a Generalized Linear Mixed Model (GLMM) (Molenberghs and Verbeke, 2005) was estimated using individual demographic variables including age, gender, education, age at onset, baseline values, time expressed in weeks, study groups, and study groups x time as fixed predictors. The risperidone dose and PANSS total score were added to the model as time-varying covariates. Remission was described by a binary variable which depended upon RSWG criteria. The model distribution of the response variable was binomial with a logit link function. The level of significance was set at 0.05 (two-tailed). As required, a Hochberg adjustment for multiple comparisons was also implemented (Hochberg, 1988).

3. Results

3.1. Demographic and clinical characteristics

Three hundred and seventy-four patients were included in this study. A baseline score for the eight PANSS items was obtained and used to define the state of remission at baseline. The baseline demographics and the clinical characteristics of the entire study cohort, as well as the comparisons among the three study groups are shown in Table 1. The rate of premature discontinuation of treatment for any reason other than relapse was 17.4% during the one year follow-up