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The effectiveness of ziprasidone in treating impaired quality of life in schizophrenia: A 12-month, open-label, flexible-dose, naturalistic observational study of patients undergoing usual care

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Abstract

Objective: Health related quality of life (HRQL) has become an important outcome measure in the treatment of psychiatric disorders. This long-term observational study examined ziprasidone-induced improvement in satisfaction with HRQL in schizophrenia patients treated under real-world conditions.
Method: Seventy schizophrenia patients with persistent symptoms or troublesome side effects were assigned to a 12-month, open-label, flexible-dose (40–160 mg/d), large-scale, naturalistic trial. Outcome measures were taken at baseline, 6, and 12 months, and included the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), severity of symptoms, distress, and side effects.
Results: Thirty-two patients fully completed the study protocol. Patients reported poorer general HRQL compared with healthy subjects. At the end of the study, significant improvement in general activity, and satisfaction with life was observed. The effect sizes for these changes were moderate (0.55, and 0.72, respectively). After Bonferroni correction for multiple comparisons improvement in satisfaction with general activity remained significant. No significant changes were noted in other Q-LES-Q dimensions. Improvement in general activity was associated with a reduction in the severity of symptoms and emotional distress, but was unrelated to the ziprasidone daily dose, side effect scores, and concomitantly prescribed antidepressants, anxiolytics, mood stabilizers, or antiparkinson drugs.
Conclusion: This study indicates that ziprasidone treatment resulted in the improvement of the satisfaction with general activity that tended to increase over time, from month 6 onwards. This effect was associated with reduction in the severity of clinical symptoms, and emotional distress.

Keywords: Naturalistic study; Quality of life; Schizophrenia; Ziprasidone

1. Introduction

Since health-related quality of life (HRQL) has become an important outcome measure in the treatment of psychiatric disorders, the pharmaceutical industry has been increasingly incorporating HRQL measures for assessment of efficacy in the drug development process. Although there is no universal operational definition of HRQL, most researchers agree that patients' statements regarding satisfaction with major life domains of daily functioning are relevant indicators of the subjective quality of life.

Ziprasidone is a novel second generation antipsychotic agent (SGA) with a unique human receptor binding profile: it has a high affinity for serotonin 5-HT_{2A} content, 5-HT_{1A} (where it

Abbreviations: DSAS, Distress Scale for Adverse Symptoms; ESRS, Extrapyramidal Symptom Rating Scale; FGAs, First-generation antipsychotic agents; GDI, General Distress Index; HRQL, Health-related quality of life; NAS, Number of Adverse Symptoms; PANSS, Positive and Negative Syndromes Scale; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; SGAs, Second-generation antipsychotic agents; SI, Symptoms' intensity; TBDI, Talbieh Brief Distress Inventory.

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acts as a partial agonist), 5-HT_{1D}, and 5-HT_{2C} receptors, and has moderate D_2 antagonism (Schmidt et al., 2001). Although ziprasidone improves positive, negative, and depressive symptoms in placebo-controlled trials (Goff et al., 1998; Allison et al., 1999; Daniel et al., 1999; Keck et al., 2001; Hirsch et al., 2002), the impact of ziprasidone therapy on HRQL improvement of chronic schizophrenia patients have not been established. To our knowledge, only two short-term studies attempted to assess changes in HRQL impairment among patients who received ziprasidone.

First, the study examined changes in HRQL scores for a 28-week, randomized, multicenter trial of patients with schizophrenia treated with olanzapine (10–20 mg/day) or ziprasidone (80–160 mg/day) (Phillips et al., 2006). The authors found nonsignificant improvement from baseline to the end of the study among patients of both treatment arms using two HRQL scales (the Medical Outcomes Study Short-Form 36-Item Health Survey, and the Quality of Life Scale). Second, Kudla et al. (2006) examined HRQL scores of 276 subjects (113 completers) with schizophrenia and schizoaffective disorder for an open-label, 12-week, prospective, flexible-dose observational trial of ziprasidone (40–160 mg/day) using the Short-Form 12-Item Health Survey (SF-12), and the Subjective Well-being under Neuroleptic treatment (SWN-K) questionnaire. Nonsignificant improvements were observed on both the SF-12 and SWN-K scales. Thus, these trials of ziprasidone-induced improvement of quality of life in two short-length samples were not substantiated.

Therefore, in response to these limitations, three questions were addressed in the present long-term study of chronic schizophrenia patients undergoing usual care. (1) Would improvement in HRQL deficit occur during 12-month ziprasidone treatment? (2) Does concomitant treatment influence HRQL impairment during the study period? (3) Are the changes in HRQL impairment related to or independent of changes in the severity of clinical symptoms, emotional distress, side effects, and ziprasidone daily dose?

2. Method

2.1. Study design

The study was a 12-month, open-labeled, flexible-dose, large-scale, naturalistic observational trial of chronic schizophrenia patients undergoing usual care but who require a change in their medication due to persistent symptoms or troublesome side effects. Data were gathered from February 2004 to September 2006. The present design enabled us to estimate the effectiveness of ziprasidone in a real-life setting with a flexible dosage regimen (40–160 mg per day). The trial included men and women aged 18–60 years. At screening, outpatients or inpatients were required to have a primary diagnosis of schizophrenia (DSM-IV), normal laboratory test results and normal ECG results, and to have negative results on a urine drug screen upon study entry.

Patients with primary DSM-IV axis I psychiatric disorders other than schizophrenia or DSM-IV-defined psychoactive substance abuse/dependence in the preceding 6 months were excluded. Exclusion criteria included systemic somatic illnesses, patients with known QTc interval-associated conditions, pregnancy, and lactation period. Patients whose depot neuroleptic medication had been discontinued were eligible only after an average dosing period had elapsed.

The design adhered to the Declaration of Helsinki and ICH/Good Clinical Practice guidelines. The Internal Review Board of Sha'ar Menashe Mental Health Center approved the study. Signed informed consent was obtained from the patients after the procedures, possible side effects, and the advantages of switching the medication to ziprasidone were explained to them.

2.2. Procedure

Patients were recruited via the case register and treatment had been initiated according to clinical indications as determined by the treating physician, which made discontinuation of previous treatment before enrolling patients in the trial. Data were collected over three visits: a baseline visit before starting ziprasidone therapy, after 6 months of treatment, and after 12 months of treatment. After screening and baseline assessments, patients were placed on oral ziprasidone. Fixed dosing regimens were used during the first week only: 40 mg b.i.d. on days 1 and 2, 60 mg b.i.d. on days 3–7. Thereafter the dosage was flexible, for example, between 40 and 160 mg per day during the study period. There were no restrictions on concomitant medications; they were allowed if deemed necessary (they were prohibited in the 24 h before cognitive testing). Patients could continue with ziprasidone as long as necessary, and decisions about medication changes were made by the attending physicians and their patients, as they occurred in usual practice.

2.3. Schizophrenia subjects

A total of 84 patients underwent screening for this study, but 14 subjects were excluded due to organic brain damage ($N=2$), comorbidity with substance dependence ($N=4$), and serious medical illness ($N=4$); 2 patients had low comprehension skills, and 2 patients refused to participate. The study was based on data from 70 subjects that met the DSM-IV criteria for a diagnosis of schizophrenia. There were 52 male subjects (74.3%), with a mean age of 35.2 years (SD=8.2; range=21–56 years); education was 11.4 (SD=2.4) years, age of onset was 23.6 (SD=7.0) years, age of first hospitalization was 24.5 (SD=7.0) years, the mean number of hospitalizations was 6.5 (SD=6.7), and the mean duration of illness was 11.6 (SD=7.9) years. Their diagnosis was paranoid ($N=56$), disorganized ($N=7$), residual type ($N=4$), undifferentiated ($N=2$), and catatonic ($N=1$) subtypes of schizophrenia. All patients were physically healthy, had undergone recent physical examinations, and had ECG, blood, and urine laboratory test results within the normal range.

2.4. Healthy subjects

The comparison group included 175 nurses' aides and practical nurses from Sha'ar Menashe hospital (Ritsner et al.,