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Efficacy and tolerability of olanzapine in the treatment of schizotypal personality disorder

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Abstract

Background: Few treatment studies of schizotypal personality disorder (SPD) have investigated the new, atypical antipsychotic drugs. This study examined the efficacy and tolerability of olanzapine, an atypical antipsychotic drug, in a series of patients with DSM-IV diagnosed schizotypal personality disorder. *Method*: This was a 26-week, open-label study with flexible dose design in 11 subjects with a diagnosis of schizotypal personality disorder based on Structured Clinical Interview for DSM-IV (SCID) and Personality Disorder Examination (PDE Journal of Psychiatric Disorders 1 (1987) 1). Subjects were treated with a low dose (average 9.32 mg/day) of olanzapine. Psychopathology was assessed at baseline and at the end of the study and analyzed with last observation carried forward analysis. *Results*: Patients showed significant improvements in psychosis and depression ratings, as well as in overall functioning. Olanzapine was well tolerated, though significant weight gain was observed. *Conclusion*: This study provides preliminary data regarding olanzapine efficacy and tolerability in schizotypal personality disorder subjects. These data need to be confirmed in larger controlled clinical trials.

Keywords: Efficacy; Tolerability; Olanzapine; Schizotypal personality disorder

1. Introduction

Schizotypal personality disorder (SPD), which affects 3–5% of population, is characterized by pervasive social and interpersonal deficits, and subtle, psychotic-like symptoms (Gunderson and Phillips, 1995). Observations that first-degree relatives of subjects with SPD have a higher risk for schizophrenia-related disorders (Baron et al., 1985; Siever et al., 1990b) suggests that SPD is a schizophrenia related disorder. Similarly, neurobiological markers such as deficits in prepulse inhibition, P50 suppression, and antisaccade paradigms reported in schizophrenic subjects are also observed in subjects with SPD (Cadenhead et al., 2002; Siever et al., 1990a). Patients with SPD also show many of the same cognitive deficits as seen in schizophrenia, though such deficits are less severe; deficits are seen in working memory, attention, and executive functioning (Park and McTigue, 1997). Additionally, up to 40% of patients with SPD may go on to develop schizophrenia as compared to about 1%

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in the general population (Fenton and McGlashan, 1989). Thus, both genetic, clinical and neurobehavioral data support the hypothesis that SPD may be a schizophrenia-spectrum disorder. This provides the rationale for treating SPD with antipsychotic drugs (APDs), similar to those used in the treatment of schizophrenia and related psychotic disorders.

Only a few studies have examined treatment of psychotic symptoms in subjects with SPD. All of these studies have employed low doses of high potency conventional APDs to avoid extra pyramidal symptoms (EPS) (Soloff et al., 1986, 1989; Stein, 1992). For example, in a predominantly SPD population, thiothixene clearly showed a greater efficacy as compared to placebo (Goldberg et al., 1986). Similarly, haloperidol was significantly effective in the treatment of mixed SPD and Borderline Personality Disorder (BPD) inpatient population (Soloff et al., 1986, 1989). In an open-label study with amoxapine (an atypical antidepressant with the neuroleptic metabolite, loxapine), BPD and SPD subjects were treated for 3 weeks and only subjects with SPD reported any beneficial effects (Jensen and Andersen, 1989).

Despite the fact that atypical APDs are replacing conventional APDs as a first line of treatment for psychotic disorders, few studies have investigated atypical APDs in the treatment of SPD. Clozapine has been clearly demonstrated to have significant superiority in treating psychotic symptoms in BPD subjects over conventional APDs (Frankenburg and Zanarini, 1993). However, since clozapine has a significant risk of agranulocytosis and lowering of the seizure threshold, the advent of newer and better-tolerated atypical APDs such as olanzapine has offered a fresh perspective in the treatment of personality disorders with psychotic symptoms. Olanzapine, like clozapine, has potent affinity for D_1, D_2, D_4, $5HT_{2a}$, $5HT_{2c}$, $5HT_3$, muscarinic, alpha$_1$-adrenergic, and histamine H_1 receptors (Bymaster et al., 1999), but unlike clozapine is not associated with agranulocytosis or lowering of the seizure threshold. Thus, olanzapine seemed to be a likely choice to be studied in the treatment of personality disorders. Indeed, olanzapine has been found to be effective in BPD (Frankenburg and Zanarini, 2001; Schulz et al., 1999). However, no study has examined the efficacy of olanzapine in SPD.

The purpose of this study was to examine the effectiveness and safety of low-dose olanzapine in 11 subjects with SPD and to find the optimal dosing range for olanzapine to design a placebo-controlled, double-blind trial as the next step in this investigation. In addition, the relative benefits and tolerability of olanzapine in the treatment of SPD was assessed in view of the safety issues, such as weight gain and metabolic syndrome associated with the use of atypical APDs.

2. Methods

2.1. Subjects

A series of 11 subjects diagnosed with SPD based on Structured Clinical Interview for DSM-IV (SCID) were recruited from consecutive outpatients at the Western Psychiatric Institute and Clinic (WPIC). We also approached participants in another ongoing study of cognitive function in SPD (Ruth Condray Principal Investigator). All study subjects were Caucasian with an average age of 39.4 ± 10.1 (range: 22–50 years) and included eight males and three females. Since subjects with SPD rarely present themselves for clinical care, some patients had comorbid diagnoses (psychotic disorder not otherwise specified, $n=1$; bipolar disorder type II, $n=1$). For the same reason, the study sample also was somewhat more severely ill than might be expected in a pure SPD sample (mean GAS score of 45.6). However, subjects diagnosed with schizophrenia or schizoaffective disorder based on SCID were excluded from the study. In addition, none of the subjects had ever received neuroleptic treatment for SPD. Other exclusion criteria were the presence of significant medical or neurological illness, mental retardation, and pregnancy or lactation.

2.2. Treatment

Following baseline assessments, the subjects ($n=11$) were started on olanzapine. The initial olanzapine doses were 2.5 or 5 mg/day (average 3.40 ± 1.26 mg/day), increased by 2.5 mg/day at weekly intervals, and increments up to a final dose of 2.5–12.5 mg (average 9.32 ± 2.75 mg/day).