Available online at www.sciencedirect.com
ScienceDirect
Progress in Neuro-Psychopharmacology & Biological Psychiatry 31 (2007) 1464–1469
Progress In Neuro-Psychopharmacology & Biological Psychiatry
www.elsevier.com/locate/pnpbp

Quetiapine as monotherapy for social anxiety disorder: A placebo-controlled study

Sandeep Vaishnavi *, Syed Alamy, Wei Zhang, Kathryn M. Connor, Jonathan R.T. Davidson

Duke University Medical Center, Department of Psychiatry, Room 4082A, Duke South, Yellow Zone, Durham, NC 27710, USA

Received 1 November 2006; received in revised form 21 June 2007; accepted 22 June 2007
Available online 4 July 2007

Abstract

Social anxiety disorder (SAD) is one of the most common anxiety disorders. Reports have suggested an effect of the atypical antipsychotic quetiapine in anxiety disorders. Given these considerations, we conducted a controlled trial of quetiapine monotherapy in SAD. Fifteen patients were randomized to quetiapine (up to 400 mg/day) or placebo for 8 weeks. The Brief Social Phobia Scale (BSPS) and the Clinical Global Impression of Improvement Scale (CGI-I) were the primary outcome measures, while the Social Phobia Inventory (SPIN) and the Sheehan Disability Inventory (SDI) were secondary measures. There was no significant difference on the BSPS score at endpoint between the quetiapine and placebo groups. There was a significant time effect but not a significant time × treatment group interaction, indicating that both the quetiapine and placebo patients did better over the course of the trial. 20% of the quetiapine patients had a 50% or greater drop in BSPS score at the end of the trial compared to baseline, while 0% had such a drop in the placebo group. There was no significant difference in responders (CGI-I score of 1 or 2) versus non-responder (CGI-I score of 3 or more) across the groups. However, 40% of quetiapine patients and 0% of the placebo patients showed much or very much improvement on the CGI-I. The Number Needed to Treat (NNT) to be a responder on the CGI-I was 3. Significant time effects were noted for the SPIN and SDI, as well as a significant time × treatment effect in favor of quetiapine on the SPIN. Additionally, quetiapine showed a large effect size on the SPIN.

Keywords: Anxiety disorders; Atypical antipsychotics; Social phobia

1. Introduction

Social anxiety disorder (SAD) is characterized by overwhelming fear and avoidance of social or performance situations. It is one of the most common anxiety disorders (Magee et al., 1996) and the third most common psychiatric disorder in the United States, with a lifetime prevalence of up to 16% in the general population (Hidalgo et al., 2001).

The disorder typically begins in adolescence and has a lifelong course (Kessler et al., 1998; Schneier et al., 1992). Socioeconomic disadvantages, impaired quality of life, and decreased treatment seeking are common among patients with SAD (Gross et al., 2005). In addition, high rates of comorbidity with other psychiatric disorders including depression and alcohol abuse, as well as general medical illnesses, are frequently reported (Stein et al., 1998).

There are data from controlled trials that show paroxetine (Stein et al., 1998), fluvoxamine (Stein et al., 1999), sertraline (Van Ameringen et al., 2001), phenelzine (Gelernter et al., 1991), moclobemide (Davidson et al., 1993), alprazolam (Gelernter et al., 1991), clonazepam (Davidson et al., 1993), and gabapentin (Pande et al., 1999) as well as cognitive behavioral therapy (CBT) (Heimberg et al., 1998) have some efficacy for treatment of SAD. Current preferred treatments

Abbreviations: SAD, Social Anxiety Disorder; BSPS, Brief Social Phobia Scale; CGI-I, Clinical Global Impression of Improvement Scale; CGI-S, Clinical Global Impression Severity Scale; SPIN, Social Phobia Inventory; SDI, Sheehan Disability Inventory; NNT, Number Needed to Treat; CBT, Cognitive Behavioral Therapy; SSRIs, Selective Serotonin Reuptake Inhibitors; PTSD, Posttraumatic Stress Disorder; OCD, Obsessive Compulsive Disorder; MINI, Mini International Neuropsychiatric Interview; ANOVA, Analysis of Variance; ES, Effect Size.

* Corresponding author. Current address: Johns Hopkins Hospital, 550 N. Broadway, Suite 308, Baltimore, MD 21205, USA.
E-mail address: sandeep.vaishnavi@gmail.com (S. Vaishnavi).

0278-5846/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2007.06.027

include CBT and the use of selective serotonin reuptake inhibitors (SSRIs) (Davidson et al., 2004). However, response rates leave much room for improvement. One meta-analysis shows a moderate mean SSRI effect size of 0.65 (Blanco et al., 2003). Meta-analyses with CBT also show a moderate mean effect size of 0.72 (Rodebaugh et al., 2004). One direct blinded comparison of fluoxetine, CBT, combination therapy, and placebo found a maximal response rate of 54% for active treatment, compared to 32% for placebo (Davidson et al., 2004). Overall, the response of SAD to available treatments is modest, with considerable symptom residue and low rates of remission.

There is clearly a need for additional therapies for SAD. Atypical antipsychotics have shown some evidence for efficacy in anxiety symptoms in schizophrenia (Tollefson et al., 1998). Additionally, these agents have now been evaluated for treatment of anxiety disorders such as posttraumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD) (Atmaca et al., 2002). There is also evidence to suggest patients with SAD have lower dopaminergic D2 receptor binding potential (Schneier et al., 2000) and decreased dopaminergic reuptake site densities in the striatum (Tiihonen et al., 1997). As such, antidopaminergic agents (such as antipsychotics) may potentially be useful in SAD. To our knowledge, one controlled pilot study has shown some efficacy for atypical antipsychotic monotherapy, with olanzapine, for SAD (Barnett et al., 2002).

Quetiapine is an atypical antipsychotic with greater serotinergic than dopaminergic effects; quetiapine acts on 5HT2A, 5HT6, 5HT7, H1, alpha-1, alpha-2, and D2 receptors (Stahl, 2000). It has reported anxiolytic properties; one study has found quetiapine to be effective against anxiety in long-term treatment of patients with schizophrenia (Kashmper, 2004) while another showed significant improvement in anxiety with bipolar patients (Calabrese et al., 2005). There is one open-label trial supporting the use of quetiapine in SAD that we are aware of (Schutters et al., 2005).

To our knowledge, there are no controlled studies of quetiapine as monotherapy for SAD. Our purpose was to study quetiapine in a double-blind, placebo-controlled pilot trial for SAD. The primary hypothesis is that monotherapy with quetiapine will be more effective than placebo in decreasing symptoms of SAD.

2. Methods

2.1. Study design

This was an eight week, randomized, double-blind, placebo-controlled treatment trial of SAD with quetiapine (50–400 mg/day) or matching placebo. Patients were recruited by advertisements in the local media. No attempt was made to recruit patients with any particular treatment history for SAD (either successful treatment history or treatment resistance). Patients were assessed for eligibility at a screening visit, with eligible patients returning for a baseline assessment in approximately 1 week, at which time they were randomized 2:1 to either quetiapine (10 patients) or placebo (5 patients); this was done by utilizing a computer code generated by a study statistician who did not have contact with subjects. Patients were then evaluated at weeks 1, 3, 5, and 8, for a total of 6 study visits (including screening and baseline visits).

2.2. Patient population

The inclusion criteria were as follows: (1) adult outpatients 18–65 years of age, (2) a primary diagnosis of SAD using DSM-IV criteria, (3) a minimum Clinical Global Impression Severity score (CGI-S) (Guy, 1976) of 4 and minimum Brief Social Phobia Scale (BSPS) (Davidson et al., 1997) score of 20 at baseline, (4) written informed consent, and (5) a negative serum pregnancy test for women of childbearing potential.

The exclusion criteria were as follows: (1) current DSM IV diagnosis of bipolar disorder, schizophrenia or other psychotic disorder, mental retardation or other pervasive developmental disorder, or cognitive disorder due to a general medical condition, (2) any current primary anxiety disorder other than SAD, (3) current primary diagnosis of major depressive disorder, (4) history of substance abuse or dependence within the last 6 months, (5) suicidal risk or serious suicide attempt within the last year, (6) clinically significant medical condition or laboratory abnormality, (7) women of childbearing potential who are unwilling to practice an acceptable method of contraception, (8) concomitant use of medication with psychotropic effects, and (9) history of hypersensitivity to quetiapine.

2.3. Assessment instruments

At screening, patients underwent a psychiatric and medical assessment, including a structured diagnostic interview (MINI, Mini International Neuropsychiatric Interview) (Sheehan et al., 1989) and a clinical examination. Other assessments included the BSPS, Clinical Global Impression of Severity (CGI-S) and improvement (CGI-I); the BSPS and CGI-I were the primary outcome measures. Self-ratings included the Social Phobia Inventory (SPIN) (Connor et al., 2000), and Sheehan Disability Inventory (SDI) (Leon et al., 1992). Safety was assessed by the inquiry of "has anything changed since last visit?," the SOSS (Severity of Symptoms Scale) (Connor et al., 2001), the Barnes Akathisia Scale (BAS) (Barnes, 1989), and the Simpson–Angus Scale (SAS) (Simpson and Angus, 1970). In addition, vital

Table 1
Demographic characteristics of study population

Demographic characteristics	Total (n=15)
Gender [n(%)]	
Male	7(46.7)
Female	8(53.3)
Ethnicity [n(%)]	
White	10(66.7)
Non-white	5(33.3)
Marital status [n(%)]	
Married	8(53.3)
Not married	7(46.7)
Age (years, mean±SD)	32.93±8.64