Drug and Alcohol Dependence 149 (2015) 18–24

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Quetiapine for the treatment of cocaine use disorder

Andre Tapp[a,*], Amanda Ernst Wood[b], Annette Kennedy[c], Patrick Sylvers[b], Nael Kilzieh[b], Andrew J. Saxon[b]

[a] VA Puget Sound Health Care System, American Lake Division (A-116), University of Washington, 9600 Veterans Drive SW, Tacoma, WA 98493, United States
[b] VA Puget Sound Health Care System, University of Washington, Tacoma, WA, United States
[c] Sheridan VAMC, University of Wyoming, Laramie, WY, United States

ARTICLE INFO

Article history:
Received 13 June 2014
Received in revised form
18 December 2014
Accepted 20 December 2014
Available online 27 January 2015

Keywords:
Cocaine use disorder
Quetiapine
Treatment trial

ABSTRACT

Background: Cocaine addiction continues to be a significant healthcare issue, yet there are no FDA approved medications for the treatment of cocaine use disorder within the United States.
Methods: This 12-week, prospective, double-blind, randomized, placebo-controlled study examined the effectiveness of quetiapine (Seroquel XR™) versus matched placebo for the treatment of DSM-IV cocaine dependence in non-psychotic individuals. Subjects randomized to quetiapine ($N = 29$) were titrated up to a target dose of 400 mg/day of quetiapine, while those in the placebo arm ($N = 31$) were given a matched placebo. All subjects had weekly clinic visits and a cognitive-behavioral therapy group session. Outcome measures included self-report of cocaine use and money spent on cocaine as well as urine drug screens (UDS).
Results: The drop-out rate was substantial at 68%. Logistic regression analysis did not find significant differences between groups in predicting end-of trial abstinence, defined as three consecutive weekly negative UDS (13.7% in the quetiapine group versus 12.9% in the placebo group; $p = .92$). Based upon a repeated measures analysis of variance, subjects in this study, as a whole, demonstrated reductions in their self-reported use of cocaine, self-reported money spent on cocaine, and number of days per week using cocaine. However, the quetiapine group did not differ significantly from the placebo group.
Conclusions: This study did not find group differences between the quetiapine and placebo arms, suggesting that quetiapine is not an efficacious treatment for DSM-IV cocaine dependence.
Published by Elsevier Ireland Ltd.

1. Introduction

Cocaine use in the United States is a significant public health concern, leading to loss of income, use of public services, and mortality. The results from the 2012 National Survey on Drug Use and Health (2013) shows that 1.6 million Americans aged 12 or older were current cocaine users (including crack cocaine), comprising .6% of the population. Despite this widespread use, there are currently no approved medications for the treatment of cocaine use disorder.

Numerous psychoactive compounds, including dopamine agonists (such as psychostimulants which, like cocaine, block monoamine neurotransmitter transporters), dopamine antagonists, antidepressants, and mood stabilizers have undergone study for the treatment of cocaine use disorder. A variety of agents have shown promise in open-label trials, but few have shown efficacy in randomized controlled trials (de Lima et al., 2002; Elkashef et al., 2005). Agents that have shown some initial efficacy in randomized, controlled trials are propranolol (Elkashef et al., 2005; Kampman et al., 2001), baclofen (Shoptaw et al., 2003), and vigabatrin (Brodie et al., 2009; Somoza et al., 2013). Topiramate has had some mixed results with some studies demonstrating efficacy (Johnson et al., 2013; Kampman et al., 2004; Kampman et al, 2013) including a study in which topiramate was combined with mixed amphetamine salts (Mariani et al., 2012). Cochrane database systematic reviews have not found support for the use of dopamine agonists for the treatment of cocaine dependence (Amato et al., 2011), and have found mixed results for the efficacy of psychostimulant medications for cocaine dependence (Castells et al., 2010), with some studies finding reductions in cocaine use (Grabowski et al., 2001; Mariani and Levin, 2012; Mooney et al., 2009), and other studies finding no benefit to psychostimulants (Schmitz et al., 2012).

Since dopaminergic and serotonergic receptors may be involved in the reinforcing effects of cocaine, medications such as

* Corresponding author. Tel.: +1 253 583 2705.
E-mail address: Andre.Tapp@va.gov (A. Tapp).

http://dx.doi.org/10.1016/j.drugalcdep.2014.12.037
0376-8716/Published by Elsevier Ireland Ltd.

second generation antipsychotics that block dopamine and serotonin receptors may reduce the rewarding effects of cocaine and thus lessen cravings for cocaine. Animal studies have given support to this hypothesis (Meil and Schechter, 1997; Sorensen, 2008). Specifically, quetiapine was shown to block the reward enhancing effect of cocaine in rats (Gallo, 2010).

The research on the use of atypical antipsychotics to treat cocaine use disorder in non-psychotic individuals has reported mixed results. In cocaine challenge studies examining pretreatment with clozapine (Farren et al., 2000) and risperidone (De La Garza et al., 2005; Newton et al., 2001), results indicated the antipsychotics reduced the euphoria associated with administration of cocaine, and risperidone also reduced cravings triggered by cocaine challenge (De La Garza et al., 2005). Furthermore, in open-label trials, treatment with risperidone was found to significantly reduce cocaine cravings in non-psychotic, cocaine users (Roy et al., 1998; Smelson et al., 1997). A 20-week study of 80 patients with cocaine or methamphetamine use disorder prescribed either olanzapine or risperidone found that both medication groups had decreased drug cravings (Nejtek et al., 2008). However, two double-blind, placebo-controlled studies of risperidone for the treatment of cocaine use disorder did not find significant reductions in cocaine cravings or use (Grabowski et al., 2000; Smelson et al., 2004).

Likewise, three double-blind, placebo-controlled studies that have evaluated the efficacy of olanzapine for the treatment of cocaine use disorder did not yield positive results (Hamilton, 2009; Kampman et al., 2003; Reid et al., 2005). Studies of aripiprazole have also been mixed. A 12-week randomized trial of aripiprazole and ropinirole found that aripiprazole was effective in reducing cocaine use (Meini, 2011). However, in a human laboratory study, aripiprazole was found to actually increase self-administration of smoked cocaine (Haney et al., 2011). A meta-analysis of randomized, placebo-controlled trials of antipsychotics for cocaine or psychostimulant dependence, did not find advantages of the antipsychotics over placebo, but quetiapine was not one of the antipsychotic medications studied (Kishi et al., 2013).

Differences in mechanisms of action may render certain atypical antipsychotics more effective and safer than others for the treatment of cocaine use disorder. Theoretically, quetiapine's relatively high affinity for both alpha1 and alpha2 adrenergic receptors (Richelson and Souder, 2000) may yield improvements in mood symptoms associated with cocaine use. Three retrospective chart reviews have found reductions in cravings and alcohol use associated with quetiapine (Monnelly et al., 2004; Pinkofsky et al., 2005; Sattar et al., 2004), however, a double-blind, placebo-controlled trial of quetiapine for alcohol dependence found no significant differences between the quetiapine and placebo groups (Litten et al., 2012).

Brown et al. (2002) found a significant decrease in subjects' cocaine cravings and an 87% reduction in the amount of money spent on cocaine in 17 outpatients with bipolar disorder and cocaine dependence who were treated with quetiapine; however, a follow-up study of 12 individuals with bipolar disorder and cocaine dependence was non-significant. Another open-label trial of quetiapine in individuals with schizophrenia found that quetiapine was associated with reductions in cocaine use (Potvin et al., 2006). Finally, our own open-label trial (Kennedy et al., 2008) examined quetiapine in 22 non-psychotic subjects with cocaine dependence over six weeks of treatment. Results found that cravings for cocaine decreased significantly over time ($\beta = -.54$; 95% CI = −.81, −.28; $p < .001$). A decrease in the number of grams of cocaine used was not statistically significant in the group of completers, but showed a trend toward significance ($\beta = -.12$; 95% CI = −.24, .01; $p = .063$). The results from this pilot study suggested that quetiapine effectively reduced cocaine cravings in non-psychotic individuals suffering cocaine use disorder.

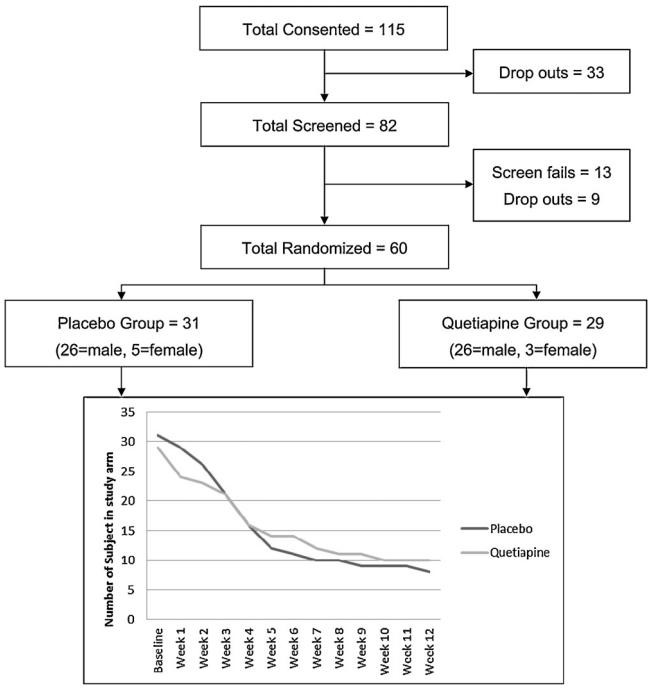

Fig. 1. Subject flow and drop-out rates.

To further investigate the hypothesis that quetiapine is efficacious for the treatment of cocaine use disorder, the authors conducted this randomized, double-blind, placebo-controlled trial to test the effectiveness of Seroquel XR™ for the treatment of cocaine use disorder in non-psychotic, community dwelling individuals. The primary objective of this study was to compare cocaine use and cravings between the quetiapine and placebo groups, leading to three hypotheses.

1.1. Hypotheses

Hypothesis 1: The quetiapine group will have significantly more individuals who demonstrate end of trial abstinence from cocaine (defined as a negative urine drug screen for three consecutive weeks) than the placebo group.

Hypothesis 2: The quetiapine group will demonstrate significantly less cocaine use and money spent on cocaine as measured by a self-report measure than the placebo group.

Hypothesis 3: The quetiapine group will have significantly more individuals who demonstrate end of trial absence of cravings (defined as a negative self-report of cravings for three consecutive weeks) than the placebo group.

2. Methods

2.1. Participants

Participants were both Veteran and non-Veteran community participants, aged 18 to 65, who were currently (within the past 30 days) using cocaine. Potential subjects with a psychotic disorder (bipolar, schizophrenia, etc.) or who were psychiatrically or medically unstable were excluded from the study, as were women who were pregnant or nursing. Since these data were collected prior to the publication of the DSM-5, all participants met criteria for cocaine dependence, as determined by administering the Structured Clinical Interview for DSM-IV-TR Axis I (SCID-I/P) during screening. All subjects provided written informed consent and were provided HIPAA information.

Of the 115 subjects who were consented, 33 dropped out before the first screening visit. A total of 82 subjects were screened, of which 14 were screen fails, 9 dropped out, and 60 were randomized to either quetiapine ($N = 29$) or to matched placebo ($N = 31$; see Fig. 1). The quetiapine group had 26 males and 3 females, while the placebo group had 26 males and 5 females. Average number of years of cocaine use was 19.6 for the placebo group and 20.7 for the quetiapine group, indicating