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Antidepressant efficacy of olanzapine as monotherapy in major depressive disorder, without psychosis: A pilot study☆

Jose Mathews[a], Keith S. Garcia[a], Mark A. Mintun[a,b], Yvette I. Sheline[a,b,*]

[a]Department of Psychiatry, Washington University School of Medicine, Box 8134, 660 S. Euclid, St. Louis, MO 63110, USA
[b]Department of Radiology, Washington University School of Medicine, St. Louis, MO, USA

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Abstract

In this pilot study we assessed the efficacy of olanzapine as monotherapy in the treatment of major depressive disorder, without psychosis. We also demonstrated the in vivo 5-HT_{2A} receptor occupancy of olanzapine using positron emission tomography. An open-label prospective 6-week study design with 14 patients who met the inclusion and exclusion criteria for the study were enrolled from the general community of the St. Louis metropolitan area. All patients met DSM-IV criteria for major depressive disorder without psychosis, had a Hamilton Depression Rating Scale ($HAMD_{17}$) score >18 and were between the ages of 18 and 65. The primary measure of efficacy was the change in HAMD 17 total score from baseline to endpoint. The data were collected between 1998 and 2004. There was a significant reduction in the $HAMD_{17}$ scores from baseline to endpoint. Half the patients ($n=6$) showed ≥50% reduction in their $HAMD_{17}$ scores. This study points to the potential of olanzapine as a therapeutic agent for the treatment of major depressive disorder without psychosis.

Keywords: Antidepressants; 5-HT_{2A} receptors; Neuroimaging; Positron emission tomography

1. Introduction

There is evidence from schizophrenia trials that olanzapine has significant effects on mood. A recent review of the published literature on the efficacy of atypical antipsychotic agents in the treatment of depression, hostility, and suicidality in patients with schizophrenia suggested that olanzapine may have an antidepressant effect and may reduce suicidality in patients with schizophrenia (Keck et al., 2000). There is also evidence for its use as an augmentation agent for the treatment of treatment-resistant major depression (Ghaemi et al., 2000; Shelton et al., 2001; Parker, 2002).

Olanzapine has also been shown to be effective in the treatment of psychotic depression in open label studies and case reports (Nelson et al., 2001; Schatzberg, 2003). In the pivotal study comparing the efficacy of olanzapine and an olanzapine–fluoxetine combination in the treatment of bipolar I depression, the olanzapine alone group showed statistically significant improvement in depressive symptoms versus the placebo group (Tohen et al., 2003). These studies hint at a possible antidepressant action of olanzapine, although

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* Corresponding author. Department of Psychiatry, Washington University School of Medicine, Box 8134, 660 S. Euclid, St. Louis, MO 63110, USA. Tel.: +1 314 362 8422; fax: +1 314 362 7599.
E-mail address: yvette@npg.wustl.edu (Y.I. Sheline).

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the question of whether olanzapine has any antidepressant effect in patients with unipolar major depression remains unanswered. There is also a dearth of literature looking at the efficacy of olanzapine in the treatment of unipolar depression as the sole agent in patients without psychosis. This pilot study tries to address the possibility of olanzapine as a monotherapy for unipolar major depression.

The pharmacokinetic profile of olanzapine shows potent 5-HT_{2A} receptor antagonism (Zhang and Bymaster, 1999); which may account for its antidepressant effects. Abnormalities in the 5-HT_{2A} receptor have been reported in patients with depression and are likely indicative of altered serotonergic function (Mann et al., 1986; Arango et al., 1992). Selective antagonism of the 5-HT_{2A} receptor with EMD 281014 showed significant increases in swimming and decreased immobility in the forced swim test paradigm in rats with congenital learned helplessness, an animal model for depression (Patel et al., 2004). Clinical studies have shown significant antidepressant properties for drugs such as mirtazapine (De Boer et al., 1995), nefazadone (Meyer et al., 1999) and trazadone (Fiorella et al., 1995) that have prominent 5-HT_{2A} receptor antagonism.

This pilot study looks at the efficacy of olanzapine as monotherapy for the treatment of major depressive disorder without psychosis to test the hypothesis that olanzapine has antidepressant efficacy for the treatment of unipolar major depressive disorder. Positron emission tomography (PET) is a powerful tool to study in vivo human brain receptor occupancy. The radio-ligand [^{18}F]altanserin is a high affinity, selective agent for imaging 5-HT_{2A} receptors (Lemaire et al., 1991) with reliable and established effects in in vivo human brain imaging (Mintun et al., 2004). A quantitative receptor binding study was done using [^{18}F]altanserin to demonstrate in vivo 5-HT_{2A} receptor occupancy of olanzapine at a clinically relevant dose, and it may be this property of olanzapine that contributes to antidepressant efficacy.

2. Methods

2.1. Study design

Fourteen patients who met the inclusion and exclusion criteria for the study were enrolled after giving informed consent. The study was designed as an open-label, prospective, 6-week trial with the primary objective of assessing the efficacy of olanzapine as an antidepressant medication in patients with major depressive disorder. All patients had a washout period of at least five antidepressant half-lives rather than a fixed time interval. This was felt to be a better way to control for antidepressant medication such as fluoxetine, with a long half-life and the longest half-life medication was used to establish a washout period when a patient was on multiple medications. Patients were started on olanzapine 2.5 mg and titrated up according to clinical response, with a maximal daily dose of 20 mg. Adjunctive use of lorazepam was permitted up to 1 mg/day for treatment of insomnia, although it was not used in any of the patients in this study. No other psychotropic medication use was permitted during the course of study. A quantitative 5-HT_{2A} receptor binding study was done using positron emission tomography and [^{18}F]altanserin to measure regional 5-HT_{2A} receptor binding in the brain. Regions of interest were determined as previously described (Sheline et al., 2002) using ANALYZE software to trace boundaries and apply these regions (see Fig. 4) to individual datasets in Talairach atlas coordinates. The PET image data were collected and processed from one patient using imaging methods described in Mintun et al. (2004).

2.2. Patients

All patients were between the ages of 18 and 65. They met DSM-IV criteria for unipolar major depressive disorder with a score on the 17-item version of the Hamilton Rating Scale for Depression ($HAMD_{17}$) (Hamilton, 1960) of $\geq$18. Participants were recruited from the general community of the St. Louis metropolitan area through advertisements and the Volunteer for Health program at the Barnes Jewish Hospital. The demographic characteristics are listed in Table 1. Diagnoses were confirmed by a psychiatrist through structured clinical interview. Exclusion criteria included a previous trial of olanzapine, diagnosis of schizophrenia, diagnosis of bipolar disorder, acute co-morbid medical

Table 1
Demographic data

Demographics		
$N=14$	Mean	S.D.
Age (years)	47.4	14.1
Gender (m, f)	5, 9	
Race		
Caucasian	10	
African American	2	
American Indian/Alaskan Indian	1	
Unknown	1	