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Journal of Affective Disorders 115 (2009) 234–240

Journal of Affective Disorders

www.elsevier.com/locate/jad

Preliminary communication

Does tachyphylaxis occur after repeated antidepressant exposure in patients with Bipolar II major depressive episode?

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Received 6 March 2008; received in revised form 2 July 2008; accepted 7 July 2008
Available online 9 August 2008

Abstract

Objective: Tachyphylaxis often refers to the loss of antidepressant efficacy during long-term treatment. However, it may also refer to the gradual loss of efficacy after repeated antidepressant exposures over time. The aim of this study was to examine the phenomenon of tachyphylaxis in patients with Bipolar II major depression treated with either venlafaxine or lithium. We hypothesized that a greater number of prior antidepressant exposures would result in a reduced response to venlafaxine, but not lithium, therapy.
Methods: 83 patients were randomized to treatment with either venlafaxine ($n=43$) or lithium ($n=40$). The primary outcome was a $\geq 50\%$ reduction in baseline Hamilton Depression Rating score. A detailed history of prior drug therapy was obtained. Logistic regression was used to test the hypothesis that prior antidepressant exposure was associated with reduced response to venlafaxine therapy.
Results: The mean number of prior antidepressant and mood stabilizer exposures was significantly higher in venlafaxine non-responders versus responders ($p=0.02$). There was no significant association between response to lithium and the number of prior antidepressant and mood stabilizer exposures ($p=0.38$). The odds of responding to venlafaxine or lithium therapy decreased with an increasing number of prior antidepressant exposures ($p=0.04$). Response was not significantly affected by the number of prior mood stabilizer exposures ($p=0.30$). Adjustment for clinical and demographic covariates sharpened the estimated impact of prior antidepressant exposure on treatment outcome.
Limitations: This study was a *post hoc* exploratory analysis. The study was not specifically powered to test the hypothesis of an association between number of prior antidepressant drug exposures and response to venlafaxine or lithium therapy.
Conclusion: These observations support earlier findings suggesting the presence of tachyphylaxis occurring after repeated antidepressant drug exposures. Possible mechanisms of tachyphylaxis may include genetic predisposition for non-response, physiological adaptation after repeated antidepressant exposures, and inherent illness and pharmacokinetic heterogeneity.

Keywords: Tachyphylaxis; Tolerance; Antidepressant; Mood stabilizer; Treatment resistant depression; Bipolar II disorder

1. Introduction

Tachyphylaxis generally refers to the loss of antidepressant efficacy during long-term therapy (Sharma, 2001; Fava, 2003). However, it may also refer to the gradual loss of efficacy after repeated antidepressant

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doi:10.1016/j.jad.2008.07.007

exposures over time (Amsterdam et al., 1994; Amsterdam and Shults, 2005; Leykin et al., 2007). While tachyphylaxis during long-term therapy may occur in 25–50% of patients (Posternak and Zimmerman, 2005; Solomon et al., 2005; Thase, 2006), tachyphylaxis after repeated antidepressant exposure may occur at a rate of 20% to 30% with each prior antidepressant exposure (Amsterdam et al., 1994; Amsterdam and Shults, 2005). Some studies have suggested that tachyphylaxis may be influenced by antidepressant class (Posternak and Zimmerman, 2005; Thase et al., 2000, 2001), with the greatest proportion occurring during selective serotonin reuptake inhibitor therapy (Posternak and Zimmerman, 2005; Thase et al., 2000, 2001; Zajecka, 2007). Tachyphylaxis may contribute to the development of treatment-resistant depression (TRD), although this has not been a universal finding (Zimmerman and Thongy, 2007). There is considerable debate as to whether TRD results from a genetic predisposition to non-response (e.g., Pollock et al., 2000; Neumeister et al., 2006), or from tachyphylaxis due to physiological adaptation in neurotransmission during antidepressant exposure (Zajecka, 2007; Leykin et al., 2007).

Some studies have suggested that tachyphylaxis may occur more frequently in patients with Bipolar type II (BP II) major depressive episode (MDE) (Lieb and Balter, 1984; Sharma, 2001; Sharma et al., 2005) and that these patients may be more likely to develop TRD (Cole et al., 1993; Nolen and Bloemkolk, 2000; Post et al., 2003; Berk and Dodd, 2005; Ei-Mallakh and Karippot, 2005; Sharma et al., 2005). Sharma et al. (2005) examined 63 unipolar MDE patients with TRD using the Structured Clinical Interview for DSM-IV (First et al., 2001) and reclassified 52% of the patients with BP spectrum disorder. Many of the patients who were resistant to antidepressant drug therapy eventually responded to mood stabilizer therapy.

In the present analysis, we examined the effect of prior antidepressant, mood stabilizer, antidepressant and mood stabilizer, and any prior pharmacotherapy on response to venlafaxine or lithium in BP II MDE patients. We hypothesized that a greater number of prior antidepressant exposures would be associated with a reduced response to venlafaxine, but not lithium, therapy.

2. Methods and materials

2.1. Study design

A description of the study design has been previously published (Amsterdam and Shults, 2008). Briefly, outpatients ≥18 years old with BP II MDE and a baseline 17-item Hamilton Depression Rating (Williams, 1988) score ≥18 were included in the study. Patients were excluded if they had prior mania or psychosis, substance abuse or dependence in the preceding 3 months, or non-response to venlafaxine or lithium within the current MDE. Patients provided informed consent in accordance with the ethical standards of the local Institutional Review Board. Oversight was provided by the local Office of Human Research and an independent data and safety monitoring board. Prior treatment history was ascertained using the SCID, self-report, and available medical records. Patients were randomized to open label monotherapy with either venlafaxine or lithium. Efficacy measures were obtained at baseline and study weeks 1, 2, 4, 6, 8, 10, and 12. Venlafaxine was administered from 37.5 mg to 450 mg daily. Lithium was administered from 300 to 2400 mg daily (with a serum lithium level ≥0.5 mmol/L). The primary outcome was the proportion of patients in each treatment group with a ≥50% reduction in baseline HAM-D 28 score. The study was powered to detect a difference in response rates of 60% for venlafaxine versus 30% for lithium, based on a two-group Chi-square test with a 2-sided 0.05 significance level. The number of subjects needed to distinguish between these response rates with 80% power was 42 subjects per group.

2.2. Statistical procedures

Initial analyses were descriptive and included summarizing the number of prior treatments in responders versus non-responders and in each treatment condition. Box-plots (not shown) were constructed to visually compare the number of prior treatment exposures in responders versus non-responders within each treatment condition. *T*-tests were used to compare the mean number of prior treatment exposures for responders versus non-responders within each treatment condition. Logistic regression was used to test the hypothesis that treatment response would be less likely with a greater number of prior antidepressant treatment exposures. The outcome for the logistic regression model was binary and took value of 1 if a patient was a responder and value of zero otherwise. We considered two regression models for each category of prior treatment. The first model included only the number of prior treatments as a covariate. The second model also included the additional covariates of venlafaxine (that took value of 1 for patients treated with venlafaxine and zero otherwise), gender (that took value of 1 for females and zero for males), race (that took value of 1 for Caucasian and zero otherwise),