



## 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

## 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 response 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.

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**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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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 Karipott, 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  $\geq 18$  years old with BP II MDE and a baseline

17-item Hamilton Depression Rating (Williams, 1988) score  $\geq 18$  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  $\geq 0.5$  mmol/L). The primary outcome was the proportion of patients in each treatment group with a  $\geq 50\%$  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),

illness duration (in years), age at first MDE, age at first hypomanic episode, current MDE duration (in months), number of prior MDEs, number of prior hypomanic episodes, number of prior sub-syndromal hypomanic episodes, and baseline HAM-D 28 score. The second model was used to see if the estimated impact of prior treatment number was modified after adjustment for clinical and demographic variables that might influence response. Adjusted and unadjusted odds ratios were calculated for each category of prior treatment, with 95% confidence intervals and a *p*-value for the test that the odds ratio is equal to 1.

To test the primary hypothesis, we modified the second regression model to include a ‘treatment × number of prior treatment exposures’ interaction term. We also considered a simpler regression model that included the covariates: (i) number of prior treatment exposures, (ii) venlafaxine, and (iii) number of prior treatment exposures × treatment interaction term. An interaction term that differed significantly from zero would indicate that the impact of number of prior treatment exposures differed between the venlafaxine and lithium groups. Because no significant interaction terms were identified in the regression models, the results of the interaction analyses are not shown below.

Logistic regression analyses were conducted for each category of prior treatment exposure, defined as: (i) number of prior antidepressant exposures, (ii) number of prior mood stabilizer exposures, (iii) number of prior antidepressants and mood stabilizer exposures, and (iv) number of any prior treatment exposure (including

antidepressant, mood stabilizer, atypical antipsychotic, neuroleptic, and stimulant).

To compare the predictive power of each prior treatment category on response, we constructed the receiver operator characteristic (ROC) curve for both regression models. The area under the curve (AUC) for each ROC curve was calculated. An AUC close to 1 indicated a model that had excellent predictive power. The assumption of linearity in the logit for continuous covariates was tested for each logistic regression model. Finally, the hypothesis of adequate fit was assessed by implementing the Hosmer–Lemeshow test.

### 3. Results

#### 3.1. Enrollment

84 patients were enrolled in the trial, and 83 patients (43 on venlafaxine and 40 on lithium) had at least one post-baseline measurement. Thirty-three patients (39.8%) discontinued treatment before completing the trial: 11 for lack of efficacy, 13 for adverse events, 2 for noncompliance, and 7 lost to follow up. Table 1 displays the clinical and demographic characteristics of the treatment groups.

#### 3.2. Prior treatment exposure

72 patients (85.71%) received prior pharmacotherapy: 72 (85.71%) received a total of 247 antidepressant trials; 29 (34.52%) received a total of 43 mood stabilizer trials; and, 25 (29.76%) received a total of 49 other drug trials.

Table 1  
Clinical and demographic characteristics of BP II MDE treatment groups

	Venlafaxine ( <i>n</i> =43)	Lithium ( <i>n</i> =40)	<i>P</i> value
Gender F:M	23:20	24:16	0.51
Caucasian	86.1%	77.5%	0.57
Age */range (yrs)	37.8 (13.3)/19–73	36.3 (13.4)/18–74	0.59
Age */range at 1st MDE	20.8 (10.5)/5–57	16.6 (5.7)/6–38	0.03
Age */range at 1st hypomanic episode	22.0 (8.8)/13–57	20.7 (6.7)/8–38	0.14
Number */range prior MDEs	6.7 (6.0)/0–30	8.5 (8.1)/0–35	0.25
Number */range prior hypomanic episodes	14.6/1–200	24.9/1–110	0.12
Number */range prior sub-syndromal hypomanic episodes	42.7 (49.2)/0–200	45.9 (59.5)/0–200	0.68
Number */range prior antidepressants	2.9 (2.37)/1–10	2.30 (0.71)/1–12	ns
Number */range prior mood stabilizers	0.58 (1.1)/0–6	0.45 (0.7)/0–3	ns
Illness duration */range (yrs)	17.3/1–46	19.8/2–55	0.66
Current MDE */range (month)	14.1/1–90	16.5/0.75–84	0.73
Baseline HAM-D 28	28.9 (7.5)	28.58 (7.5)	0.72
Baseline YMRS*	0.26 (0.85)	1.2 (2.58)	0.02
Daily Dosage (mg)**	185.6 (92.04)	966.24 (410.9)	–
Serum Lithium Level (mmol/L)	–	0.64 (0.265)	–

\*\*Averaged of maximum dose for all treatment visits.

\*Mean (SD).

### 3.3. Treatment response

We observed a greater reduction in HAM-D 28 scores during venlafaxine (versus lithium) (95% CI = (-11.97, -1.18)) ( $p=0.017$ ). There was also a greater proportion of venlafaxine (versus lithium) patients classified as treatment responders ( $p<0.0005$ ). There was no significant difference in mean Young Mania Rating Scale (YMRS) (Young et al., 1978) scores over time in the venlafaxine (versus lithium) group, and no significant increase in mean YMRS scores at any study visit versus baseline for either treatment condition (Amsterdam and Shults, 2008).

### 3.4. Prior treatment exposure versus response

The mean number of prior antidepressant and mood stabilizer exposures was significantly greater in venlafaxine non-responders versus responders ( $p=0.02$ ). In contrast, there was no association between the number of prior antidepressant and mood stabilizer exposures and response to lithium ( $p=0.38$ ). Similarly, a significantly greater number of any prior pharmacotherapy exposure was seen in venlafaxine non-responders versus responders ( $p=0.01$ ). In contrast, the number of any prior pharmacotherapy exposure was not significantly associated with lithium response ( $p=0.33$ ). There was a non-significant trend for a greater number of prior antidepressant exposures to be associated with venlafaxine non-response ( $p=0.06$ ); although the number of prior antidepressant exposures was not significantly associated with lithium response ( $p=0.09$ ). Finally, a greater number of prior mood stabilizer exposures was associated with good response to both venlafaxine ( $p=0.02$ ) and lithium ( $p=0.01$ ). We note, however, that the number of prior mood stabilizer exposures was limited in both treatment groups.

### 3.5. Prior treatment exposure and odds of response

Table 2 displays the unadjusted and adjusted odds ratio associated with each category of prior treatment exposure. The unadjusted odds of responding to venlafaxine or lithium therapy were significantly reduced in proportion to the number of prior antidepressant, but not mood stabilizer, exposures. Adjustment for the influence of clinical and demographic variables sharpened the estimated impact of the effect of prior antidepressant exposure on response. An odds ratio  $<1$  indicated that the odds of response was reduced with each prior antidepressant exposure. An adjusted odds ratio of 0.62 indicated that the odds of response to therapy were reduced by  $1 \times 0.62$  with each prior antidepressant exposure.

ROC analysis showed that the predictive power of the number of prior antidepressant exposures, the number of prior mood stabilizer exposures, and the number of antidepressant and mood stabilizer exposures was similar. This was suggested by the fact that the AUC did not differ significantly for the ROC curves corresponding to the prior treatment categories. As expected, ROC analysis using the adjusted regression models found that the addition of the clinical and demographic covariates resulted in greater predictive power of response than models that only included the prior treatment exposure.

## 4. Discussion

Prior studies have suggested that some patients with unipolar depression may develop tachyphylaxis after repeated antidepressant exposure (Amsterdam et al., 1994; Nierenberg et al., 1994, 2003; Amsterdam and Shults, 2005; Rush et al., 2006a). In the present analysis, we hypothesized that a greater number of prior antidepressant exposures was associated with a reduced response to venlafaxine, but not to lithium, therapy in patients with BP II MDE. We also hypothesized that there would be a negative association between the number of prior antidepressant, but not mood stabilizer, exposures and response to venlafaxine or lithium therapy. Our observations support earlier findings of tachyphylaxis developing after repeated antidepressant exposure. Our observations also suggest that tachyphylaxis after repeated antidepressant exposure may not be limited to unipolar depression, but may also occur in patients with BP II MDE. The adjusted odds of a BP II MDE patient responding to venlafaxine therapy decreased by a factor of  $1 \times 0.62$  with each prior antidepressant exposure ( $p=0.04$ ), and by  $1 \times 0.70$  with each prior exposure to any pharmacotherapy ( $p=0.01$ ). This indicated that the odds of achieving response (i.e.,  $\geq 50\%$  reduction in baseline HAM-D 28

Table 2

Unadjusted and adjusted odds ratios of treatment response using logistic regression models

Prior treatment	Unadjusted odds-ratio (95% CI) and $p$ -value	Adjusted odds-ratio (95% CI) and $p$ -value
Antidepressant	0.77 (0.62,0.96) $p=0.02$	0.62 (0.40,0.97) $p=0.04$
Mood stabilizer	0.87 (0.53,1.42) $p=0.58$	0.64 (0.27,1.48) $p=0.30$
Antidepressant and mood stabilizer	0.81 (0.68,0.98) $p=0.03$	0.71 (0.51,0.99) $p=0.045$
Any pharmacotherapy	0.80 (0.67,0.95) $p=0.01$	0.70 (0.53,0.93) $p=0.01$

score) decreased by 38% with each prior antidepressant exposure, and by 30% with each prior pharmacotherapy exposure. In contrast, there was no apparent negative effect of prior mood stabilizer exposure on response to venlafaxine or lithium. However, because the number of prior mood stabilizer exposures was limited, and because prior mood stabilizer therapy was often prescribed in conjunction with other pharmacotherapy, it was difficult to differentiate between the impact of prior mood stabilizer therapy *per se* versus other pharmacotherapy.

The cause of tachyphylaxis is not well understood. Intrinsic disease heterogeneity or inter-individual differences in pharmacokinetic and pharmacodynamic variables may contribute to response variability to a particular therapy. While some researchers have suggested that some antidepressant classes may produce physiological adaptation that manifests as tachyphylaxis (Posternak and Zimmerman, 2005; Thase et al., 2000, 2001), it is equally possible that tachyphylaxis results from a genetic predisposition to non-response (Pollock et al., 2000; Neumeister et al., 2006), although this has not been universally observed (Kim et al., 2000; Yoshida et al., 2002; Murphy et al., 2004). A genetic predisposition to non-response would likely result in the exposure to more pharmacotherapy interventions with partial or poor response.

It is also possible that tachyphylaxis may result from a physiological adaptation that occurs after repeated antidepressant exposure. In a prior analysis of 149 unipolar MDE patients treated with fluoxetine, we found a negative association between the number of prior antidepressant exposures and response to fluoxetine (odds ratio=0.80,  $p<0.03$ ) (Amsterdam et al., 1994). There was no significant association between treatment response and age, gender, number of prior MDEs, illness duration, or MDE length. Nierenberg et al. (1994) observed a 42% response rate with venlafaxine in TRD patients unresponsive to  $\geq 3$  prior antidepressant trials, but only a 13% response rate in patients who also had electroconvulsive therapy. Similarly, we observed tachyphylaxis in 59 patients with TRD who were unresponsive to as many as 15 prior antidepressant trials (Amsterdam and Shults, 2005). We found a significant negative association between the number of prior antidepressant trials and response to MAOI therapy, with an odds ratio=0.68, or a 32% reduction in the likelihood of response to MAOI therapy with each prior antidepressant trial. There was no association between age, gender, illness duration, episode length, or MAOI dosage and response. In that study, 32.5% of MAOI trials resulted in a final clinical global impressions change (CGI/C) score of 1 (i.e., ‘very much improved’) in patients with  $\leq 3$  prior antidepressant trials versus 12.1% of MAOI trials resulting in a CGI/C

score of 1 in patients who received  $\geq 4$  prior antidepressant trials ( $p=0.04$ ) (Amsterdam and Shults, 2005).

Tachyphylaxis after repeated antidepressant exposure was also observed in the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study (Fava et al., 2006; McGrath et al., 2006; Rush et al., 2006b; Trivedi et al., 2006). Remission rates diminished from 36.8% at treatment level 1 to 30.6%, 13.7%, and 13.0% at treatment levels 2, 3, and 4, respectively. In addition, STAR\*D patients who required more antidepressant trials to achieve remission also experienced a greater relapse rate during follow up therapy (i.e., tachyphylaxis during continuation therapy) (Rush et al., 2006a). Subsequently, Leykin et al. (2007) examined the influence of prior antidepressant exposure on response to either paroxetine ( $n=80$ ) or cognitive therapy ( $n=80$ ). After controlling for age, gender, race, marital status, educational status, baseline HAM-D score, age at illness onset, episode duration, and number of prior MDEs, only the number of prior antidepressant exposures showed a significant negative association with outcome to paroxetine ( $p<0.001$ ), but not to cognitive therapy ( $p=0.83$ ). This observation suggests that cognitive therapy may exert its therapeutic action via a different mechanism than that of antidepressant drug therapy, and may be less affected by the physiological adaptation resulting from prior drug exposure (Goldapple et al., 2004).

Finally, other pharmacologic lines of evidence support the possibility that repeated antidepressant exposure may cause gradual tachyphylaxis due to physiologic adaptation. For example, repeated administration of benzodiazepines is associated with progressive physiological adaptation in  $\gamma$ -amino butyric acid receptors that can result in drug tolerance and tachyphylaxis (Bateson, 2002; Bonavita et al., 2002; Biggio et al., 2003). Gradual changes in dopamine neurotransmission have been associated with repeated administration of some neuroleptic agents resulting in tardive dyskinesia (Casey, 1993; Simpson, 1997). Thus, it is possible that repeated administration of antidepressants may also result in physiological adaptation of serotonin (or other) neurotransmitter systems that manifests clinically as tachyphylaxis.

There are a number of caveats that should be considered in the interpretation of our findings. For example, the present study was a *post hoc* exploratory analysis of data derived from a clinical trial. The trial was not powered to specifically test the hypothesis of an association between prior antidepressant exposure and response to venlafaxine or lithium. We had limited power to detect an interaction effect between prior antidepressant exposures and response to venlafaxine versus lithium. While the present results suggest that

the number of prior antidepressant exposure has a negative impact on future response, this does not appear to be the case with prior mood stabilizer exposure. However, the fact that the number of prior mood stabilizer exposures was limited in both treatment groups limits our ability to assess the true impact of prior mood stabilizer therapy on future treatment response. In addition, 82% of patients with no prior mood stabilizer therapy were exposed to some other type of prior pharmacotherapy. Thus, the comparison of treatment groups based upon prior mood stabilizer exposure is tenuous. Furthermore, it is possible that the subgroup of BP II MDE patients who had no response to venlafaxine did so by chance alone, or did so because they had BP II, rather than unipolar, MDE. It is also possible that our finding of tachyphylaxis represents a statistical artifact. We note that our present observations only suggest the presence of tachyphylaxis, as the study design did not directly demonstrate a progressive loss of antidepressant efficacy with successive antidepressant exposures. In order to directly demonstrate progressive tachyphylaxis, efficacy would need to be examined after repeated antidepressant exposures in the same individual who is randomly assigned to successive therapies. This design was utilized in the STAR\*D study that did demonstrate a progressive reduction in antidepressant response with successive treatment trials. The STAR\*D study also found a higher relapse rate (i.e., tachyphylaxis) during follow up therapy in recovered patients who previously had more treatment exposed (Rush et al., 2006a).

Because this was a *post hoc* analysis, we had a limited ability to independently verify the number and adequacy of prior antidepressant and mood stabilizer therapy, pill-taking compliance, or the extent of prior treatment response. In addition, the number of prior treatment exposures was not limited to treatments obtained during the most recent MDE. It is possible that some prior treatments were discontinued due to side effects (rather than lack of efficacy). Inter-individual pharmacological variables may also have influenced the response to venlafaxine or lithium. Finally, we note that prior treatment failure (as a predictor of future antidepressant response) may differ from tachyphylaxis that occurs during maintenance therapy in patients who have previously responded to antidepressant therapy.

## 5. Conclusion

We found a negative association between the number of prior antidepressant exposures and response to venlafaxine, but not lithium, therapy in the present study. A similar association of the number of prior mood sta-

bilizer exposures and clinical response was not observed. The odds of responding to venlafaxine in the present study were reduced with each prior antidepressant exposure. These observations support prior studies suggesting the possibility that gradual tachyphylaxis may occur after repeated antidepressant exposures, and that this phenomenon may occur as a result of gradual physiologic adaptation of central neurotransmitter systems to repeated antidepressant exposure.

### Role of funding source

The work presented in this manuscript resulted from an investigator-initiated trial that was funded by the Stanley Medical Research Institute (SMRI). The SMRI had no direct involvement in study design, procedure, or data analysis.

### Conflict of interest

Dr. Amsterdam currently receives research grant support from the NIMH, NIH/NCCAM, Lilly Research Laboratories, Novartis, Inc., and Sanofi-Aventis, Inc. He is on the speaker's bureau of Wyeth and Bristol-Myers-Squibb. Dr. Shults receives research grant support from the NIH, NIMH, and the NIH/NCCAM.

### Acknowledgements

This research was supported by a grant from The Stanley Medical Research Institute, and The Jack Warsaw Fund for Research in Biological Psychiatry (Depression Research Unit, University of Pennsylvania Medical Center).

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