Published in final edited form as:

Bipolar Disord. 2016 November ; 18(7): 563–570. doi:10.1111/bdi.12442.

Step-wise loss of antidepressant effectiveness with repeated antidepressant trials in bipolar II depression

Jay D Amsterdam^a, Lorenzo Lorenzo-Luaces^{a,b,c}, and Robert J DeRubeis^{a,b}

^aDepression Research Unit, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA

^bDepartment of Psychology, University of Pennsylvania, Philadelphia, PA

^cMethods to Improve Diagnostic Assessment and Services (MIDAS) Project, Brown University, Providence, RI, USA

Abstract

Objective—This study examined the relationship between the number of prior antidepressant treatment trials and step-wise increase in pharmacodynamic tolerance (or progressive loss of effectiveness) in subjects with bipolar II depression.

Methods—Subjects 18 years old with bipolar II depression ($n = 129$) were randomized to double-blind venlafaxine or lithium carbonate monotherapy for 12 weeks. Responders ($n = 59$) received continuation monotherapy for six additional months.

Results—After controlling for baseline co-variates of prior medications, there was a 25% reduction in likelihood of response to treatment with each increase in the number of prior antidepressant trials [odds ratio (OR) = 0.75, $B = -0.29$, $SE = 0.12$; $\chi^2 = 5.70$, $p < 0.02$], as well as a 32% reduction in the likelihood of remission with each prior antidepressant trial (OR = 0.68, $B = -0.39$, $SE = 0.13$; $\chi^2 = 9.71$, $p = 0.002$). This step-wise increase in pharmacodynamic tolerance occurred in both treatment conditions. Prior selective serotonin reuptake inhibitor (SSRI) therapy was specifically associated with step-wise increase in tolerance, whereas other prior antidepressants or mood stabilizers were not associated with pharmacodynamic tolerance. Neither the number of prior antidepressants, SSRIs, or mood stabilizers, were associated with an increase in relapse during continuation therapy.

Corresponding author: Jay D. Amsterdam, M.D., Depression Research Unit, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, 3535 Market Street, Philadelphia, PA 19104, USA, Fax: 856-428-1392, jamsterd@mail.med.upenn.edu.

Disclosures

JDA, LL-L, and RJD are not members of any pharmaceutical industry-sponsored advisory board or speaker's bureau, and have no financial interest in any pharmaceutical or medical device company.

Author contributions

JDA was principal investigator on the project, designed the trial, obtained grant support, recruited subjects, implemented and conducted the research, oversaw the trial and data management and wrote the first and subsequent drafts of the manuscript. LL-L performed data quality assurance, data analyses, data interpretation, and participated in drafting the first and subsequent drafts of the manuscript. RJD was co-principal investigator on the project, performed data interpretation and participated in drafting the first and subsequent drafts of the manuscript. All authors had access to the clinical and statistical data, participated in manuscript preparation, and take full responsibility for the accuracy of data and data reporting.

Conclusions—The odds of responding or remitting during venlafaxine or lithium monotherapy were reduced by 25% and 32%, respectively, with each increase in the number of prior antidepressant treatment trials. There was no relationship between prior antidepressant exposure and depressive relapse during continuation therapy of bipolar II disorder.

Keywords

antidepressant; bipolar disorder; depression; drug tolerance; loss of response; lithium; SNRI; SSRI; tachyphylaxis; treatment resistant depression; venlafaxine

A gradual increase in pharmacodynamic tolerance (or a gradual loss of initial antidepressant effectiveness) has been reported during long-term antidepressant administration (1-7). However, this phenomenon may also occur as a step-wise reduction in effectiveness over time after repeated antidepressant drug trials (1, 2, 8). Studies have suggested that step-wise tolerance to antidepressant therapy may occur in 20% to 50% of patients after repeated antidepressant drug trials (1, 2, 8-10). It occurs in both unipolar (1, 2, 8-11) and bipolar (2) disorder, and may be especially common after repeated exposure to selective serotonin reuptake inhibitors (SSRIs) (3, 12, 13), although it also occurs with other antidepressant classes (9, 11).

There is considerable debate as to whether step-wise loss of antidepressant effectiveness results from a genetic predisposition to treatment resistance (14, 15) or whether, instead, it results from physiologic adaptation of neurotransmitter systems to repeated antidepressant exposures (8). The latter possibility is particularly concerning because it would suggest that some cases of resistant depression result from repeated exposure to antidepressant therapy *per se* (9, 10, 16, 17). If this is so, the growing proportion of patients with treatment-resistant depression may, in part, result from antidepressant-induced medication-resistance whereas a similar phenomenon may not be at work after repeated psychotherapeutic interventions (8).

The primary aims of this study were to examine whether the number of prior antidepressant trials was associated with: (i) a step-wise reduction in the likelihood of observed response to acute venlafaxine or lithium monotherapy in subjects who were in a bipolar II major depressive episode; and/or (ii) a higher likelihood of relapse during continuation venlafaxine or lithium monotherapy in subjects who recovered from their major depressive episode. We hypothesized that, as the number of prior antidepressant trials increased, a step-wise loss of response would occur to acute venlafaxine or lithium monotherapy and/or a higher relapse rate during continuation venlafaxine or lithium monotherapy.

Methods

Subjects

This is an exploratory analysis of data obtained from a randomized controlled comparison of venlafaxine monotherapy versus lithium monotherapy for bipolar II depression ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00602537) identifier: NCT00602537). The primary study outcomes and design features have been described elsewhere (18, 19).

Briefly, outpatient subjects 18 years old were included if they met DSM IV-TR criteria for bipolar II disorder and a current major depressive episode via the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (20). Subjects had a minimum 17-item Hamilton Rating Scale for Depression (HRSD) (21) score 16. Exclusion criteria were: history of prior mania or psychosis, substance use disorder within the preceding three months, sensitivity or non-response to venlafaxine or lithium within the current episode, unstable medical condition, or concurrent use of antidepressant or mood stabilizer medication.

Procedures

Informed consent was obtained in accordance with the ethical standards of the Institutional Review Board, using Good Clinical Practice guidelines (22) with oversight by the local Office of Human Research and an independent Data and Safety Monitoring Board. Prior antidepressant, mood stabilizer, and other psychotropic drug therapy during the current and prior affective episodes was ascertained via the SCID format (20) and available medical and pharmacy records. Adequacy of prior dosage and treatment duration was ascertained using an adaptation of the Harvard Antidepressant Treatment History of the SCID (23, 24). Trials of unverified adequacy were excluded; while trials of borderline adequacy were examined individually by the investigators for consensus determination. Best estimates of the number of prior DSM IV defined major depressive and hypomanic episodes since the onset of the disorder were obtained from subjects using SCID format. Structured 17-item HRSD and Young Mania Rating Scale (YMRS; 25) measures were obtained by a study clinician blind to treatment condition. Blocked randomization was performed as previously described (18, 19).

Treatment

Acute treatment was administered for 12 weeks with outcome measures obtained at baseline and weeks 1, 2, 4, 6, 8, 10, and 12. Response was defined as a 50% reduction in baseline HRSD score plus a final Clinical Global Impression / Severity (CGI/S) (26) score 3. Remission was defined as a final HRSD score 8 plus a final CGI/S score of 2. Responders were invited to enroll in continuation monotherapy on their established dose of double-blind medication for 6 additional months. Outcome measures were obtained at continuation weeks 16, 20, 24, 30 and 36. Relapse was defined as a rise in the 17-item HRSD score to 14 or higher plus a CGI/S score of 4 for 14 days. Venlafaxine was initiated at 37.5mg daily and increased (as clinically warranted and tolerated) to a maximum dose of 375mg daily by week 4 of treatment. Lithium was initiated at 300mg daily and increased to a dose 1200mg daily by week 4 of treatment based upon clinical response and a serum lithium level of 0.8-1.5mEq/L. Subjects unable to sustain a minimum lithium level 0.5mEq/L were discontinued from the trial. Blinded treatment conditions were maintained as previously described (18, 19).

Statistical procedures

Analyses were conducted using IBM SPSS version 21 (IBM Corporation, New York, NY, USA) according to the intent-to-treat principle. Analyses and results of the primary and secondary outcome measures have previously been described (18, 19). Initial analyses

summarized the demographic and clinical variables at baseline and after response at week 12 for the entire subject sample and for subjects randomized to continuation therapy using Fisher's exact test for categorical variables. T-tests were used to compare means of continuous variables. Bivariate correlations were used to examine the effect of baseline variables on the number of prior antidepressant trials. Variables that were significant at $p < 0.05$ were entered into a simultaneous regression analysis as control variables.

Acute treatment outcomes were analyzed as a function of treatment condition, number of prior antidepressant trials (i.e., 0, 1, 2, 3, 4, 5, or 6+), and by the interaction of treatment condition by the number of prior trials. The primary outcome variables for acute treatment outcome were response (versus nonresponse) and symptom remission (vs. non-remission). As categorical outcomes, these variables were analyzed using binary logistic regression. Because fewer than expected lithium-treated subjects responded to acute treatment, and fewer patients in the lithium condition were thus unavailable for continuation therapy, outcomes for the continuation phase of the study were analyzed for the entire sample, controlling for treatment condition but without analyzing treatment interactions. The main outcome for the continuation phase was relapse, using Cox regression. Additionally, we explored whether the number of prior SSRIs and mood stabilizers were specifically associated with outcomes.

Results

Clinical and demographic features

One-hundred twenty-nine subjects were randomized to venlafaxine ($n=65$) or lithium ($n=64$). There were no statistically significant differences between treatment conditions on any demographic or clinical variable (Table 1) (18,19). Overall, subjects received a mean [standard deviation (SD)] total of 2.69 (2.00) prior trials of any antidepressant before study enrollment. Only 17% ($n = 22$) were medication-naïve. There was no significant difference between the conditions in the number of prior antidepressant trials ($p = 0.53$) (see Table 1).

Table 2 shows the proportion of prior antidepressants by antidepressant treatment class. Caucasian subjects received more prior antidepressant trials [mean = 2.94 (SD = 2.04)] relative to non-Caucasian subjects [mean = 1.69, SD = 1.51, $t(50.52) = -3.48$, $p = 0.001$]. Subjects who met the criteria for inter-episode recovery received fewer prior antidepressant trials (mean=1.69, SD=1.51) than subjects who did not show inter-episode recovery [mean = 2.94, SD = 2.04, $t(127) = 2.88$, $p = 0.005$]. Subjects with higher baseline severity HRSD scores received more prior antidepressant treatment trials ($r = 0.35$, $p < 0.001$) (Table 3). Similarly, subjects with more prior depressive episodes received a greater number of prior antidepressant trials ($r = 0.24$, $p = 0.008$). Finally, subjects with younger age of depression onset received a greater number of prior antidepressant trials ($r = -0.21$, $p = 0.02$) (Table 3).

When these variables were included in model predicting the number of prior antidepressant trials, all but age of first depression ($B = -0.04$, $SE = 0.02$, $t = 1.61$, $\beta = -0.13$, $p = 0.11$) predicted number of prior antidepressant trials at $p < 0.05$. The final model, which included being Non-Hispanic White, ($B = 1.16$, $SE = 0.39$, $t = 3.00$, $\beta = 0.41$, $p < 0.01$), baseline depression severity ($B = 0.17$, $SE = 0.04$, $t = 4.02$, $\beta = 0.32$, $p < 0.001$), inter-episode recovery ($B = -0.87$,

SE=0.38, $t=-2.26$, $\beta=-0.18$, $p=0.02$), and prior depressive episodes ($B=0.02$, SE=0.01, $t=2.57$, $\beta=0.20$, $p=0.01$) accounted for 24% of the variance in the number of prior antidepressant trials.

Response and remission during acute therapy

Even after accounting for the effect of treatment and the baseline variables associated with prior medications, there was a significant association between the number of prior antidepressant trials and the likelihood of response [odds ratio (OR) = 0.75, $B=-0.29$, SE = 0.12; $\chi^2=5.70$, $p<0.02$] and remission (OR=0.68, $B=-0.39$, SE=0.13; $\chi^2=9.71$, $p=0.002$). The number of prior medications explained variance in response (5%) and remission (10%) above and beyond the treatment conditions and the baseline variables (Table 4) and neither of the baseline characteristics that co-varied with prior medications predicted response or remission (all $p>0.19$).

Overall rates of response and remission are presented in Figure 1. The interaction between the number of prior antidepressant trials and treatment condition was not a predictor of response ($p=0.47$) or remission ($p=0.20$). An increase in the number of prior SSRI trials was specifically associated with a reduction in acute response (OR=0.75, $B=-0.28$, SE=0.12, $\chi^2=5.22$, $p=0.02$) and remission (OR=0.78, $B=-0.26$, SE=0.13, $\chi^2=4.05$, $p=0.04$). In contrast, an increase in the number of prior mood stabilizer trials was not associated with reduced response (OR=1.26, $B=0.23$, SE=0.32, $\chi^2=0.52$, $p=0.47$) or remission (OR=1.13, $B=0.12$, SE=0.32, $\chi^2=0.15$, $p=0.70$). Similarly, no other drug class was associated with reduced likelihood of response (all $p>0.19$).

The association between the number of prior SSRI trials and response (OR=1.29, $B=0.26$, SE=0.25, $\chi^2=1.01$, $p=0.32$) or remission (OR=1.50, $B=0.40$, SE=0.27, $\chi^2=2.24$, $p=0.14$) did not differ as a function of treatment condition. Similarly, the treatment condition did not interact with the number of prior mood stabilizer trials to moderate response (OR=0.41, $B=-0.88$, SE=0.55, $\chi^2=2.60$, $p=0.11$) or remission (OR=0.33, $B=-1.10$, SE=0.59, $\chi^2=3.54$, $p=0.06$).

Relapse during continuation therapy

Relapse on venlafaxine or lithium was not predicted by number of prior antidepressant trials (OR=1.24, $B=0.22$, SE=0.21, $\chi^2=1.11$, $p=0.29$), number of prior SSRIs (OR=1.29, $B=0.25$, SE = 0.26, $\chi^2=0.93$, $p=0.34$), or number of prior mood stabilizer trials (OR=0.84, $B=-0.18$, SE=0.54, $\chi^2=0.11$, $p=0.74$).

Discussion

The phenomenon of a step-wise increase in antidepressant drug tolerance after repeated antidepressant trials was initially suggested by Lieb and Balter (27) in a very small sample of patients with treatment-resistant depression; and was subsequently confirmed in a larger study by Amsterdam (1) in depressed subjects who demonstrated an increased step-wise tolerance rate of at least 20% with each increase in the number of prior antidepressant treatment trials. In that study, the investigators controlled for the effects of age, gender, illness severity, illness duration, and episode length with only the number of prior

antidepressant exposures significantly predicting a loss of response to fluoxetine therapy. Subsequent studies, including the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) have also supported observations of step-wise loss of antidepressant effectiveness (2, 8-11, 16, 28-30). For example, reduction in remission and response rates were observed in the STAR*D study with each increase in the number of prior antidepressant drug exposures. Remission rates declined from 36.8% at level 1, to 30.6%, 13.7%, and 13.0% at levels 2, 3 and 4, respectively. Moreover, STAR*D subjects who required more antidepressant therapy during acute treatment had higher relapse rates during follow-up evaluation (32).

The findings of the current analysis confirm earlier observations by our group of step-wise loss of antidepressant responsiveness after repeated antidepressant exposures (1, 2, 8, 11, 30). We have also reported that this step-wise phenomenon is not limited to individuals with unipolar or treatment-resistant depression; rather, it can also occur in individuals with bipolar II disorder (2, 11). Some have suggested that this type of loss of response may be even more evident with SSRIs (3, 12, 13). Although there has been a proliferation of SSRIs and other antidepressant drugs over the past four decades, the likelihood of achieving response and remission with these drugs has not changed and the number of patients with persistent depression may have increased (31).

The cause of step-wise loss of antidepressant effectiveness is unknown. It is possible that disease heterogeneity or inter-individual differences in response to different antidepressant drug classes may contribute to it. Increased tolerance may also result from a genetic predisposition to non-response to certain drugs (14, 15, 33, 34), although this has not been a universal finding (35-37). Additionally, some antidepressant drugs may produce a persistent physiological adaptation over time that manifests as progressive tolerance and this eventual loss of effectiveness may result from repeated antidepressant administration *per se* (8). This idea is supported by a study in which a step-wise loss of response was observed for subjects with unipolar major depression treated with paroxetine but the same decrease in likelihood of achieving response was not observed for subjects in that study who were randomized to cognitive therapy (8). In the analysis by Leykin and colleagues (8), age, gender, illness severity, illness duration, episode length, and number of prior depressive episodes were included as co-variables and only the number of prior antidepressant trials predicted a negative association with acute remission rates to paroxetine ($p<0.001$), but not to cognitive therapy ($p=0.83$). This suggests that exposure to prior antidepressants may be a predictor of poor response to subsequent drug trials and that other treatment approaches should be considered.

In the present study, we controlled for baseline symptom severity, inter-episode recovery, and number of prior depressive episodes, all of which may be associated with illness heritability. However, we found no association between these variables and treatment outcomes. This may suggest that the presence of step-wise loss of effectiveness observed in the current study is not a genetic predisposition to non-response; rather, it suggests that it is repeated exposure to prior antidepressants that influenced the effectiveness of venlafaxine and lithium response. In a similar analysis, Nierenberg et al. (28) observed a 42% response rate during venlafaxine therapy in subjects with partial or poor response to 3 prior

antidepressant drug trials; but only a 13% response rate in subjects who also had prior partial or poor response to electroconvulsive therapy as part of their treatment. In another study of 92 subjects exposed to 5 prior antidepressant drug trials, Nierenberg et al.(29) found only a 12% remission rate; findings similar to those observed during level 4 of STAR*D (9, 10, 16, 17) and similar to those of our group (2, 11).

Other lines of evidence suggest that step-wise loss of antidepressant effectiveness may result from antidepressant-induced physiological adaptation. For example, repetitive administration of benzodiazepines may result in persistent physiological adaptation in γ -amino-butyric acid receptors resulting in drug tolerance and loss of effectiveness (38, 39). Similarly, a change in dopamine neurotransmitter function has been observed after repeated neuroleptic exposures resulting in a step-wise development of irreversible tardive dyskinesia (40).

Several caveats should be considered before interpreting the current results. For example, the current study was a *post hoc* exploratory analysis of data derived from a randomized 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 also had limited power to detect an interaction effect between prior antidepressant exposures and response to venlafaxine versus lithium.

It is possible that subjects in the current study with poor acute response to treatment had, by chance alone, more prior exposure to antidepressant trials (versus responders and remitters), and that our finding represents a statistical artifact. For example, some subjects may have had poor response to venlafaxine or lithium for reasons other than progressive tolerance (e.g., dosage limitations due to side effects, reduced compliance) or other pharmacological variables (i.e., variation in pharmacokinetic or pharmacodynamic activity). Additionally, it is possible that past antidepressant administration occurred in such a way as to promote non-response to the current study drugs. Although information on the number of prior antidepressant trials was not limited to the current depressive episode, independent verification of prior treatment adequacy and compliance and the extent of response to antidepressant therapy was often limited and could not always be independently verified.

Our current estimate of step-wise antidepressant tolerance was retrospective in nature and not based upon direct observation of progressive loss of effectiveness after repeated antidepressant trials over time. However, other studies like STAR*D employed a repetitive treatment design and reported a similar step-wise reduction in response and remission rates with successive antidepressant trials. Furthermore, the STAR*D study found a greater likelihood of depressive relapse during continuation antidepressant therapy in subjects with more prior antidepressant (9, 10, 16, 17). Additionally, we note that step-wise loss of response during acute antidepressant therapy may be different than loss of effectiveness that occurs during continuation therapy in individuals who have previously responded to antidepressant therapy.

While the current results suggest that the number of prior antidepressant trials is a negative predictor of future venlafaxine and lithium response, this does not appear to be the case with

prior mood stabilizer trials. This finding supports prior observations in bipolar II depressed subjects treated with venlafaxine or lithium (2). However, we note that the number of prior adequate mood stabilizer exposures in both the treatment groups was limited, and this factor limits our ability to assess the true impact of prior mood stabilizer therapy on the rate of future loss of response. There is great variability in the rate of mood stabilizer use in bipolar patients and the rate of mood stabilizer use appears to be lowest in patients with bipolar II disorder and who present with an index depressive episode (41) (i.e., the patient population that we studied). Thus, it is plausible that an effect of prior mood stabilizers would emerge in patient populations that have greater exposure to mood stabilizers.

There was no significant effect of prior antidepressant or mood stabilizer exposure on relapse rates during continuation therapy. This finding comports with prior observations by our group in bipolar II depressed subjects treated with venlafaxine or lithium (2). However, it contrasts with findings from the STAR*D study (9). The failure to detect a significant effect of prior treatment on relapse in the present study may result from a lack of statistical power to detect increased tolerance during continuation therapy. Alternatively, it may be the case that the effects of prior medications on treatment outcomes are most evident during the acute phase of treatment, such that when patients respond they have an approximately equal rate of relapse irrespective of the number of prior antidepressant treatment trials.

Conclusions

We observed a negative association between the number of prior antidepressant trials and the likelihood of acute antidepressant response to venlafaxine or lithium, but no relationship between the number of prior antidepressant trials and relapse during continuation antidepressant or mood stabilizer therapy. The odds of responding or remitting during acute venlafaxine or lithium monotherapy in the current study were reduced by approximately 25% and 32%, respectively, with each increase in the number of prior antidepressant trials at any time over the course of the affective illness. These observations support prior studies suggesting the possibility that step-wise loss of effectiveness may occur after repeated antidepressant, but not repeated mood stabilizer trials over time, and that this phenomenon may occur as a result of physiologic adaptation of central neurotransmitter systems to repeated antidepressant treatment trials.

Acknowledgements

This research was supported by NIMH grant MH060353. Additional support for the preparation of this manuscript was provided by NIH grant MH080097 and The Jack Warsaw Fund for Research in Biological Psychiatry of the University of Pennsylvania Medical Center. Results from this study have not been previously presented in abstract form, and are not under consideration for publication elsewhere. The [clinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/BP02000602) identifier for the study is BP02000602.

References

1. Amsterdam JD, Maislin G, Potter L. Fluoxetine efficacy in treatment resistant depression. *Progress in Neuro-Psychopharmacol Biological Psychiatr*. 1994; 18:243–261.
2. Amsterdam JD, Shults J. Does tachyphylaxis occur after repeated antidepressant exposure in patients with Bipolar II major depressive episode? *J Affect Disord*. 2009; 115:234–240. [PubMed: 18694599]

3. Posternak MA, Zimmerman M. Dual Reuptake Inhibitors Incur Lower Rates of Tachyphylaxis Than Selective Serotonin Reuptake Inhibitors. *J Clin Psychiat.* 2005; 66:705–707.
4. Solomon DA, Leon AC, Mueller TI, Coryell W, Teres JJ, Posternak MA, Judd LL, Endicott J, Keller MB. Tachyphylaxis in Unipolar Major Depressive Disorder. *J Clin Psychiat.* 2005; 66:283–290.
5. Sharma V. Loss of response to antidepressants and subsequent refractoriness: diagnostic issues in a retrospective case series. *J Affect Disord.* 2001; 64:99–106. [PubMed: 11292524]
6. Thase ME. Preventing relapse and recurrence of depression: a brief review of therapeutic options. *CNS Spectrums.* 2006; 11:12–21. [PubMed: 17146414]
7. Thase ME, Haight BR, Richard N, Rockett CB, Mitton M, Modell JG, VanMeter S, Harriett AE, Wang Y. Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: A meta-analysis of original data from 7 randomized controlled trials. *J Clin Psychiat.* 2005; 66:1, 478–981.
8. Leykin Y, Amsterdam JD, DeRubeis RJ, Gallop R, Shelton RC, Hollon SD. Progressive resistance to a selective serotonin reuptake inhibitor but not to cognitive therapy in the treatment of major depression. *J Consul Clin Psych.* 2007; 75:267–276.
9. Rush A. Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. *Am J Psychiat.* 2006; 163:1905. [PubMed: 17074942]
10. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M. Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clin Practice. *Am J Psychiat.* 2006; 163:28–40. [PubMed: 16390886]
11. Amsterdam JD, Shults J. MAOI efficacy and safety in advanced stage treatment-resistant depression—A retrospective study. *J Affect Disord.* 2005; 89:183–188. [PubMed: 16213594]
12. Zimmerman M, Thongy T, How Often. Do SSRIs and Other New-Generation Antidepressants Lose Their Effect During Continuation Treatment? *J Clin Psychiat.* 2007; 68:1271–1276.
13. Thase ME. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Brit J Psychiat.* 2001; 178:234–241.
14. Smeraldi E, Zanardi R, Benedetti F, Bella DD, Perez J, Catalano M. Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. *Molecular Psychiat.* 1998; 3:508–511.
15. Pollock B. Allelic Variation in the Serotonin Transporter Promoter Affects Onset of Paroxetine Treatment Response in Late-Life Depression. *Neuropsychopharm.* 2000; 23:587–590.
16. Fava M. A Comparison of Mirtazapine and Nortriptyline Following Two Consecutive Failed Medication Treatments for Depressed Outpatients: A STAR*D Report. *Am J Psychiat.* 2006; 163:1161. [PubMed: 16816220]
17. McGrath P. Tranylcypromine Versus Venlafaxine Plus Mirtazapine Following Three Failed Antidepressant Medication Trials for Depression: A STAR*D Report. *Am J Psychiat.* 2006; 163:1531. [PubMed: 16946177]
18. Amsterdam JD, Lorenzo-Luaces L, Soeller I, Li SQ, Mao JJ, DeRubeis RJ. Safety and effectiveness of continuation antidepressant versus mood stabilizer monotherapy for relapse-prevention of bipolar II depression: A randomized, double-blind, parallel-group, prospective study. *J Affect Disord.* 2015; 185:31–37. [PubMed: 26143402]
19. Amsterdam JD, Lorenzo-Luaces L, Soeller I, Li SQ, Mao JJ, DeRubeis RJ. Short-term venlafaxine v. lithium monotherapy for bipolar type II major depressive episodes: effectiveness and mood conversion rate. *Brit J Psychiat.* 2016; 208:359–365.
20. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB. Structured Clin Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition With Psychotic Screen (SCID-I/P W/ PSY SCREEN). Biometrics Research, New York State Psychiatric Institute; New York, NY: 2001.
21. Williams JBW. A Structured Interview Guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiat.* 1988; 45:742. [PubMed: 3395203]
22. Baber N. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH). *Brit J Clin Pharmacol.* 1994; 37:401–404. [PubMed: 8054244]

23. Nierenberg AA, Amsterdam J. Treatment-resistant depression: definition and treatment approaches. *Clin Psychiat.* 1990; 51:39–47.
24. Nierenberg A, Keck P, Samson J, Rothschild A, Schatzberg A. Methodological considerations for the study of treatment-resistant depression. *Advances in Neurosychiat Psychopharmacol.* 1991; 2:1–12.
25. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Brit J Psychiat.* 1978; 133:429–435.
26. Guy, W. ECDEU assessment manual for psychopharmacology. US Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976.
27. Lieb J, Balter A. Antidepressant tachyphylaxis. *Medical Hypotheses.* 1984; 15:279–291. [PubMed: 6521674]
28. Nierenberg AA, Feighner JP, Rudolph R, Cole JO, Sullivan J. Venlafaxine for Treatment-Resistant Unipolar Depression. *J Clin Psychopharm.* 1994; 14:419–423.
29. Nierenberg AA, Papakostas GI, Petersen T, Kelly KE, Iacoviello BM, Worthington JJ, Tedlow J, Alpert JE, Fava M. Nortriptyline for Treatment-Resistant Depression. *J Clin Psychiat.* 2003; 64:35–39.
30. Amsterdam JD, Williams D, Michelson D, Adler LA, Dunner DL, Nierenberg AA, Reimherr FW, Schatzberg AF. Tachyphylaxis after Repeated Antidepressant Drug Exposure in Patients with Recurrent Major Depressive Disorder. *Neuropsychobiol.* 2009; 59:227–233.
31. Whitaker, R. Anatomy of an epidemic: Magic bullets, psychiatric drugs, and the astonishing rise of mental illness in America. Broadway; 2011.
32. Fava GA. Can Long-Term Treatment With Antidepressant Drugs Worsen the Course of Depression? *J Clin Psychiat.* 2003; 64:123–133.
33. Jacobs N, Kenis G, Peeters F, Derom C, Vlietinck R, van Os J. Stress-Related Negative Affectivity and Genetically Altered Serotonin Transporter Function. *Arch Gen Psychiat.* 2006; 63:989. [PubMed: 16953001]
34. Neumeister A, Hu X-Z, Luckenbaugh DA, Schwarz M, Nugent AC, Bonne O, Herscovitch P, Goldman D, Drevets WC, Charney DS. Differential Effects of 5-HTTLPR Genotypes on the Behavioral and Neural Responses to Tryptophan Depletion in Patients With Major Depression and Controls. *Arch Gen Psychiat.* 2006; 63:978. [PubMed: 16953000]
35. Kim DK, Lim S-W, Lee S, Sohn SE, Kim S, Hahn CG, Carroll BJ. Serotonin transporter gene polymorphism and antidepressant response. *NeuroReport.* 2000; 11:215–219. [PubMed: 10683861]
36. Yoshida K, Ito K, Sato K, Takahashi H, Kamata M, Higuchi H, Shimizu T, Itoh K, Inoue K, Tezuka T, Suzuki T, Ohkubo T, Sugawara K, Otani K. Influence of the serotonin transporter gene-linked polymorphic region on the antidepressant response to fluvoxamine in Japanese depressed patients. *Progress Neuropsychopharm Biol Psychiat.* 2002; 26:383–386.
37. Murphy GM, Hollander SB, Rodrigues HE, Kremer C, Schatzberg AF. Effects of the Serotonin Transporter Gene Promoter Polymorphism on Mirtazapine and Paroxetine Efficacy and Adverse Events in Geriatric Major Depression. *Arch Gen Psychiat.* 2004; 61:1163. [PubMed: 15520364]
38. Biggio G, Dazzi L, Biggio F, Mancuso L, Talani G, Busonero F, Mostallino MC, Sanna E, Follesa P. Molecular mechanisms of tolerance to and withdrawal of GABAA receptor modulators. *Euro Neuropsychopharm.* 2003; 13:411–423.
39. Bonavita CD, Bisagno V, Bonelli CG, Acosta GB, Rubio MC, Wikinski SI. Tolerance to the sedative effect of lorazepam correlates with a diminution in cortical release and affinity for glutamate. *Neuropharmacol.* 2002; 42:619–625.
40. Simpson GM, Lindenmayer J-P. Extrapyramidal Symptoms in Patients Treated With Risperidone. *J Clin Psychopharm.* 1997; 17:194–201.
41. Blanco C, Laje G, Olfson M, Marcus SC, Pincus HA. Trends in the treatment of bipolar disorder by outpatient psychiatrists. *Am J Psychiat.* 2002; 159:1005–1010. [PubMed: 12042190]

Fig. 1.
Likelihood of treatment response and remission according to the number of prior antidepressant medications patients reported at baseline.

Table 1

Baseline characteristics of subjects randomized to venlafaxine or lithium carbonate

	Venlafaxine (n = 65)		Lithium (n = 64)		p-value
	n	%	n	%	
Females ^a	35	53.8	38	59.4	0.60
Non-Caucasian ^a	9	13.8	17	26.6	0.08
Rapid cycling ^a	30	46.2	25	39.1	0.48
Inter-episode recovery ^a	13	20.3	15	23.1	0.92
	Mean	SD	Mean	SD	
No. of prior antidepressant trials ^b	2.80	1.99	2.57	2.04	0.53
Age, years ^b	43.0	13.1	42.7	14.3	0.92
Age first MDE, years ^a	18.6	7.7	17.2	7.0	0.28
Age first hypomanic episode, years ^b	20.6	8.0	20.5	10.7	0.92
No. prior MDEs ^b	24.1	42.2	24.0	32.3	0.99
No. prior hypomanic episodes ^b	43.9	61.0	44.4	99.1	0.97
Baseline HRSD ^b	20.0	3.7	20.2	3.8	0.64
Baseline YMRS ^b	0.6	1.4	0.5	1.4	0.93
Duration of depressive episode, months ^b	11.53	14.68	14.13	15.52	0.33

MDE = major depressive episode; HRSD = Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale; SD = standard deviation.

^aFisher's exact test.^bStudent t-test.

Table 2

Frequency of prior psychotropic drug trials for those subjects previously exposed to drug therapy

Antidepressants	No. of prior medication trials	n	%
Any	0	22	17.05
	1	23	17.83
	2	20	15.50
	3	19	14.73
	4	14	10.85
	5	15	11.63
	6+	16	12.40
SSRIs	0	26	20.2
	1	35	27.1
	2	18	14.0
	3	20	15.5
	4	17	13.2
	5+	13	10.0
Mixed action antidepressants^a	0	84	65.1
	1	27	20.9
	2	14	10.9
	3+	4	3.2
Venlafaxine	0	103	79.8
	1	23	17.8
	2	3	2.3
TCAs	0	115	89.1
	1	11	8.5
	2+	3	2.5
MAOIs	0	122	94.6
	1+	7	5.4
Other medications			
Mood stabilizer	0	97	75.2
	1	19	14.7
	2	10	7.8
	3+	3	2.5
Lithium	0	107	82.9
	1	20	15.5
	2+	2	1.7
Atypical antipsychotics	0	110	85.3
	1	12	9.3

Antidepressants	No. of prior medication trials	n	%
	2	5	3.9
	3+	2	1.7

SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; MAOI = monoamine oxidase inhibitor.

^aMixed action antidepressants include medications such as serotonin antagonist and reuptake inhibitor (SARI) and norepinephrine-dopamine reuptake inhibitor (NDRI).

Table 3

Clinical and demographic correlates of number of prior antidepressant trials

	<i>r</i>	p-value
Females	0.11	
Non-Caucasian	−0.25	< 0.01
Rapid cycling	−0.11	
Inter-episode recovery	−0.25	< 0.01
Age, years	0.16	
Age first MDE, years	−0.21	< 0.05
Age first hypomanic episode, years	−0.03	
No. prior MDEs	0.24	< 0.01
No. prior hypomanic episodes	0.15	
Baseline HRSD	0.35	< 0.001
Baseline YMRS	−0.05	
Duration of depressive episode, months	0.06	

MDE = major depressive episode; HRSD = Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale.

Table 4

Prediction of response and remission from baseline characteristics and treatment (Step 1) and the number of prior antidepressant medications patients report at baseline

Dependent variable: responder status	Step 1					Step 2				
	B	S.E.	Wald	OR	p-value	B	S.E.	Wald	OR	p-value
Venlafaxine (versus lithium)	1.52	0.40	14.28	4.56	< 0.001	1.67	0.42	15.59	5.29	<0.001
Caucasian (versus other ethnicities)	−0.56	0.51	1.22	0.57		−0.21	0.53	0.16	0.81	
Inter-episode recovery	0.81	0.49	2.68	2.24		0.63	0.51	1.49	1.88	
Baseline HRSD	−0.08	0.05	2.54	0.92		−0.04	0.06	0.42	0.96	
No. prior episodes	0.00	0.01	0.15	1.00		0.01	0.01	0.94	1.01	
No. prior antidepressants						−0.29	0.12	5.70	0.75	< 0.01
Chi square				15.37					28.31	
Nagelkerke <i>R</i> square				0.21					0.26	
Dependent variable: symptom remission										
Venlafaxine (versus lithium)	1.27	0.39	10.53	3.56	< 0.001	1.49	0.42	12.43	4.44	< 0.001
Caucasian (versus other ethnicities)	0.25	0.51	0.25	1.29		0.69	0.53	1.69	1.99	
Inter-episode recovery	0.57	0.47	1.45	1.76		0.30	0.51	0.34	1.35	
Baseline HRSD	−0.10	0.05	3.63	0.90		−0.04	0.06	0.52	0.96	
No. prior episodes	0.00	0.01	0.01	1.00		0.01	0.01	0.49	1.01	
No. prior antidepressants						−0.39	0.13	9.71	0.68	< 0.01
Chi square				19.05					29.88	
Nagelkerke <i>R</i> square				0.18					0.28	

HRSD = Hamilton Rating Scale for Depression; OR = odds ratio.