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DYNAMIC PREDICTION OF TREATMENT RESPONSE IN LATE-LIFE DEPRESSION

Ian Joel, BS¹, Amy E. Begley, MA¹, Benoit H. Mulsant, MD², Eric J. Lenze, MD³, Sati Mazumdar, PhD⁴, Mary Amanda Dew, PhD¹, Daniel Blumberger, MD, PhD², Meryl Butters, PhD¹, Charles F. Reynolds III, MD^{1,*}, and for the IRL GREY Investigative Team^{**}

¹University of Pittsburgh School of Medicine, Department of Psychiatry, Pittsburgh, PA USA

²Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Ontario, Canada

³Washington University, Department of Psychiatry, St. Louis MO USA

University of Pittsburgh Graduate School of Public Health, Department Biostatistics, Pittsburgh, PA USA

Abstract

Objective—1) identify actionable predictors of remission to antidepressant pharmacotherapy in depressed older adults and 2) use signal detection theory to develop decision trees to guide clinical decision making

Method—We treated 277 participants with current major depression using open-label venlafaxine XR (up to 300 mg/day) for 12 weeks, in an NIMH-sponsored randomized, placebo-controlled augmentation trial of adjunctive aripiprazole. Multiple logistic regression and signal detection approaches identified predictors of remission in both completer and intent-to-treat samples.

Results—Higher baseline depressive symptom severity (OR, 0.86, 95% CI, 0.80-0.93; $p < 0.001$), smaller symptom improvement during the first two weeks of treatment (OR, 0.96, 95% CI, 0.94-0.97; $p < 0.001$), male sex (OR, 0.41 95% CI, 0.18-0.93, $p = 0.03$), duration of current episode ≥ 2 years (OR, 0.26 95% CI, 0.12-0.57, $p < 0.001$) and adequate past depression treatment (ATHF ≥ 3) (OR, 0.34 95% CI, 0.16-0.74, $p = 0.006$) predicted lower probability of remission in the completer sample. Subjects with Montgomery Asberg (MADRS) decreasing by $> 27\%$ in the first two weeks and with baseline MADRS scores of < 27 (percentile rank = 51) had the best chance of remission (89%). Subjects with small symptom decrease in the first 2 weeks with adequate prior treatment and younger than 75 yrs old had the lowest chance of remission (16%).

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*Corresponding Author: Charles F. Reynolds III, M.D., University of Pittsburgh, 3811 O'Hara Street BT 758, Pittsburgh, PA 15213, 412-246-6426, reynoldscf@upmc.edu.

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Conclusion—Our results suggest the clinical utility of measuring pre-treatment illness severity and change during the first two weeks of treatment in predicting remission of late-life major depression.

INTRODUCTION

Major depressive disorder (MDD) is prevalent in older adults (1–3% point prevalence)(1) and can be difficult to treat, with at least 50% of patients failing to respond adequately to first-line antidepressant pharmacotherapy.(2–4) Slower response to initial treatment predicts shorter time to recurrence,(5; 6) and persistence of residual depressive symptoms consistently predicts a less durable recovery in these patients.(7) Achieving remission quickly is paramount in the treatment of late-life depression (LLD); prolonged illness amplifies suffering and disability, increases caregiver burden, non-adherence with treatment and dropout, poor adherence with other medical treatments, and increased mortality including death by suicide.(8)

Given the clinical importance of achieving remission early in treatment, research to date has focused on identifying pre-treatment characteristics that predict slow or incomplete response to initial pharmacotherapy in older adults with major depression. Such predictors could help clinicians make early decisions about intervention strategies, such as switching, combining, or augmenting medications vs. “staying the course”. Greater comorbid medical burden(9), larger depressive symptom burden(10), higher levels of comorbid anxiety(11), poor previous response to antidepressant treatment(12), poor social support(13), the presence of suicidal ideation(14), a past history marked by recurrent rather than single-episode depression(15), and the use of concomitant psychotropic medication (CPM)(16), have all been identified as predictors of delayed or incomplete treatment response. Additionally, in studies of predominantly midlife patients, minimal improvement in depressive symptoms early in treatment reliably predicts poor treatment response (8);(17–21). The literature is inconclusive regarding the effects of lifetime age of onset(13; 22);(23) and executive dysfunction(24) on treatment response.

Although several predictors of treatment response have been identified, identification of the most clinically actionable ones remains incomplete, especially in older adults with major depression. Also unknown is whether predictors in the context of one type of treatment also serve as predictors for other types. Moreover, many published studies have focused on different parameters of treatment response variability(13) and used varying outcome measures to define response. In this context, Andreescu and colleagues(22) integrated a select group of putative predictors of response to SSRIs into a dynamic, clinically useful algorithm based on signal detection theory, identifying symptom change in the first four weeks of pharmacotherapy as a predictor of final response status(20). More recently, identification of early improvers at two weeks (improvement of 20% in pretreatment depression ratings) has been shown to predict remission in midlife patients treated with adjunctive aripiprazole(20). To our knowledge, however, no study has previously examined similar dynamic predictors of response status to SNRI antidepressants(20). Moreover, the preponderance of studies that have examined response prediction with other types of antidepressant agents have done so using trials of short duration and sub-maximal dosage (25; 26), thus employing less stringent criteria for reliably determining final response status.(27)

The aim of this study was thus to extend these findings by characterizing baseline demographic, clinical, and early-symptom-change correlates of remission to 12-week, open-label venlafaxine XR monotherapy. We sought to: 1) identify clinically actionable predictors of treatment remission to SNRI therapy in depressed older adults and 2) use signal detection

theory to develop decision trees that can facilitate prediction early in the course of treatment. We asked whether a combination of baseline measures and depressive symptom change as early as 2 weeks of treatment would yield clinically useful tools for prediction of final remission in older adults.

METHOD

Participants

Between July 20, 2009, and April 13, 2012, we screened 759 depressed patients aged 60 and older, with 351 excluded because of failure to satisfy inclusion/exclusion criteria of the study. We excluded patients with a lifetime diagnosis of bipolar disorder, schizophrenia, schizoaffective or other psychotic disorders; current psychotic symptoms; dementia; scores of 20 or less on the Folstein Mini-Mental Status Examination (MMSE); a history of alcohol or substance abuse within the past 3 months; high risk for suicide; unstable medical illness; or a contraindication to venlafaxine XR or aripiprazole. Of the 408 who were eligible and agreed to participate, 102 dropped out before starting treatment; 306 began treatment, of whom 29 are active still in the first phase of the study. Of the 277 participants who participated in this study phase, 219 completed the 12-week trial, and 58 withdrew after starting venlafaxine. Of the 58 dropouts, 23 withdrew consent (desired alternative treatments or felt too burdened by the protocol); 35 were removed by investigators due to medical issues, adverse events, noncompliance, or administrative reasons. Data from the 219 participants completing the 12-week trial are presented in this report. Results from intent to treat analyses are also summarized (data from intent to treat analyses are available upon request).

Pathways leading to participation included referral from primary care and specialty mental health sectors; self-referral in response to advertisements in the media or on websites including a study website www.latelivedepression.org and clinicaltrials.gov; and solicitation of potentially eligible patients enrolled in research registries or being treated in collaborating primary care practices. All participants were experiencing a non-psychotic, unipolar major depressive episode, as established by the Structured Clinical Interview for DSM-IV,(28) and had a baseline rating of 15 or higher on the Montgomery-Asberg Depression Rating Scale (MADRS). The study was conducted after approval from the institutional review boards of the three sites involved, and all participants provided written informed consent.

Assessment

We assessed depressive symptoms using the MADRS (main outcome measure; Cronbach's $\alpha=0.65$) and the 17-item Hamilton Rating Scale for Depression (Cronbach's $\alpha=0.60$). Other pre-treatment assessments focused on suicidal ideation (21-item Scale for Suicide Ideation, SSI(29); Cronbach's $\alpha=0.90$), general anxiety symptoms (Brief Symptom Inventory, BSI-anxiety(30); Cronbach's $\alpha = 0.87$), severity and uncontrollability of worry (Penn State Worry Questionnaire, brief version, PSWQ(31); Cronbach's $\alpha = 0.92$), comorbid medical burden (Cumulative Illness Rating Scale for Geriatrics, CIRS-G),(32) global cognitive function (Repeatable Battery for the Assessment of Neuropsychological Status, RBANS),(33) executive function (two tests from the Delis-Kaplan Executive Function Scale, DKEFS),(34) response to previous antidepressant treatment (Anti-depressant Treatment History Form, ATHF),(35) as well as basic demographic information (age, gender, race, education) and clinical variables (age at onset of first lifetime depressive episode, duration of current episode, single vs. recurrent presenting episode, any outside psychotherapy participation during treatment, any history of substance abuse, and the percentage using benzodiazepines during treatment).

Participants were seen once a week for the first two weeks and then every 2 weeks by study clinicians under the supervision of physician investigators. During each of these visits, the research team assessed depressive symptoms (MADRS), suicidal ideation (SSI), vital signs, and adverse effects (UKU side effects rating scale)(17). Finally, at the end of treatment, independent assessors administered the MADRS. The three site PIs then conjointly adjudicated final remission status for each participant.

Intervention

We treated participants openly with venlafaxine XR, starting at 37.5 mg/day and titrated (in 37.5 mg increments, at least every 3 days) to a target dose of 150 mg/day. At the end of week 6, non-remitters (MADRS>10) had their dose of venlafaxine increased further (in 37.5-75 mg increments every 3 days) to a target dose of 300 mg/day. To assess remission status, we followed participants for at least 4 weeks on the maximum tolerated dose. At any time during treatment, participants who experienced adverse effects could receive a reduced dose. Participants were permitted to use lorazepam (up to 2 mg/day) as needed for sleep or anxiety. Participants were also allowed to continue using medications for sleep, including zolpidem, zopiclone, trazadone, low-dose amitriptyline, and to participate in outside psychotherapy, if these therapies could not be discontinued during the study. Throughout the study, pharmacotherapy was embedded in a model of depression care management, that is, supportive clinical care focusing on psychoeducation about depression and its treatment, depressive symptoms, suicidal ideation, countermeasures for medication adverse effects, and treatment adherence, but not incorporating any depression-specific psychotherapy.(18)

Analysis

We generated descriptive statistics to provide a multidimensional characterization of the completer study group (n=219). For all analyses, we categorized subjects into remitters and non-remitters, based on the following criterion: two consecutive MADRS scores ≤ 10 at the end of treatment. There were 58 subjects who dropped out prior to completing the study. To determine the outcome of the dropouts, imputations were performed for both intermittent missing and monotone missing observations, so that each subject had a MADRS score at each time point (weeks 0, 1 and bi-weekly weeks 2 through 12). A static imputation was arrived at through multiple iterations using the Markov Chain Monte Carlo (MCMC) option of the multiple imputation procedure in SAS. We examined the imputed classification of each subject in each of 45 imputed datasets. Individuals were classified as remitted or non-remitted based on which was the majority in the imputed datasets. Of these dropouts, 57 were classified as non-remitters and 1 was classified a remitter. (Rates of dropout and non-remission did not differ across three participating sites.) The frequency of imputed outcomes differed between the groups who were eventually determined to be remitters versus “non-remitters” (1% (1/106) vs. 33% (57/171), Fisher Exact $p<0.001$). The reasons for dropout indicate that the dropouts were not dependent on observed data and could be considered MAR (missing at random).

After examining data for normality and using transformation when necessary, we assessed differences in key demographic and clinical characteristics between remitters and non-remitters in the completer sample, using t-tests for continuous variables and chi-square or Fishers exact tests for categorical variables. Variables significantly associated with remission at $p<0.05$ in the univariate models were forced into a multiple logistic regression model. The Pearson correlations between all predictor variables were examined before running the model. The same predictors included in the logistic regression model were also incorporated into a receiver-operating characteristic (ROC) model using signal detection. The purpose of the ROC model was to develop a clinically useful tool for predicting remission based on the clinical predictors identified in the univariate analysis. We asked

what combination of characteristics best predicted remission after taking into account the clinical consequences of misclassifications. We used the ROC5 program (<http://www.stanford.edu/~yesavage/ROC.html>), public domain software designed to perform signal detection computations. The program allows the user to weight the importance of sensitivity (i.e., more emphasis on avoiding false negatives; that is, falsely concluding that the patient would eventually not remit) vs. specificity (i.e., more emphasis on avoiding false positives that is, falsely concluding that the patient would eventually remit) by specifying the threshold. For example, a threshold of 50 will weight sensitivity and specificity evenly, while a threshold of 30 will calculate a 30/70 split to the kappa emphasizing specificity (70%) over sensitivity (30%). We ran two models, one with a threshold of 30 and the other with a threshold of 70. We also repeated all analyses using the intent to treat sample as a sensitivity analysis (and, as reported below, found virtually identical results). Unless otherwise noted all statistical analyses were conducted using SAS version 9.2 statistical software (SAS Institute Inc., Cary, North Carolina).

RESULTS

As presented in Table 1 (univariate analyses of the completer sample), 105 participants (48.0%) were classified as remitters and 114 (52.0%) as non-remitters, with no significant differences in referral sources or use of benzodiazepines between them. Non-remitters received higher end-phase doses (mg/d) of venlafaxine than did remitters (279 vs. 201). Twelve variables were associated with remission at $p < .05$ and were included in the multivariate models: age, gender, education, baseline depressive symptom severity (MADRS), anxiety severity (BSI), age of onset of first lifetime depressive episode, current episode duration ≥ 2 years, adequacy of past antidepressant trial, outside psychotherapy during trial, history of suicide attempt, presence of suicidal ideation (SIS), and percentage change in MADRS score in the two weeks. Several key variables-of-interest — comorbid medical burden, and cognitive impairment—did not differ significantly between groups.

In the intent to treat sample 106 participants (38.3%) were classified as remitters and 171 (61.7%) as non-remitters (data not shown; available upon request). Contrasts between remitters and non-remitters were identical to the completer sample except that, age, age of onset of first lifetime episode, adequate prior antidepressant trial, and whether or not subject received outside psychotherapy were no longer significant at $p < 0.05$. Eight variables continued to be associated with remission at $p < .05$ and were included in the multivariate models: gender, education, baseline depressive symptom severity (MADRS), anxiety severity (BSI), percentage with current episode duration ≥ 2 years, history of suicide attempt, suicide ideation (SIS) and percent change in MADRS score in the first two weeks.

Table 2 shows the results of the multiple logistic regression in the completer sample ($n=219$). (Results from intent to treat analyses will be summarized here; data are available upon request.) Male gender, higher MADRS score at baseline, duration of current episode ≥ 2 years, adequate prior antidepressant trial, and lower percent decrease in MADRS in first 2 weeks predicted lower probability of remission. In the intent-to treat analysis [$n=277$], male gender, higher MADRS score at baseline, duration of current episode ≥ 2 years, lower percent change in MADRS during first 2 weeks also predicted lower remission rate. For all logistic regression models, the same predictors were significant whether all variables are forced into the model or whether a forward or backward stepwise regression was used.

Results of the signal detection analyses in the completer sample are shown in Figures 1 and 2. In the first model (Figure 1), we set the sensitivity cutoff point at 30 to favor specificity of prediction in clinical situations when an aggressive approach would be needed (e.g., in the context of disabling depression or high suicide risk) because falsely concluding that the

patient would eventually remit to treatment could be harmful. The significant predictors of remission in this model were higher percent improvement in symptoms (MADRS score) during first 2 weeks and lower level of depressive symptoms at baseline, adequacy of prior treatment, age and onset of first lifetime episode. Thus, as depicted in figure 1, subjects with MADRS scores decreasing by more than 28% in the first two weeks and with baseline MADRS score < 27 (percentile rank = 51) had the best chance of remission (88.5%). Subjects who had small change in MADRS scores in the first 2 weeks, who had had adequate prior treatment, and who were less than 75 years old had low chance of remission (15.5%).

In the second model (Figure 2), we set the sensitivity cutoff point at 70 to favor sensitivity of prediction in clinical situations when a conservative approach would be needed (e.g., in the context of a history of previous delayed or incomplete response to treatment), because falsely concluding that the patient would be a non-remitter could lead to giving up prematurely on a treatment that would eventually be beneficial. The significant predictors of remission were higher percentage of improvement in the first two week, lower baseline depression severity, shorter duration of current episodes, inadequate prior treatment, and older age. As depicted in Figure 2, subjects whose symptom severity did not change much in the first 2 weeks (< 26.5%) had a lower chance of remitting compared to those whose symptoms decreased more (26.5% vs. 70.3%) Subjects whose MADRS scores changed by less than 26.5% in the first 2 weeks, who had adequate prior treatment and who were less than 75 had the lowest probability of remitting (12.3%). Subjects whose MADRS score changed by more than 26.5% in the first 2 weeks and had MADRS at baseline < 27 (percentile rank = 51) had the highest probability of attaining remission (86%).

In signal detection analyses using the intent to treat sample (n=277; data not shown but available upon request), high specificity models (30% sensitivity) showed the primary predictors were also symptom reduction during the first two weeks of treatment (MADRS percent change) and baseline severity of depressive symptoms (MADRS). In addition, education was also a significant predictor. In the high sensitivity models (70% sensitivity), percent change in MADRS score after two weeks, baseline MADRS scores and anxiety were significant predictors.

DISCUSSION

In depressed older adults, easily measured patient characteristics —gender, baseline level of depressive symptoms and evidence of symptomatic improvement at week 2—predicted the likelihood of remission after 12 weeks of treatment with venlafaxine XR. If a profile suggests treatment resistance, the clinician and patient can consider other treatment strategies, such as switching medication or augmentation of the initial antidepressant early in the course of treatment. Conversely, for older patients with profiles indicating a high chance of remission “staying the course” would be appropriate. While some studies have used signal detection theory to demonstrate that a patient’s symptomatic response after 4–6 weeks of treatment reliably predicts their response status at 12 weeks,(19; 22) the current data suggest that after as little as 2 weeks of treatment, improvement in depressive symptoms can be utilized in conjunction with baseline severity to predict remission. These results are consistent with Sackeim and Roose³⁶, who also reported that symptomatic change during 6 weeks of antidepressant treatment reliably predicted final response status. Other studies in midlife patients have reached similar conclusion. (20; 21; 36–38) Early prediction of non-response should lead to earlier treatment change (dose, addition, etc.) rather than waiting a month or more. Early benefit, of whatever cause, is a reason to be encouraged.

We note several limitations of this study. First, we utilized data from an open-label trial lacking a placebo control group and are therefore unable to distinguish whether the observed symptomatic changes were treatment-specific or were due to non-specific factors (e.g., time or attention). Lower scores at baseline may mean that it is easier to have a lower score at end point but do not argue for a specific benefit of treatment. Consistent with this observation, a recent analysis (using logistic regression and classification/regression tree methods) of 1017 placebo-treated patients with major depression consistently identified as the best predictors of remission less severe depression symptoms, younger age, less anxiety, and shorter current MDD episode duration(39). Second, replication of our findings is needed to verify their stability. Prediction models developed from the use of signal detection show variability that reflects their recursive nature. Thus, the first cut point is made using the best predictor and yielding the optimal prediction of remitter/non-remitter status. The program runs again on those subgroups to identify the next optimal cuts within those subpopulations. Given the recursive nature of the signal detection procedure, it is possible to come up with different branching. Third, our patients received depression care management in addition to pharmacotherapy(18) and thus they may not be generalizable to pharmacotherapy provided under “usual care” conditions. Finally, we did not examine all possible clinical markers or any putative biological markers of treatment resistance that could potentially bolster the overall explanatory power of the models.

An understanding of predictors that can best be used in the clinic or at the bedside to guide treatment decision making and minimize exposure to ineffective medications is an important first step toward personalizing depression treatment. However, without the systematic use of a standardized assessment tool to measure changes in symptom status during treatment, it is difficult to implement care tailored to each patient’s need. It is unlikely that rater-administered measures such as the Montgomery Asberg would be used by clinicians in clinical practice. More likely is the use of a self-report scale, such as the QIDS (Quick Inventory of Depressive Symptoms)(40) or PHQ-9 (patient Health Questionnaire-9).(41) Whether the current results would hold up with the use of a self-report scale would also be important to demonstrate.

In summary, the current results suggest that measuring change in clinical status as early as week 2 in conjunction with pretreatment severity measures of depression can inform clinical decision making early in treatment of older adults with major depression.

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References List

1. Mulsant BH, Ganguli M. Epidemiology and diagnosis of depression in late-life. *J Clin Psychiatry*. 1999; 60(suppl):9–15. [PubMed: 10513852]
2. Bruce ML, McAvay G. Epidemiology of psychiatric disorders in late life. *Primary Psychiatry*. 1998; 5:59–65.
3. Thomas L, Mulsant BH, Solano FX, et al. Response speed and rate of remission in primary and specialty care of elderly patients with depression. *Am J Geriatr Psychiatry*. 2002; 10:583–591. [PubMed: 12213693]
4. Whyte EM, Basinski J, Farhi P, et al. Geriatric depression treatment in non-responders nonresponders to selective serotonin reuptake inhibitors. *J Clin Psychiatry*. 2004; 65(12):1634–1641. [PubMed: 15641868]

5. Flint AJ, Rifat SL. Maintenance treatment for recurrent depression in late-life. *Am J Geriatr Psychiatry*. 2000; 8:112–116. [PubMed: 10804071]
6. Whyte EM, Dew MA, Gildengers A, et al. Time course of response to antidepressants in late-life major depression: Therapeutic implications. *Drugs Aging*. 2004; 21(8):531–554. [PubMed: 15182217]
7. Dombrowski, AY.; Szanto, K.; Siegle, GJ., et al. *Suicidal Elderly Discount Future Rewards*. Vancouver, Canada: Biological Psychiatry; 2009.
8. Mulsant BH, Houck PR, Gildengers AG, et al. What is the optimal duration of a short-term antidepressant trial when treating geriatric depression? *J Clin Psychopharmacol*. 2006; 26(2):113–120. [PubMed: 16633138]
9. Dew MA, Whyte EM, Lenze EJ, et al. Recovery from major depression in older adults receiving augmentation of antidepressant pharmacotherapy. *Am J Psychiatry*. 2007; 164(6):892–899. [PubMed: 17541048]
10. Gildengers AG, Houck PR, Mulsant BH, et al. Trajectories of treatment response in late-life depression: Psychosocial and clinical correlates. *Journal of Clinical Psychopharmacology*. 2005; 25(Suppl 1):S8–S13.
11. Andreescu C, Lenze EJ, Dew MA, et al. Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: Controlled study. *The British Journal of Psychiatry*. 2007; 190:344–349. [PubMed: 17401042]
12. Tew JD, Mulsant BH, Houck PR, et al. Impact of prior inadequate treatment exposure on response to antidepressant treatment in late life. *Am J Geriatr Psychiatry*. 2006; 14(11):957–965. [PubMed: 17068318]
13. Dew MA, Reynolds CF, Houck PR, et al. Temporal profiles of the course of depression during treatment: Predictors of pathways toward recovery in the elderly. *Arch Gen Psychiatry*. 1997; 54:1016–1024. [PubMed: 9366658]
14. Szanto K. Suicidal behavior in the elderly. (Special Report). *Psychiatric Times*. 2003:52–54.
15. Driscoll HC, Basinski J, Mulsant BH, et al. Late-onset major depression: Clinical and treatment-response variability. *International Journal of Geriatric Psychiatry*. 2005; 20:661–667. [PubMed: 16021664]
16. Shelton RC, Hollon SD, Wisniewski SR, et al. Factors associated with concomitant psychotropic drug use in the treatment of major depression: a STAR*D Report. 2009; 9:487–498. *CNS Spectrums*.
17. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl*. 1987; 334:1–100. [PubMed: 2887090]
18. Reynolds CF, Dew MA, Martire LM, et al. Treating depression to remission in older adults: A controlled evaluation of combined interpersonal psychotherapy versus escitalopram with depression care management. *International Journal of Geriatric Psychiatry*. 2010; 25:1134–1141. [PubMed: 20957693]
19. Sackeim HA, Roose SP, Lavori PW. Determining the duration of antidepressant treatment: Application of signal detection methodology and the need for duration adaptive designs (DAD). *Biol Psychiatry*. 2006; 59(6):483–492. [PubMed: 16517241]
20. Muzina DJ, Chambers JS, Camacho TA, et al. Adjunctive aripiprazole for depression: predictive value of early assessment. *Am J Manag Care*. 2011; 17(12):793–801. [PubMed: 22216750]
21. Trivedi MH, Baker SM. Clinical significance of monitoring early symptom change to predict outcome. *J Clin Psychiatry*. 2001; 62(Suppl 4):27–33. [PubMed: 11229785]
22. Andreescu C, Mulsant BH, Houck PR, et al. Empirically derived decision trees for the treatment of late-life depression. *Am J Psychiatry*. 2008; 165(7):855–862. [PubMed: 18450930]
23. Alexopoulos GS, Meyers BS, Young RC, et al. The "vascular depression" hypothesis. *Arch Gen Psychiatry*. 1997; 54(10):915–922. [PubMed: 9337771]
24. McLennan SN, Mathias JL. The depression-executive dysfunction (DED) syndrome and response to antidepressants: a meta-analytic review. *Int J Geriatr Psychiatry*. 2010; 25(10):933–944. [PubMed: 20872927]

25. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007; 68(6):843–853. [PubMed: 17592907]
26. Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2008; 28(2):156–165. [PubMed: 18344725]
27. Nelson JC, Delucchi K, Schneider LS. Efficacy of second generation antidepressants in late-life depression: a meta-analysis of the evidence. *Am J Geriatr Psychiatry*. 2008; 16(7):558–567. [PubMed: 18591576]
28. First, M.; Spitzer, RL.; Gibbon, M., et al. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P). New York: New York State Psychiatric Institute; 1995.
29. Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: The Scale for Suicide Ideation. *J Consult Clin Psychol*. 1979; 47:343–352. [PubMed: 469082]
30. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med*. 1983; 13(3):595–605. [PubMed: 6622612]
31. Meyer TJ, Miller ML, Metzger RL, et al. Development and validation of the Penn State Worry Questionnaire. *Behav Res Ther*. 1990; 28(6):487–495. [PubMed: 2076086]
32. Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: Application of the Cumulative Illness Rating Scale. *Psychiatry Res*. 1992; 41(3):237–248. [PubMed: 1594710]
33. Randolph C, Tierney MC, Mohr E, et al. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol*. 1998; 20(3):310–319. [PubMed: 9845158]
34. Delis DC, Kaplan E, Kramer JH. *Dellis Kaplan Executive Function System Examiner's Manual*. The Psychological Corporation. 2001
35. Oquendo MA, Baca-Garcia E, Kartachov A, et al. A computer algorithm for calculating the adequacy of antidepressant treatment in unipolar and bipolar depression. *J Clin Psychiatry*. 2003; 64(7):825–833. [PubMed: 12934985]
36. Nierenberg AA, McLean NE, Alpert JE, et al. Early nonresponse to fluoxetine as a predictor of poor 8-week outcome. *Am J Psychiatry*. 1995; 152(10):1500–1503. [PubMed: 7573590]
37. Szegedi A, Muller MJ, Anghelescu I, et al. Early improvement under mirtazapine and paroxetine predicts later stable response and remission with high sensitivity in patients with major depression. *J Clin Psychiatry*. 2003; 64(4):413–420. [PubMed: 12716243]
38. Szegedi A, Jansen WT, van Willigenburg AP, et al. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. *J Clin Psychiatry*. 2009; 70(3):344–353. [PubMed: 19254516]
39. Nelson JC, Zhang Q, Deberdt W, et al. Predictors of remission with placebo using an integrated study database from patients with major depressive disorder. *Curr Med Res Opin*. 2012; 28(3):325–334. [PubMed: 22292447]
40. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003; 54(5):573–583. [PubMed: 12946886]
41. Kroenke K, Spitzer R. The PHQ-9: A new depression and diagnostic severity measure. *Psychiatric Annals*. 2002; 32:509–521.

Figure 1.

Hierarchy of predictors of treatment remission with an aggressive treatment approach (i.e., a threshold of 30% for sensitivity) using intent to treat sample.

Figure 2.
Hierarchy of predictors of treatment remission with a conservative treatment approach (i.e., a threshold of 70% for sensitivity).

Table 1

Demographic and clinical characteristics of remitters and non-remitters: completer sample

	Whole Group N=219 Mean(SD) or % (N)	Remitters N=105 Mean(SD) or % (N)	Non-remitters N=114 Mean(SD) or % (N)	
Age	68.3 (6.8)	69.6 (7.6)	67.1 (5.7)	t(217)=-2.77, p=0.006
%Male	33.3 (n=73)	24.8 (n=26)	41.2 (n=47)	$\chi^2(1)=6.67$, p=0.01
%Caucasian	88.6 (n=194)	86.7 (n=91)	90.4 (n=103)	$\chi^2(1)=0.73$, p=0.39
Education	14.3 (2.8)	14.8 (2.8)	13.9 (2.8)	t(217)=-2.42, p=0.02
Hamilton Depression Rating Scale at baseline	19.4 (5.0) n=217	18.6 (4.4) n=104	20.1 (5.4) n=113	t(215)=2.28, p=0.02
Montgomery-Asberg Depression Rating Scale (MADRS) at baseline	26.7 (5.8) range = 13-43	24.6 (5.3) range=13-39	28.7 (5.6) Range=15-43	t(217)=5.57, p<.001
Brief Symptom Inventory, Anxiety (BSI Anxiety)	1.4 (1.0)	1.3 (0.9)	1.6 (1.0)	t(217)=2.46, p=0.02
Penn State Worry Questionnaire (PSWQ)	59.6 (12.8) n=214	58.1 (12.4) n=103	60.9 (13.0) n=111	t(212)= 1.62, p=0.11
Cumulative Illness Rating Scale (CIRS-G) Total	9.9 (4.5) n=218	9.7 (4.4) n=104	10.2 (4.5)	t(216)=0.85, p=0.40
Count	6.3 (2.4) n=218	6.0(2.5) n=104	6.3 (2.4)	t(216)=-0.71, p=0.48
%Recurrent depression	73.1 (n=160)	75.2 (n=79)	71.1 (n=81)	$\chi^2(1)=0.49$, p=0.49
Age of onset of first lifetime episode	40.9 (21.4) n=218	44.4 (21.2) n=104	37.7 (21.2)	t(216)=-2.35, p=0.02
Duration of current episode (weeks) ^b	355.0 (743.6) n=217	216.8 (543.0)	484.5 (874.4) n=112	t(215)=4.09, p<0.001
%Duration of current episode $\geq$ 2 years	45.6 (n=99/217)	31.4 (n=33/105)	58.9 (n=66/112)	$\chi^2=16.52$, p<0.001
Strength of highest rated antidepressant trial (ATHF) % $\geq$ 3	66.5 (n=143/215)	56.3 (n=58/103)	75.9 (n=85/112)	$\chi^2(1)=9.24$, p=0.0024
% with outside psychotherapy during trial	12.3 (n=27)	7.6 (n=8)	16.7 (n=19)	$\chi^2(1)=4.14$, p=0.04
% with history of a suicide attempt	15.2 (n=33/217)	6.8 (n=7/103)	22.8 (n=26/114)	$\chi^2(1)=10.8$, p=0.001
% Scale for Suicide Ideation (SSI) at baseline >0	32.4 (n=71)	23.8 (n=25)	40.4 (n=46)	$\chi^2(1)=6.83$, p=0.009
% with history of substance abuse	17.8 (n=39)	14.3 (n=15)	21.1 (n=24)	$\chi^2(1)=17.1$, p=0.19
% Benzodiazepines use	43.8 (n=96)	40.0 (n=42)	47.4 (n=54)	$\chi^2(1)=12.1$, p=0.27
Percent change in MADRS during first 2 weeks	-24.8 (26.9)	-36.1 (26.0)	-14.5 (23.5)	t(215)=-6.41, p<.001
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Total	95.1 (16.3) n=214	95.1 (14.5) n=101	95.1 (17.8) n=113	t(212)=-0.01, p=0.99
Delayed Memory	95.7 (16.8) n=217	96.2 (16.1) n=103	95.3(17.4) n=114	t(215)=-0.41, p=0.68
Coding Task	94.4 (20.6) n=217	95.6 (18.8) n=103	93.4 (22.1)	t(215)=-0.77, p=0.44
Delis-Kaplan Executive Function Scale (DKEFS) Trails-simple vs. alternating	8.5 (3.6) n=209	8.5 (3.5) n=99	8.5 (3.6) n=110	t(207)= 0.03, p=0.97
Color-word interference errors scaled score ^b	10.3 (2.7) n=208	10.4 (2.8) n=99	10.2 (2.7) n=109	t(206)=0.08, p=0.94
Montgomery-Asberg Depression Rating Scale	14.4 (10.9)	4.4 (3.1)	23.6 (6.5)	t(163.7)=28.31, p<.001

	Whole Group N=219 Mean(SD) or % (N)	Remitters N=105 Mean(SD) or % (N)	Non-remitters N=114 Mean(SD) or % (N)	
(MADRS) at end of trial a				
Venlafaxine dose at the end of trial ^{a,b}	241.4 (73.1)	201.1 (74.8)	278.5 (47.4)	t (217)= 9.21, p<.001

^a Satterthwaite method used due to unequal variances.

^b Means and standard deviations reported in the original units. LN(X) transformation used in the analyses.

Table 2

Results of multiple logistic regression using the completer sample (n = 219), forcing significant univariate variables where $p < 0.05$

	Estimate (Stderr)	Wald Chisquare (df=1)	p-value	Odds Ratio [95% CI]
Age	0.04 (0.03)	2.15	0.14	1.05 [0.99–1.11]
Male	−0.90 (0.42)	4.60	0.03	0.41 [0.18–0.93]
Education	0.10 (0.07)	1.98	0.16	1.11 [0.96–1.27]
Montgomery-Asberg Depression Rating Scale (MADRS) at baseline	−0.15 (0.04)	13.21	<0.001	0.86 [0.80–0.93]
Brief Symptom Inventory, Anxiety (BSI Anxiety)	−0.002 (0.23)	0.0001	0.99	1.00 [0.64–1.55]
Age of onset of first lifetime episode	−0.005 (0.01)	0.28	0.59	1.00 [0.98–1.02]
Duration current episode ≥ 2 years	−1.33 (0.39)	11.43	<0.001	0.26 [0.12–0.57]
Adequate prior antidepressant trial (ATHF ≥ 3)	−1.07 (0.39)	7.46	0.006	0.34 [0.16–0.74]
Received outside psychotherapy during trial	−0.06 (0.65)	0.008	0.93	0.94 [0.26–3.37]
History of suicide attempt	−0.83 (0.63)	1.76	0.19	0.44 [0.13–1.49]
Scale for Suicide Ideation (SIS) > 0	−0.81 (0.44)	3.33	0.07	0.45 [0.19–1.06]
Percent change in Montgomery-Asberg Depression Rating Scale (MADRS) during first 2 weeks	−0.04 (0.01)	26.65	<0.001	0.96 [0.94–0.97]