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What Are the Clinical Implications of New Onset or Worsening Anxiety During the First Two Weeks of SSRI Treatment for Depression?

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Abstract

Objective—To evaluate the prevalence of new onset or worsening of anxiety symptoms, as well as their clinical implications, during the first two weeks of Selective Serotonin Reuptake Inhibitor (SSRI) pharmacotherapy for depression.

Method—Adult outpatients with non-psychotic major depressive disorder were enrolled in an 8-week acute phase SSRI treatment trial at 15 clinical sites across the US. Worsening anxiety was defined as a greater than 2 point increase on the Beck Anxiety Inventory (BAI) between baseline and Week 2. New onset of anxiety symptoms was ascribed when the BAI baseline rating was 0 and the Week 2 value was greater or equal to 2 points on the BAI.

Results—Overall, after two weeks of treatment, 48.8% (98 of 201 participants) reported improvement in anxiety symptoms, 36.3% (73 of 201) reported minimal symptom change, and 14.9% (30 of 201) reported worsening of anxiety symptoms. No association was found between change in anxiety symptoms within the first two weeks and change in depressive symptoms or remission at the end of 8 weeks of treatment. For participants with clinically meaningful anxiety symptoms at baseline, however, worsening of anxiety during the first two weeks of treatment was associated with worsening depressive symptoms by 8 weeks (p = .054).

Conclusions—The trajectory of anxiety symptom change early in SSRI treatment is an important indicator of eventual outcome for outpatients with major depression and baseline anxiety symptoms.

Keywords

anxiety; change; depression; SSRI; outcome

INTRODUCTION

~~Selective Serotonin R~~euptake Inhibitors (SSRIs), the most widely prescribed antidepressants

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world-wide[1], are effective and well-tolerated medications.[2] In a large scale meta-analysis of 102 randomized clinical trials (with over 10,000 depressed patients), SSRI medications had a slightly greater advantage with regards to tolerability and lower side effects compared to tricyclic medications.[2] To complement this, results from a meta-analysis of ten double-blind randomized clinical studies[3] indicate no difference between antidepressant medications at the acute phase outcome point, with regards to the trajectory of response during treatment, or with emergent anxiety. More specific comparisons, for example comparing an SSRI (i.e., sertraline) with non-SSRI medication (i.e., buproprion hydrochloride sustained release, an aminoketone that serves a noradrenergic and/or dopaminergic function), data indicate no differences in baseline anxiety, number of weeks in which anxiety emerged or attenuated during treatment, and the mean change of anxiety symptoms during the acute phase.[4,5]

Nonetheless, adverse events are reported among SSRI patients and there are individual differences in adjustment during the first four to six weeks with the emergence of unpleasant psychological and physiological anxiety symptoms with SSRI use.[6] Evaluating the effects of treatment-related emergent anxiety symptoms during the early phase of pharmacotherapy is critically important because an estimated 50%–70% of patients with depression report anxiety (agitation, tremors, insomnia, headaches), across both community samples[7] and outpatient samples in randomized clinical trials.[8–10] These symptoms, however, may be related to the neurotransmitter serotonin and not necessarily mediated by the presence of anxiety, highlighting the importance of careful evaluation of psychiatric adjustment to SSRIs during early phase of treatment. Without treatment, comorbid depression and anxiety[11–12] is associated with poor functional impairment[13–16], and amplified risk of depressive relapse and recurrence.[16,17] Depressed individuals with anxiety at baseline treated with SSRIs demonstrate show slower treatment response,[10,18] lower remission rates, and poorer treatment compliance.[10]

Quantifying the odds of early worsening of anxiety with SSRIs, using measures that reliably discriminate symptoms of anxiety from those related to depression, has had minimal research attention. Prior studies have samples with limited representation of typical outpatients who seek pharmacotherapy in primary care and psychiatric care settings. We conducted a secondary analysis using data from an eight week acute phase, single blind, randomized clinical trial of SSRI treatment in patients with nonpsychotic MDD who were enrolled at six primary and nine psychiatric care sites across the United States (Suicide Assessment Measure Study, [SAMS]; M. H. Trivedi, MD, unpublished data, January 2009). This study employed a representative sample of treatment-seeking patients. Such data would guide clinicians in making decisions regarding choice of medication and the likelihood of positive response to SSRI antidepressants.

This report outlined the following pre-planned questions:

1. What is the incidence of new onset or worsening anxiety symptoms during the first two weeks of SSRI treatment in depressed outpatients?
2. Are changes in anxiety symptoms during the first two weeks of SSRI treatment related to depressive symptom outcomes after eight weeks of SSRI treatment?
3. Does a change in anxiety symptoms during the first two weeks of SSRI treatment have a differential effect on the eight week outcome for those with and without anxious features at baseline?

METHODS

Study Description

The primary objective of the multicenter National Institutes of Mental Health (NIMH) sponsored SAMS was to evaluate clinician- and patient-oriented measures of suicidality and associated symptoms. The secondary objectives were: 1) to describe and measure the occurrence and course of treatment-emergent suicidality and associated symptoms in depressed outpatients after initiation and dose escalation of SSRI pharmacotherapy, and 2) to evaluate and compare suicidality assessment methods in representative clinical primary and psychiatric practice settings.

The current study was overseen by the Depression Trials Network (DTN) National Coordinating Center (NCC) (The University of Texas Southwestern Medical Center), the Data Coordinating Center (DCC) (Epidemiological Data Center at the University of Pittsburgh), and 15 Regional Centers. The Institutional Review Boards at the NCC, the DCC, and each regional center approved and oversaw the study protocol. A Data Monitoring and Safety Board reviewed the study protocol and participant consent prior to study enrollment, and monitored participant safety throughout the course of the study.

Study Population

Prior to enrollment, all participants were informed of the risks, benefits and potential adverse events, and all provided written informed consent. From August 2007 through February 2008, 265 outpatients 18–75 years of age who were diagnosed with nonpsychotic MDD were enrolled at six primary and nine psychiatric care sites across the United States. Nonpsychotic MDD was diagnosed clinically and confirmed using the Psychiatric Diagnostic Screening Questionnaire (PDSQ)[18,19] and the Quick Inventory of Depressive Symptomatology – Clinician-rated (QIDS-C_{16}),[24–26] a 16-item structured interview based upon the 9 DSM-IV-TR criteria used to define an MDE (scores ranging 0 to 27, with higher numbers indicating greater severity).[20] Eligibility criteria is outlined in another report.

Patients were ineligible if they had bipolar disorder; schizophrenia; schizoaffective disorder; MDD with psychotic features (lifetime); a current primary diagnosis of anorexia nervosa, bulimia nervosa, or obsessive-compulsive disorder; current substance abuse or dependence; required inpatient treatment at the time of study entry; or had a well-documented history of nonresponse (in the current MDE) to two adequately-delivered SSRI treatments (in terms of both dose and duration). Patients were also ineligible if they were breast-feeding, pregnant, or intending to become pregnant; had taken an antipsychotic medication within 4 months of study entry; or had taken antidepressants in the two weeks prior to screening (four weeks for fluoxetine and 6 weeks for MAOIs). Suicidality was acceptable as long as acute inpatient treatment was not indicated at the baseline visit. Patients were excluded if they had current substance abuse or dependence.

Patients were treated for 8 weeks with an SSRI selected by the physician. Choices included citalopram, escitalopram, fluoxetine, paroxetine, paroxetine-CR or sertraline.[1] Patients received medications and doses that are routinely received in clinical practice for a period of time that reflects consensually-recommended preferred practices.

To provide appropriately vigorous yet tolerable dosing, clinical management was informed by critical decision-point dosing tables and Measurement-Based Care (MBC).[21–23] MBC was based on the itemized measurement at each clinic visit of 1) depressive symptom

[1]Frequency table of medication use is described in Warden et al., 2010. We also include this on page 19.

severity using the QIDS-C_{16}, and 2) measurement of side effects and medication tolerability using the following instruments: the Systematic Assessment for Treatment Emergent Events – Systematic Inquiry (SAFTEE-SI),[27] a 55-item self-report that rates the most commonly reported side effects expected with the study medications; the 3-item Frequency, Intensity, and Burden of Side Effects Rating (FIBSER),[28] a self-report measure which provides global ratings of frequency, intensity and overall burden due to side effects attributable to the antidepressant treatment; and a self-rated medication treatment adherence questionnaire to assess compliance with the prescribed antidepressant. MBC was used successfully in clinical practice settings in the STAR*D trial.[29,30]

Protocol visits were to occur at weeks 0, 2, 4, 6, and 8. In addition, the QIDS-C_{16} and FIBSER were collected by telephone at weeks 1, 3, 5, and 7. Participants were also contacted by telephone on Mondays, Wednesdays and Fridays during the first 2 weeks following medication initiation and following a dose increase (week 4 or later) to evaluate the presence of suicidal ideation and emergence of associated symptoms.

Assessments

At the screening/baseline visit, CRCs collected sociodemographic and clinical information, including the Beck Anxiety Inventory (BAI)[31] a 21-item self-report inventory that distinguishes anxiety from depressive symptoms, and measures severity of anxiety symptoms including physiologic hyperarousal and cognitive anxiety. A score of 15 or lower on the BAI indicates a mild level of anxiety; scores ≥16 indicate a moderate level of anxiety. CRCs completed the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$),[32,33] a 17-item questionnaire that identifies the type and severity of depressive symptoms present.

Course of Treatment Measures

Study clinicians used MBC guidelines and assessed symptom severity and tolerability at each visit to make dose adjustments and clinical decisions. Depressive symptoms were measured at each clinic visit using the QIDS-C_{16}. Anxiety symptom severity was obtained at each clinic visit using the BAI.

Safety Assessments

Side effects were monitored clinically. Serious adverse events were monitored using a multi-tiered approach[28] that involved the CRCs, study clinicians, the clinical manager, safety officers, regional center directors, and the NIMH Data Safety and Monitoring Board.

Concomitant Medications

Concomitant treatments for current General Medical Conditions (GMCs), associated symptoms of depression (e.g., sleep and agitation), and citalopram side effects were permitted at study entry and during the treatments, based on clinical judgment.

Statistical Analysis

Of 265 enrolled participants, 65 did not have adequate data to calculate the change in anxiety symptoms during the first two weeks of treatment and were excluded from these analyses.[2] Change in depressive symptoms was measured using the QIDS-C_{16} (QIDS-C_{16}

[2]Sixty-five participants terminated the study prior to Week 2. No significant differences were noted between patients who terminated prior to week 2 and patients who completed the treatment on the majority of demographic, clinical, and medication use variables. Chi-square analyses revealed differences by ethnicity group, $\chi^2 = 8.42$ (df = 2), $p = 0.01$. T-test showed differences between the two groups on the QIDS-C^{16} change score between Week 0 and exit of study, $\chi^2 = 2.8$ (df = 263), $p = 0.005$.

endpoint value minus QIDS-C_{16} at baseline). Remission was defined as a score ≤ 5 on the QIDS-C_{16} at exit or the last observed QIDS-C_{16}.

Change of anxiety symptoms was classified using the BAI (BAI score at 2 weeks minus BAI score at baseline). BAI anxiety symptoms were classified into three groups: (a) Early improvement was defined as a > 2 point decrease on the BAI between baseline and Week 2 of treatment; (b) Minimal change was defined as a change of ≤ 2 points (increase or decrease) on the BAI between baseline and Week 2; (c) Early worsening was defined as a > 2 point increase on the BAI between baseline and Week 2.

Descriptive statistics are presented as means, medians, or percentages of the sociodemographic and clinical characteristics. Frequency distributions of the change in BAI scores from baseline to Week 2 were calculated. A Spearman's Correlation Coefficient estimated the association between change in anxiety from baseline to Week 2, as measured by the BAI, and change in depressive symptoms, as measured by the QIDS-C_{16}.

A chi-square test was used to determine if the remission rate was different among participants with and without a 2-point increase of their BAI scores during the first 2 weeks of treatment.

To determine whether there is a differential effect of change in anxiety level on depressive symptom severity based on the presence of anxious depression at baseline, a linear regression model was fit with main effects for change in BAI and presence of anxious depression at baseline, as well as the two-way interaction. Anxious depression at baseline was based a score ≥ 7 on the clinician-based interview (the 6-item $HRSD_{17}$ Anxiety/Somatization Factor score,[35,36] which includes $HRSD_{17}$ Item 9 [agitation], Item 10 [psychic anxiety], Item 11 [somatic anxiety], Item 12 [gastrointestinal somatic], Item 13 [general somatic], and Item 15 [hypochrondriasis]).

Statistical significance for all analyses was defined as a 2-sided p-value of < 0.05. No adjustments were made for multiple comparisons, so results should be interpreted accordingly.

RESULTS

Baseline sociodemographic and clinical characteristics, including the BAI and $HRSD_{17}$ Anxiety/Somatization Factor scores, are outlined in Table 1.

To evaluate the incidence of new onset or worsening anxiety symptoms during the first 2 weeks of SSRI treatment in depressed outpatients, we conducted a frequency distribution of the change in BAI scores from baseline to Week 2, classifying the change in anxiety symptoms into three groups: The first group consisted of 48.5% (97 of 200) of participants who reported early improvement of anxiety symptoms (Mean = −9.81, SD = 6.67, Range = −47.0 to −3.0); in the second group, 36.5% (*n* = 73 of 200) (Mean = −0.16, SD = 1.33, Range = −2.0 to 2.0) reported a minimal change in anxiety symptoms; and, in the third group, 15.0% (30 of 200) (Mean = 7.20, SD = 4.01, Range = 3.0–17.0), reported early worsening of anxiety symptoms.

The majority of patients took Citalopram (*n* = 95, 50.5%), followed by Fluoxetine (*n* = 31, 16.5%), Escitalopram (*n* = 29, 15.4%), Sertraline (*n* = 24, 12.8%) and Paroxetine (*n* = 9, 4.8%). Chi-square analyses indicated no significant differences on frequency of use of medications between participants who completed the study and those who terminated prior to Week 2, $\chi^2 = 1.83(df = 4)$, $p = 0.77$.

We conducted a Spearman correlation coefficient to determine if changes in anxiety symptoms during the first 2 weeks of SSRI treatment were related to depressive symptom outcomes after 8 weeks of SSRI treatment. Results indicated that the correlation was significantly different from zero ($r = 0.10$, $p = 0.16$, n = 200).

In addition, using a Chi-Square analyses between change of QIDS (binary) and remission, we found no association between a categorical classification of worsening of anxiety (yes, no), defined by a 2-point increase in BAI score, and depressive symptom remission (yes, no) at Week 8 ($p = 0.31$). Of the total 200 participants for this analysis, 158 participants reported no change of anxiety symptoms: Within this subsample, 46.8% (N = 74) did not achieve remission, with the remaining 53.2% (N = 84) who did not experience remission. Likewise, for the 42 participants who reported an increase of anxiety symptoms early in treatment, 38.1% (N = 16) reported remission, while 61.9% (N = 26) reported lack of remission by Week 8. Though this association was not statistically significant (χ^2 (38, 200) = 34.71 p = . 62), a clinically meaningful effect was observed in a direction that was expected, with a reduction of 8% of participants in the early anxiety group who did not achieve remission by Week 8.

Using logistic regression, we measured the extent to which early worsening of anxiety influenced depressive symptoms at baseline (i.e., with and without anxious depression using $HRSD_{17}$ Anxiety/Somatization factor score). A logistic regression model was fit with main effects for change in BAI and the presence of anxious depression at baseline, as well as the two-way interaction between the two main effects. The results of the model indicated a borderline significant ($p = .0536$) interactive effect. The results of the model can be interpreted as follows: For those without anxious depression at baseline, then the slope associated with the change on the BAI is −0.07. This means that for participants without anxiety at baseline, a one unit increase of the change of the BAI is associated with a decrease in the change of the QIDS-C_{16} by 0.07 points. Because change in the QIDS-C_{16} is measured as exit minus baseline, this would mean a decrease in the QIDS-C_{16} score, representing symptom improvement. If, on the other hand, anxiety is present at baseline, then the slope associated with the change in the BAI is 0.12. This means than that for participants with anxious depression at baseline, a one unit increase (worsening) of the change of the BAI is associated with an increase (worsening) in the change of the QIDS-C_{16} by 0.12 points.

DISCUSSION

Change in Depression and Anxiety Symptoms

The majority of participants (> 80%) experienced significant improvement of their depressive symptoms after eight weeks of SSRI treatment, which reflects prior studies.[36–38] A small subset of patients (5%) reported a worsening depression by end of treatment.

About 15% of patients showed early worsening of anxiety emergent within the first two weeks of SSRI treatment. SSRIs may exert an activating effect, and this disposition, in turn, activates neurobiological mechanisms that increase HPA activation and diminish sleep quality,[39] and dysfunction of neurotransmitter modulatory circuits (subgenual cingulate cortex).[40] Also, individual differences in genetic polymorphisms of medication metabolizing enzymes (e.g., cytochrome P450 (CYP) isoenzyme CYP2D6))[40] and copharmacy[41] may account for adverse anxiety reactions early treatment. Specifically, fluoxetine and paroxetine, 2D6 inhibitors, may elevate meta-chlorophenylpiperazine (m-CPP), increasing the risk for anxiety and panic. [41] In contrast, venlafaxine, bupropion, mirtazipine, sertraline, (potent 3A, but weak 2D6 inhibitors) are less likely to interact, though measurable anxiogenic effects remain to be investigated.

Almost half of patients showed early improved anxiety, and one third reported either minimal or no change in anxiety symptoms. The improvement of anxiety may be due to the effects of medication on the central nervous system, though tests of biological effects of SSRIs would be necessary to confirm this.[42] Also, physiologic symptoms of anxiety may improve as depressive symptoms improve. We were unable to discern the relative contribution of these characteristics from our present analyses.

Association of Change in Anxiety Symptoms with Change in Depressive Symptoms and Treatment Outcome

The degree to which anxiety symptoms changed during the first two weeks of treatment was not associated with the extent to which depressive symptoms changed after eight weeks of SSRI treatment. This was confirmed with analyses that examined change of anxiety as either a continuous variable or as a grouping variable (e.g., BAI groups categorized as having either an early improvement, no change, or early worsening).

Our analyses found no association between a change in anxiety symptoms and remission. This finding contrasts with those of earlier studies which reported that a worsening of anxiety during the first weeks of treatment indicated a worse outcome (e.g., an absence of remission).[43,44] We did, however, find a clinically meaningful difference, with patients who had an increase in anxiety symptoms being less likely to reach remission than those who had no change in anxiety symptoms.

Effect of Baseline Anxiety

The level of anxiety at baseline had a differential effect on the gradient of change in depression symptoms. For patients with high $HRSD_{17}$ anxiety/somatization scores at baseline, the incremental worsening of anxiety during the first two weeks of SSRI treatment was associated with increased depressive symptoms. Patients without anxiety at baseline showed no increase in depressive symptoms with a worsening of anxiety over the first two weeks of treatment. This suggests that patients with high and low baseline anxiety follow different trajectories of depression worsening during SSRI treatment (i.e., high anxiety at baseline is associated with an increased risk of higher severity of depression symptoms).[10] These findings suggest a differential effect of SSRIs on anxiety.

For individuals with low anxiety at baseline, anxiety symptoms may reflect medication effects rather than a worsening of the illness. In comparison, the individuals with high anxiety at baseline who have worsening anxiety experience a progressive downturn in depressive symptoms, which makes treatment gains that much harder to achieve. In the clinical context, these findings suggest that data on baseline anxiety and during the first two weeks of SSRI treatment signal the potential trajectory of depressive symptoms for clinicians who are considering prescribing SSRI antidepressants.

The worsening of anxious symptoms during SSRI treatment highlights the role of the clinician's expertise in handling amplified anxiety either through additional of anxiolytics or behavioral techniques during the early phase of treatment, while optimizing the SSRI dosage. This is especially relevant given that data suggests that many individuals who suffer from anxious depression are treated in primary care facilities[10] and are, therefore, less likely to receive fully optimal medication dosages.

Strengths and Limitations

Strengths include the use of a measure that reliably discriminates anxiety from depression, a clinical interview to ascertain depressive symptom severity, careful control of covariates, and a large and diverse sample to permit generalizable conclusions. The extent to which the

emergent anxiety symptoms were correlated with medication-related side effects from this study is reported elsewhere (Warden, Trivedi, Wisniewski, Kurian, Zisook, 2010). Emergent anxiety is unlikely to reflect inadequate dosing, given our reliance on the MBC approach to ensure optimal treatment.

Conclusions

About 15% of patients with MDD experienced a worsening of anxiety symptoms after two weeks of SSRI treatment. Changes in anxiety symptoms after two weeks of SSRI treatment were not associated with a change in depressive symptoms or treatment outcome after eight weeks of treatment. We did find a differential effect of change in anxiety level based on anxiety at baseline: patients with high anxiety at baseline and who showed early worsening of anxiety were significantly more likely to have more severe depression. Clinicians may use this early indicator to determine the viability of continuing with SSRIs with their patients.

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References

1. Preskorn, SH.; Stanga, CY.; Ross, R. Selective serotonin reuptake inhibitors. In: Preskorn, SH.; Stanga, CY.; Feighner, JP.; Ross, R., editors. Antidepressants: Past, Present, and Future. Vol. 157. Berlin; New York: Springer; 2004. p. 241-262.
2. Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: A meta-analyses of efficacy and tolerability. Journal of Affective Disorders. 2000; 58:19–36. [PubMed: 10760555]
3. Papakostas GI, Trivedi MH, Alpert JE, Seifert CA, Krishen A, Goodale EP, Tucker VL. Efficacy of bupropion and the selective serotonin reuptake inhibitors in the treatment of anxiety symptoms in major depressive disorder: a meta-analysis of individual patient data from 10 double-blind, randomized clinical trials. J Psychiatric Res. 2008; 42:134–140.
4. Rush AJ, Trivedi MH, Ibrahim HM, et al. Response in relation to baseline anxiety levels in major depressive disorder treated with bupropion sustained release or sertraline. Neuropsychopharmacology. 2001; 24:131–138. [PubMed: 11377926]
5. Trivedi MH, Rush AJ, Carmody, et al. Do bupropion SR and sertraline differ in their effects on anxiety in depressed patients? J Clin Psychiatry. 2001; 62:776–781. [PubMed: 11816866]
6. Beasley CM Jr, Dornseif BE, Pultz JA, Bosomworth JC, Sayler ME. Fluoxetine vs. trazodone: efficacy and activating-sedating effects. J Clin Psychiatry. 1991; 52:294–299. [PubMed: 2071559]
7. Kessler RC, Nelson CB, McGonagle KA, Liu J, Swartz M, Blazer DG. Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. Br J Psychiatry Suppl. 1996; 30:S17–S30.
8. Fava M, Alpert JE, Carmin C, et al. Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. Psychol Med. 2004; 34:1299–1308. [PubMed: 15697056]

9. Fava M, Rush AJ, Alpert JE, et al. What clinical and symptom features of comorbid disorders characterize outpatients with anxious major depressive disorder: a replication and extension. Can J Psychiatry. 2006; 51:823–835. [PubMed: 17195602]
10. Fava M, Rush AJ, Alpert JE, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. Am J Psychiatry. 2008; 165:342–351. [PubMed: 18172020]
11. Fawcett J, Kravitz HM. Anxiety symptoms and their relationship to depressive illness. J Clin Psychiatry. 1983; 44:8–11. [PubMed: 6874657]
12. Marcus SM, Kerber KB, Rush AJ, et al. Sex differences in depression symptoms in treatment-seeking adults: confirmatory analyses from the Sequenced Treatment Alternatives to Relieve Depression study. Compr Psychiatry. 2008; 49:238–46. [PubMed: 18396182]
13. Joffe RT, Bagby RM, Levitt A. Anxious and nonanxious depression. Am J Psychiatry. 1993; 150:1257–1258. [PubMed: 8328574]
14. Jeste ND, Hays JC, Steffens DC. Clinical correlates of anxious depression among elderly patients with depression. J Affect Disord. 2006; 90:37–41. [PubMed: 16325261]
15. Davidson JR, Meoni P, Haudiquet V, Cantillon M, Hackett D. Achieving remission with venlafaxine and fluoxetine in major depression: its relationship to anxiety symptoms. Depress Anxiety. 2002; 16:4–13. [PubMed: 12203668]
16. Van Valkenburg C, Akiskal HS, Puzantian V, Rosenthal T. Anxious depressions: clinical, family, history, and naturalistic outcome: comparisons with panic and major depressive disorders. J Affect Disord. 1984; 6:67–82. [PubMed: 6231331]
17. Ramana R, Paykel ES, Cooper Z, Hayhurst H, Saxty M, Surtees PG. Remission and relapse in major depression: a two-year prospective follow-up study. Psychol Med. 1995; 25:1161–1170. [PubMed: 8637946]
18. Zimmerman M, Mattia JI. The Psychiatric Diagnostic Screening Questionnaire: development, reliability and validity. Compr Psychiatry. 2001a; 42:175–189. [PubMed: 11349235]
19. Zimmerman M, Mattia JI. A self-report scale to help make psychiatric diagnoses: the Psychiatric Diagnostic Screening Questionnaire. Arch Gen Psychiatry. 2001b; 58:787–794. [PubMed: 11483146]
20. American Psychological Association. Diagnostic and Statistical Manual of Mental Disorders – Text Revision. Washington, DC: American Psychiatric Association; 2000.
21. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006; 163:28–40. [PubMed: 16390886]
22. Trivedi MH, Daly EJ. Measurement-based care for refractory depression: a clinical decision support model for clinical research and practice. Drug Alcohol Depend (Suppl). 2007; 88:S61–S71.
23. Trivedi MH, Rush AJ, Gaynes BN, et al. Maximizing the adequacy of medication treatment in controlled trials and clinical practice: STAR*D measurement-based care. Neuropsychopharmacology. 2007; 32:2479–2489. [PubMed: 17406651]
24. Rush AJ, Carmody TJ, Reimitz PE. The Inventory of Depressive Symptomatology (IDS): clinician (IDS-C) and self-report (IDS-SR) ratings of depressive symptoms. Int J Methods Psychiatr Res. 2000; 9:45–59.
25. 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; 54:573–583. [PubMed: 12946886]
26. Trivedi MH, Rush AJ, Ibrahim HM, et al. The Inventory of Depressive Symptomatology, clinician rating (IDS-C) and self-report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, clinician rating (QIDS-C) and self-report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychol Med. 2004; 34:73–82. [PubMed: 14971628]
27. Levine J, Schooler NR. SAFTEE: a technique for the systematic assessment of side effects in clinical trials. Psychopharmacol Bull. 1986; 22:343–381. [PubMed: 3774930]

28. Wisniewski SR, Rush AJ, Balasubramani GK, Trivedi MH, Nierenberg AA. Self-rated global measure of the frequency, intensity, and burden of side effects. J Psychiatr Pract. 2006; 12:71–79. [PubMed: 16728903]
29. Fava M, Rush AJ, Trivedi MH, et al. Background and rationale for the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Psychiatr Clin North Am. 2003; 26:457–494. [PubMed: 12778843]
30. Rush AJ, Fava M, Wisniewski SR, et al. Sequenced Treatment Alternatives to Relieve Depression (STAR*D): rationale and design. Control Clin Trials. 2004; 25:119–142. [PubMed: 15061154]
31. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988; 56:893–897. [PubMed: 3204199]
32. Hamilton M. A rating scale for depression. J Neurol, Neurosurg Psychiatry. 1960; 23:56–62. [PubMed: 14399272]
33. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. 1967; 6:278–296. [PubMed: 6080235]
34. Demyttenaere K, Enzlin P, Dewe W, et al. Compliance with antidepressants in a primary care setting, 1: beyond lack of efficacy and adverse events. J Clin Psychiatry (Suppl). 2001; 62:S30–S33.
35. Cleary P, Guy W. Factor analysis of the Hamilton Depression Scale. Drugs Exp Clin Res. 1977; 1:115–120.
36. Tollefson GD, Holman SL, Sayler ME, Potvin JH. Fluoxetine, placebo, and tricyclic antidepressants in major depression with and without anxious features. J Clin Psychiatry. 1994; 55:50–59. [PubMed: 8077155]
37. Montgomery SA. The efficacy of fluoxetine as an antidepressant in the short and long term. International Clinical Psychopharmacology (Suppl.). 1989; 4:113–119.
38. Rush AJ, Zimmerman M, Wisniewski SR, Fava M, Hollon SD, Warden D, Biggs MM, Shores-Wilson K, Shelton RC, Luther J, Thomas B, Trivedi MH. Comorbid psychiatric disorders in depressed outpatients: Demographic and clinical features. J Affect Disord. 2005; 87:43–55. [PubMed: 15894381]
39. Fava M, Rosenbaum JF, Hoog SL, Tepner RG, Kopp J, Nilsson ME. J Affect Disord. 2000; 59:119–126. [PubMed: 10837880]
40. Harvey AT, Preskorn SH. Cytochrome P450 enzymes: interpretation of their interactions with selective serotonin reuptake inhibitors. Part II. Journal of Clin Psychopharmacology. 1996; 16(5): 345–55.
41. Ereshefsky L, Riesenmann C, Lam YW. Antidepressant drug interactions and the cytochrome P450 system. The role of cytochrome P450 2D6. Clinical Pharmacokinet. 1995; 29(1):10–19.
42. Ressler KJ, Mayberg HS. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. Nat Neurosci. 2007; 10:1116–1124. [PubMed: 17726478]
43. Flint AJ, Rifat SL. Two-year outcome of elderly patients with anxious depression. Psychiatry Research. 1997; 66:22–31.
44. Roose S, Glassman, Walsh B, Woodrin S. Tricyclic responders: Phenomenology and treatment. Am J Psychiatry. 1986; 143:345–348. [PubMed: 3953869]
45. Warden D, Trivedi MH, Wisniewski SR, Kurian B, Zisook S, Kornstein SG, Friedman ES, Miyahara S, Leuchter AF, Fava M, Rush AJ. Early Adverse Events and Attrition in SSRI Treatment: A Suicide Assessment Methodology Study (SAMS) Report. Journal of Clinical Psychopharmacology. 2010; 30(3):259–266. [PubMed: 20473060]

Table 1

Baseline characteristics of the sample

Variable	N	%
Race		
White	131	65.5
Black	41	20.5
Other	28	14.0
Gender		
Male	62	31.0
Female	138	69.0
Hispanic		
No	178	89.0
Yes	22	11.0
Employment		
Unemployed	70	35.0
Employed	120	65.0
Retired	10	5.0
Marital Status		
Never married	63	31.5
Married	73	36.5
Divorced/separated	57	28.5
Widowed	7	3.5
Insurance		
Private	87	44.4
Public	37	18.9
None	72	36.7
Age of Onset (≥18)		
No	76	38.2
Yes	123	61.8
Family history of alcohol/drug		
No	111	55.5
Yes	89	45.5
Family history of suicide		
No	192	96.0
Yes	8	4.0
Number of Depressive Episodes (≥2)		
No	59	32.2
Yes	124	67.8
Chronic Depression (≥2years)		
No	130	68.2
Yes	58	30.8
Anxious features		

Variable	N	%
No	66	33.0
Yes	134	67.0
	N	**Mean(SD)**
Age (years)	200	41.9(13.2)
Education (years)	200	13.6(2.8)
$HRSD_{17}$	199	21.6(4.5)
QIDS-C_{16}	201	14.7(3.2)
GMC severity	201	3.1(3.5)