Do Suicidal Thoughts or Behaviors Recur During a Second Antidepressant Treatment Trial?

Roy H. Perlis, MD, MSc; Rudolf Uher, MD, PhD; Nader Perroud, MD; and Maurizio Fava, MD

ABSTRACT

Objective: A subset of patients undergoing initial antidepressant treatment experience worsening of symptoms, including thoughts of suicide or suicidal behavior. The present study explores whether this subset of patients is also more likely to experience recurrence or worsening of these symptoms during a second treatment trial with a different antidepressant.

Method: We examined data collected between July 2001 and September 2006 from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, a multicenter effectiveness study of outpatients with major depressive disorder diagnosed by a *DSM-IV* checklist. In that study, subjects who did not remit with citalopram treatment were randomized among next-step treatment options. The main outcome measure for this post hoc analysis, presence of suicidal thoughts and behaviors, was assessed using the suicide item on the 16-item Quick Inventory of Depressive Symptomatology—Self-Rated. Logistic regression was used to examine association between emergence or worsening of these symptoms with the first-step (level 1) citalopram treatment and emergence or worsening with next-step (level 2) pharmacologic or psychosocial treatment, including augmentation with bupropion or buspirone; switch to sertraline, venlafaxine, or bupropion; or addition of or switch to cognitive therapy.

Results: Of 1,240 subjects entering level 2 with a score less than 3 on the suicide item, 102 (8.2%) experienced emergence or worsening of suicidal thoughts or behaviors. Emergence or worsening at level 1 was strongly associated with reemergence or worsening at level 2 (crude OR = 4.00 [95% CI, 2.45–6.51], adjusted OR = 2.95 [95% CI, 1.76–4.96]). Overall magnitude of risk was similar among next-step pharmacologic augmentation versus switching.

Conclusions: These results suggest that individuals who experience emergence or worsening of suicidal thoughts or behaviors with one antidepressant treatment may warrant closer follow-up during the next-step treatment, as these symptoms may recur regardless of which modality is selected.

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Corresponding author: *Roy H. Perlis, MD, MSc, Center for Experimental Drugs and Diagnostics, Massachusetts General Hospital, 185 Cambridge St, 6th Floor, Boston, MA 02114 (rperlis@partners.org).*

A small subset of patients treated with antidepressants will experience emergence or worsening of suicidal thoughts and behaviors after initiation of treatment, a phenomenon sometimes referred to as *treatment-emergent suicidal ideation*. A meta-analysis[1] of placebo-controlled antidepressant studies suggested this phenomenon to be more common among drug- than placebo-treated patients 24 years or younger, leading to a change in US Food and Drug Administration labeling for all antidepressants.[2]

Many individuals who experience worsening of suicidal thoughts still achieve symptomatic improvement after an adequate treatment trial.[3,4] However, some patients with worsening may require treatment change in order to achieve remission. While we and others have reported clinical features associated with this emergence or worsening of suicidal thoughts,[3–6] the implications of treatment-emergent suicidal ideation for selecting or monitoring *next-step* treatment have, to our knowledge, not been studied. When a patient experiences treatment-emergent suicidal ideation with a first treatment trial and does not reach remission, is such a phenomenon likely to recur and is the risk comparable across next-step treatments?

To examine these clinically salient questions, we utilized data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. We first investigated whether emergence or worsening of suicidal thoughts or behaviors during citalopram treatment of major depressive disorder (MDD) was predictive of further worsening with next-step treatment, based on self-report or clinician rating of the suicide item on a depression rating scale, the Quick Inventory of Depressive Symptomatology (QIDS), at each visit.[7] Then, we explored prevalence of these treatment-emergent/worsening symptoms in individual next-step treatment groups, including cognitive-behavioral therapy.

METHOD

Study Design

The STAR*D study was a multicenter investigation conducted at 41 primary care or psychiatric sites in the United States to determine which of several next-step treatment options are most effective for individuals with nonpsychotic MDD who did not remit with or tolerate first-line pharmacotherapy with citalopram. Full study details have been reported elsewhere.[8,9] The study consisted of sequential levels of treatment intervention; at each level, treatment visits occurred at 0, 2, 4, 6, 9, and 12 weeks, with an optional 14-week visit if needed. The first (level 1) treatment utilized open-label citalopram, while subsequent levels utilized multiple randomized treatments. Citalopram was suggested to be initiated at 20 mg/d and increased to 40 mg/d by week 4 and 60 mg/d by week 6. However, the dose could be adjusted as needed to maximize tolerability and optimize likelihood of clinical improvement.

On entering level 2, treatment was assigned according to a process of equipoise-stratified randomization,[10] in which patients could

Clinical Points

- Patients with major depressive disorder who experience emergence or worsening of suicidal thoughts or behaviors with an initial antidepressant treatment are at increased risk for experiencing the same symptoms when a next-step treatment is started.
- These symptoms may recur even when a non-SSRI medication is initiated.
- Still, the majority of patients will not experience recurrence of these symptoms with next-step treatment, and patients who did not experience these symptoms initially may still experience them with next-step treatment.

express a preference for 1 or more categories of treatment (though not specific medications) and would be randomly assigned to treatment only from among their preferences. Available level 2 treatment arms were augmentation of citalopram or switch to another antidepressant. Randomly assigned augmentation strategies included buspirone or bupropion sustained release, with citalopram continued at stable dosage; randomly assigned switch strategies included sertraline, venlafaxine extended release, or bupropion sustained release. In addition, a subset of patients received cognitive therapy either as monotherapy or in combination with citalopram at stable dosage; only subjects indicating a willingness to be randomly assigned to cognitive therapy could be assigned this treatment. Because of the small number of subjects entering subsequent treatment levels, they were not considered in the present analysis.

Study Population

STAR*D enrolled only subjects seeking treatment at one of the study sites; to maximize generalizability, no advertisements were permitted. Inclusion and exclusion criteria were likewise broad, including outpatients 18–75 years of age, with a *DSM-IV* diagnosis of nonpsychotic MDD and a baseline score ≥ 14 on the 17-item Hamilton Depression Rating Scale,[11] provided the treating clinician had determined that outpatient antidepressant treatment was appropriate. Subjects were excluded for lifetime psychotic features, schizophrenia, schizoaffective disorder, or bipolar disorder I, II, or not otherwise specified, based on a clinician checklist or self-report, or for a documented history of nonresponse or intolerance in the current major depressive episode to adequate doses[12] of 1 or more medications utilized in the first 2 protocol treatment steps. Subjects with concurrent psychiatric disorders felt to be likely to require hospitalization within 6 months, such as severe substance use disorder or primary diagnosis of eating disorder or obsessive-compulsive disorder, were also excluded. Concurrent medical or psychiatric conditions and medications were permitted provided they did not contraindicate a protocol treatment. Data were collected between July 2001 and September 2006.

Outcome Measure

The definition of suicidal thoughts or behaviors remains complex and subject to debate, with competing definitions utilizing different thresholds and metrics. Here, we focused a priori on self-report measures of depressive symptoms, which were collected at study entry and at each follow-up visit, as this represented the most complete data set available. The Quick Inventory of Depressive Symptomatology—Self-Rated is a 16-item measure[7] that includes 1 item (Item 12) inquiring about hopelessness and suicidal thoughts and behaviors. The anchor points are as follows: 0 = I do not think of suicide or death, 1 = I feel life is empty or is not worth living, 2 = I think of suicide/death several times a week for several minutes, and 3 = I think of suicide/death several times a day in detail or have made specific plans or attempted suicide. The outcome of interest was emergence or worsening of suicidal thoughts or behaviors at any visit following level entry, defined as a 1-point or greater increase in the suicide item score to a minimum of 2 on at least 1 follow-up visit. (To maximize face validity, an increase to 1, representing a feeling that life is empty, is not classified as positive identification of suicidal thinking/behavior, consistent with prior work from our group and others.[3])

For comparison, we also report the hopelessness or suicidal thinking/behavior item from the corresponding clinician-rated measure, the Quick Inventory of Depressive Symptomatology—Clinician Rated (QIDS-C),[7] which was collected at every visit by the unblinded study clinician and utilizes the same anchor points.

Analysis

In primary analyses, 2-by-2 tables and simple logistic regression were applied to examine association between presence or absence of worsening at study level 1 and worsening at study level 2. To avoid a ceiling effect, individuals with the maximum suicide item score of 3 at entry to either level 1 or level 2 were excluded since they were not at risk for further worsening on this rating scale. To address potential confounding effects of age, sex, primary versus specialty care setting, race, prior suicide attempt, and overall depression severity defined by QIDS at entry to level 2 (omitting item 12), an additional logistic regression model was fit incorporating these covariates.

Incidence of emergence or worsening of suicidal thoughts or behaviors, among those who experienced this symptom with citalopram treatment, was also examined descriptively within treatment arms in level 2, consistent with the methodology advocated by Kraemer et al[13] and Leon[14] for initial exploration of subgroup effects. As treatment assignment incorporated patient preference as well as randomization, the augmentation, switch, and cognitive therapy strategies are not formally comparable,[10] though we hypothesized that magnitude of effect could still be informative.

Table 1. Adjusted Regression Model for Emergence or Worsening of Suicidal Thoughts or Behaviors With Next-Step Treatment

	n	%	Odds Ratio (univariate[a])	Odds Ratio (full model)	*P* Value	95% Confidence Interval
Emergence or worsening on QIDS-SR item 12 at level 1	121	9.8	4.00	2.95	< .001	1.76–4.96
Prior suicide attempt	204	16.5	2.07	2.19	.002	1.34–3.58
Male sex	518	41.8	1.71	1.83	.01	1.18–2.84
Primary care setting (vs specialty)	456	36.8	0.50	0.55	.02	0.33–0.90
White	1,000	80.7	0.64	0.79	.35	0.48–1.29
	Mean	SD				
Age, y	42.4	12.6	1.01	1.00	.64	0.99–1.02
Baseline QIDS-SR score at level 2[b]	12.1	4.8	1.11	1.09	< .001	1.05–1.15

[a]Odds ratio for unadjusted association of variable with emergence or worsening of suicidal thoughts or behaviors in logistic regression.
[b]Model is fit with level 2 baseline QIDS-SR score excluding the suicide item, but mean and standard deviation are reported here for the full scale.
Abbreviation: QIDS-SR = Quick Inventory of Depressive Symptomatology—Self-Rated.

RESULTS

In all, 1,423 participants entered level 2. Of these, we excluded 39 participants who had a suicide item score of 3 or a missing score at entry to level 1, 16 with a score of 3 at entry to level 2, and 128 who failed to return for a postbaseline visit at level 2; this yielded 1,240 subjects in the at-risk cohort. Of these at-risk subjects, 102 (8.2%) experienced emergence (n = 94; 7.6%) or worsening (n = 8; 0.6%) during next-step treatment—75/1,118 (6.7%) of those *without* emergence or worsening at level 1 and 27/121 (22.3%) of those *with* emergence or worsening at level 1 ($\chi^2_1 = 35.3$; $P < .001$).

In logistic regression, the crude odds ratio (OR) for emergence or worsening at level 2, based on level 1, was 4.00 (95% CI, 2.45–6.51); adjusted for age, ethnicity, sex, care setting, lifetime suicide attempts, and baseline depression severity (Table 1), the OR was 2.95 (95% CI, 1.76–4.96).

A sensitivity analysis with the clinician-rated QIDS-C confirmed that the association between emergence or worsening of suicidal thoughts with subsequent treatments was robust and was not limited to self-reported outcomes: emergence or worsening was observed among 88/1,113 (7.9%) of individuals without prior experience of this phenomenon and 21/127 (16.5%) with prior experience of this phenomenon ($\chi^2_1 = 10.6$; $P = .001$). In simple logistic regression, the OR was 2.31 (95% CI, 1.38–3.87); in an adjusted model, the OR was 1.92 (95% CI, 1.11–3.32).

Finally, we examined incidence of emergence or worsening at level 2 by treatment strategy, focusing on those who experienced emergence or worsening at level 1: switch, augmentation, or cognitive therapy (either alone or in combination with citalopram). Emergence or worsening in suicidal thoughts occurred in 1/11 (9%) receiving cognitive therapy, 11/51 (22%) of those receiving pharmacologic augmentation, and 15/59 (25%) receiving switch to bupropion, venlafaxine, or sertraline (Fisher exact $P = .586$). When analysis was restricted to the antidepressant switch arms, incidence was numerically but not statistically greater in the non-serotonergic (bupropion) arm—7/20 (35%) versus 4/21 (19%) for sertraline and 4/18 (22%) for venlafaxine (Fisher exact $P = .489$). In light of the modest group sizes and absence of true randomization between switch and augmentation, or cognitive therapy, these values must be interpreted with extreme caution.

DISCUSSION

In this analysis of data from more than 1,200 depressed outpatients receiving at least 2 sequential antidepressant treatments in the STAR*D study, we find that emergence or worsening of suicidal thoughts or behaviors with next-step treatment is not uncommon and is strongly associated with having experienced that phenomenon with initial citalopram treatment. Among those individuals with emergence or worsening during initial citalopram treatment, incidences were broadly similar across next-step treatment strategies, but may be diminished among those receiving cognitive-behavioral therapy. Consistent with prior reports[15] and with level 1 of STAR*D,[3] we also identify elevated risk associated with history of suicide attempt.

A key question for clinicians who observe the emergence of suicidal thoughts or behaviors during initial antidepressant treatment is, "What is the appropriate next step?" Previous reports suggest that many individuals who experience this initial emergence or worsening will nonetheless go on to improve with the initial antidepressant.[3,4] Still, for those who do not, a treatment change is typically considered. Our results suggest that 1 in 5 of these individuals will have a similar experience with the next treatment, indicating that risk for emergence or worsening of suicidal thinking is greater for those who experience this phenomenon initially. Thus, such patients merit closer follow-up in subsequent treatment steps, as they remain at elevated risk. We note, however, that the majority of individuals who experienced this symptom at initial treatment did not reexperience it with next-step treatment, while a majority of individuals experiencing this symptom with next-step treatment had not had this symptom with initial treatment.

In light of small sample size and treatment assignment that was not fully randomized, comparisons of next-step

treatments must be considered in purely descriptive terms. Whether next-step treatment selection should be influenced by initial emergence or worsening of suicidal thoughts or behaviors merits further investigation; our results may be helpful in generating hypotheses about interventions with greater or lesser risk.

An important caveat is that our analysis is not intended to directly address treatment-specificity, or lack thereof, of this phenomenon. The association between initial and next-step emergence or worsening does suggest some degree of cross–treatment-class effect: this effect would quite likely be obscured if, for example, this phenomenon was only associated with selective serotonin reuptake inhibitors. Consideration of change on a rating scale is also qualitatively different from analyses of suicidal behavior, which are generally practical only in meta-analysis or large population-based studies. A particular obstacle here is the wording of the QIDS anchor points, which do not clearly distinguish between thoughts of one's own death and suicide per se: it would be possible for a patient to become increasingly preoccupied with his or her own death without having thoughts of committing suicide, and therefore to score a 3. Item 3 of the Hamilton Depression Rating Scale is more specific, requiring suicidal ideation to score a 3 or 4, but has a similar limitation to score a 2; in the present study, however, this scale was not collected at each visit. Limitations of existing depression rating scales for the assessment of suicidal thoughts and behaviors led the US Food and Drug Administration to advise incorporation of suicide-specific assessments, such as the Columbia Classification Algorithm for Suicide Assessment, in future trials.[16,17]

In summary, the present analysis suggests that onset or worsening of suicidal thoughts or behaviors is not uncommon in next-step treatment of depression, and that risk persists from one treatment course to the next. More generally, these results indicate the importance of monitoring for symptomatic worsening any time treatment is initiated or changed.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), buspirone (BuSpar and others), citalopram (Celexa and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Author affiliations: Massachusetts General Hospital and Harvard Medical School, Boston (Drs Perlis and Fava); Institute of Psychiatry, King's College London, United Kingdom, and Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada (Dr Uher); and Department of Psychiatry, University Hospitals of Geneva, Geneva, Switzerland (Dr Perroud).

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Additional information: Requests for access to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) dataset are made to the National Institute of Mental Health (NIMH), sponsor of the trial. See http://www.nimh.nih.gov/trials/datasets/nimh-procedures-for-requesting-data-sets.shtml for information.

REFERENCES

1. Stone M, Laughren T, Jones ML, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ*. 2009;339(2):b2880.
2. Food and Drug Administration. Suicidality and antidepressant labeling: revisions to product labeling. http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM173233.pdf. Accessibility verified July 18, 2012.
3. Perlis RH, Purcell S, Fava M, et al. Association between treatment-emergent suicidal ideation with citalopram and polymorphisms near cyclic adenosine monophosphate response element binding protein in the STAR*D study. *Arch Gen Psychiatry*. 2007;64(6):689–697.
4. Perroud N, Uher R, Marusic A, et al. Suicidal ideation during treatment of depression with escitalopram and nortriptyline in Genome-Based Therapeutic Drugs for Depression (GENDEP): a clinical trial. *BMC Med*. 2009;7(1):60.
5. Perlis RH, Beasley CM Jr, Wines JD Jr, et al. Treatment-associated suicidal ideation and adverse effects in an open, multicenter trial of fluoxetine for major depressive episodes. *Psychother Psychosom*. 2007;76(1):40–46.
6. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. *JAMA*. 2004;292(3):338–343.
7. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med*. 1996;26(3):477–486.
8. Rush AJ, Fava M, Wisniewski SR, et al; STAR*D Investigators Group. Sequenced Treatment Alternatives to Relieve Depression (STAR*D): rationale and design. *Control Clin Trials*. 2004;25(1):119–142.
9. Trivedi MH, Rush AJ, Wisniewski SR, et al; STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006;163(1):28–40.
10. Lavori PW, Rush AJ, Wisniewski SR, et al. Strengthening clinical effectiveness trials: equipoise-stratified randomization. *Biol Psychiatry*. 2001;50(10):792–801.
11. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
12. Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry*. 2003;53(8):649–659.
13. Kraemer HC, Stice E, Kazdin A, et al. How do risk factors work together? mediators, moderators, and independent, overlapping, and proxy risk factors. *Am J Psychiatry*. 2001;158(6):848–856.
14. Leon AC. Two clinical trial designs to examine personalized treatments for psychiatric disorders. *J Clin Psychiatry*. 2011;72(5):593–597.
15. Perroud N, Aitchison KJ, Uher R, et al. Genetic predictors of increase in suicidal ideation during antidepressant treatment in the GENDEP project. Neuropsychopharmacology. 2009;34(12):2517-2528.
16. Center for Drug Evaluation and Research (CDER). Suicidality: Prospective Assessment of Occurrence in Clinical Trials. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf. Updated August 25, 2010. Accessed June 29, 2012.
17. Posner K, Oquendo MA, Gould M, et al. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. 2007;164(7):1035–1043.