Time Course and Predictors of Suicidal Ideation During Citalopram Treatment in the STAR*D Trial

Catherine G. Coughlin, BS[a]; Ewgeni Jakubovski, MA[a]; and Michael H. Bloch, MD, MS[a,b,*]

ABSTRACT

Objective: Selective serotonin reuptake inhibitors are first-line treatment for major depressive disorder (MDD), but their impact on suicidal ideation is equivocal. Our goal is to examine the time course and clinical predictors of citalopram-induced suicidal ideation during phase 1 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.

Methods: Of the 4,041 subjects with *DSM-IV* nonpsychotic MDD in the STAR*D trial phase 1 (2001–2006), we included in our analysis 3,577 subjects who reported side-effect data and had received citalopram (20–60 mg/d) for 8–14 weeks. Suicidal ideation was reported on item 12 of the Quick Inventory of Depressive Symptomatology, Self-Report. Survival analysis and receiver operating characteristic analysis were used to assess baseline characteristics associated with emergence and worsening of suicidal ideation.

Results: Suicidal ideation was more likely to occur early in citalopram treatment, with few subjects showing emergence or worsening occurring after 6 weeks of treatment. Clinical variables explained very little of the variance in worsening or emergence of suicidal ideation with citalopram treatment (generalized $R^2 \leq 2\%$ in survival analysis). Being Hispanic, taking sedative medications, increased depression severity, absence of hypersomnia, and cardiac comorbidity were significantly ($P \leq .04$) associated with greater likelihood of emergence of suicidal ideation in patients without suicidal ideation at baseline. Being widowed, better work performance, weight loss at baseline, and the presence of vascular or neurologic comorbidities were associated with a greater likelihood of worsening of suicidal ideation.

Conclusions: Baseline clinical variables were poor predictors of emergence or worsening of suicidal ideation. As such, increased research focusing on clinical correlates rather than clinical predictors of suicidal ideation may be useful, as intervening events may be crucial in bringing about increased suicidality.

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[a]Yale Child Study Center, [b]Department of Psychiatry, Yale School of Medicine, New Haven, Connecticut
**Corresponding author:* Michael H. Bloch, MD, MS, Child Study Center, Yale University School of Medicine, PO Box 2070900, New Haven, CT 06520 (michael.bloch@yale.edu).

Suicidal ideation is a common but serious psychiatric emergency, strongly correlated with a history of mental illness.[1] Given that only a third of patients who attempt suicide have contact with mental health services within a year of their suicide attempt,[2] finding other predictive and protective factors related to suicidal ideation is of paramount clinical importance. Selective serotonin reuptake inhibitors (SSRIs), the most common treatment for major depressive disorder (MDD), have been associated with increased risk of suicidal ideation in meta-analyses[3,4] of randomized, placebo-controlled trials in children and adults under 24 years. As a result, the US Food and Drug Administration (FDA) added a black box warning[5] of suicidality for children and young adults aged 18–24 years for all antidepressants. This increased risk of suicidal ideation with SSRIs did not persist among adults aged 25–64 years,[3,4] and SSRIs have demonstrated an advantage over other medication classes in reducing suicidal ideation.[6] In fact, SSRIs are protective against suicide in elderly adults.[7] There is additional evidence that suggests that any initial increase in suicidal ideation with SSRIs is offset by a long-term antidepressant protective benefit from SSRI maintenance.[8] While the role of antidepressant medication in exacerbating or ameliorating suicidal ideation is both unclear and controversial despite the FDA warning, the period immediately after the initiation of treatment represents a high-risk period of suicidal ideation.[9]

Research examining predictors of suicidal ideation with antidepressant treatment is sparse and contradictory. Randomized control trials and meta-analyses of these trials are limited by short study periods and the exclusion of high-risk patients, while observational and ecological studies are often limited by confounding.[10] Analysis of predictors of suicidal ideation in SSRI trials has suggested that increased depression severity, treatment-refractory depression, hopelessness, unemployment, and comorbid substance use or anxiety disorders are correlated with an increased risk of suicide.[11–13] Furthermore, SSRI-induced psychomotor agitation and racing thoughts may increase suicidal ideation.[14] Women are slightly less likely than men to experience suicidal ideation during SSRI treatment initiation, and on average, onset of suicidal ideation in women occurs a few days later than in men.[15]

The National Institute of Mental Health (NIMH)–funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study was conducted to determine the effectiveness of different treatments for people with MDD. Over a 6-year period (2001–2006), the study enrolled more than 4,000 outpatients, 62% through mental health centers, aged 18–75 years with MDD, who were all initially treated with 8–14 weeks of citalopram. The study sample included participants with past suicidal attempts, current suicidal ideation, and the presence of known risk factors for suicide. Analysis of the STAR*D trial dataset is particularly advantageous, as it represents a practical clinical trial conducted in real-world settings. Previous analyses (eg, Zisook et al[16]) have explored suicidal ideation in the STAR*D dataset, finding that an increase in treatment-emergent suicidal ideation was associated with concurrent drug abuse, severe depression, or melancholic features. This analysis, while well

Clinical Points

- The effects of selective serotonin reuptake inhibitors (SSRIs) on suicidal ideation are poorly understood, and further characterization of the time course and predictors of suicidal ideation is warranted.
- Emergence or worsening of suicidal ideation in patients with major depressive disorder was most likely to occur within 6 weeks of initiation of SSRI treatment.
- Baseline clinical predictors explained extremely little of the variance in emergence or worsening of suicidal ideation.
- Some baseline characteristics are significantly associated with emergence (eg, taking a sedative and worse depression symptoms) or worsening (eg, improved work performance) of suicidal ideation or both (sleep disturbances and medical comorbidity).

done, did not examine many clinical predictors available at baseline and did not examine the change in suicidal ideation across all time points. The goal of the current study was to use data from phase 1 of the STAR*D trial to examine (1) the time course of emergence of (and worsening of existing) suicidal ideation and (2) predictors of their emergence and worsening using logistic regression and receiver operating characteristic (ROC) analysis.

METHODS

Study Overview

The rationale, design, and methods of the STAR*D trial have been described in depth elsewhere.[17,18] Of the 4,041 total subjects who participated in the phase 1 trial, we included the 3,629 subjects who reported side-effect data. All subjects were given citalopram (20–60 mg/d) in a nonblinded, noncontrolled fashion for 8–14 weeks. Suicidal ideation was reported on item 12 of the Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR).[18–21] The study was registered on ClinicalTrials.gov (identifier: NCT00021528).

Subjects

Subjects were recruited from 18 primary care centers and 23 psychiatric clinical sites throughout the United States. To be included in the STAR*D trial, outpatients needed to be adults aged 18–75 years and present with a nonpsychotic major depressive episode. They were required to have a score at baseline of greater than 13 on the 17-item Hamilton Depression Rating Scale (HDRS-17).[22,23] Patients were excluded from the STAR*D trial if they were pregnant or breast-feeding or had a primary psychiatric diagnosis of bipolar disorder, a psychotic disorder, obsessive-compulsive disorder, or an eating disorder. Subjects were also excluded if they had a general medical condition that was a contraindication for the use of any antidepressant agents used in the first 2 treatment phases of STAR*D or had a clear history of nonresponse or intolerance to these agents. For this analysis[18] of citalopram-induced suicidal ideation, subjects were additionally required to have at least 1 postbaseline assessment of side effects on the QIDS-SR.

Assessment

A checklist based on *DSM-IV* criteria was used to confirm the diagnosis of nonpsychotic MDD. At baseline, self-reports were obtained to provide information on demographic characteristics, past treatment history, and family history of Axis I psychiatric disorders. The Psychiatric Diagnostic Screening Questionnaire[24] was used to establish the presence of comorbid Axis I psychiatric diagnosis. The QIDS-SR and the HDRS-17 assessed depression severity. Health status was measured with the Short-Form Health Survey (SF-12).[25] Other baseline measures were the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[26] and Work and Social Adjustment Scale (WSAS).[27] The presence and severity of suicidal ideation was assessed using item 12 of the QIDS-SR at every treatment visit. Item 12 probes about thoughts of suicide or death. Specifically, the item asks respondents to select the most appropriate response over the last 7 days from the following options: (0) "I didn't think of suicide or death," (1) "I felt that life was empty or wondered if it was worth living," (2) "I thought of suicide or death several times for several minutes over the past 7 days," and (3) "I thought of suicide or death several times a day in some detail, or I made specific plans for suicide or actually tried to take my life." Clinical visits were suggested at 2, 4, 6, 9, and 12 weeks of citalopram treatment.

Intervention

Citalopram was prescribed in an open-label, unblinded manner to all subjects enrolled in the STAR*D protocol. The starting dose of citalopram was 20 mg per day, which was increased to 40 mg by week 4 and a maximum dose of 60 mg by week 6. The treatment protocol allowed for individualized starting doses and dose adjustments. Medication management was informed by QIDS ratings. Patients were allowed to discontinue citalopram before 12 weeks if (1) they had intolerable side effects, (2) an optimal dose was not possible due to side effects or patient choice, or (3) significant depressive symptoms (QIDS-Clinician ≥ 9) were present after 9 weeks of treatment with citalopram at the maximum-tolerated dose.

Statistical Analysis

Data preparation was conducted using SAS version 9.2 (SAS Institute) and Microsoft Excel (MicroSoft Corp). Both survival analysis and signal detection methodology were used to find the best prediction model for emergence of suicidal ideation. SAS was used for simple and multiple logistic regression models. The ROC analysis was performed using free software available online (http://www.stanford.edu/~yesavage/ROC.html). Data utilized in this study were obtained from the NIMH-supported STAR*D limited access dataset, version 2.

Survival analysis assessed the association of demographic, social, and clinical characteristics with emergence of suicidal ideation. Participants were stratified at baseline by the presence or absence of suicidal thoughts. Participants with a QIDS-SR item 12 score of 0 ("I didn't think of suicide or death") were defined as having no baseline suicidal ideation, whereas

participants with a score ≥ 1 ("I felt that life was empty or wondered if it was worth living") as having baseline suicidal ideation. We examined predictors of time to emergence of suicidal ideation in the group with no suicidal ideation and time to worsening of suicidal ideation in the group of participants with baseline suicidal ideation. For the analysis of emergence of suicidal ideation, we defined clinically significant suicidal ideation as a QIDS-SR item 12 score ≥ 2 ("I thought of suicide or death several times for several minutes") over the past 7 days. We chose to use a threshold of 2 rather than the threshold of 1 utilized in previous analyses of this dataset (1) because many individuals endorsing a QIDS-SR item 12 score of 1 may not be experiencing suicidal ideation (eg, a participant experiencing "life is empty" but not wondering "if it was worth living") and (2) to ensure similar definitions of suicidal ideation outcomes across the 2 groups. In supplementary material, we also include results when a threshold of 1 (rather than 2) was utilized for QIDS-SR item 12 (see Supplementary Analysis, eTable 1, and eFigure 1). For the analysis of worsening of suicidal ideation from baseline, we required that participants experience at least a 1-point increase from baseline (thus also requiring a QIDS-SR item 12 score ≥ 2). Participants with a QIDS-SR item 12 score = 3 at baseline (n = 52), the maximum possible score, were excluded from this analysis, as their suicidal ideation could not worsen on this item during the course of the study. Thus, the total number of participants included in our analyses was 3,577.

Survival analysis utilized the Cox proportional hazards model (Proc PHREG in SAS 9.0) using the outcome (worsening or emergence of suicidal ideation) and time (time-point at which worsening or emergence of suicidal ideation was reported or the last assessment time point). Survival analysis models were calculated with the following predictor variables individually:

- Demographic predictors: age, race (Caucasian and African American [yes/no]), ethnicity (Hispanic vs non-Hispanic), gender, and site (primary care vs mental health clinic).
- Socioeconomic predictors: years of education, academic degrees (high school dropout, high school diploma, some college and/or graduate school), employment status (employed/unemployed), income (categorized as < $10,000, $10,000–$20,000, $20,000–$40,000 and > $40,000), and marital status.
- Clinical predictors: age at onset of MDD; length of the current depressive episode; family history of depression; history of resistance to SSRI treatment; benzodiazepine, sedative/hypnotic, or antipsychotic use; history of resistance to antidepressant treatment; past suicide attempts; and comorbid Axis I disorders (posttraumatic stress disorder, bulimia, panic disorder, agoraphobia, social phobia, alcohol dependence, drug dependence, generalized anxiety disorder, somatization disorder, obsessive-compulsive disorder, hypochondriasis). Sedative/hypnotic agents were defined as medications other than benzodiazepines, barbiturates, and antidepressants used for sleep.
- Baseline rating scales: HDRS, QIDS-SR, WSAS, Q-LES-Q (all items and total scores), and 12-SF Health.
- Medical comorbidities: heart, vascular, genitourinary, musculoskeletal, neurologic, and endocrine/metabolic, scored 0 (no problem) to 4 (extremely severe impairment).

All predictor variables were tested for main effects. Significant predictors ($P < .05$) from the simple survival analysis models were entered into a backward stepwise survival analysis model to assess the unique and independent contribution of these variables to side-effect emergence rates. Individual predictor variables were excluded from the backward stepwise survival analysis model based on P values until only significant predictors ($P < .05$) remained. We additionally computed a generalized R^2 statistic using the likelihood ratio statistic for the best-fitting survival analysis result for each outcome.

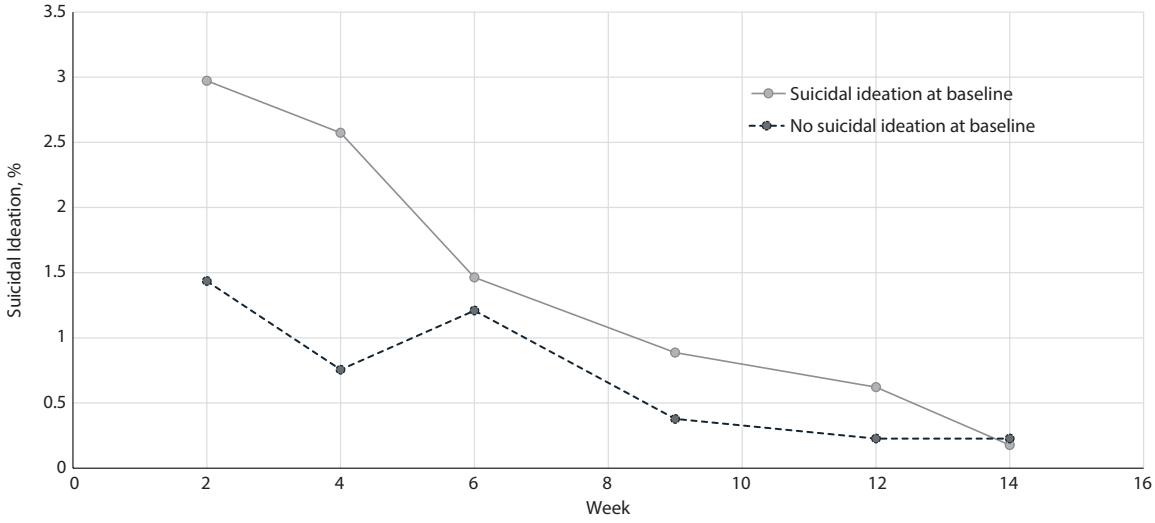
Receiver operating characteristic analysis was used as an alternative prediction model. ROC analysis is a nonparametric method that operates via recursive partitioning. It aims at identifying subgroups of individuals who have a higher or lower probability of achieving a particular binary outcome.[28] Emergence of suicidal ideation at any time was utilized as the binary outcome for ROC analysis. For each measured potential predictor, cutoff points were generated at all values observed in the variable. The quality of a cutoff point is defined by its ability to divide the sample into 2 subsamples, maximally distinct in the specified binary outcome. The cutoff point that yields the best prediction is identified across all values of all variables. That cutoff point is then used to divide the total sample into 2 subsamples. The same procedure is repeated systematically in each of the 2 subsamples. This iterative process continues until a stopping criterion is reached. The stopping criteria for ROC analysis are either a subgroup size of less than 10 individuals or a failure to reach a significant group difference at $P < .05$ for any candidate cutoff value.[28] With a sample as large as the STAR*D trial, following these common stopping rules would result in a large number of high-order interaction terms, which would be difficult to interpret. Therefore, we decided a priori to introduce additional stopping rules, namely stopping the analysis once the 3-way interaction level was reached. After the last step of the ROC analysis was reached, we calculated the probability of worsening and emergence and presented results as hierarchical decision tree diagrams. The models were calculated using the same predictors as previous regression models.

RESULTS

Time Course of Emergence and Worsening of Suicidal Ideation During Short-Term Citalopram Treatment

Participants (N = 1,323) completing at least 1 follow-up rating reported no suicidal ideation at baseline, and 2,254

Figure 1. Time Course of Emergence and Worsening of Suicidal Ideation During Citalopram Treatment[a]



[a]This graph depicts the time course and likelihood of occurrence of emergence (in participants with no baseline suicidal ideation) and worsening of suicidal ideation (in participants with suicidal ideation at baseline).

Table 1. Predictors of Emergence and Worsening of Suicidal Ideation in Survival Analysis[a]

Emergence of Suicidal Ideation					Worsening of Suicidal Ideation				
Predictor	HR	95% CI		*P*	Predictor	HR	95% CI		*P*
Hispanic	1.94	1.03	3.68	.04	Widowed	1.96	1.07	3.60	.03
Sedative	9.18	2.05	41.01	.004	QIDS-SR, hypersomnia	0.83	0.69	1.00	.046
HDRS total score	1.06	1.01	1.11	.02	QIDS-SR, weight decrease	1.16	1.01	1.34	.04
QIDS-SR, hypersomnia	0.64	0.41	1.00	.047	Q-LES-Q, work performance	1.22	1.06	1.41	.005
Q-LES-Q, vision	0.78	0.61	0.99	.04	Vascular comorbidity	1.19	1.01	1.40	.04
Cardiac comorbidity	1.74	1.29	2.35	.0003	Neurologic comorbidity	1.25	1.03	1.51	.02
Multiple Regression					Multiple Regression				
Sedative $R^2 = 0.012$	9.81	2.19	43.87	.003	Q-LES-Q, work performance $R^2 = 0.003$	1.19	1.00	1.41	.049

[a]Subjects were initially stratified by whether they did (QIDS-SR item) or did not have suicidal ideation on QIDS-SR item 12. Participants with a QIDS-SR item 12 score of 0 ("I didn't think of suicide or death") were defined as having no baseline suicidal ideation, whereas participants with a score ≥ 1 ("I felt that life was empty or wondered if it was worth living") as having baseline suicidal ideation. Subjects were required to have a QIDS-SR item 12 score ≥ 2 ("I thought of suicide or death several times for several minutes") over the past 7 days in order to qualify as having worsening or emergence of suicidal ideation.

Abbreviations: HDRS = Hamilton Depression Rating Scale; HR = hazard ratio; QIDS-SR = Quick Inventory of Depressive Symptomatology, Self-Report; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

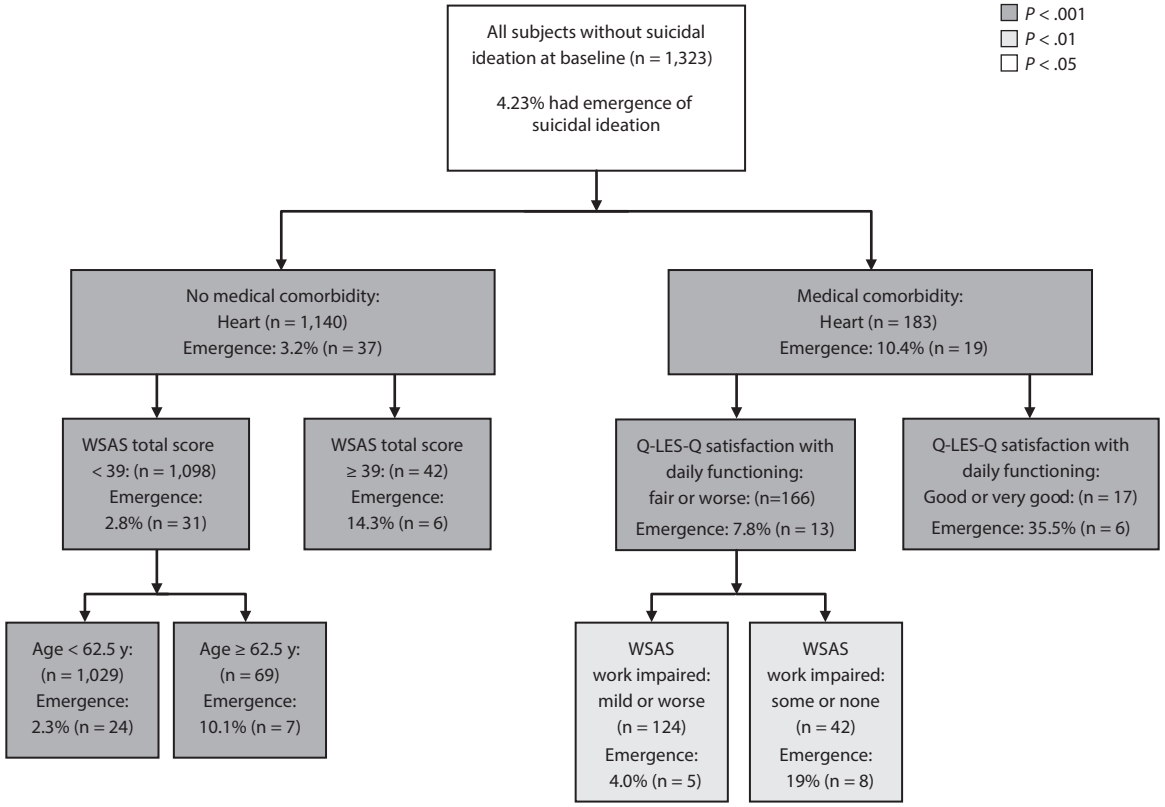
participants reported suicidal ideation at baseline. Of the participants who reported no suicidal ideation at baseline, 4.2% experienced emergence of suicidal ideation (QIDS-SR item 12 ≥ 2) during short-term citalopram treatment. Of the participants experiencing suicidal ideation at baseline, 8.7% reported worsening of suicidal ideation during short-term citalopram treatment. Figure 1 depicts the time course of emergence and worsening of suicidal ideation across the first phase of the STAR*D trial. Both worsening and emergence of suicidal ideation was most likely to be reported at the first assessment point (week 2) and was decreasingly likely to be reported at each subsequent visit. However, worsening (up to week 4) or emergence (up to week 6) of suicidal ideation was still commonly reported (1%–1.5%). Initial worsening or emergence of suicidal ideation was much less likely to be reported during or after the assessment at 9 weeks of citalopram treatment (0.25%–0.75%).

Baseline Predictors of Emergence of Suicidal Ideation With Citalopram Treatment

Table 1 depicts baseline characteristics associated with emergence of suicidal ideation in univariate survival analysis. Being Hispanic, taking a sedative, a higher baseline HDRS score, and the presence of cardiac comorbidity were associated with a greater likelihood of emergence of suicidal ideation in patients without suicidal ideation at baseline. The presence of hypersomnia (QIDS-SR item 4) at baseline was associated with a lower likelihood of emergent suicidal ideation. In backward stepwise survival analysis, the best-fitting model, which explained only 1.2% of the variance in outcome, contained only whether participants took a sedative at baseline.

Figure 2 depicts hierarchical prognostic subgroups for emergence of suicidal ideation in participants who did not report suicidal ideation at baseline. Baseline clinical

Figure 2. Empirically Derived Prognostic Subgroups for Emergence of Suicidal Ideation During Citalopram Treatment in Subjects With No Suicidal Ideation at Baseline (QIDS-SR item 12 score ≥ 2)[a]



[a]The figure depicts empirically derived prognostic subgroups for treatment-emergent suicidal ideation (in participants with no baseline suicidal ideation). Receiver operating characteristic analysis is a nonparametric method that aims at identifying subgroups of individuals who have a higher or lower probability of achieving a particular binary outcome (in this case, emergence of suicidal ideation). For each measured potential predictor, cutoff points are generated at all values observed in the variable. The quality of a cutoff point is defined by its ability to divide the sample into 2 subsamples, maximally distinct in the specified binary outcome. The cutoff point that yields the best prediction is identified across all values of all variables. That cutoff point is then used to divide the total sample into 2 subsamples. The same procedure is repeated systematically in each of the 2 subsamples. This iterative process continues until a stopping criterion is reached.

Abbreviations: Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, WSAS = Work and Social Adjustment Scale.

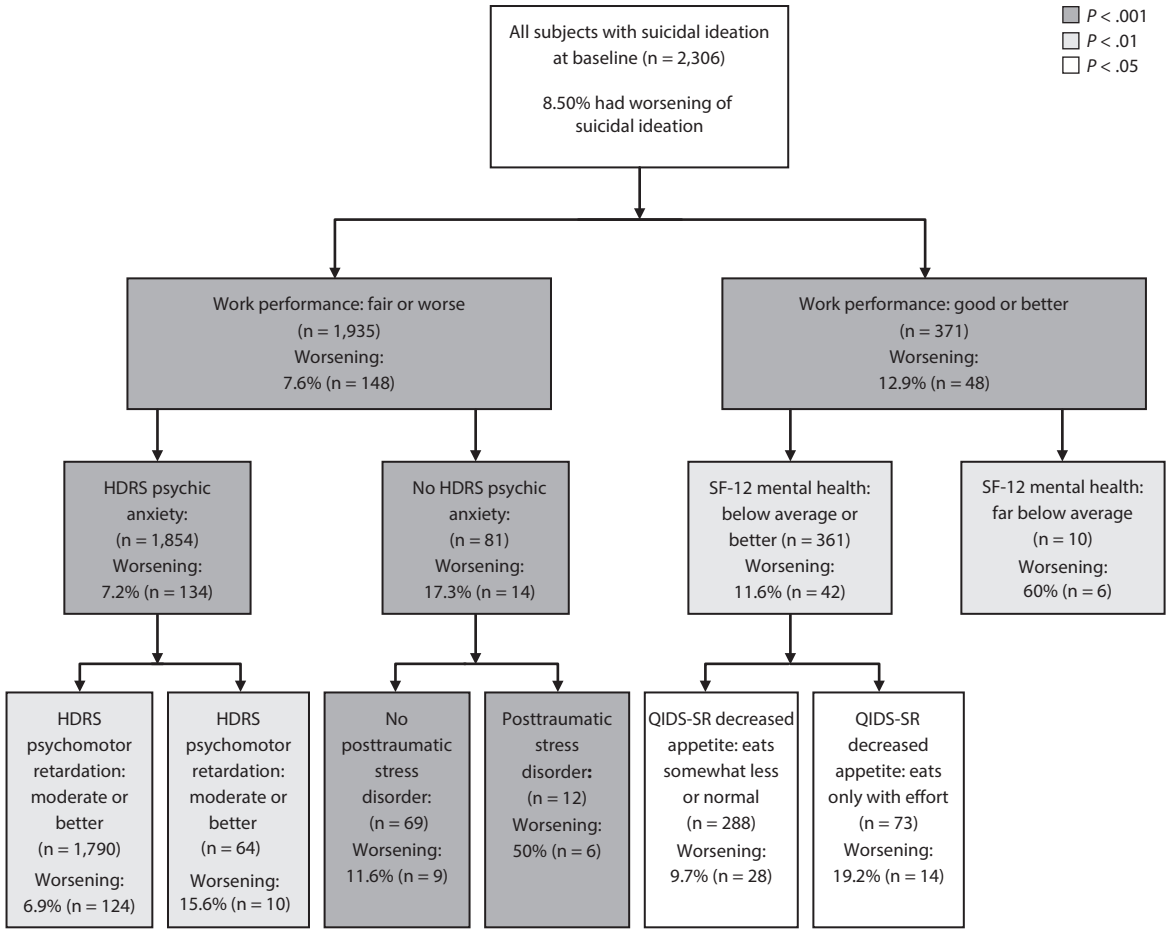
characteristics were able to identify subgroups with a likelihood of emergence of suicidal ideation as low as 2.3% (no cardiac comorbidity, WSAS total score < 39, age < 62.5 years) to as high as 35.3% (presence of a cardiac comorbidity and Q-LES-Q satisfaction with daily functioning good or very good, item 7 score ≥ 4). The presence of cardiac disease at baseline was the most discriminative predictor for emergence of suicidal ideation with citalopram treatment ($\chi^2 = 19.8$, $P < .001$).

Baseline Predictors of Worsening of Suicidal Ideation With Citalopram Treatment

Table 1 depicts baseline characteristics associated with worsening of suicidal ideation with citalopram treatment. Being widowed, better work performance (item 3 on Q-LES-Q), weight loss in the previous 2 weeks at baseline, and the presence of vascular or neurologic comorbidities were associated with a greater likelihood of worsening of suicidal ideation with citalopram treatment. A higher degree of work impairment (item 1 on WSAS) and hypersomnia were associated with a lower likelihood of worsening of suicidal ideation with citalopram treatment. In backward stepwise survival analysis, the best-fitting model, which explained less than 1% of the variance in outcome, contained only baseline work impairment.

Figure 3 depicts the hierarchical prognostic subgroups for worsening of suicidal ideation in participants who reported suicidal ideation at baseline. Baseline clinical characteristics were able to identify subgroups with a likelihood of worsening of suicidal ideation as low as 6.9% (fair or worse work performance Q-LES-Q item 3; presence of HDRS psychic anxiety, score ≥ 1 item 10; and HDRS psychomotor retardation item 8 moderate or higher, score ≥ 3) to as high as 60% (good or better work performance, Q-LES-Q item 3, score ≥ 4; SF-12 mental health far below average, score < 16.77). Work performance at baseline was the most discriminative predictor for worsening of suicidal ideation after citalopram treatment, with better work performance at baseline being associated with increased likelihood of worsening suicidal ideation ($\chi^2 = 10.9$, $P < .001$).

Figure 3. Empirically Derived Prognostic Subgroups for Worsening of Suicidal Ideation During Citalopram Treatment in Subjects With Suicidal Ideation at Baseline[a]



[a]The figure depicts empirically derived prognostic subgroups for worsening of suicidal ideation (in participants with suicidal ideation at baseline). Receiver operating characteristic analysis is a nonparametric method that aims at identifying subgroups of individuals who have a higher or lower probability of achieving a particular binary outcome (in this case, worsening of suicidal ideation). For each measured potential predictor, cutoff points are generated at all values observed in the variable. The quality of a cutoff point is defined by its ability to divide the sample into 2 subsamples, maximally distinct in the specified binary outcome. The cutoff point that yields the best prediction is identified across all values of all variables. That cutoff point is then used to divide the total sample into 2 subsamples. The same procedure is repeated systematically in each of the 2 subsamples. This iterative process continues until a stopping criterion is reached.

Abbreviations: HDRS = Hamilton Depression Rating Scale; QIDS-SR = Quick Inventory of Depressive Symptomatology, Self-Report; SF-12 = Short-Form Health Survey.

DISCUSSION

In this secondary analysis of phase 1 of the STAR*D trial, we were able to demonstrate that worsening or emergence of suicidal ideation is most common in the first few weeks of citalopram treatment and much less likely after 6 weeks of treatment. We conducted empirical and data-driven approaches to identify baseline predictors of emergence and worsening of suicidal ideation and were able to identify some baseline characteristics significantly associated with emergence (eg, taking a sedative and worse depression symptoms) or worsening (eg, improved work performance) of suicidal ideation or both (absence of hypersomnia and medical comorbidity). However, perhaps the most striking results of these analyses were the relative inability for these baseline predictors to predict outcome—2% or less of the variance in outcomes explained in backward stepwise logistic regression models.

Two findings from this study are of potential importance to clinicians: (1) the time course of emergence and worsening of suicidal ideation and (2) a few baseline predictors of outcome that were strongly associated with emergence or worsening suicidal ideation but were relatively uncommon at baseline (so did not contribute much to explaining outcome in the overall sample). These included (1) taking sedative medications and (2) medical comorbidity. Previous research has established that hypnotic drugs, as well as insomnia, are predictive of suicidal ideation.[29] Taking sedatives may be a proxy for preexisting anxiety, agitation, and/or sleep problems at baseline, which are perhaps associated with treatment-emergent SSRI-related side effects. Similarly, the relationship between cardiac disease and suicidal ideation

is well documented.[30,31] Additionally, for clinicians, data suggesting that emergence or worsening of suicidal ideation is fairly uncommon after 6–9 weeks of citalopram treatment create a time point at which clinical monitoring can be tapered in a patient whose depression is improving. Our data are consistent with previous studies of SSRI-induced suicidal ideation that estimate that patients are at an increased suicide risk for the first month of suicide treatment.[9,15]

The lack of power of baseline clinical characteristics in predicting emergence or worsening of suicidal ideation has important implications for suicide research. Although not exhaustive, clinical assessments at baseline in the STAR*D trial were fairly extensive and were nonetheless shockingly poor at predicting emergence or worsening of suicidal ideation.[14,15,17] Two alternative research strategies that may help to mitigate the lack of predictive utility of clinical baseline assessments are to (1) examine other potential data available at baseline (eg, genetic[14] or neuropsychological predictors[32]) and (2) examine correlates of worsening suicidal ideation. Several previous studies[33,34] have examined genetic predictors of emergence of suicidal ideation, including in this STAR*D sample.[35,36] These analyses, on the whole, have largely failed to provide consistent genetic risk factors and explained a fairly small proportion of suicidal outcomes. Studies examining predictors using neuropsychological testing have occurred on a much smaller scale but have pinpointed cognitive inflexibility as a potential risk factor for future suicidal ideation.[32] Another possibility that remains is that baseline predictors will have little predictive power because unpredictable, subsequent intervening events may have a large impact on changes in suicidal ideation across time. In this case, as researchers, we should concentrate on correlates, rather than predictors, of worsening suicidal ideation that may help identify inter-assessment events or changes that may cause worsening suicidality. Unfortunately, because STAR*D was designed as a practical clinical trial to minimize subject burden, few of these baseline clinical assessments were repeated at regular study intervals throughout the clinical trial. On the other hand, some of the baseline predictors suggest potential vulnerabilities to intervening events, which may increase the likelihood of emerging and worsening suicidal ideation. For instance, higher, as opposed to lower, baseline work functioning was associated with increased risk of worsening suicidal ideation. This result raises the possibility that in individuals with baseline suicidal ideation and good occupational performance, workplace difficulties or decreased functioning might influence suicidal ideation.

There are several limitations in our study. Survival analysis and ROC analysis of predictors of emergence are not hypothesis driven; they are empirically derived. These exploratory analyses typically provide an overly optimistic evaluation of the power of identified predictors. The restrictive inclusion criteria of the sample (ie, patients were excluded if they had primary psychiatric disorder, history of SSRI nonresponse, etc), limits the generalizability of these results to more heterogeneous clinical populations of depressed outpatients. Additionally, previous research has suggested a relationship between emergence or worsening of suicidal ideation and risk of dropout. Therefore, by relying on regular study assessments to assess suicidal ideation, we may have missed some subjects who had an emergence or worsening of suicidal ideation, as they may have dropped out prior to the next scheduled study assessment. Another limitation to this analysis was the use of QIDS-SR to determine suicidal ideation, as there are many methods to evaluate suicidal ideation; moreover, definitions of suicidal ideation are not consistent within the field. Furthermore, SSRI-induced suicidal ideation is most likely better evaluated as a continuous variable, rather than a dichotomous outcome. However, continuous rating scales of assessing suicidality were not conducted regularly in the STAR*D protocol.

Suicidal ideation induced by an SSRI was most likely to occur early in treatment. A few baseline predictors of emerging or worsening suicidal ideation with citalopram treatment were identified, but they explained a clinically insignificant portion of likelihood of experiencing emergence or worsening suicidal ideation. Further work is warranted on the predictors of both suicidal ideation and suicide attempts, with a specific focus on clinical relevance and application. Research examining treatment-emergent suicidal ideation should also concentrate on (1) examining other potential baseline predictors of outcome (eg, genetic or neuropsychological testing) or (2) examining correlates of worsening suicidal ideation. As both clinicians and researchers, we may benefit by focusing on intervening events that occur after the initiation of treatment (eg, relationship problems, social stresses, etc) that are correlated with emergence or worsening of suicidal ideation rather than focusing on baseline characteristics of patients that seem to have poor predictive value.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Time Course and Predictors of Suicidal Ideation During Citalopram Treatment in the STAR*D Trial

Authors: Catherine G. Coughlin, BS; Ewgeni Jakubovski, MA; and Michael H. Bloch, MD, MS

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List of Supplementary Material for the article

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This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Material:

Alternative Emergence of Suicidal Ideation Analysis Utilizing QIDS-SR item 12≥1 (*felt that life was empty or wondered if it was worth living).*

The Supplementary Table depicts baseline characteristics associated with emergence of suicidal ideation in univariate survival analysis. Being widowed, the presence of cardiac, musculoskeletal and neurologic comorbidity, decreased QLESQ social relationship score and increased impairment on the WSAS total and on the WSAS private activities item were associated with a greater likelihood of emergence of suicidal ideation in patients without suicidal ideation at baseline. Having received a higher educational degree was associated with a lower likelihood of emergent suicidal ideation. In backward stepwise survival analysis, the best-fitting model, which explained only 1.7% of the variance in outcome, contained being widowed, highest educational degree received, WSAS impairment in private activities and musculoskeletal comorbidities.

The Supplementary Figure depicts hierarchical prognostic subgroups for emergence of suicidal ideation in participants who did not report suicidal ideation at baseline. Baseline clinical characteristics were able to identify subgroups with a likelihood of emergence of suicidal ideation as low as 12.2% (no cardiac comorbidity, WSAS Impairment in Private Activities < 7 and WSAS Impairment in Close Relationships<6) to as high as 35.3% (WSAS Impairment in Private Activities≥7 and no psychomotor retardation on HAM-D). WSAS Impairment in Private Activities was the most discriminative predictor of emergence of suicidal ideation.

Supplementary Table: Predictors of Emergence of Suicidal Ideation with Citalopram Treatment

Emergence of Suicidal Ideation				
Predictor	HR	95% CI		p
widowed	1.90	1.18	3.07	0.01
Highest Degree Received	0.92	0.85	0.99	0.03
WSAS-Impairment in Private Activities	1.06	1.01	1.12	0.03
WSAS Total Score	1.02	1.00	1.03	0.03
QLES - Social Relationships	0.87	0.76	0.98	0.02
Cardiac Comorbidity	1.26	1.05	1.50	0.01
Musculosketal Comorbidity	1.19	1.05	1.35	0.01
Neurologic Comorbidity	1.23	1.04	1.44	0.01
Multiple Regression				
widowed	1.83	1.12	3.01	0.02
Highest Degree Received	0.92	0.85	0.99	0.03
QLES - Social Relationships	0.87	0.77	0.99	0.03
Musculosketal Comorbidity	1.23	1.08	1.40	0.002
R^2=	0.017			

Supplementary Figure: Empirically-Derived Prognostic Subgroups for Emergence of Suicidal Ideation