Predicting Worsening Suicidal Ideation With Clinical Features and Peripheral Expression of Messenger RNA and MicroRNA During Antidepressant Treatment

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ABSTRACT

Objective: To investigate how the combination of clinical and molecular biomarkers can predict worsening of suicidal ideation during antidepressant treatment.

Methods: Samples were obtained from 237 patients with major depressive disorder (*DSM-IV* criteria) treated with either duloxetine or placebo in an 8-week randomized controlled trial. Data were collected between 2007 and 2011. The relationship between treatment-worsening suicidal ideation (TWSI) and a number of clinical variables, as well as peripheral expression of messenger RNA (mRNA) and microRNA (miRNA), was assessed at baseline. We generated 4 predictive models for TWSI: clinical, mRNA, miRNA, and a combined model comprising the best predictive variables from clinical, mRNA, and miRNA data.

Results: Eleven patients (9.8%) presented with TWSI in the duloxetine group. Among the clinical variables, only baseline depressive severity was found to be mildly predictive of TWSI. Two mRNAs (stathmin 1 [*STMN1*] and protein phosphatase 1 regulatory subunit 9B [*PPP1R9B*]) and 2 miRNAs (miR-3688 and miR-5695) were identified that were significantly predictive of TWSI when mRNA and miRNA were assessed separately ($P = .002$, .044, .004, and .005, respectively). The best model included baseline depression severity and expression of *STMN1* and miR-5695 and predicted TWSI with area under the curve = 0.94 ($P < .001$). Additionally, the combined model did not significantly predict TWSI in the placebo group.

Conclusions: This study generated a predictive tool for TWSI that combines both biological and clinical variables. These biological variables can be easily quantified in peripheral tissues, thus rendering them viable targets to be used in both clinical practice and future studies of suicidal behaviors.

Trial Registration: ClinicalTrials.gov identifiers: NCT00635219, NCT00599911, and NCT01140906

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Suicidal behavior is the most serious complication of mood disorders, and suicidal ideation is an important correlate of suicidal behavior.[1] Although there has been a debate over the last decade about the occurrence of treatment-induced suicidal behavior, antidepressant treatment is one of the most effective strategies for suicide prevention, and most patients have a reduction of suicide ideation during antidepressant treatment. However, increased suicidal ideation during antidepressant treatment may occur in up to 30% of patients.[2–4] This increased ideation may be characterized as either treatment-worsening suicidal ideation (TWSI) or, in patients who do not display suicidal ideation initially, as treatment-emergent suicidal ideation (TESI). Both TWSI and TESI, along with suicidal behavior, represent a major concern in daily patient care.

Suicidal behavior and variation in suicidal ideation during antidepressant treatment are difficult to predict. A complete clinical interview is the gold standard to evaluate suicide risk in daily clinical practice, but such interviews have been of limited value when it comes to predicting TWSI or TESI because clinical variables explain very little of the variance of suicidal ideation occurring during antidepressant treatment.[5] In addition, combining a large set of clinical factors does not seem to improve the ability to predict suicidal behavior.[6] Similarly, while the addition of psychometric scales to the clinical assessment renders the prediction more structured, it does not significantly increase specificity and is not part of routine clinical evaluation.[7] Moreover, prediction is especially difficult because of variability across time in suicidal intent, which may be sudden and impulsive.[8]

Clinical Points

- Treatment-worsening suicidal ideation is an important concern during antidepressant treatment of patients with major depressive disorder.
- A combination of biomarkers, including expression of stathmin 1 (STMN1) and miR-5695, along with baseline Montgomery-Asberg Depression Rating Scale severity scores may be used to predict worsening of suicidal ideation during antidepressant treatment.

The assessment of biomarkers may improve the identification of patients most likely to experience TWSI and TESI. Pharmacogenomic studies have described several genetic polymorphisms associated with a greater risk of suicide events during antidepressant treatment.[4] The study of messenger RNA (mRNA) and microRNA (miRNA) expression is also a promising approach because these are dynamic molecular markers that may change with treatment.[9] Numerous studies have shown altered expression of mRNA, RNA molecules that are transcribed into proteins, in major depressive disorder (MDD) and in relation to suicidal behavior.[10,11] Although less well investigated, miRNAs, small noncoding RNA molecules that regulate gene expression, have also been implicated in MDD and suicide.[12,13] Moreover, high-throughput technologies investigating mRNA and miRNA allow for hypothesis-free biomarker discovery, but to our knowledge there are no reports to date of prediction of TESI or TWSI using these markers. Finally, only a few studies[14–16] have combined biomarkers and clinical data to improve the accuracy of biomarker prediction. Thus, their application to suicide prevention or the prediction of suicidality in the context of antidepressant treatment has yet to be determined.

In this study, we aimed to investigate the utility of molecular biomarkers, specifically peripheral mRNA and miRNA measures, to predict worsening of suicidal ideation during antidepressant treatment. We investigated depressed patients who were treated with duloxetine or placebo as part of a double-blind, randomized, placebo-controlled trial and used high-throughput technologies to study mRNA and miRNA as a function of TESI or TWSI.

METHODS

Patients and Clinical Data

We included data from 237 participants with MDD who were part of double-blind, randomized, placebo-controlled trials of duloxetine (ClinicalTrials.gov identifiers: NCT00635219, NCT00599911, and NCT01140906). Participants, aged 18–75 years, were recruited based on a primary diagnosis of MDD and a major depressive episode lasting at least 3 months, with a severity score on the Montgomery-Asberg Depression Rating Scale (MADRS)[17] at baseline of ≥ 22. Participants resistant to at least 2 previous antidepressant treatments or who had received electroconvulsive therapy in the 6 weeks prior to study beginning were excluded. Other exclusion criteria were major depressive episode in bipolar disorder, presence of psychotic features, and recent substance use disorder. Psychiatric diagnoses were made using the Mini-International Neuropsychiatric Interview according to *DSM-IV* criteria.[18] All patients included in this analysis were free of medication at study inclusion and then received treatment with duloxetine (60 mg) or placebo for 6–8 weeks. A total of 112 patients were treated with duloxetine and 125 were treated with placebo. This study was approved by the local institutional review board, and written informed consent was obtained from all subjects.

Suicidal ideation was assessed 6 times: at baseline (before treatment) and 1, 2, 4, 6, and 8 weeks after treatment initiation (NCT00635219 and NCT01140906) or at baseline and 1, 2, 3, 4, and 6 weeks after treatment initiation (NCT00599911). Ideation was assessed using item 10 from the MADRS, "suicidal thoughts" with scores ranging from 0 (enjoys life or takes it as it comes) to 6 (explicit plans for suicide when there is an opportunity; active preparations for suicide). Although not ideal, the use of a single suicide item from a depression scale has been included in several previous studies and has also been validated as an appropriate tool to evaluate suicidal ideation in prospective studies.[19] Treatment-worsening suicidal ideation was defined as an increase of at least 1 point on MADRS item 10 at any time during the follow-up. TWSI was the primary outcome measure. Treatment-emergent suicidal ideation was defined as an increase of at least 1 point on MADRS item 10 at any time during the follow-up in patients who did not present with suicidal ideation at baseline (ie, baseline MADRS item 10 score = 0).

Severity of depressive symptoms was measured using the MADRS total score at each visit. Anxiety severity at baseline was evaluated using the Hamilton Anxiety Rating Scale.[20] Family history was evaluated using a standardized questionnaire to assess potential occurrence of psychiatric disorders or suicide in parents and grandparents. Due to small sample sizes in each category of diagnosis, we combined positive family history in a unique variable by considering the presence of at least 1 major psychiatric diagnosis (major depression, bipolar disorder, schizophrenia, suicide, substance use disorder) in at least 1 family member.

Biological Assessments

Whole blood samples were collected at baseline using PAXgene Blood RNA Tubes (PreAnalytiX GmbH; Hombrechtikon, Switzerland). Total RNA was extracted using the miRNeasy Micro Kit (QIAGEN; Hilden, Germany) with DNase treatment. RNA integrity was evaluated using an Agilent Bioanalyzer (Agilent Technologies; Santa Clara, California). All samples had an RNA integrity number (RIN) > 6.

To study mRNA, RNA was hybridized to the Illumina HumanHT-12 v4 microarray (Illumina, Inc; San Diego, California). Samples were randomized to avoid batch effects. All array probes and samples were subjected to quality

Table 1. Description of the Patients Included in the Study[a]

Variable	Whole Cohort (N = 237)	Patients Treated With Duloxetine (n = 112)	Patients Treated With Placebo (n = 125)
Age, mean (SD), y	46.8 (12.8)	47.5 (12.9)	46.1 (12.9)
MADRS score at baseline, mean (SD)	31.2 (3.7)	31.0 (3.5)	31.4 (3.9)
HARS score before treatment, mean (SD)[b]	20.4 (6.5)	20.7 (6.7)	20.1 (6.4)
Total no. of MDEs, mean (SD)[b]	3.0 (1.6)	3.2 (1.9)	2.8 (1.2)
Patients with TWSI	32 (13.5)	11 (9.8)	21 (16.8)
Female	165 (69.6)	81 (72.3)	84 (67.2)
Current melancholic features	156 (65.8)	68 (60.7)	37 (29.6)
Current first MDE	19 (8.0)	7 (6.3)	12 (9.6)
Antidepressant-naive patients at study inclusion[c]	35 (14.8)	17 (21.0)	18 (18.6)
Positive familial psychiatric history[c]	73 (30.8)	38 (46.9)	35 (36.1)

[a] Values shown as n (%) unless otherwise noted.

[b] Data available for only 216 subjects (101 duloxetine and 115 placebo).

[c] Data available for only 178 subjects (81 duloxetine and 97 placebo).

Abbreviation: HARS = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDE = major depressive episode, TWSI = treatment-worsening suicidal ideation.

control using Flexarray (NetApp, Inc; Sunnyvale, California). Data were normalized using background adjustment and log$_2$ transformation, variance stabilization transformation (VST) correction, and quantile normalization. In total, 47,323 probes were present in the microarray. All probes were filtered using a detection P value < .01 in at least 10% of the samples, resulting in available expression data for 16,674 remaining probes.

miRNA were analyzed using the Illumina TruSeq Small-RNA protocol (Illumina, Inc; San Diego, California) as previously described.[21,22] Samples were sequenced at the McGill University and Genome Quebec Innovation Centre (Montreal, Canada) using the HiSeq2500 Illumina sequencer with 50-nucleotide single-end reads (Illumina, Inc; San Diego, California). We used a detection threshold of 10 counts per miRNA (present in at least 80% of libraries tested). A total of 281 miRNAs survived our criteria and were included in the analysis. All small RNA–sequencing data were normalized with the Bioconductor DESeq2 package using the variance-stabilizing transformation method.[23]

Statistical Analyses

Data were expressed as proportions and frequency for categorical variables and as means and standard deviations for continuous variables. We first conducted our analysis on patients treated with an active antidepressant (duloxetine).

To select the best mRNAs and miRNAs to be used as predictive biomarkers, expression levels were first analyzed at the transcriptome-wide level. Mean differences of RNA expression for each mRNA or miRNA were assessed between patients with or without TWSI during the follow-up using t tests and correction for multiple testing. The best potential mRNA and miRNA predictive biomarkers were selected according to a false discovery rate (FDR) threshold below 10%.[24]

We aimed to build 4 different models to predict occurrence of TWSI: best clinical variables ("clinical model"), best predictive mRNAs ("mRNA model"), best predictive miRNAs ("miRNA model"), and a model that combined the best predictive variables from clinical, mRNA, and miRNA data ("combined model"). For each model, variables were selected according to univariate logistic regression with occurrence of TWSI as dependent variable. Variables were included in subsequent multivariate analysis if $P < .1$ in the univariate analyses. For clinical variables, due to missing data, we used a multiple imputation strategy,[25] and we computed both univariate logistic regressions before and after imputation of missing data. We included in the clinical model only variables that achieved statistical threshold in both analyses. For mRNA, unlog value of expression was used to avoid large odds ratios.

Models were built using a stepwise multiple logistic regression, and predictive scores were calculated for each model. A binormal smoothing was performed for building receiver operating characteristic (ROC) curves. A resampling method with a bootstrap strategy was used to calculate confidence intervals of area under the curve (AUC), sensitivity, and specificity. We then compared the AUC of the 3 first models (clinical, mRNA, and miRNA) to the final combined model using pROC package (R software; R Foundation). Finally, we tested the AUC of the combined model in the cohort of patients treated with placebo.

RESULTS

A total of 237 participants were included in the study (69.6% female; mean ± SD age = 46.8 ± 12.8 years): 112 treated with duloxetine and 125 treated with placebo (Table 1). Mean ± SD baseline MADRS score was 31.2 ± 3.7. During the follow-up, TWSI was identified in 32 participants (13.5%): 11 (9.8%) treated with duloxetine and 21 (16.8%) treated with placebo. TESI was identified in only 2 participants (0.8% of total), both treated with placebo. No suicide attempts were reported in this sample.

Clinical Predictive Model

In the duloxetine group, before and after imputation of missing data, only depression severity at baseline, as measured

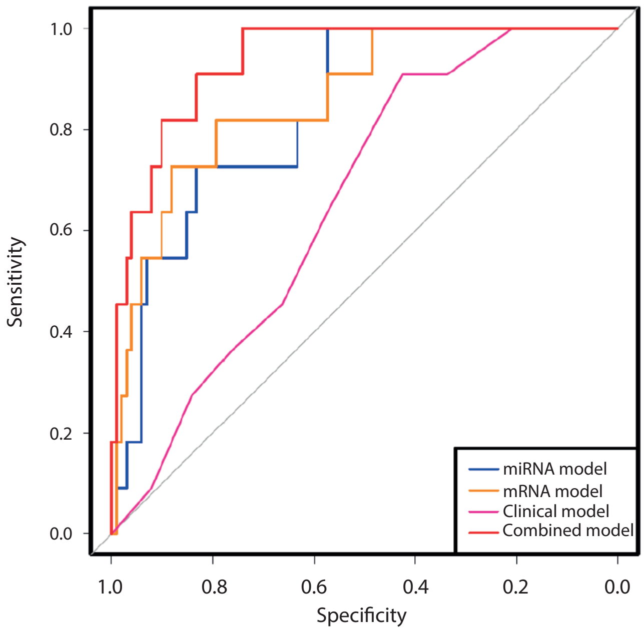
Table 2. Receiver Operating Characteristic Curves for 4 Different Models to Predict Treatment-Worsening Suicidal Ideation

Predictive Model (Variables Included)	AUC (95% CI[a])	Standard Error	*P* Value	Sensitivity, % (95% CI[a])	Specificity, % (95% CI[a])
Clinical (MADRS total score at inclusion)	0.66 (0.52–0.80)	0.070	.08	90.9 (62.8–100)	42.6 (20.8–59.4)
mRNA (PPP1R9B mRNA and *STMN1* mRNA)	0.86 (0.75–0.97)	0.05	<.001	81.8 (45.5–100)	79.2 (46.5–95.1)
miRNA (miR-3688 and miR-5695)	0.83 (0.73–0.97)	0.05	<.001	100.0 (54.6–100)	57.4 (47.5–80.2)
Combined (MADRS total score at inclusion, *STMN1* mRNA, and miR5695)	0.94 (0.88–0.99)	0.03	<.001	100.0 (72.7–100)	74.3 (72.7–100)

[a] 95% CIs were determined by bootstrap resampling method.

Abbreviations: AUC = area under the curve, MADRS = Montgomery-Asberg Depression Rating Scale, miRNA = microRNA, mRNA = messenger RNA, *PPP1R9B* = protein phosphotase 1 regulatory subunit 9B, *STMN1* = stathmin 1.

Figure 1. Receiver Operating Characteristic Curves for the 4 Models Used to Predict Treatment-Worsening Suicidal Ideation



Abbreviations: miRNA = microRNA, mRNA = messenger RNA.

by MADRS total score, predicted TWSI in univariate logistic regressions ($P < .1$). We found no association between TWSI and age, sex, level of anxiety symptoms, melancholic features, total number of major depressive episodes, familial history of psychiatric disorders, and history of antidepressant treatment (Supplementary Table 1). As a result, we built a predictive model using only the baseline MADRS total score for our clinical model. MADRS at baseline demonstrated a trend to be predictive for TWSI with an AUC = 0.66 (95% CI, 0.52–0.80; $P = .08$), sensitivity = 90.9%, and specificity = 42.6% (Table 2 and Figure 1).

mRNA Predictive Model

In patients treated with duloxetine, after the analysis of the expression of 16,674 probesets, followed by correction for multiple testing with FDR < 10%, we found the expression of 2 probesets to be significantly associated with TWSI. Protein phosphatase 1 regulatory subunit 9B (*PPP1R9B*) was underexpressed before treatment in patients who presented with TWSI (fold change [FC] = –1.21, $P = 1.13 \times 10^{-5}$). Stathmin 1 (*STMN1*) was overexpressed before treatment in patients who presented with TWSI (FC = 1.20, $P = 5.99 \times 10^{-6}$). The expression levels of these 2 mRNAs were predictive of suicidal ideation in logistic regressions (Supplementary Table 2). We built a multivariate regression model using these 2 mRNA biomarkers. When combined, they predicted suicidal ideation with an AUC = 0.86 (95% CI, 0.75–0.97; $P < .001$), sensitivity = 81.8%, and specificity = 79.2% (Table 2 and Figure 1).

miRNA Predictive Model

After small-RNA sequencing, we found 2 miRNAs associated with TWSI in patients treated with duloxetine (FDR < 10%): both miR-3688 (FC = 2.10, $P = 6.1 \times 10^{-4}$) and miR-5695 (FC = 1.84, $P = 1.72 \times 10^{-4}$) were overexpressed in patients who presented with TWSI. Levels of these 2 miRNAs were predictive of suicidal ideation in logistic regression (Supplementary Table 3). We built a multivariate regression model including these 2 miRNA biomarkers. When combined, they predicted suicidal ideation with an

AUC = 0.83 (95% CI, 0.73–0.97; *P* < .001), sensitivity = 100%, and specificity = 57.4% (Table 2 and Figure 1).

Combined Model

Using the same procedure, we included in a multiple logistic regression all biomarkers and clinical data that were predictive of TWSI in univariate analyses. Using a stepwise multivariate logistic regression, we found that miR-5695, *STMN1* mRNA, and MADRS score at baseline significantly predicted TWSI during the follow-up (Supplementary Table 4). Based on multivariate logistic regression, we built a combined variable that allowed prediction of TWSI. Based on logistic regression β-coefficients, the probability was calculated as follows:

$$e^{(-9.522191 + 2{,}825924 \times \mathrm{miR5695} + 0.359468 \times \mathrm{STMN1} - 0.531583 \times \mathrm{MADRS})} /$$
$$(1 + e^{(-9.522191 + 2.825924 \times \mathrm{miR5695} + 0.359468 \times \mathrm{STMN1} - 0.531583 \times \mathrm{MADRS})})$$

Using ROC-curve analysis, we found an AUC = 0.94 (95% CI, 0.88–0.99; *P* < .001), sensitivity = 100%, and specificity = 89.1% for the combined model (Table 2 and Figure 1).

Comparing the AUCs of these 4 different models, we found that the AUC of the combined model is significantly higher than the AUC of the clinical model (*P* < .001) and the AUC of the miRNA model (*P* = .005). The AUC of the combined model was higher than that of the mRNA model, although the difference was not significant (*P* = .23).

Combined Model in Patients Treated With Placebo

Finally, we tested our combined model among placebo-treated patients. We found no predictive value for placebo's worsening suicidal ideation of our combined model with an AUC = 0.52 (*P* = .812).

DISCUSSION

In this study, we analyzed a large number of clinical and molecular variables and generated 3 models that significantly predicted TWSI. We identified 2 mRNAs and 2 miRNAs that were significantly predictive of TWSI when assessing mRNA or miRNA separately. Furthermore, we determined that combining clinical information with mRNA and miRNA expression values yielded the best ability to predict TWSI in our cohort. Our final combined model included the clinical variable of baseline depression severity (MADRS score) and the expression of the mRNA *STMN1* and the miRNA miR-5695. The high accuracy and sensitivity of our tool allowed us to predict TWSI in the majority of patients. However, our model did not significantly predict TWSI in the placebo group, indicating that it is specific to antidepressant treatment. This model satisfies a number of key characteristics of biomarkers, namely clinical validity, clinical utility, clinical usefulness, and biological plausibility.[26]

Among all the clinical variables examined, only baseline MADRS was mildly predictive of TWSI, which is consistent with the findings that clinical variables explain very little of the variance of suicidal ideation occurring during antidepressant treatment.[5]

In the mRNA predictive model, our analyses identified 2 mRNAs, *PPP1R9B* and *STMN1*, whose expression values at baseline were predictive of TWSI. *PPP1R9B*, also known as spinophilin, is a scaffold protein involved in the development of dendritic spines and synapses.[27] Additionally, this protein has been linked to (or associated with) the effects of environmental enrichment on neuronal plasticity in rodents,[28] regulation of μ-opioid receptor function,[29] and noradrenergic responses to the antidepressant desipramine.[30] *STMN1* encodes the protein stathmin, a neuronal growth–associated protein involved in regulating microtubule dynamics that has been associated with neuronal plasticity, fear, and anxiety responses.[31,32] Although the relationship between the functions of these 2 mRNAs and their expression in the blood is unknown, their potential relevance to the pathophysiology of suicidal behavior indicates biological plausibility, an important characteristic for biomarkers.

Our miRNA predictive model identified 2miRNAs, miR-3688 and miR-5695. These 2 miRNAs have not been associated previously with any psychiatric phenotype. miRNAs are known to target a large number of mRNAs for either destruction or translational repression. However, the targets of these 2 miRNAs have yet to be established. We thus performed a target identification based on convergent results of 4 algorithms (miRWalk, miRanda, RNAhybrid, and Targetscan), and we conducted a gene ontology analysis using a set of shared predicted targets of these 2 miRNAs. We found that the most significantly enriched term was regulation of neurogenesis (GO:0050769, analysis not shown). As miRNAs can be packaged into extracellular vesicles and secreted into the blood from all bodily tissues, including the brain,[33] it is possible that our findings here represent a plausible pathologic process occurring elsewhere in the body. Additional work will be necessary to identify their relevant gene targets in order to better understand their potential role in TWSI.

Although encouraging, our results should be interpreted with caution. Firstly, our analysis comprised a relatively small sample of patients with major depression. However, previous studies also included limited sample sizes and/or more heterogeneous phenotypes.[15,16,31,34] Moreover, the relatively low frequency of TWSI (< 10% in our sample) reduces the ability to detect biomarkers of TWSI. In the same vein, we choose a more inclusive definition of TWSI (ie, increase of 1 point), while other studies have utilized a 2-point increase[35] or used a composite score based on several tools.[2] In our cohort, the majority of patients exhibiting TWSI displayed an increase of 1 point, with the exception of 2 patients in the duloxetine group with an increase of 2 points. The maximum severity (score) of MADRS item 10 was 3. As a consequence, our results may suffer from low specificity or overestimation. However, one previous study[36] also demonstrated the accuracy of this definition as a biomarker of suicidal ideation. Moreover, at least theoretically, a stricter definition would also be associated with lower sensitivity, which is, based on a clinical point of view, the more important parameter when predicting severe complications such suicide ideation and its potential consequences. Overall, this is a common issue in randomized controlled trials, from which patients with higher suicide risk are often excluded. As such, larger samples including patients with higher risk for suicidal behaviors are needed to overcome this issue.

Secondly, we did not replicate previous findings investigating clinical variables as predictors of suicidal behavior, aside from a trend for depression severity to be associated with TWSI. However, it is worth noting that most of these previous findings suggested a low effect size for clinical predictors.[5]

The identification of biomarkers that allow for the diagnosis of psychiatric disorders, and prediction of clinical outcomes, is an important research goal. Numerous studies have identified both clinical and biological variables that may be used for these purposes; however, many of these findings have failed to be replicated. Ultimately, biomarkers must demonstrate replicability, accuracy, and cost-effectiveness to warrant their inclusion in clinical practice.

Although our predictive tool is promising, its clinical utility remains to be demonstrated. It is worth noting that the generalization of our findings to suicidal ideation in general is unclear, as we focused our analyses on suicidal ideation specifically associated with antidepressant treatment and not during placebo treatment. Our study design did not allow us to test if the use of our predictive tool may significantly improve the prognosis of patients treated with antidepressants. On the basis of our findings, a randomized controlled trial comparing treatment management with and without our predictive tool would be the only method to test the efficacy of these biomarkers. However, to date, the prediction of suicidal ideation and suicide behavior is based only on clinical interviews, and the accuracy of such practice has not been demonstrated. As such, we could speculate that the predictive tools described herein have a clinical utility that is at least comparable to current standard practice.

In summary, we report a predictive tool for TWSI during antidepressant treatment that combines both biological and clinical variables. These biological variables can be easily quantified in peripheral tissues, thus rendering them viable targets to be used in both clinical practice and future studies of suicidal behaviors.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.

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Supplementary Material

Article Title: Predicting Worsening Suicidal Ideation During Antidepressant Treatment With Clinical Features and Peripheral Expression of Messenger RNA and Micro RNA

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List of Supplementary Material for the article

1. **Table 1** Univariate Logistic regression, clinical variables after imputation of missing data
2. **Table 2** Univariate Logistic regression for best mRNAs
3. **Table 3** Univariate Logistic Regression for best miRNAs
4. **Table 4** Multivariate logistic regression for final model

SUPPLEMENTARY MATERIALS

Supplementary Table 1: Univariate Logistic regression, clinical variables after imputation of missing data

Variables	**Odds Ratio**	**95% confidence interval**	**p-value**
Age	1.01	0.96-1.06	0.66
HAM-A at baseline	1.02	0.93-1.13	0.62
Melancholic features at baseline	0.55	0.14-2.19	0.40
Total number of MDE	0.93	0.62-1.36	0.68
Familial history of psychiatric disorders	0.33	0.06-1.82	0.20
Antidepressant naïve patients	2.33	0.45-12.02	0.30
MADRS at baseline	0.82	0.65-1.03	0.09
Gender	4.23	0.52-34.49	0.18

HAM-A: Hamilton Anxiety Rating Scale, MADRS: Montgomery Åsberg Depression Rating Scale, MDE: major depressive episode

Supplementary Table 2: Univariate Logistic regression for best mRNAs

Variables	Odds Ratio	95% confidence interval	p-value
PPP1R9B mRNA at baseline	0.71	0.50-0.99	0.044
STMN1 mRNA at baseline	1.20	1.07-1.34	0.002

Supplementary Table 3: Univariate Logistic Regression for best miRNAs

Variables	**Odds Ratio**	**95% confidence interval**	**p-value**
miR-3688 at baseline	2.80	1.4-5.7	0.004
miR-5695 at baseline	5.04	1.6-15.7	0.005

Supplementary Table 4: Multivariate logistic regression for final model

Variables	Odds Ratio	95% confidence interval	p-value
MADRS at baseline	0.59	0.38-0.89	0.012
STMN1 mRNA at baseline	1.43	1.13-1.82	0.003
miR-5695	16.87	2.7-104.3	0.002