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Positron Emission Tomographic Imaging of the Serotonergic System and Prediction of Risk and Lethality of Future Suicidal Behavior

Maria A. Oquendo, MD,
New York State Psychiatric Institute, New York

Department of Psychiatry, Columbia University, New York, New York

Hanga Galfalvy, PhD,
New York State Psychiatric Institute, New York

Department of Psychiatry, Columbia University, New York, New York

Gregory M. Sullivan, MD,
Tonix Pharmaceuticals, LLC, New York, New York

Jeffrey M. Miller, MD,
New York State Psychiatric Institute, New York

Department of Psychiatry, Columbia University, New York, New York

Matthew M. Milak, MD,
New York State Psychiatric Institute, New York

Department of Psychiatry, Columbia University, New York, New York

M. Elizabeth Sublette, MD, PhD,
New York State Psychiatric Institute, New York

Department of Psychiatry, Columbia University, New York, New York

Sebastian Cisneros-Trujillo, MD,

Corresponding Author: Maria A. Oquendo, MD, Department of Psychiatry, Columbia University, 1051 Riverside Dr, Unit 3, New York, NY 10032 (mao4@cumc.columbia.edu).

Author Contributions: Drs Oquendo and Galfalvy contributed equally. Dr Galfalvy had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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New York State Psychiatric Institute, New York

Department of Psychiatry, Columbia University, New York, New York

Ainsley K. Burke, PhD,
New York State Psychiatric Institute, New York

Department of Psychiatry, Columbia University, New York, New York

Ramin V. Parsey, MD, PhD, and
Department of Psychiatry and Behavioral Science, Stony Brook University School of Medicine, Stony Brook, New York

J. John Mann, MD
New York State Psychiatric Institute, New York

Department of Radiology, Columbia University, New York, New York

Abstract

IMPORTANCE—Biomarkers that predict suicidal behavior, especially highly lethal behavior, are urgently needed. In cross-sectional studies, individuals with depression who attempt suicide have lower midbrain serotonin transporter binding potential compared with those who do not attempt suicide, and higher serotonin$_{1A}$ binding potential in the raphe nuclei (RN) is associated with greater lethality of past suicide attempts and suicidal intent and ideation.

OBJECTIVES—To determine whether serotonin transporter binding potential in the lower midbrain predicts future suicide attempts and whether higher RN serotonin$_{1A}$ binding potential predicts future suicidal ideation and intent and lethality of future suicide attempts.

DESIGN, SETTING, AND PARTICIPANTS—In this prospective 2-year observational study, a well-characterized cohort of 100 patients presenting for treatment of a major depressive episode of at least moderate severity underwent positron emission tomography using carbon 11-labeled *N*-(2-(1-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl))-*N*-(2-pyridyl)-cyclohexanecarboxamide ([^{11}C]WAY-100635), a serotonin$_{1A}$ antagonist; a subset of 50 patients also underwent imaging with carbon 11-labeled 3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)- benzonitrile ([^{11}C]DASB), a serotonin transporter radioligand. Imaging was performed at Columbia University Medical Center from May 3, 1999, to March 11, 2008. Follow-up was completed on May 28, 2010, and data were analyzed from August 1, 2013, to March 1, 2016.

EXPOSURES—Patients were treated naturalistically in the community and followed up for 2 years with documentation of suicidal behavior, its lethality, and suicidal ideation and intent.

MAIN OUTCOMES AND MEASURES—Suicide attempt or suicide.

RESULTS—Of the 100 patients undergoing follow-up for more than 2 years (39 men; 61 women; mean [SD] age, 40.2 [11.2] years), 15 made suicide attempts, including 2 who died by suicide. Higher RN serotonin$_{1A}$ binding potential predicted more suicidal ideation at 3 (b = 0.02; t = 3.45; P = .001) and 12 (b = 0.02; t = 3.63; P = .001) months and greater lethality of subsequent suicidal behavior (b = 0.08; t = 2.89; P = .01). Exploratory analyses suggest that the serotonin$_{1A}$ binding potential of the insula (t = 2.41; P = .04), anterior cingulate (t = 2.27; P = .04), and dorsolateral prefrontal cortex (t = 2.44; P = .03) were also predictive of lethality. Contrary to our hypotheses,

suicidal intent was not predicted by serotonin$_{1A}$ binding potential in any brain region ($F_{1,10}$ = 0.83; P = .38), and midbrain serotonin transporter binding potential did not predict future attempts (log-rank χ^2_1 = 0.4; P = .54), possibly owing to low power.

CONCLUSIONS AND RELEVANCE—Greater RN serotonin$_{1A}$ binding potential predicted higher suicidal ideation and more lethal suicidal behavior during a 2-year period. This effect may be mediated through less serotonin neuron firing and release, which affects mood and suicidal ideation and thereby decision making.

Suicidal behavior occurs in the context of a diathesis characterized by impairments in mood and emotion regulation, decision making, problem solving, and social appraisal.[1] Suicidal behavior is also associated with specific biomarkers,[2] mostly involving the serotonergic system and hypothalamic pituitary adrenal axis. We found individuals with major depressive disorder (MDD) who attempt suicide (attempters) have lower in vivo midbrain serotonin transporter binding compared with those who do not attempt suicide (nonattempters or control individuals),[3,4] suggesting that the differences in the proportions of suicide attempters studied may contribute to discrepant positron emission tomography (PET) findings in MDD.[5,6] Similarly, attempters with MDD showed lower serotonin transporter binding in the midbrain and pons[4] compared with controls. In contrast, a small study using iodine 123-labeled beta [3H]2-beta-carbomethoxy-3-beta-[4'-iodophenyl]tropane[7]single-photon emission computed tomography linked higher serotonin transporter binding in the globus pallidus to suicidal behavior. Using fluorodeoxyglucose F 18-labeled PET, a previous investigation[8] found attempters with MDD had lower regional rates of cerebral glucose metabolism in the right dorsolateral prefrontal cortex (PFC) compared with nonattempters with MDD, a discrepancy that roughly doubled after fenfluramine administration, which suggested impaired serotonergic response.[9] In a serotonin$_{2A}$ binding study using ^{123}I-5-I-R91150 and single-photon emission computed tomography, deliberate self-harming patients who did not use medication had less frontal serotonin$_{2A}$ binding compared with controls. Thus, most studies implicate serotonergic dysfunction in suicidal behavior.

Moreover, high-lethality attempters with depression showed lower PFC rates of cerebral glucose metabolism than low-lethality attempters, a difference enhanced after fenfluramine administration.[10] Lower ventromedial PFC activity was associated with lower impulsivity, higher suicidal intent, and more lethal suicide attempts. Likewise, Leyton et al[11] found that, compared with controls, higher-lethality attempters had less carbon 11-labeled α-methyl L-tryptophan trapping in orbital PFC and less tracer uptake inversely correlated with suicidal intent. A recent study[12] reported that raphe nuclei (RN) serotonin$_{1A}$ binding potential was greater in high-compared with low-lethality attempters and positively correlated with suicidal ideation, lethality, and intent of the most recent suicide attempt. Of note, PFC serotonin$_{1A}$ binding potential correlated with suicidal ideation, but not lethality.[12] Hence, more pronounced serotonergic dysfunction may lead to more lethal suicidal behavior.

No brain imaging study has examined these biomarkers prospectively to evaluate their capacity for predicting suicidal behavior. Given the findings in MDD of lower midbrain serotonin transporter binding in past suicide attempters and higher RN serotonin$_{1A}$ binding correlated with more severe suicidal ideation and greater lethality and intent of past

attempts, our primary hypotheses were that, in patients with depression, PET scanning will demonstrate that (1) lower midbrain serotonin transporter binding potential predicts future suicide attempts and (2) greater RN serotonin$_{1A}$ binding potential predicts attempts of greater lethality and intent and greater suicidal ideation during a 2-year follow-up.

Methods

One hundred patients with MDD aged 18 to 65 years with Hamilton Depression Rating Scale[13] (17-item) scores greater than 15 were included in the study. Exclusion criteria consisted of lifetime exposure to 3,4-methylenedioxymethamphetamine (Ecstasy) more than 2 times, alcohol or substance use disorders in the previous 6 months, unstable medical conditions, pregnancy, lactation, psychosis, and schizophrenia. Participants had been medication free for at least 3 weeks (6 weeks for fluoxetine hydrochloride and 4 weeks for antipsychotics); 62 patients required a medication washout period. Short-acting benzodiazepines for anxiety or insomnia were permitted as needed until 72 hours before scans. Data were collected from May 3, 1999, to March 11, 2008. This study was approved by the institutional review board of New York State Psychiatric Institute, and all patients provided written, informed consent.

Portions of this sample have been included in previous publications (eMethods in the Supplement).[3,12,14–16] Assessments included a history and physical examination, routine blood tests, pregnancy test, urine toxicologic screen, the Structured Clinical Interview for *DSM-IV*,[17] Hamilton Depression Rating Scale,[13] Beck Depression Inventory,[18] Global Assessment Scale,[19] Beck Scale for Suicide Ideation (BSSI),[20] Brown Goodwin Aggression History Scale,[21] Buss-Durkee Hostility Inventory,[22] and Barratt Impulsivity Scale.[23] Suicidal behavior was documented with the Columbia Suicide History Form,[24] using Columbia Classification Algorithm of Suicide Assessment.[25] For attempters only, the Beck Suicide Intent Scale[26] and Medical Lethality Scale[26] rated each attempt's intent and medical sequelae (range, 0 [no injury] to 8 [fatal]).

Radiochemistry, Input Function Measurement, and Image Acquisition and Analysis

Carbon 11-labeled *N*-(2-(1-(4-(2-methoxyphenyl)-1-piperazinyl) ethyl))-*N*-(2-pyridyl)-cyclohexanecarboxamide ([^{11}C]WAY-100635), a serotonin antagonist, and carbon 11-labeled 3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile ([^{11}C]DASB), a serotonin transporter radioligand, were synthesized with assessment of arterial input function, metabolites, and plasma free-fraction (f_P) measurements as previously described.[27,28] Image acquisition and binding estimation were as previously reported for [^{11}C]DASB[3] and [^{11}C]WAY-100635.[12]

Outcome Measures for Midbrain Serotonin Transporter and Serotonin$_{1A}$ Region of Interest Binding Potential

We derived [^{11}C]DASB midbrain volume of distribution (V_T) values using likelihood estimation in the graphical approach to reduce inherent noise-dependent bias.[29,30] The [^{11}C]DASB V_T/f_P was calculated as before,[3] as were outcome measures for sensitivity analyses (BP_F,BP_P, and BP_{ND}[31]). For serotonin$_{1A}$ region-of-interest (ROI) binding potential

(BP_F), the ROI contours and BP_F were generated as previously reported.[12] The ROIs included the RN, amygdala, hippocampus, parahippocampal gyrus, anterior cingulate, medial and dorsolateral PFC, and insular, parietal, temporal, orbital, and occipital cortices. Imaging data acquisition and processing details are found in eMethods in the Supplement.

Prospective Assessments

Patients received treatment in the community. At 3, 12, and 24 months, suicidal ideation was assessed. For each follow-up suicide attempt, suicidal intent and lethality were assessed, as at baseline. Follow-up was completed on May 28, 2010, and data were analyzed from August 1, 2013, to March 1, 2016.

Statistical Analysis

Midbrain [^{11}C]DASB Binding Potential and Future Suicide Attempts—Survival analysis using the log-rank test evaluated the time to the first suicide attempt in 2 groups defined by a median split of midbrain [^{11}C]DASB V_T/f_P. To account for technical variability in [^{11}C]DASB V_T/f_P, a sensitivity analysis used an analysis of variance model with log-transformed midbrain [^{11}C]DASB V_T/f_P (to reduce skewness) as the dependent variable and with each observation weighted by the inverse squared errors of the respective [^{11}C]DASB V_T/f_P. These SEs were estimated using a bootstrap algorithm that accounts for errors in metabolite, plasma, and brain data.[32] Weighting based on the precision of binding potential estimates ensures that more reliable observations have more influence on results. Weights were also winsorized at the 90th percentile to avoid having outliers in the weight function, which also prevents a small number of patients from having an outsized influence on model parameters. Suicide attempt status during follow-up was the independent variable. Sensitivity analyses using the same analytic strategy assessed BP_F, BP_P, and BP_{ND}.

RN [^{11}C]WAY-100635 BP_F, Future Attempt Lethality and Intent, and Future Suicidal Ideation—Log-transformed RN serotonin$_{1A}$ BP_F was modeled using a weighted linear regression model with maximal attempt lethality during follow-up and sex as independent variables. Weights were based on the BP_F estimate's precision, as above. Associations between lethality and log-transformed serotonin$_{1A}$ BP_F in all 12 ROIs were explored using a single mixed-effects model with the following fixed effects: maximal attempt lethality during follow-up, ROI, lethality by ROI indicator interaction, and sex. A patient-specific random intercept term accounted for intrapatient correlation in BP_F across ROIs. If the interaction term was not significant, it was removed from the model and only the main effect was reported. If the interaction term was significant, exploratory ROI-specific analyses similar to that for the RN were conducted for the remaining 11 ROIs. The ROI-specific exploratory models were adjusted using the Benjamini-Hochberg approach to control the false discovery rate.

Primary and exploratory analyses of serotonin$_{1A}$ BP_F and the Beck Suicide Intent Scale score for the most lethal attempt during follow-up were identical to those for lethality. In analyses examining the relationship between serotonin$_{1A}$ BP_F and future BSSI, we included attempters and nonattempters whose Hamilton Depression Rating Scale score was greater than 10, a score below which few have suicidal ideation.[33] Three separate models tested the

association at 3 (51 of 134 patients), 12 (47 or 134 patients), and 24 (39 of 134 patients) months, using the same strategy used for maximum lethality (eg, 1 primary analysis examining the association between future BSSI score and RN serotonin$_{1A}$ BP_F and exploratory analyses of the association between future BSSI score and serotonin$_{1A}$ BP_F in all 12 ROIs [all regions in 1 model]; and follow-up exploratory analyses of future BSSI and serotonin$_{1A}$ BP_F in each ROI, if appropriate). Exploratory analyses used the Benjamini-Hochberg adjustment.

We conducted several sensitivity analyses. Given our cross-sectional findings,[12] we calculated the correlation between base-line and future lethality scores and examined the association between RN serotonin$_{1A}$ BP_F and future lethality while controlling for baseline lethality and sex. Sensitivity analyses excluding attempters whose attempt was of zero lethality assessed whether nondamaging attempts were biologically different. We also adjusted our model for clinical predictors of attempt lethality to explore whether binding provides additional information to that provided by these measures. Finally, we explored the effect of recent medication status on RN serotonin$_{1A}$ BP_F's association with follow-up attempt lethality by adjusting the weighted regression model described above using an indicator variable (medication washout vs no washout).

Results

One hundred patients (39 men; 61women; mean [SD] age, 40.2 [11.2] years) underwent [^{11}C]WAY-100635 PET scans and 50 also underwent [^{11}C]DASB scans; all had follow-up data (median follow-up, 748 days; range, 76–1294 days; time censored at 800 days). Fifty-one participants were past suicide attempters. During follow-up, 13 patients made a nonfatal attempt and 2 additional patients died by suicide. Clinical and demographic data are found in Table 1.

Midbrain [^{11}C]DASB BP_F and Future Suicide Attempts

Only 5 patients with [^{11}C]DASB data manifested suicidal behavior during follow-up, which limited statistical power. Future suicidal behavior was not associated with lower midbrain serotonin transporter V_T/f_P (log-rank $\chi^2_1 = 0.4$; $P = .54$). Similarly, a weighted analysis of variance model showed no difference in midbrain serotonin transporter V_T/f_P between future attempters and nonattempters (log scale difference: b = 0.006; SE = 0.08; $t = 0.07$; $P = .94$). Sensitivity analyses with 3 other [^{11}C]DASB outcome measures (BP_P, BP_F, and BP_{ND}) were not different in future attempters.

V_T/f_P, Future Attempt Lethality and Intent, and Future Suicidal Ideation

Higher lethality of future attempts was associated with higher RN serotonin$_{1A}$ BP_F in the weighted regression model testing our primary hypothesis (b = 0.08; $t = 2.89$; $P = .01$) (Figure 1) and remained significant after adjusting for baseline lethality ($P = .02$). The mixed-effects exploratory model with BP_F in 12 ROIs (including RN) as a response variable and ROI, lethality, and their interaction as independent variables showed an interaction between ROI BP_F and lethality ($F_{11,14} = 1.91$; $P = .04$), indicating that the relationship between lethality and BP_F was not uniform across ROIs. We found an association between

future lethality and higher serotonin$_{1A}$ BP_F in the insula, but not after adjustment for multiple testing (Table 2).

After removing 3 patients with zero-lethality follow-up attempts in an exploratory analysis, we found a positive correlation between serotonin$_{1A}$ BP_F and future lethality (b = 0.09; t_9 = 2.38; P = .04) across all ROIs (interaction with ROI: $F_{11,11}$ = 0.99; P = .45). The ROI-specific post hoc analyses without these 3 patients showed significant associations between future lethality and serotonin$_{1A}$ BP_F in the RN, anterior cingulate, dorsolateral PFC, and insula. After Benjamini-Hochberg correction, these regions showed a strengthened but nonsignificant association (Table 2).

Adjusting for the presence of a comorbid personality disorder did not affect results, and we found no evidence of a differential correlation between future lethality and BP_F based on comorbid diagnoses. Adjusting for clinical or demographic variables at the time of the baseline scan (Table 1), such as age, severity of depression, aggression, impulsivity, and suicidal ideation, did not alter the significance of lethality's association with RN serotonin$_{1A}$ BP_F. Indeed, RN serotonin$_{1a}$ BP_F, adjusted for sex, explained more variability than independent variables such as the Beck Depression Inventory score (adjusted R^2 = 0.33 [P = .03] vs adjusted R^2 = 0.16 [P = .19], respectively).

Suicidal intent associated with the most lethal suicide attempt during follow-up was not associated with RN serotonin$_{1A}$ BP_F (b = −0.006; t = −0.20; P = .84). An exploratory model with all 12 ROIs was not significant ($F_{1,10}$ = 0.83; P = .38). Removing zero-lethality attempters did not change results.

The BP_F of RN serotonin$_{1A}$ correlated positively with suicidal ideation severity (BSSI score) at 3 (b = 0.02; t = 3.45; P = .001) and 12 (b = 0.02; t = 3.63; P = .001) months of follow-up, but not at 24 months (Figure 2). In mixed-effects exploratory models encompassing all 12 ROIs, higher BSSI scores at 3 and 12 months were associated with higher serotonin$_{1A}$ BP_F ($F_{11,40}$ = 9.64 [P = .03] and $F_{11,34}$ = 5.11 [P = .03], respectively), but not 24 months, with differences in the strength of the association across ROIs at both time points (interactions with ROI: P = .003 at 3 months and P < .001 at 1 year) (Table 3). This association was present for every ROI at 3 months and all ROIs except the amygdala at 12 months. Sensitivity analyses showed that recent medication status (required washout vs no washout) did not affect serotonin$_{1A}$ BP_F in any ROI ($F_{1,97}$ = 0.008; P = .93) and did not predict future attempts (log-rank test χ^2_1 = 0.2; P = .68) or lethality (t_{13} = 0.98; P = .34).

Discussion

This study is the first prospective examination of whether serotonin transporter and serotonin$_{1A}$ binding in vivo predict suicidal behavior and its lethality. Consistent with postmortem studies of suicides with depression suicide [34,35] and with cross-sectional imaging findings,[12] higher RN serotonin$_{1A}$ BP_F predicted greater lethality of future suicidal behavior during 2 years. These results suggest that RN serotonin$_{1A}$ BP_F represents a predictive biomarker of more lethal suicidal behavior, a serious clinical outcome.

Higher RN serotonin$_{1A}$ BP_F may lead to more lethal suicidal behavior via more severe suicidal ideation, and, indeed, higher RN serotonin$_{1A}$ BP_F predicted greater suicidal ideation at 3 and 12 months. However, the association between RN serotonin$_{1A}$ BP_F and suicidal intent for future suicide attempts was not detected, possibly owing to insufficient statistical power, because only 15 subsequent suicidal acts were reported.

V_t/f_p and Likelihood of Future Suicide Attempts

Lower serotonin transporter binding in ventromedial PFC and other brain regions is found in suicides in postmortem studies.[36–40] These and cross-sectional findings[3] led us to hypothesize that lower midbrain serotonin transporter V_t/f_p would predict suicide attempts during a 2-year period. This prediction was not verified in our subsample, perhaps because only 5 attempts occurred during follow-up.

Although 2 meta-analyses examining the serotonin transporter LPR polymorphism report an association of suicidal behavior and the serotonin transporter LPR low-expressing S allele,[41,42] we and others[3,43–49] have reported no association of in vivo binding with lower-expressing alleles in the gene, although not all studies agree.[50–52] A more robustly powered study with a larger sample of future suicide attempters may determine whether serotonin transporter binding predicts suicide risk.

RN [^{11}C]WAY-100635 BP_F, Future Attempt Lethality and Intent, and Future Suicidal Ideation

Serotonin$_{1A}$ somatodendritic autoreceptors inhibit RN serotonin neuron firing.[53] Thus, more autoreceptors can lead to less firing and serotonin release from nerve terminals.[53,54] That higher RN serotonin$_{1A}$ BP_F predicts more lethal suicidal behavior agrees with cross-sectional studies showing that higher-lethality attempters have low cerebrospinal fluid levels of 5-hydroxyindoleacetic acid, a marker of low serotonin turnover,[55] and with reports of blunted prolactin response to serotonergic challenge in high-lethality suicide attempters.[10] The effect of higher RN serotonin$_{1A}$ BP_F on lethality of future suicidal behavior is also consistent with the observation that low cerebrospinal fluid 5-hydroxyindoleacetic acid levels predict suicide death among discharged inpatients.[56,57]

How might elevated RN serotonin$_{1A}$ BP_F lead to a complex outcome such as a suicide attempt? We observed that RN serotonin$_{1A}$ BP_F predicted more pronounced suicidal ideation at 3 and 12 months, which could lead to more lethal attempts. Moreover, other parameters associated with low serotonergic tone, as would be expected in individuals with greater RN serotonin$_{1A}$ BP_F, are predictors of more lethal suicidal behavior. For example, we found that a lower response to fenfluramine, an index of serotonergic hypofunction, was associated with higher-lethality behavior and low impulsivity.[10] Low impulsivity may increase lethality owing to careful planning,[10,58] although impulsive individuals may make high-lethality attempts if they choose very lethal methods (eg, firearms, jumping). On the other hand, we have previously reported that those with low serotonin$_{1A}$ BP_F—the opposite of what we found here—have greater aggression,[59] found in some studies to be linked to more lethal suicidal behavior.[60,61] Our sample had relatively low aggression (mean score, 18.5), perhaps indicating that aggression was not a key driver of suicidal behavior for this study population.

Exploratory post hoc analyses suggested that greater serotonin$_{1A}$ BP_F in insula, in addition to RN, predicted more lethal attempts. When those whose future suicide attempts had zero lethality were excluded, serotonin$_{1A}$ BP_F in anterior cingulate cortex and dorsolateral PFC also predicted greater lethality, although these findings did not survive the Benjamini-Hochberg adjustment. The anterior insula has close neuroanatomic connections to the anterior cingulate cortex. Together, they are pivotal to decision making involving risk[62] (weighing risks and benefits of a decision) and in emotional and social cognition, putatively mediated by von Economo neurons,[63] and implicated in suicidal behavior previously.[1] Thus, lethality may be a consequence of the individual's underestimate of the risk of a negative effect on loved ones during decision making about whether to attempt suicide.[64] Similarly, disturbances in emotional and social cognition could lead to underestimation of the social and emotional consequences of the suicidal behavior for others. This insula-anterior cingulate cortex system is also implicated in switching from default mode network to executive mode, which enlists the dorsolateral PFC,[62,65] critical for reappraisal and contextual processing to assess the salience of negative stimuli.[66] Moreover, inhibitory effects of serotonin$_{1A}$ heteroreceptors on glutamatergic and γ-aminobutyric acid-transmitting cells that drive hemodynamic responses to functional demands are hypothesized to regulate activation of the default mode network.[67] Thus, attempt lethality may result from excessive default network activity leading to negative ruminative states,[66] perhaps potentiating suicidal preoccupation.

We did not find an association of serotonin$_{1A}$ BP_F with the suicidal intent associated with future suicide attempts, in contrast to findings in past suicide attempters. However, higher RN serotonin$_{1A}$ BP_F predicted more suicidal ideation (BSSI score) at 3 and 12 months, and exploratory analyses showed that greater serotonin$_{1A}$ BP_F in 12 ROIs also predicted a greater BSSI score at 3 and 12 months, but with differences in the strength of that relationship across ROIs. Although more severe suicidal ideation at 3 and 12 months of follow-up may lead to well-planned, more lethal suicide attempts, we were unable to detect such an association in this study. In addition, whether elevated BSSI scores at 3 and 12 months reflect more persistent or chronic suicidal ideation, thereby increasing risk, is unknown. We are currently investigating this question.

Systems other than serotonergic neurotransmission are linked to suicidal behavior, for example, γ-aminobutyric acid, glutamatergic, hypothalamic-pituitary-adrenal, and noradrenergic systems.[2] Many of these systems interact with the serotonin system. Too few future suicide attempts limit statistical power, but this study is one of the largest prospective PET brain imaging studies in mood disorders ever published. We did not have data regarding medication exposure during follow-up. Finally, [^{11}C]WAY-100635, a serotonin$_{1A}$ antagonist, binds to high- and low-affinity states, limiting its utility for examining high-affinity agonist receptors.

Conclusions

We found that greater RN serotonin$_{1A}$ BP_F, measured with [^{11}C]WAY-100635 PET, predicted more lethal suicidal behavior during a 2-year period. Our results suggest that this association is at least partly mediated through more severe suicidal ideation. Identifying

neurobiological characteristics of high-lethality suicide attempters has intrinsic scientific importance, and discovery of molecular-level markers of high-lethality behavior may eventually improve clinical screening to detect those at risk for suicide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

Are in vivo brain serotonergic indices predictive of more lethal suicidal behavior?

Findings

The binding potential of the serotonin$_{1A}$ receptor in the raphe nuclei predicts more lethal suicidal behavior and greater suicidal ideation during a 2-year follow-up.

Meaning

Serotonin system hypofunction is a key risk factor for suicidal behavior with greater morbidity and mortality; treatments that target this system pharmacologically or that impact the effects of low serotonergic tone on suicidal ideation, such as cognitive therapy for suicidal behavior, may aid in stemming the epidemic of suicides.

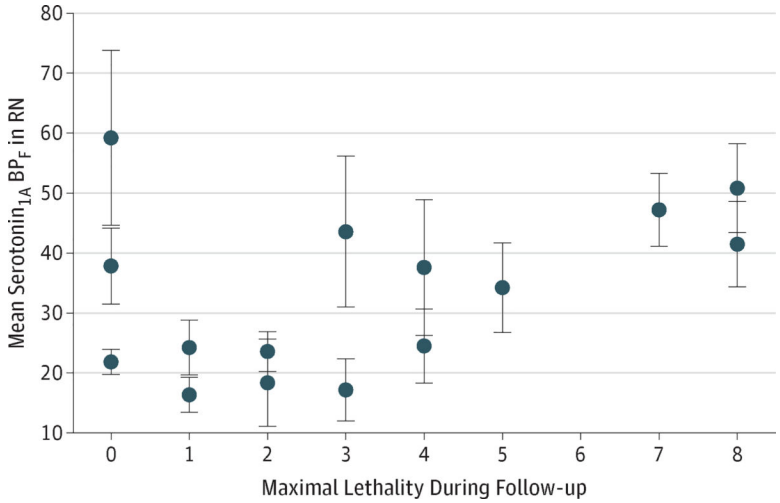

Figure 1. Correlation Between Maximal Lethality of Suicide Attempts During Follow-up and Serotonin$_{1A}$ Binding Potential (BP_F) in the Raphe Nuclei (RN)

Each data point represents the mean RN BP_F for a single suicide attempter; error bars indicate SEs. Lethality is scored from 0 to 8, with 0 indicating no injury and 8 indicating fatal injury, using the Beck Suicide Intent Scale[20] and Medical Lethality Scale.[26]

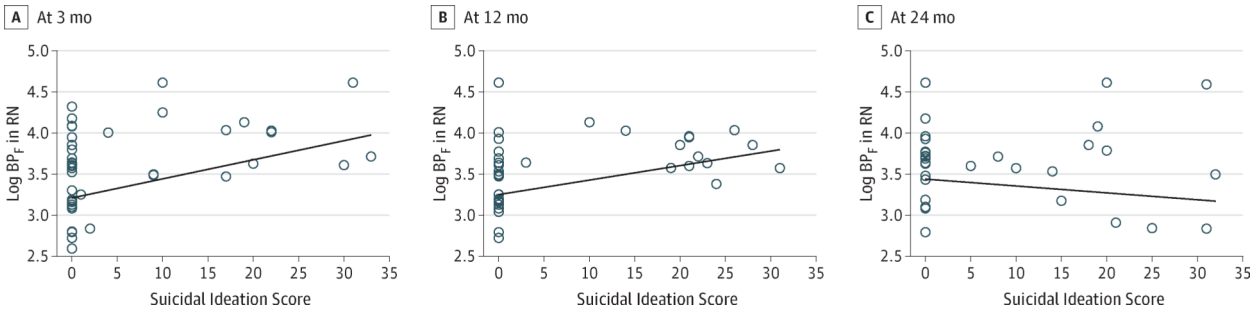

Figure 2. Serotonin$_{1A}$ Binding Potential (BP$_F$) in Raphe Nuclei (RN) by Suicide Ideation Severity

Serotonin$_{1A}$ BP$_F$ was measured at baseline; suicide ideation severity was measured at 3, 12, and 24 months using the Beck Scale for Suicide Ideation.[20] Scores ranged from 0 to 30, with higher scores indicating more severe ideation. Standard errors of the BP estimates were adjusted for in the calculation of the regression estimates.

Table 1.

Baseline Characteristics of the 100 Participants

Characteristic	Patients
Male sex, No. (%)	39 (39)
Childhood, No. (%)	
Abuse	51(51)
Separation younger than 15y (n = 99)	38 (38)
Comorbid past substance abuse, No. (%) (n = 99)	28 (28)
Cigarette smoking, No. (%) (n = 99)	24 (24)
Borderline personality disorder, No. (%) (n = 95)	17(18)
History of suicide attempt, No. (%)	51 (51)
Age, mean (SD), y	40.2 (11.2)
Hamilton Depression Rating Scale score, mean (SD)[a]	19.5 (4.9)
Beck Depression Inventory score, mean (SD) (n = 99)[b]	28.6 (10.1)
Beck Hopelessness Scale score, mean (SD)[c]	12.0 (5.8)
Scale for Suicidal Ideation[d]	
2 wk prior (n = 85)	8.9 (9.3)
Current (n = 99)	6.2 (7.3)
Brown-Goodwin Aggression History Scale score, mean (SD) (n = 98)[e]	18.5 (5.6)
Buss-Durkee Hostility Inventory score, mean (SD) (n = 88)[f]	38.7 (11.9)
Barratt Impulsivity Scale score, mean (SD) (n = 88)[g]	57.7 (18.2)
No. of past suicide attempts, mean (SD) (n = 51)	2.4 (1.9)
Maximal lethality of suicide attempts score, mean (SD) (n = 51)[h]	2.6 (1.7)

[a] Scores range from 0 to 54, with higher scores indicating more severe depression.

[b] Scores range from 0 to 63, with higher scores indicating more severe depression.

[c] Scores range from 0 to 20, with higher scores indicating more severe hopelessness.

[d] Scores range from 0 to 48, with higher scores indicating more severe ideation.

[e] Scores range from 10 to 40, with higher scores indicating more severe aggression.

[f] Scores range from 0 to 66, with higher scores indicating more severe hostility.

[g] Scores range from 0 to 96, with higher scores indicating more severe impulsivity.

[h] Scores range from 0 to 8, with higher scores indicating fatal injury.

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Table 2.

Association Between Serotonin$_{1A}$ BP_F in 12 ROIs and Lethality of Follow-up Suicide Attempts[a]

	With Zero-Lethality Attempters				Without Zero-Lethality Attempters			
Log-Transformed PB_F per ROI	**Estimate**	***t* Value**	***P* Value**	**Adjusted[b]**	**Estimate**	***t* Value**	***P* Value**	**Adjusted[b]**
RN	0.08	2.88	.01	NA	0.12	4.43	.002	NA
Amygdala	0.01	0.48	.64	0.64	0.02	0.68	.51	0.51
Hippocampus	0.05	1.61	.13	0.15	0.07	1.82	.10	0.11
Parahippocampal gyrus	0.05	1.65	.12	0.15	0.07	2.13	.06	0.08
Temporal lobe	0.05	1.64	.12	0.15	0.08	2.13	.06	0.08
Anterior cingulate gyrus	0.06	1.79	.09	0.15	0.09	2.27	.04	0.08
Dorsal PFC	0.07	1.84	.09	0.15	0.10	2.44	.03	0.08
Medial PFC	0.06	1.65	.12	0.15	0.09	2.05	.07	0.08
Orbital PFC	0.05	1.56	.14	0.15	0.09	2.13	.06	0.08
Insula	0.05	2.31	.04	0.15	0.07	2.41	.04	0.08
Occipital lobe	0.05	1.71	.11	0.15	0.09	2.17	.05	0.08
Parietal lobe	0.06	1.71	.11	0.15	0.09	2.24	.05	0.08

Abbreviations: BP_F, binding potential; NA, not applicable in primary analysis; PFC, prefrontal cortex; RN, raphe nuclei; ROI, region of interest.

[a]Patients underwent imaging with carbon 11-labeled 3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile ([^{11}C]DASB).

[b]Significance levels for exploratory analyses are adjusted using the Benjamini-Hochberg method.

Table 3.

Serotonin$_{1A}$ ROI Analysis Results for Suicidal Ideation During Follow-up[a]

	3 mo			12 mo			24 mo		
Log-Transformed PB_F per ROI	**Estimate**	***P* Value**	**Adjusted[b]**	**Estimate**	***P* Value**	**Adjusted[b]**	**Estimate**	***P* Value**	**Adjusted[b]**
RN	0.02	.001	NA	0.01	<.001	NA	−0.008	.21	NA
Amygdala	0.02	<.001	0.002	0.004	.26	0.26	−0.01	.03	0.29
Hippocampus	0.02	<.001	0.002	0.009	.03	0.03	−0.007	.18	0.29
Parahippocampal gyrus	0.01	.01	0.02	0.01	.004	0.02	−0.009	.10	0.29
Temporal lobe	0.01	.005	0.01	0.007	.02	0.03	−0.008	.11	0.29
Anterior cingulate gyrus	0.01	.02	0.02	0.009	.004	0.02	−0.008	.12	0.29
Dorsal PFC	0.01	.02	0.02	0.009	.01	0.02	−0.006	.24	0.29
Medial PFC	0.01	.01	0.02	0.008	.01	0.02	−0.005	.29	0.29
Orbital PFC	0.01	.02	0.02	0.007	.03	0.03	−0.006	.24	0.29
Insula	0.01	.006	0.01	0.009	.006	0.02	−0.005	.29	0.29
Occipital lobe	0.01	.01	0.02	0.008	.01	0.02	−0.006	.22	0.29
Parietal lobe	0.01	.02	0.02	0.008	.01	0.02	−0.007	.16	0.29

Abbreviations: BP_F, binding potential; NA, not applicable in the primary analysis; PFC, prefrontal cortex; RN, raphe nuclei; ROI, region of interest.

[a]Patients underwent imaging with carbon 11-labeled 3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile ([^{11}C]DASB).

[b]Significance levels for exploratory analyses are adjusted using the Benjamini-Hochberg method.