Prediction of Suicidal Behavior in Clinical Research by Lifetime Suicidal Ideation and Behavior Ascertained by the Electronic Columbia-Suicide Severity Rating Scale

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ABSTRACT

Objective: To evaluate whether lifetime suicidal ideation with intention to act and/or suicidal behaviors reported at baseline predict risk of prospectively reporting suicidal behavior during subsequent study participation.

Method: Data from studies using the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) to prospectively monitor suicidal ideation and behaviors between September 2009 and May 2011 were analyzed. Studies included patients with major depressive disorder, insomnia, posttraumatic stress disorder, epilepsy, and fibromyalgia. Records for 35,224 eC-SSRS assessments were extracted. Incomplete assessments and eC-SSRS records from patients missing a baseline assessment or with no prospective follow-up assessments were excluded. Baseline lifetime eC-SSRS reports were categorized as negative (no lifetime ideation with intent to act or prior suicidal behavior) or positive (lifetime ideation with intent to act but no prior behavior, no ideation with intent to act but prior behavior, or both lifetime ideation with intent and prior behavior).

Results: 3,776 patients completed a baseline and 1 or more follow-up assessments. The mean follow-up period was 64 days. Of patients with negative lifetime reports, 2.4% subsequently reported suicidal behavior during study participation, compared to 12.0% of patients with lifetime ideation with intent only (OR = 5.55; 95% CI, 2.65–11.59), 9.6% of patients with lifetime behavior only (OR = 4.33; 95% CI, 2.94–6.39), and 18.3% of patients with both (OR = 9.13; 95% CI, 6.47–12.88). Sensitivity and specificity of positive reports for identifying suicidal behaviors were 0.67 and 0.76, respectively.

Conclusions: Patients reporting lifetime suicidal ideation with intent to act and/or prior suicidal behavior at baseline are 4 to 9 times more likely to prospectively report suicidal behavior during study participation.

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Suicide is a major public health challenge, and reduction or prevention depends on accurate identification of at-risk patients. The most reliable predictor of future risk for suicidal behavior is a past history of suicidal behavior and the severity of lifetime suicidal ideation.[1–3] Use of a precise, uniform evaluation across the full spectrum of lifetime suicidal behaviors and ideation might provide more accurate ascertainment of risk in clinical research studies.

Questions concerning suicidal ideation and behavior have been raised in randomized clinical trials involving both pediatric and adult patients,[4,5] prompting the US Food and Drug Administration (FDA) to draft and revise the industry guidance *Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials*.[6] The guidance recommends assessment and active querying about suicidal thoughts and behavior to improve data quality and ensure prompt recognition of at-risk patients. Prospective assessment of suicidal ideation and behavior is recommended in all trials across several FDA divisions to obtain more complete, reliable, and timely identification of possible treatment-emergent symptoms by eliminating bias associated with retrospective interpretation of spontaneously reported adverse events. Use of uniform definitions and common data collection instruments can also facilitate meta-analysis of data across studies and diagnoses. The data review presented here demonstrates the potential to advance the goals and objectives of the FDA's guidance, protect patient safety, and improve data quality and analysis of clinical research studies.

The Columbia-Suicide Severity Rating Scale (C-SSRS)[7] is a semistructured, rater-based interview to prospectively assess the severity and frequency of suicidal ideation and behaviors. The C-SSRS preceded development of the Columbia Classification Algorithm for Suicide Assessment,[8] which was commissioned by the FDA to retrospectively quantify suicidal ideation and behaviors on the basis of spontaneous adverse event reports. The C-SSRS identifies the full range of suicidal ideation and behavior, was developed to monitor change from visit to visit, and has predictive safety referral criteria derived from longitudinal studies.[7]

The electronic C-SSRS (eC-SSRS) is a fully structured clinical interview designed and developed for computer administration using interactive voice response technology. Patients respond to standardized clinical questions, presented in a uniform fashion and faithfully branching between queries that adhere to C-SSRS clinical conventions, via touch-tone telephones. A previous study[9] supported the validity of the eC-SSRS as comparable to the C-SSRS. The eC-SSRS has been incorporated into randomized clinical trials to evaluate clinical validity, improve procedural reliability, reduce rating bias, and facilitate more complete self-disclosure.[10–12]

The FDA guidance drew public comments questioning the relevance of lifetime suicidal ideation and behavior (other than outright suicide attempts) for evaluating patient risk of subsequent suicidal behavior.[13,14] Lifetime ideation has demonstrated predictive utility in a suicidal adolescent population,[7] but more research is needed to quantify the relationships across and within different patient populations to aid in determining a patient's risk level. Testing predictive relationships is difficult to address on a study-by-study basis because of the low base rate of suicidal behavior in clinical trials. The existing set of eC-SSRS assessments, collected from thousands of patients across multiple studies, provided an opportunity to evaluate the predictive relationships between lifetime ideation and behaviors reported at study baseline with suicidal behaviors subsequently reported during trial participation.

DATA SOURCES AND STUDY SELECTION

Between September 2009 and May 2011, eC-SSRS assessments were administered to participants in clinical trial research by ERT, a clinical services provider to the biopharmaceutical industry. In May 2011, a total of 35,224 eC-SSRS records from all ongoing and completed research studies were extracted for analysis. Treatment indications included major depressive disorder (MDD), epilepsy, posttraumatic stress disorder (PTSD), insomnia, and fibromyalgia.

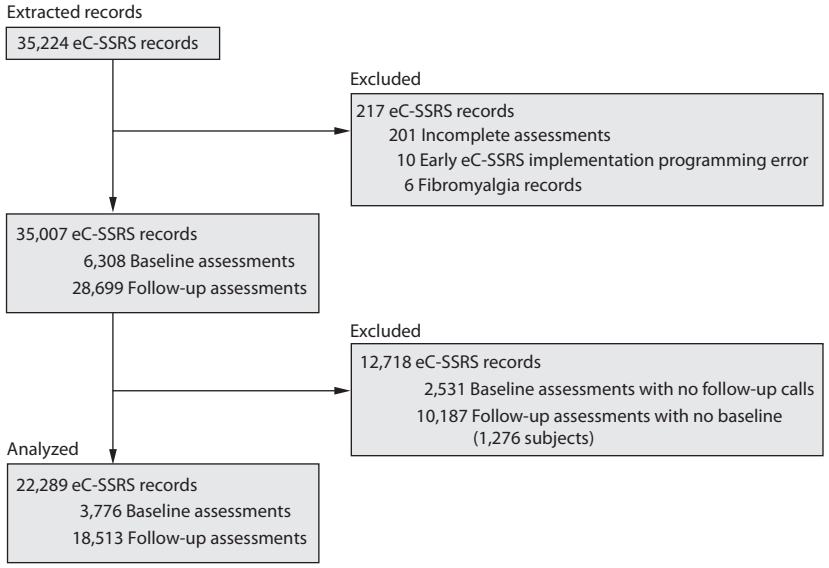
DATA EXTRACTION

Data records were extracted from a centralized database as comma-separated value (.csv) text files, merged in Excel spreadsheets, and imported to an SPSS (v20; IBM Corporation, Armonk, New York) data file for analysis. Each record was uniquely identified by a patient ID number and contained the responses to each eC-SSRS question as well as date and time stamps for the start and end of each assessment. No demographic, treatment blind, or personally identifying information was available. Figure 1 shows the data cleaning and analysis process for the results presented below. Of the 35,224 extracted records, 217 (0.6%) were excluded for one of the following reasons: 201 records were excluded due to incomplete assessments, 10 records were excluded due to an early system error that predated correction, and 6 fibromyalgia records were excluded because only 5 baseline assessments and 1 follow-up assessment were available. An additional 12,718 records (36.1%) were excluded because either no prospective follow-up assessments were collected (n = 2,531) or the eC-SSRS was used exclusively for prospective follow-up (10,187 assessments) without an assessment of lifetime ideation at baseline (n = 1,267).

Clinical Points

- Severity of lifetime suicidal ideation and behavior predicts patient risk for subsequent suicidal behavior, which is of critical importance for clinical practice and monitoring of patients.
- Computer-automated assessments, such as the electronic Columbia-Suicide Severity Rating Scale, reduce clinician burden, encourage patient self-disclosure, facilitate clinical follow-up, and streamline electronic patient medical records.
- Such procedures improve the quality of information for monitoring change in patient safety and assessing clinical improvement. This can inform care delivery and provide a foundation to support evidence-based decision-making.

Figure 1. Data Extraction of All Records From Ongoing and Completed Trials and eC-SSRS Record Selection Process for Reported Analyses

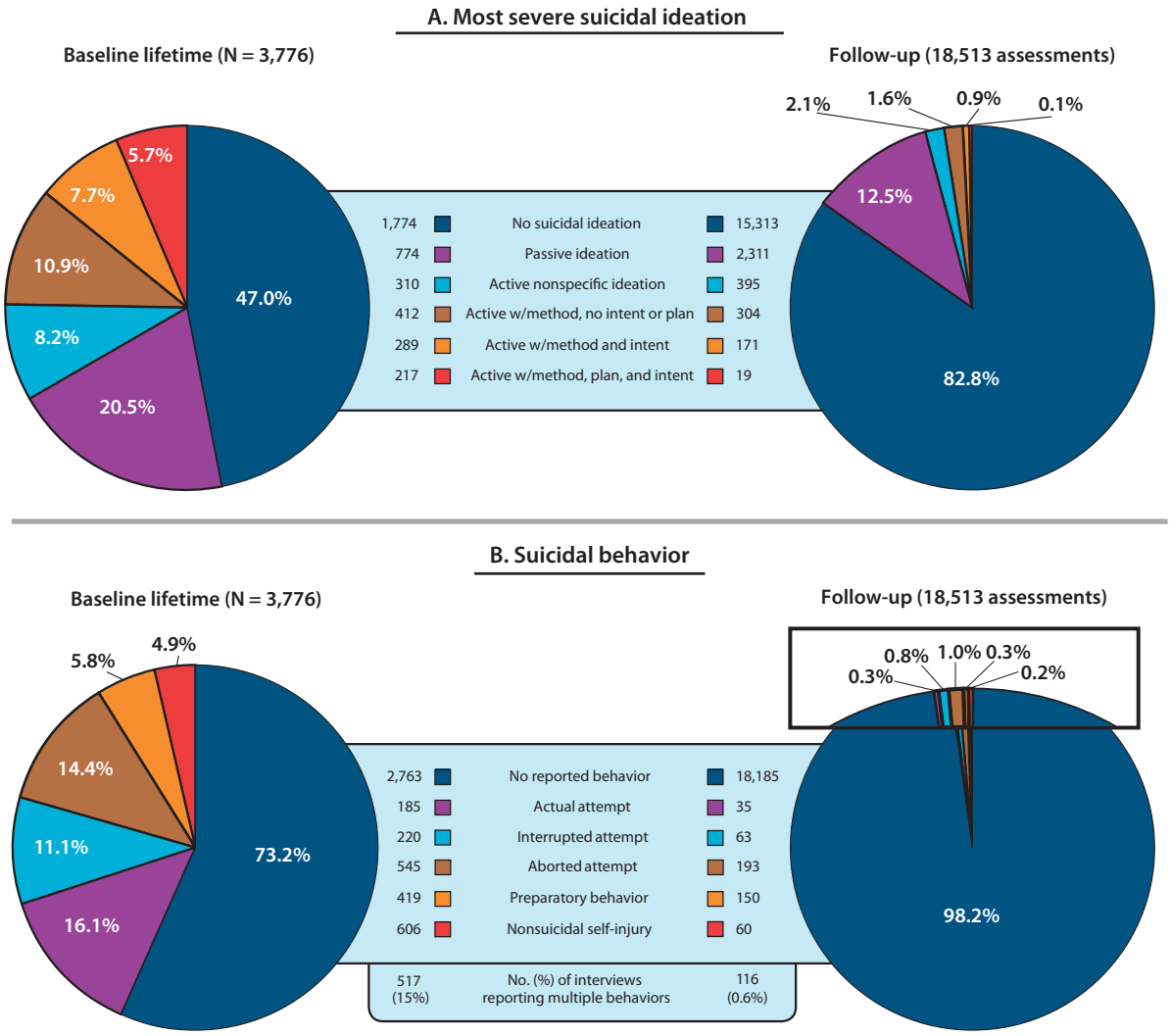


Abbreviation: eC-SSRS = electronic Columbia-Suicide Severity Rating Scale.

RESULTS

A total of 3,776 baseline assessments and 18,513 prospective follow-up assessments were analyzed. The number of prospective follow-up visits ranged from 1 to 13 (median = 6; interquartile range, 3–7), with a mean (SD) follow-up duration of 63.7 (51.0) days. Each eC-SSRS record was scored and coded with regard to the presence or absence of suicidal ideation and/or behavior. Reported suicidal ideation, when present, was graded along the 5-point severity subscale of the C-SSRS[7] suggested by the FDA guidance: (1) passive ideation; (2) active ideation, nonspecific; (3) active ideation with method, but no intent or plan; (4) active ideation with a method and intent, but no plan; and (5) active ideation with a method, intent, and plan. Reported suicidal behaviors documented by the C-SSRS behavior subscale

Figure 2. Lifetime Reports of (A) Most Severe Suicidal Ideation and (B) Frequencies of Suicidal Behaviors Obtained at Baseline and Follow-Up eC-SSRS Assessments[a]



[a]Only 1 ideation level was identified as most severe in each assessment; however, multiple behaviors could be reported at each assessment.
Abbreviation: eC-SSRS = electronic Columbia-Suicide Severity Rating Scale.

include (1) actual attempts involving actual or potential lethality, (2) interrupted attempts, (3) aborted attempts, and (4) preparatory actions. Nonsuicidal self-injurious behavior was also documented.

Figure 2A shows the overall frequency of the most severe level of suicidal ideation at the baseline and follow-up assessments. The percentages of baseline and follow-up eC-SSRS assessments reporting each type of suicidal behavior are shown in Figure 2B. It is possible for multiple types of behavior to be reported during a given assessment, so the sum is greater than 100%.

Each eC-SSRS report was categorized as a "positive" or "negative" case instance with regard to suicide risk concern. Positive cases included reports of suicidal ideation with intent to act (severity of 4 or 5) and reports of actual, aborted, or interrupted suicide attempts or a behavior preparatory for making an attempt. Reported ideation and behavior not meeting these criteria was classified as a negative case. Reports of nonsuicidal self-injurious behavior (not accompanied by reports of suicidal ideation with intent to act or another suicidal behavior) were classified as negative reports.

Across all baseline reports of lifetime ideation and behavior, 984 were identified as positive cases and 2,792 were classified as negative cases. To ascertain whether lifetime ideation and behavior, reported at baseline, influenced the risk of subsequent suicidal behavior occurring during study participation, the baseline reports were used to assign each patient a Safety Concern Code (SCC). Patients with negative baseline reports were assigned an SCC of "None." Patients with positive reports due to ideation severity of 4 or 5, but no reported suicidal behavior were assigned an SCC of "I." Patients with positive baseline reports on the basis of reported suicidal behavior but lifetime ideation severity of 3 or less were assigned an SCC of "B." Patients with positive baseline reports reflecting both ideation severity of 4 or 5 and prior suicidal behavior were assigned an SCC of "Both."

Table 1 provides the sample sizes for each of the clinical populations, the frequencies of positive and negative eC-SSRS baseline reports, and the distribution of SCCs within each clinical population.

Table 2 provides descriptive statistics for the 18,513 prospective follow-up assessments provided by the subjects with respect to the numbers of patients in each treatment indication, total eC-SSRS assessments, mean numbers of follow-up assessments and durations, mean intervals between assessments, and relative frequencies of negative and positive eC-SSRS reports for each clinical population.

Across all eC-SSRS assessments, the mean completion time was 3.8 (SD = 1.9) minutes and required patients to respond to a mean of 10.4 (SD = 4.8) queries. The 1,398 positive eC-SSRS reports required patients to reply to more follow-up questions (mean = 22.4, SD = 5.7) compared to the 20,891 negative reports (mean = 9.6, SD = 3.5; $t_{22,287} = -125.3$, $P < .001$). The time in minutes required to complete positive reports (mean = 7.7, SD = 2.9) was about double the time required to complete negative reports (mean = 3.6, SD = 1.5; $t_{22,287} = -89.4$; $P < .001$).

Of the 18,513 follow-up assessments, 293 (1.58%) were prospective reports of suicidal behavior (actual, interrupted, or aborted attempt, or behavior preparatory to an attempt). Of the 3,776 patients included in the analyses, 201 (197 with MDD and 4 with PTSD) prospectively reported suicidal behavior during study participation; 47 (44 with MDD and 3 with PTSD) did so at multiple follow-up visits.

Figure 3 shows the number of patients who provided a baseline and 1 or more prospective eC-SSRS reports categorized by the SCCs determined by their baseline assessments. The percentages of patients in each SCC group (None, I, B, and Both) who prospectively reported suicidal behaviors during follow-up visits were 2.4%, 12.0%, 9.6%, and 18.3%, respectively. The 2,792 patients with negative lifetime assessments at baseline (SCC of None) served as the reference group in cross-tabulations for computing common odds ratios and confidence intervals using the Mantel-Haenszel estimate for each of the other SCC groups. The forest plot of Figure 3 shows that subjects reporting lifetime suicidal ideation with intent to act on a method or plan and/or prior suicidal behavior at baseline (I, B, or Both) are 4.7 to 8.7 times more likely to prospectively report a suicidal behavior during study participation than subjects with negative baseline reports.

Receiver operating characteristics (ROCs) of the SCCs were computed using the final outcome of each patient as positively or negatively reporting a suicidal behavior during study participation (coded 0 or 1, respectively) as the state variable, and the patient's SCC of None, I, B, or Both (coded 0, 1, 2, or 3, respectively) was entered as an ordinal test variable. The area under the ROC curve was 0.73 (95% CI = 0.69–0.77; $P < .001$). In comparing negative baseline reports (SCC of None) against all positive baseline instances (all other SCCs combined), the sensitivity of using positive lifetime report to identify patients who subsequently reported suicidal behavior prospectively was 0.67, and specificity was 0.76. The positive predictive value of patients with positive baseline reports to subsequently report a suicidal behavior during study participation was 0.14, and the negative predictive value of a negative baseline report was 0.98.

Table 1. Sample Sizes for Each Clinical Population, Proportions of Negative and Positive eC-SSRS Baseline Reports, and Distributions of Safety Concern Codes[a] for Assessing Risk of Suicidal Behavior Occurring During Study Participation

		Positive Lifetime Cases, No. (%)	
	Negative Lifetime Cases, No. (%)[b]	Total	Safety Concern Code at Baseline
MDD	2,526 (73.4)	914 (26.6)	I: 73 (2.1) B: 442 (12.9) Both: 399 (11.6)
PTSD	71 (53.0)	63 (47.0)	I: 2 (1.5) B: 31 (23.1) Both: 30 (22.4)
Insomnia	174 (97.7)	4 (2.3)	I: 0 (0.0) B: 3 (1.7) Both: 1 (0.6)
Epilepsy	21 (87.5)	3 (12.5)	I: 0 (0.0) B: 2 (8.3) Both: 1 (4.2)
Complete data set	2,792 (73.9)	984 (26.1)	I: 75 (2.0) B: 478 (12.7) Both: 431 (11.4)

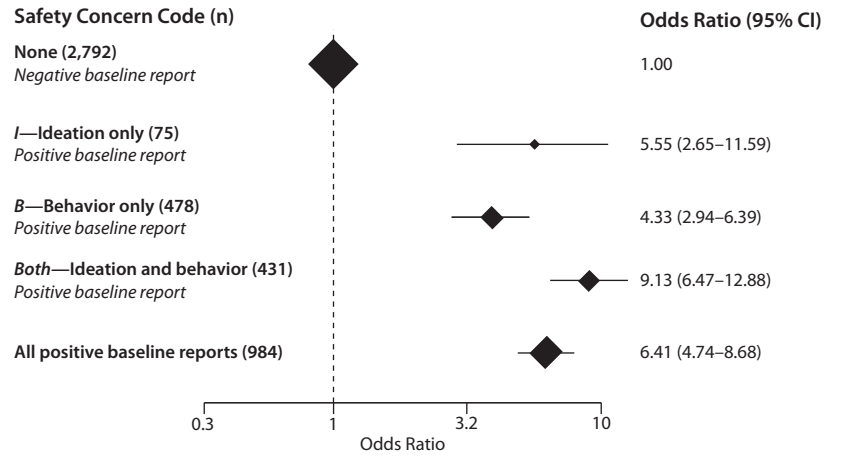
[a]Safety Concern Codes:
None = negative baseline report. No suicide ideation with intent to act or prior suicide attempts or preparatory behaviors.
I = positive baseline report. Suicide ideation with intent to act (ideation severity of 4 or 5), but no prior suicide attempts or preparatory behaviors.
B = positive baseline report. No suicide ideation with intent to act (lifetime ideation severity of 3 or less), but prior suicide attempts and/or preparatory behaviors.
Both = positive baseline report. Suicide ideation with intent to act and prior suicide attempts and/or preparatory behaviors.
[b]Safety Concern Code of None.
Abbreviations: eC-SSRS = electronic Columbia-Suicide Severity Rating Scale, MDD = major depressive disorder, PTSD = posttraumatic stress disorder.

Table 2. Descriptive Statistics for eC-SSRS Follow-Up Assessments for Each Clinical Patient Population

	Total Patients	Total Follow-Up Assessments, No. (%)	No. of Follow-Up Assessments, Mean (SD)	Days of Follow-Up, Mean (SD)	Days Between Follow-Up Assessments, Mean (SD)	Negative Reports	Positive Reports
MDD	3,440	17,466 (94.3)	5.1 (2.3)	83.8 (51.9)	12.6 (9.3)	17,063	403
PTSD	134	776 (4.2)	5.8 (2.7)	69.9 (35.2)	12.1 (4.7)	765	11
Insomnia	178	224 (1.2)	1.3 (0.8)	51.9 (39.6)	41.3 (20.4)	224	0
Epilepsy	24	47 (0.3)	2.0 (2.3)	99.4 (50.9)	50.8 (54.0)	47	0
Total	3,776	18,513	4.9 (2.5)	63.7 (51.0)	13.0 (10.3)	18,099	414

Abbreviations: eC-SSRS = electronic Columbia-Suicide Severity Rating Scale, MDD = major depressive disorder, PTSD = posttraumatic stress disorder.

Figure 3. Odds Ratios of Prospectively Reporting Suicidal Behavior During Study Participation for the Safety Concern Code Groups With Positive Lifetime Reports Obtained at Baseline Relative to Patients Reporting No Lifetime Ideation or Behavior at Baseline



DISCUSSION

Suicide and suicidal behavior are important public health concerns, and the development of valid methods for prospectively identifying patients at greater risk for engaging in suicidal behavior has important implications for research and suicide prevention. The FDA recommends prospective assessment of suicidal ideation and behavior in clinical studies both to ensure timely recognition and treatment of patients experiencing ideation and behavior and to provide data on suicidal ideation and behavior risk during treatment that can guide clinical expectations when medications are used in more naturalistic treatment settings.

This study analyzes data collected from over 3,700 subjects completing over 22,000 assessments of suicidal ideation and behavior and provides strong evidence that baseline information regarding lifetime suicidal ideation and behavior conveys clinically important information regarding risk of prospectively reporting suicidal behavior. Improving methods for identifying patients who are at greater risk of engaging in suicidal behavior has significant implications for research and suicide prevention.

The overall prevalence of lifetime behaviors found in this analysis of eC-SSRS assessments is comparable to the 15%–53% prevalence rates of lifetime suicide attempts reported by others in patients diagnosed with MDD.[3,15] Baseline rates of suicidal behavior vary among different patient populations and are higher in those with psychiatric disease than in other patient populations such as those being treated for smoking cessation, acne, or other dermatologic complaints.[15] The prevalence of prospectively reported suicidal behavior found in the present analysis is lower than that reported in a longer, 2-year prospective follow-up study of MDD and bipolar patients.[3,15] This difference may reflect the comparatively short mean follow-up duration of the present data set, since prospective prevalence of suicide attempts in patients with MDD and bipolar disorder is dependent on follow-up duration.[16] Although most attempts occur in the first month or two of follow-up, the risk may remain elevated for many years and warrant long-term monitoring.[16] The present analysis cannot directly address whether the eC-SSRS encourages greater disclosure of suicidal behavior and ideation compared to live interviewers, as has been found in prior studies.[10,12,17–21] This data set does not contain the necessary control data to permit such comparisons, but greater disclosure to the eC-SSRS compared to the clinician-administered C-SSRS when both were obtained has been reported elsewhere.[11]

The most important finding of the present study is the predictive relationship between lifetime suicidal ideation and behaviors, reported at study baseline, and the risk of prospectively reporting suicidal behavior during subsequent study participation. Even with the relatively short mean follow-up period, of about 9 weeks, patients reporting lifetime ideation with an intention to act, prior suicidal behaviors, or both at baseline were roughly 4 to 9 times more likely to report suicidal behavior during a study follow-up visit than patients who reported no lifetime ideation with intent to act or prior behavior.

Several limitations of this analysis should be noted. First, these data are predominately from patients participating in depression studies; the comparatively fewer assessments from patients with PTSD, insomnia, and epilepsy limit confidence in the generalizability of these results to other disorders. Second, these data do not address whether the recency of the lifetime ideation and behaviors reported at baseline influenced the risk of prospectively reporting suicidal behavior during study participation. Other studies suggest that severity of suicidal ideation tends to be a short-term predictor of suicide attempts[2] and that the most severe type of lifetime suicidal ideation is a longer term predictor of suicide.[22] The limitation related to the recency of suicidal ideation and behaviors will be addressed by forthcoming implementations of the eC-SSRS.

Third, the analyses presented do not address the extent to which prospective self-reports of suicidal behavior were subsequently confirmed by clinical follow-up. Finally, the data extracted for these analyses cannot address potential differences between the blinded treatment conditions, as the study blinds were not unlocked.

CONCLUSIONS

Predictive relationships between the risk of reporting suicidal behavior during study participation and lifetime experiences reported at baseline were evident for both suicidal

ideation and suicidal behaviors, substantiating the need to assess lifetime suicidal ideation and behavior at baseline. While fewer than 2.5% of patients with negative baseline reports reported suicidal behavior during subsequent study participation, over 13% of patients with positive baseline reports did so. These data demonstrate that suicidal behavior, while infrequently reported at any given study visit, is reported frequently enough to remain an important safety concern in the conduct of clinical research.

Computer-automated clinical interviews of suicidal ideation and behaviors can reduce clinician burden, as in-person interviews of this sensitive topic are often difficult and awkward for both the clinicians and patients. Greater patient disclosure of suicidal thoughts and behaviors with the use of consistent, systematic methods of inquiry has been found in adult and adolescent patients for many years.[10,12,17–21] The eC-SSRS systematically evaluates the full spectrum of suicidal ideation and behaviors that many clinicians may be reluctant to discuss. It provides immediate documentation for clinical review and follow-up and improves the likelihood of detecting emergent suicidal behavior during treatment. Computer-automated clinical interviews capture these critical assessments electronically, facilitating analysis of study results. Capturing electronic data directly from patients also reduces data entry and cleaning burdens. It may also provide a unique means for routine assessment that could enhance comprehensive approaches to suicide prevention and patient safety.

Aggregation of rare event data, such as emergent suicidal ideation and behaviors, facilitates meta-analyses through electronic storage of patient assessment records over time and across different treatments and studies. This, in turn, makes possible more rapid detection of differences between treatments and more accurate estimates of risk among similar treatments (eg, placebo) across different studies. Thus, standardization of data collection procedures improves patient safety and data quality. Centralized storage of commonly formatted patient data facilitates longitudinal, multistudy meta-analyses for increasingly sensitive and generalizable results.

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Author contributions: Dr Mundt had full access to all of the data analyzed in this review. Comma-separated value data files were provided for each study from a centralized database and merged for the reported analyses. Dr Mundt takes responsibility for the integrity of the data and accuracy of the analyses. Dr Mundt was responsible for the initial drafting of the manuscript; all coauthors participated in multiple revisions of the manuscript for important intellectual content and approved the final version. All coauthors were also involved in the conceptualization and design of the study or in the data analysis and interpretation of the results.

Potential conflicts of interest: **Dr Mundt** conducted the data analyses and prepared manuscript drafts as an independent consultant to ERT, a health-related outcomes laboratory and provider of clinical services to the biopharmaceutical industry; is a minor stock shareholder in Healthcare Technology Systems, Inc (HTS), which receives royalty payments for the development of the eC-SSRS; and has received research support grants from GlaxoSmithKline, Pfizer, Eli Lilly, Eisai, National Institutes of Health (NIH), and United States Department of Agriculture. **Dr Greist** was compensated as a consultant to ERT for work on this manuscript; is a major shareholder in HTS, which receives royalty payments for the eC-SSRS; and has consulted with GlaxoSmithKline, Jazz, Eli Lilly, Novo Nordisk, and Pfizer. In the past 2 years, Dr Greist has been a salaried investigator on research grants from AstraZeneca, Forest, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, Otsuka, Pfizer, Takeda, Transcept, and UCB. **Dr Jefferson** was compensated as a consultant to ERT for work on this manuscript; is a major shareholder in HTS, which receives royalty payments for the eC-SSRS; is a stock shareholder in Bristol-Myers Squibb, GlaxoSmithKline, and SciClone; and has served on speakers or advisory boards of Perdue, Sunovion, and GlaxoSmithKline. In the past 2 years, Dr Jefferson has been a salaried investigator on research grants from AstraZeneca, Forest, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, Otsuka, Pfizer, Takeda, Transcept, and UCB. **Mr Federico** is an employee of ERT. **Dr Mann** has 2 past grants from GlaxoSmithKline and Novartis for imaging studies unrelated to the subject of this article; receives research funding from NIH and private research foundations such as the Brain & Behavior Foundation; and receives royalties from the C-SSRS. **Dr Posner** is director of the Center for Suicide Risk Assessment; receives royalties from ERT through the Research Foundation for Mental Hygiene; and has received support from Abbott, Albany Molecular Research, Alfresa, Alkermes, Amgen, AstraZeneca, Biodelivery Sciences, Biomarin, Bristol-Myers Squibb, Canam, Cato Research, Cephalon, Cetero Research, Covance, CRI Worldwide, Depomed, Douglas, Eisai, Euthymics, Forest, GlaxoSmithKline, GW Pharma, Human Genome Sciences, i3 Research, ICON, IntelGenx Corp, Intracellular Therapies, Johnson & Johnson, Kendle Early Stage, Eli Lilly, Lundbeck, MedImmune, Medtronic, Merck, Neurosearch, Next Wave, Novartis, Noven, Novo Nordisk, Orexigen, Otsuka, Parexel, Pfizer, PGx Health, Pharmaceutical Product Development Inc, Psyadon, QED, Quintiles, Reckitt Benckiser, Roche, Sanofi-Aventis, Schering-Plough, SCOPE International, Sepracor/Sunovion, Shire, Siena Biotech, Supernus, Synosia Therapeutics, Takeda, Theravance, Upsher-Smith, Valeant, Vivus, World Wide Clinical Trials, and Wyeth.

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