Suicidality and Risk of Suicide—Definition, Drug Safety Concerns, and a Necessary Target for Drug Development: A Consensus Statement

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Objective: To address issues concerning potential treatment-emergent "suicidality," a consensus conference was convened March 23–24, 2009.

Participants: This gathering of participants from academia, government, and industry brought together experts in suicide prevention, clinical trial design, psychometrics, pharmacoepidemiology, and genetics, as well as research psychiatrists involved in studies of major depression, bipolar disorder, schizophrenia, substance abuse/dependence, and other psychiatric disorders associated with elevated suicide risk across the life cycle. The process involved reviews of the relevant literature, and a series of 6 breakout sessions focused on specific questions of interest.

Evidence: Each of the participants at the meeting received references relevant to the formal presentations (as well as the slides for the presentations) for their review prior to the meeting. In addition, the assessment instruments of suicidal ideation/behavior were reviewed in relationship to standard measures of validity, reliability, and clinical utility, and these findings were discussed at length in relevant breakout groups, in the final plenary session, and in the preparation of the article. Consensus and dissenting views were noted.

Consensus Process: Discussion and questions followed each formal presentation during the plenary sessions. Approximately 6 questions per breakout group were prepared in advance by members of the Steering Committee and each breakout group chair. Consensus in the breakout groups was achieved by nominal group process. Consensus recommendations and any dissent were reviewed for each breakout group at the final plenary session. All plenary sessions were recorded and transcribed by a court stenographer. Following the transcript, with input by each of the authors, the final paper went through 14 drafts. The output of the meeting was organized into this scholarly article, which has been developed by the authors with feedback from all participants at the meeting and represents a consensus view. Any areas of disagreement have been noted.

Conclusions: The term *suicidality* is not as clinically useful as more specific terminology (*ideation, behavior, attempts*, and *suicide*). Most participants applauded the FDA's effort to promote standard definitions and definable expectations for investigators and industry sponsors by endorsing the terminology in the Columbia Classification Algorithm of Suicide Assessment (C-CASA). Further research of available assessment instruments is needed to verify their utility, reliability, and validity in identifying suicide-associated treatment-emergent adverse effects and/or a signal of efficacy in suicide prevention trials. The FDA needs to build upon its new authority to systematically monitor postmarketing events by encouraging the development of a validated instrument for postmarketing surveillance of suicidal ideation, behavior, and risk within informative large health care–related databases in the United States and abroad. Over time, the FDA, industry, and clinical researchers should evaluate the impact of the current Agency requirement that all CNS clinical drug trials must include a C-CASA–compatible screening instrument for assessing and documenting the occurrence of treatment-emergent suicidal ideation and behavior. Finally, patients at high risk for suicide can safely be included in clinical trials, if proper precautions are followed, and they need to be included to enable premarket assessments of the risks and benefits of medications related to suicidal ideation, suicidal behavior, and suicide in such patients.

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Research on suicide has been plagued historically by methodological problems including lack of definitional clarity and inaccurate reporting by health agencies and institutions.[1,2] The problem of definition has become more complicated since the introduction of the nonspecific term *suicidality*, which lumps together suicidal ideation, self-injurious behavior, suicide attempts, and suicide despite their very different consequences for the patient.

This caveat has often been overlooked in the major public and professional concern about "suicidality" as a potential treatment-emergent adverse event associated with various central nervous system (CNS) drugs.[3–8] The US Food and Drug Administration (FDA) has been at the center of a controversy among some medical professionals, as well as some in Congress, the media, and the general public, over 2 key questions: (1) whether there is a link between antidepressant drug use and the emergence of suicidal ideation and behavior in children and adolescents and, if there is such a risk, why the FDA failed to detect and warn about this risk earlier; and (2) whether the "black box" warning on antidepressant drugs about the risk of treatment-emergent "suicidality" in pediatric patients resulted in a decrease in prescribing for this population and a consequent reversal in the decline in the annual suicide rate among adolescents.[9,10] The controversy intensified with a subsequent FDA meta-analysis of 199 placebo-controlled trials of 11 different antiepileptic drugs.[11] The Agency reported a statistically significant drug/placebo difference in treatment-emergent "suicidality" (68% of which was suicidal ideation), with 142 outcome events among 43,892 research participants. The FDA required the addition of "warnings and precautions" (but not a black box warning) to the label for the anticonvulsant drugs, in spite of concerns by neurologists and patient advocacy groups about possible consequent medication nonadherence.

One issue that has plagued the discussion is the perceived discrepancy* between the results of the FDA-initiated meta-analyses of randomized controlled trials (RCTs) that led to the black box and/or "warnings and precautions" additions to the labels of certain CNS drugs on the one hand and findings from observational and pharmacoepidemiologic studies and medical claims data on the other hand.[12] In the case of antidepressant treatment of adolescents, a number of pharmacoepidemiologic studies had reported that a steep decline in adolescent suicides that began in the early 1990s (reversing a steady annual increase over several decades) was related to the increasing use of antidepressant drugs in this population.†[2,13–18] Given that each approach (the FDA-sponsored meta-analyses and the pharmacoepidemiologic studies) has methodological limitations, there is a need for a critical review of the quality and interpretation of the evidence to better inform clinical practice.

Following initial concerns that antidepressant drugs might increase suicide risk in younger populations, the FDA commissioned a study by investigators at Columbia University to oversee the classification of all events in the pediatric antidepressant trials database that might represent "suicidality."[19] On the basis of consensus recommendations and empirical findings regarding suicide-related definitions, the investigators developed the Columbia Classification Algorithm of Suicide Assessment (C-CASA),[19] which systematically categorizes potential suicidal adverse events, as well as events that were reviewed and either were not suicidal or were events for which a determination of suicidal intent could not be made. The FDA Division of Psychiatry Products now requires that all participants in clinical trials of CNS-active drugs be evaluated at baseline and during active treatment using a scale that maps to the C-CASA algorithm to detect suicidality as a potential treatment-emergent adverse event.‡ The C-CASA terminology currently favored by the FDA represents an effort to define *suicidal ideation, suicidal behavior, nonsuicidal self-injurious behavior,* and *accidental injuries* in the context of treatment-emergent adverse events in clinical trials. It will be important to determine the broader utility and validity of the C-CASA definitions across cultures in clinical efficacy studies and epidemiologic research§ applications. Clinicians, in particular, need to know how to weigh possible risks and benefits associated with anxiolytic, antidepressant, and other CNS-active drug treatment. Treatment-emergent suicidal ideation and suicidal behavior may be influenced by risk or protective factors that were not fully considered in the clinical trials databases. How should these factors be considered in the context of drug safety and efficacy questions? Moreover, the typical exclusion from industry-sponsored pivotal trials of patients with significant suicidal risk (based on recent suicidal behavior and/or severity of suicidal ideation) has served to limit the information available to practitioners about the effects of approved drugs on these high-risk patients in their practices.

To address the issues that have emerged in recent years concerning potential treatment-emergent "suicidality,"¶ a consensus conference of participants from academia, government, and industry was organized to bring together experts in suicide prevention, clinical trial design, psychometrics, pharmacoepidemiology, and genetics, as well as research psychiatrists involved in studies of major depression, bipolar disorder, schizophrenia, substance abuse/dependence, and other psychiatric disorders associated

*One FDA staff physician (M. B. Stone, MD, electronic communication, December 2009) has argued that while the Agency's analysis did not identify any suicides in the pediatric trials, it was necessary to bring the increase in suicidal ideation and behavior in the drug-treated young patients to the attention of clinicians and the public in the form of the black box warning. He further observed that this does not mean that antidepressant drugs cannot, as a net effect, reduce risk and rate of actual suicide in the general population over a longer period of time because of their beneficial effects on depressed mood. He cited a nonpsychiatric example. "Erythropoietin (Epogen) is used to treat anemia, but it can cause red cell aplasia in some patients. An epidemiologic study of Epogen and anemia would probably find that Epogen reduced the number of patients with anemia, but that does not mean that the phenomenon of erythropoietin-induced red cell aplasia is not real."

†And, the corollary: that decreasing use of antidepressants would be associated with increased suicide rates.

‡The Division of Psychiatry Products has also encouraged studies of drugs to reduce the risk of suicide in high-risk patients.

§The new Centers for Disease Control and Prevention self-directed violence surveillance definitions of suicidal behavior (*attempted*, *interrupted*, and *aborted*) are now consistent with the C-CASA definitions (A. Crosby, MD, MPH; unpublished manuscript; 2010).

¶While the initial concerns were mostly focused on children, adolescents, and young adults, the FDA requirement to include assessment of treatment-emergent "suicidality" in clinical trials of all CNS drugs extends this concern to other age groups. Studies of drug treatments that might reduce suicide risk also apply to all age groups involving individuals at risk (as in the FDA clozapine approval).

with elevated suicide risk across the life cycle. The objective was to achieve consensus* on the following issues:

1. Definitions: to seek consensus on the value of the term *suicidality* or alternatives, as well as the relative advantages and disadvantages of instruments proposed for assessing the occurrence, severity, and intent of suicidal ideation and behavior in clinical trials of CNS drugs.
2. Evidence: to weigh the relative merits, limitations, and standards of evidence ("logic of inference") of data analyses from randomized controlled trials (RCTs), meta-analyses of published and unpublished data from RCTs, and population-based studies in assessing the question of treatment-emergent adverse events related to suicidal ideation and behavior.
3. Risk factors: to seek consensus on risk factors and moderator and mediator variables that should be considered, and their relative weight, in evaluating the question of treatment-emergent adverse events related to suicidal ideation/behavior/intent and suicide and to evaluate the efficacy of pharmacotherapy in reducing the risk of suicide in high-risk patients.
4. Ethics: to consider possible ethical and scientifically sound study designs that include research participants at risk of suicide in clinical trials in which suicidal ideation, suicidal behavior, or suicide is a potential treatment-emergent serious adverse event (SAE) and in which elevated risk of suicide is the target of pharmacotherapy intervention.

The conference was convened in Washington, DC, March 23–24, 2009, by the Department of Psychiatry at Beth Israel Deaconess Hospital, Boston, Massachusetts, and organized by Best Practice Project Management, Inc. Conclusions arising from the conference are the basis of this report.

DEFINITIONS

Self-directed violence encompasses a range of aggressive behaviors, including acts of fatal and nonfatal suicide attempts and nonsuicidal intentional self-harm. Although many governmental, international, and nongovernmental organizations collect information on fatal and nonfatal self-directed violence, there is considerable disagreement about how to define the phenomenon and how to best estimate the risk of suicide and suicide-related behaviors. Definitions vary by jurisdiction and differ depending on whether they are intended or developed for legal, medical, administrative, or other purposes. These differences affect the findings of population-based studies, including research on risk and protective factors. Different definitions may account, at least in part, for inconsistent results between studies. Consistency of terminology, with standardized definitions, would improve the quality of surveillance, treatment, preventive interventions, and research. Importantly, it would facilitate the interpretation of data garnered from different sources in population-based studies and across clinical trials.

The general term *suicidality* is not considered to be adequately specific or as clinically useful as more precise terminology (*ideation, behavior, attempts,* and *suicide*) that can be defined across data sets from clinical trials and pharmacoepidemiologic studies and that can be more readily understood by clinicians and the public. Clearly, there are major differences in clinical severity and importance between suicidal ideation and death due to suicide or suicide attempts.

Assessment Issues

A number of instruments have been developed to assess suicidal ideation, suicidal behavior, and suicide risk. In addition, information on suicidal ideation and behavior is incorporated into many depression rating scales and structured psychiatric interviews. The American Psychiatric Association (APA) Practice Guideline for the Assessment and Treatment of Patients With Suicidal Behaviors[20] emphasizes the importance of obtaining information from outside informants and carefully assessing the use of alcohol and drugs. The APA does not encourage the use of suicide assessment scales in the clinical treatment of patients, arguing that they have been developed for research purposes and lack the predictive validity necessary for use in routine clinical practice.† However, a checklist of basic questions performs better in terms of detecting suicide attempts than examination by a clinician in the emergency room or inpatient unit. Multiple review articles and chapters have compared assessment instruments, especially in relationship to their psychometric properties.[24–28] Most of the conventionally reported psychometric parameters, such as internal consistency, reliability, factor structure, and convergent validity, are only indirectly related to the goals of detecting SAEs or efficacy in clinical trials. The most relevant features of the scales for these purposes are retest stability, effect sizes from blinded treatment studies, and diagnostic accuracy. These characteristics have been reported to only a limited degree.[29] Whereas high diagnostic sensitivity is important at the level of individual cases, high specificity is actually more valuable at reducing bias in detecting rare events in clinical trials. Combining multiple sources of information and treating a positive result on any of them as evidence of "suicidality" is a useful clinical strategy, but it can produce inflated estimates of absolute risk, which can be a problem in RCTs. In addition, the differences in quality of external data sources may increase variance in clinical trials. Finally, assessments that have utility in detecting treatment-emergent SAEs in

*The process involved a 2-day conference that included reviews of the relevant literature, and a series of 6 breakout sessions focused on specific questions of interest. The output of the meeting was organized into this scholarly article, which has been developed by the authors with feedback from all participants at the meeting and represents a consensus view. Any areas of disagreement have been noted.

†The Scale for Suicide Ideation is one of the few measures that has established longer term predictive validity for completed suicide, but it does not help with short-term risk.[21–23]

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clinical trials may not be equally useful in detecting efficacy in reducing the risk of suicidal behavior, or in the clinical assessment and management of suicide risk.

Table 1 provides a template overview that should be considered in evaluating the utility of available instruments in assessing treatment-emergent suicide-related ideation and behavior and/or efficacy in reducing suicidal ideation, behavior, and risk. Tables 2 and 3 present an evaluation of existing instruments that assess treatment-emergent suicidal ideation, suicidal behavior, and suicide or an outcome measure of efficacy in reducing the risk of suicide in at-risk patients in RCTs. Table 2 shows how well each instrument reflected the 9 elements of C-CASA as required by the FDA: completed suicide, suicide attempt (with intent assessment), preparatory acts, suicidal ideation, self-injurious behavior (intent unknown), fatality (not enough information to determine whether suicide), nonsuicidal self-injury, other (accident, etc), and nonfatal injury (not enough information to determine intent). Footnotes to Table 2 highlight efforts by 2 scale developers as of December 2009 to adapt their scales to C-CASA, but at this writing (January 2010), the Agency has determined that only the Columbia Suicide Severity Rating Scale (C-SSRS)[19,39–41] fully matches to all 9 elements.* Supporters of the FDA position argue that this will improve the quality of any subsequent meta-analyses through improved reliability (C.M.B., electronic communication; December 2009). Critics of the FDA position argue that it is premature to endorse 1 scale until the construct validity has been further validated across cultures and languages, in prospective clinical studies, and in pharmacoepidemiologic research. Moreover, if 1 scale is to be used as an indicator of both benefit and risk, sensitivity to change should have been demonstrated in relationship to treatment-emergent adverse events *and* efficacy (where reduction of suicidal behavior or ideation is the primary endpoint).[42–44]

Table 3 compares these instruments in terms of their utility (ease of administration, length of administration, mode of administration [clinician- or self-administered via paper and pencil, computer, or interactive voice response system {IVRS}], and time for training in administration) and functionality (scalability, whether they obtain separate measures of ideation and behavior, and whether they have been evaluated in different clinical populations and on different cultural/linguistic groups). Footnotes to Table 3 indicate that the time for training and the time necessary for the administration of the assessment instruments came from the developers of the scales and have not been independently validated. We have no cost-related information regarding training. Table 4 provides a comparative assessment of a broader group of structured interviews, semistructured interviews, and self-report instruments in terms of the availability of normative data, established information on reliability (internal consistency, interrater reliability, and test-retest), and validity (content, construct, generalization, treatment sensitivity, and clinical utility). In the long run, the assessment instrument that will be most valued by industry and by regulators will be the one that is the most sensitive in discriminating drug from placebo in detecting treatment-emergent suicidal ideation and behavior (and/or documenting antisuicidal efficacy) in smaller sample sizes, and earlier in drug exposure. Historically, in the area of psychotropic drug development, it has been easier to establish sensitivity to change over time (end of treatment compared with baseline in drug- and placebo-treated patients) than to meet the stricter criteria of sensitivity to drug/placebo differences.

Table 1. Criteria for Judging the Utility of Available Instruments in Assessing Treatment-Emergent Suicide-Related Ideation and Behavior

Ease, length, and means of administration[a]
Time and expense for training in accurate administration
Availability of formal training materials to support administration and scoring
Learning effects that can change the subject's response during a clinical trial
Scalability[b]
Reliability (How reproducible are scores on the test?)[c]
Validity including content and construct validity, validity generalization, criterion validity, and predictive or discriminative validity[30]
Sensitivity to change—do scale scores show change in response to treatment?
Generalizability—are the results generalizable across different patient populations and across cultures?
Separate measures of suicidal ideation and behavior and a methodology for securing data on suicide
Validated composite score with implications for referral for clinical assessment by an experienced mental health professional

[a]Self-administered by paper and pencil, computer, or Interactive Voice Response Systems (IVRS) or clinician-administered.
[b]Although scores usually will not achieve an "equal interval" level of measurement and may not behave linearly, *scalability* refers to the items achieving at least a rank order level of measurement where items can be summed meaningfully and where change in the total score means something (ie, higher scores mean greater severity). Items that code nominal categories (such as type or means of attempt) cannot usually be added to create a composite score.
[c]A variety of forms of reliability are commonly reported, including interrater, test-retest, and internal consistency (eg, split half or Cronbach α coefficient).

Description of Specific Instruments

The C-SSRS is the prospective counterpart of the C-CASA and completely reflects its contents.[19,39–41] It includes elements to facilitate the investigator's appropriate identification of suicidal occurrences—definitions of terms (required by FDA for any approved scale) and corresponding probes. If the C-SSRS is used, it eliminates the need for creating narratives, because categorization is done at the time that the information is collected. The C-SSRS includes family information, and it is one of the few scales that recommends routinely obtaining information from more than 1 source. It has been adapted for self-administration via IVRS,

*In this regard, the FDA has been quite explicit in wanting to see the actual implementation of the scale(s) and see some data comparing them with the C-SSRS in a direct head-to-head comparison. "There needs to be an instrument that not only, on face, can map to C-CASA, but also has instructions and training that permit its use, and there should be evidence that it is usable and correlates well with what we consider the gold standard, ie, the C-SSRS" (T. P. Laughren, MD; electronic communication; January 2010).

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Table 2. How Available Suicide Assessment Scales Map Onto C-CASA[a–c]

Scale	Completed Suicide	Suicide Attempt (with intent assessment)[d]	Preparatory Acts	Suicidal Ideation	Self-Injurious Behavior, Intent Unknown	Not Enough Information (fatal)	Nonsuicidal Self-Injury	Other (accident, etc)	Not Enough Information (nonfatal)
C-SSRS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
HASS Demo (interview), 1 and 2 (self report questionnaire)[31e]	No	Yes	Partial: some information about aborted and interrupted attempts, no preparatory behavior	Yes	No	No	No	No	No
S-STS (both clinician- and patient-rated versions)[32f]	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
ISST[33g]	No	No	No	Yes	No	No	No	No	No
SBQ-R[35]	No	Yes	No	Yes	No	No	No	No	No
SSI[36]	No	No	Yes	Yes	No	No	No	No	No
BSI[37]	No	No	Yes	Yes	No	No	No	No	No
SITBI[38]	No	Yes	Yes	Yes	Yes	No	Yes	No	No
SIQ[195]	No	No	No	Yes	No	No	No	No	No

[a]Since the March 2009 consensus meeting, the US Food and Drug Administration (FDA) has indicated that it cannot approve the use of an assessment instrument mapping to C-CASA as a stand-alone assessment in clinical trials until the Agency reviews validation study data of these instruments and finds that they correlate well with the C-SSRS in head-to-head comparisons. For this to happen, the developers and sponsors of the C-SSRS will need to collaborate with the FDA and the developers of these other scales. The FDA should encourage this process. The FDA will also need to review and approve the instruction and training materials for those instruments being considered for endorsement.

[b]Yes = sufficient coverage to approximate similar content in C-CASA, no = insufficient coverage; partial coverage noted separately.

[c]The C-CASA was designed to analyze retrospective data, which required the creation of the 9 categories shown in the table. For prospective studies, it is assumed that information essential to the classification of behaviors will be obtained; hence, there is no actual need for any of the instruments to match to "not enough information" for fatal and nonfatal events, which was a part of C-CASA.

[d]On the question of intent, the 2 psychometricians who participated in the meeting and in the preparation of this article (and who have no connection with any of the assessment instruments) believe that no assessment instrument should be deemed sufficient to determine intent in relationship to self-injurious behavior and/or ideation because this determination should be made by a mental health professional.

[e]Demo is interview format; 1 is a questionnaire asking about the last 2 weeks; 2 is a questionnaire asking about lifetime *except* for the last 2 weeks.

[f]Since the Consensus meeting in March 2009, a modified version of the S-STS (Version 9–9-09) has been developed that tracks completed suicide directly on the form, rather than referring to a separate serious adverse events document. Instructions state (consistent with C-CASA definitions) that interrupted and aborted attempts are classified as "preparatory acts" on item 9 and not as suicide attempts on item 11.

[g]Since the Consensus meeting in March 2009, a modification of the ISST has been developed to address some of the limitations with respect to assessment of suicidal behavior. An as yet unpublished presentation describes the intent to modify the scale to map to the C-CASA.[34]

Abbreviations: BSI = Beck Scale for Suicidal Ideation, C-CASA = Columbia Classification Algorithm of Suicide Assessment, C-SSRS = Columbia Suicide Severity Rating Scale, HASS = Harkavy Asnis Suicide Survey, ISST = InterSePT Scale for Suicidal Thinking, SBQ-R = Suicidal Behaviors Questionnaire—Revised, SIQ = Suicidal Ideation Questionnaire, SITBI = Self-Injurious Thoughts and Behaviors Interview, SSI = Scale for Suicide Ideation, S-STS = Sheehan Suicidality Tracking Scale.

but this version needs to be validated against the clinician-administered scale.* According to its developers, the C-SSRS has been translated into 90 languages and it has been used in hundreds of international trials (K.P., oral communication, November 2009). Nevertheless, state-of-the-art validation across cultures must necessarily go beyond translation, and the developers of the scale are aware that cross-cultural validation is essential.†

The Sheehan Suicidality Tracking Scale (S-STS)[32] is based on the Mini-International Neuropsychiatric Interview (MINI),[53] a brief structured psychiatric interview based on *DSM-IV* criteria. While the MINI has been extensively utilized in clinical trials, at the time of the consensus conference, the S-STS had some limitations in meeting the FDA-required matching to all elements of the C-CASA algorithm. The S-STS has been modified so that it can be completed as a self-report questionnaire or as a clinician-administered interview. It has information about preparatory acts and evaluates suicidal ideation, plans, and attempts. The published psychometric properties are based on the self-report version only,[32] and additional psychometric information would be helpful about both administration formats. The version of the S-STS published by Coric et al[32] in 2009 utilizes SAE forms to chart data on suicide, which complicates matching to the C-CASA algorithm. However, according to the developers of the scale (D.V.S., oral communication, December 2009), a revised version (Version 9-9-09) is now available that records on the S-STS itself whether a visit was missed due to suicide or for another reason, thus consolidating the relevant

*A pilot study demonstrated that the self-administered version could differentiate suicidal ideation/behavior in a modest number of patients who had been admitted for suicidal behavior at an inpatient facility in Wisconsin from self-reports among an equal number of staff members at the same institution (K.P., electronic communication, December 2009).

†The documented variability in suicide rates, associated stigma, and reporting biases across countries and cultures[48,49] and the cultural differences in the expression of mood disorders and other forms of psychopathology[50,51] indicate that empirical validation is essential, and accurate translation by itself is a necessary but insufficient step toward having fully validated tools. Adaptation of scales requires a process of translation, back-translation, expert bilingual committee review, and field trials. This process is essential to ensure that the same constructs are being measured in the different cultural contexts and provides for the possibility that manifestations of psychiatric illness vary depending on cultural factors.[52]

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Table 3. Design Features, Administration Details, Training Time, and Status of Validated Translations of Suicide Assessment Scales

Scale	Ease of Administration	Length of Administration[a]	Clinician, Self, or Computer Administration	Time for Rater Training[a]	Scalability?	Separate Measures of Ideation and Behavior?	Tested in Different Populations Diagnostically? In Different Languages/Cultures?
C-SSRS	Easily administered and scored	6 screening items (2 ideation and 4 behavior); 19 items maximum (2–15 min)	Clinician (IVR in process of validation)[39]	20–40 min	Partial	Yes	Translations but no published validation yet
HASS Demo, 1, and 2	Easily administered and scored	Self-report = 44 items (5–10 min). Interview = 10–15 min. Total ≈25–30 min	Self-report and clinician. Intended to be used in combination	Not reported	Partial	Yes	Multiple English-speaking samples
S-STS[b]	Brief and straightforward; easy and clear scoring algorithms	8 items (1–2 min) (Coric 2009[32] version)	Clinician or self-report	< 15 min	Yes	Yes	Translations but no published validation yet
ISST	Rater needs experience with schizophrenia and structured assessments used with psychiatric patients	12 items (15–20 min)	Clinician	20–40 min	Yes	No	No
SBQ-R	Easily administered and scored	4 items (3–5 min)	Self-report	NA	Yes	No	Multiple English-speaking samples
SSI	Easily administered and scored	21 items (10 min)	Clinician	< 15 min	Yes	Yes	Yes
BSI	Easily administered and scored	21 items (10 min)	Self-report	NA	Yes	Yes	Yes
SITBI	Easily administered and scored	Long form, 169 items; short form, 72 items (3–15 min)	Clinician	Several hours	Partial	Yes	Multiple English-speaking samples
SIQ	Easily administered and scored	30-item version (SIQ) and 15-item version (SIQ-JR)	Self-report	NA	Yes	No	Multiple English-speaking samples

[a]Each of the scale developers provided the estimated time required for training in administration. There is no independent validation. It may take more or less time, depending on the site, the study, and the instrument.
[b]Extensive reliability, validity, and trainability testing have been done on the Mini International Neuropsychiatric Interview, but no separate and independent testing has been published on the S-STS except for the Coric et al 2009[32] description of an 8-item version; this was revised into the current 11-item version following discussion at the meeting and consultation with the US Food and Drug Administration (referred to as the "9-9-09 version").
Abbreviations: BSI = Beck Scale for Suicidal Ideation, C-SSRS = Columbia Suicide Severity Rating Scale, HASS = Harkavy Asnis Suicide Survey, ISST = InterSePT Scale for Suicidal Thinking, IVR = interactive voice response, NA = not applicable, SBQ-R = Suicidal Behaviors Questionnaire—Revised, SIQ = Suicidal Ideation Questionnaire, SITBI = Self-Injurious Thoughts and Behaviors Interview, SSI = Scale for Suicide Ideation, S-STS = Sheehan Suicidality Tracking Scale.

information onto a single source document (scale available from D.V.S.).

Although the S-STS, the Self-Injurious Thoughts and Behaviors Interview,[38] the C-SSRS, the InterSePT Scale for Suicidal Thinking (ISST),[33] used in the International Suicide Prevention Trial, and perhaps other scales appear to have clinical utility, there are limited data about their sensitivity to change in terms of the appearance of treatment-emergent suicidal ideation and behavior and the reduction of suicide risk (measure of efficacy).[54] The Harkavy Asnis Suicide Survey (HASS) Demo, the HASS 1, and the HASS 2, a series of 3 clinician-administered instruments designed to capture suicide attempts,[31] assess preparatory acts as well as information about suicidal ideation and may identify treatment-associated suicidal ideation and behavior. Like all of the other scales except the C-SSRS, at the time of the consensus conference (March 2009), they did not completely correspond to the C-CASA criteria. The Scale for Suicide Ideation has been shown to have predictive utility for suicide in the long term.[55] The C-SSRS has operationalized criteria for triggering referral to a mental health professional (K.P., oral communication, November 2009). The Suicidal Behaviors Questionnaire–Revised[35] also has a cutoff value indicating when a mental health professional should be contacted. The ISST has data on predictive utility comparing olanzapine and clozapine treatment of patients with schizophrenia (in terms of suicides, attempts, or hospitalization),[96] and it has been used to assess levels of suicidal thinking for which interventions should be made.

Not all participants at the conference were prepared to second the FDA's endorsement of the C-SSRS as the primary tool in safety and efficacy assessment of suicidal ideation and behavior, and the classification of an event as suicide, in clinical trials. As with the other assessment instruments, there are still limited data available on reliability and validity (indicated in Table 4 by fewer than 3 plus signs or "??") and on scalability, and there is a lack of published validation on the cultural and linguistic differences relevant to international clinical trials (Table 3). In addition, as described in the footnote in Table 2, there were also concerns about relying on *any* of the assessment instruments to determine intent. Risk of suicide should always be assessed by a trained mental health professional. The participants at the meeting included developers of other competing scales, as well as several

Table 4. Reliability and Validity of Measures for Assessing the Presence of Self-Injurious Thoughts and Behaviors in Children, Adolescents, and Adults[a]

		Reliability			Validity				
Scale	Normative Data	Internal Consistency	Interrater	Test-Retest	Content	Construct	Generalization	Treatment Sensitivity	Evidence for Clinical Utility
Structured interviews									
SITBI	++	NA	+++	+	++	+	++	??	+
SASII[45]	+	++	+++	+++	+	++	+	++	++
PSS	??	+	??	??	+	++	++	??	+
Semistructured interviews									
SSI	+	+++	+++	??	++	+++	+++	+++	+++
SSI-W	+	++	++	+	++	+++	++	??	+
MSSI[46]	??	++	+++	–	++	+++	++	+	+++
C-SSRS[b]	++	++	+++	??	++	++	+	++	++
HASS Demo	+	??	??	??	+	??	??	??	+
ISST	+	++	++	??	+	++	++	+	+
Self-report measures									
BSI[47]	+	+++	NA	++	++	+++	+	??	++
SMSI	??	??	NA	??	–	+	+	+	+
SPS	+	++	NA	+	??	+++	++	+	+
PANSI	??	++	NA	??	+	++	+++	+	+
ASIQ	??	+++	NA	+	??	+++	+++	??	+
SIS	??	++	NA	??	+	+	+	??	+
SBQ	??	++	NA	+	+	++	+	+	++
SBQ-R	+	++	NA	??	+	++	+	??	++
SHBQ	??	++	NA	+	+	++	–	??	+
SHI	+	+	NA	??	+	++	+	??	+
SIQ	??	++	NA	+	+	++	+	??	+
DSHI	??	++	NA	++	+	+	+	??	+
SRS	??	++	NA	??	+	+	+	??	+
HASS 1 and 2	+	+++	NA	??	+	+	+	??	+
S-STS[c]	++	??	??	??	++	++	??	++	++

[a]Data from Nock et al 2008,[26] with the addition of scales from an unpublished White Paper (PhRMA, December 2008) and discussion at meeting.
[b]A paper presenting many of the psychometric aspects of this instrument was under peer review at the time of the consensus meeting and preparation of this paper.
[c]The S-STS has been designed so that it could be completed as either a self-report or clinician-rated instrument. However, the published psychometric properties are based on the self-report version of administration.[32]
Abbreviations: ASIQ = Adult Suicide Ideation Questionnaire, BSI = Beck Scale for Suicidal Ideation, C-SSRS = Columbia Suicide Severity Rating Scale, DSHI = Deliberate Self-Harm Inventory, HASS = Harkavy Asnis Suicide Survey, ISST = InterSePT Scale for Suicidal Thinking, MSSI = Modified Scale for Suicidal Ideation, NA = not applicable, PANSI = Positive and Negative Suicide Ideation Inventory, PSS = Paykel Suicide Scale, SASII = Suicide Attempt Self-Injury Interview, SBQ = Suicidal Behaviors Questionnaire, SBQ-R = Suicidal Behaviors Questionnaire-Revised, SHBQ = Self-Harm Behavior Questionnaire, SHI = Self-Harm Inventory, SIQ = Suicidal Ideation Questionnaire, SIS = Suicide Ideation Scale, SITBI = Self-Injurious Thoughts and Behaviors Interview, SMSI = Self-Monitoring Suicidal Ideation Scale, SPS = Suicide Probability Scale, SRS = Suicide Risk Scale, SSI = Scale for Suicide Ideation, SSI-W = Scale for Suicide Ideation-Worst, S-STS = Sheehan Suicidality Tracking Scale.
Symbols: – = less than adequate, + = adequate, ++ = good, +++ = excellent, ?? = unavailable in published peer-reviewed article or technical manual.

experts who were skeptical of the FDA's "suicidality" event assessments, data collection, and documentation requirements for all premarketing clinical trials of CNS drugs. With input received at the meeting, and in the preparation of this consensus statement, the authors have tried to be balanced in their presentation of the pros and cons of each instrument, as well as provide footnoted updates on information received since the meeting.

EFFECTS OF MEDICATION

Suicidal Ideation/Behavior as a Treatment-Emergent Adverse Event

Since the early 1800s, the paradoxical emergence of suicidal ideation and behavior early in a patient's recovery from depression has been noted.[56–58] More recently, the idea that antidepressant medication might *cause* suicidal behavior/ideation surfaced in 1990 when 6 cases of treatment-emergent suicidal ideation were reported in patients taking fluoxetine.[59] An FDA advisory committee looked at data from a meta-analysis of fluoxetine and suicidal ideation/behavior in adults and concluded that there was no association.[60] In addition, an analysis of suicide rates from FDA reports of the controlled clinical trials for 9 FDA-approved antidepressants found no overall difference in suicide risk between antidepressant- and placebo-treated depressed subjects and no difference between selective serotonin reuptake inhibitors (SSRIs) and other types of antidepressants.[61]

However, in 2003, the FDA noted suggestions of increased suicidal ideation or behavior in studies of paroxetine in pediatric populations. The manufacturer also found some evidence of this, particularly in 1 study of major depressive disorder. The FDA then requested sponsor data on possible "suicidality" among pediatric patients who had been treated with 8 other antidepressant drugs, and the Agency conducted its own meta-analysis of data from 23 industry-sponsored trials and 1 trial sponsored by the National Institute of Mental Health (NIMH) on the effectiveness of antidepressants in depressed children and adolescents.[4,62] Estimates of "suicidality risk" were obtained for each drug relative to

placebo, for SSRIs as a group, and for all the evaluable trials using C-CASA. *Suicidality* was defined to include completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, and suicidal ideation. Two additional categories were grouped as (1) indeterminate or potentially suicidal events or self-injurious behavior suicidal intent unknown and (2) injury events with insufficient information to determine whether they represented deliberate suicidal behavior. Because the data that the FDA collected came from studies that did not focus on suicidal ideation or behavior, this information was based entirely on the collection and documentation of adverse event information obtained through interviews by trained raters or medical personnel using open-ended questions (rather than a standard assessment instrument). These staff had latitude with respect to recording and documenting the events that occurred. Suicide item scores on depression rating scales failed to pick up a signal.[4]

Companies provided additional trial- and patient-level data to augment information not available from published reports. They were asked to search their data using a standard strategy for specific text strings and to provide information on all deaths and side effects. An expert panel blindly classified all possibly suicide-related events into the categories described above. Two-thirds of the pediatric trials involved patients with major depression, whereas the rest studied patients with obsessive-compulsive, generalized anxiety, separation anxiety, or social anxiety disorders. *Importantly, no deaths from suicide were reported in any of the 24 pediatric trials involving 4,582 patients.*[4] An NIMH-sponsored multicenter trial[4] was the only individual study to show a statistically significant risk ratio for "suicidality" associated with drug treatment. Looking at all indications, the risk ratio for "suicidality" was 1.95 (95% CI, 1.28–2.98), suggesting an increase in risk of "suicidality" broadly defined. When the analysis was restricted to just SSRIs for major depression, the confidence interval was still significant but the risk ratio was somewhat diminished (1.66; 95% CI, 1.02–2.68).* There was not a real difference between results for ideation and behavior.

Although the initial focus was on pediatric trials, studies in adults were later analyzed. The aggregate adult data set was much larger, with 99,231 patients in 372 trials.[8] The overall odds ratio for the primary endpoint of "suicidality" was 0.85 (95% CI, 0.71–1.02), suggesting a possible slight protective effect of the drugs, in particular in relationship to suicidal ideation. Further examination of the data by age cohort showed that in young adults (aged 18 to 24 years), the results were close to being statistically significant in terms of increased risk of "suicidality" but lacked power (OR = 1.62, 95% CI, 0.97–2.71); in adults 25 to 65 years, the effect of antidepressants on "suicidality" was neutral; and in patients 65 years and older, the trend was in the other direction (OR = 0.37; 95% CI, 0.18–0.76).[8] In sum, the FDA found a suggestion of an age-related increased risk of "suicidality" related to antidepressant treatment that was statistically significant only in the pediatric/adolescent age group.

In 2006, Hammad and colleagues published the results of the FDA analysis and concluded that the use of antidepressant drugs in pediatric patients appeared to be associated with a modest increase in "risk of suicidality."[4,64] However, they urged caution in the interpretation of their post hoc analysis, given the lack of concordance between "suicidality" reported spontaneously as an adverse event compared with suicide item ratings on clinician-rating scales. The FDA decided to require a black box warning about increased risk of "suicidality" as a possible antidepressant treatment–emergent serious adverse event in pediatric, adolescent, and young adult populations. Assuming that the results and interpretation of the meta-analyses are correct, many questions remain about how and why antidepressants might increase suicidal ideation and behavior in young patients. Is the emergence of suicidal ideation and behavior at the beginning of treatment a result of a delay in treatment efficacy, rather than a side effect of treatment?[65] Risk generally declines after the onset of efficacious psychotherapy or medication treatment, and the time of greatest risk of suicidal behavior is the month prior to commencing treatment.[66] However, the delayed efficacy effect cannot explain the drug/placebo difference in treatment-emergent suicidal ideation and behavior. Alternatively, at the beginning of treatment, adolescents may be more sensitive than adults to adverse activating events such as increased anxiety, restlessness, irritability, anger, and akathisia—all of which may increase the risk of suicidal ideation and behavior.[67] Increased suicidal ideation and behavior could also represent an unrecognized switch into hypomania.

One of the most persistent questions for clinicians about the FDA meta-analysis is the extent to which it can be considered definitive in establishing a cause-and-effect relationship between antidepressant drug use and the emergence of suicidal ideation and/or behavior in younger patients. Association in a meta-analysis does not mean causality,[68]† and data from case-control and other studies would need to confirm the association before more definitive statements of causality can be made. A case-control study of Medicaid beneficiaries from all 50 states who received inpatient treatment for depression compared suicide attempts and suicide deaths in severely depressed children (aged 6–18 years) and adults (19–64 years) treated with any antidepressant (vs controls).[69] The results were consistent with the results of the FDA meta-analyses in adults and in children and adolescents. In contrast to the conclusions of the meta-analysis, autopsy studies of people who have committed suicide rarely have found evidence of recent exposure to SSRI antidepressants. In a study[70] in Utah of 151 teen suicides, only 4 of those who committed suicide had evidence of any psychiatric medication during a toxicology screen. In another study,[16] of 42 teen suicides, none of the individuals were treated with an SSRI during the last 2 weeks

*A subsequent meta-analysis[63] that included 7 additional pediatric trials not covered in the FDA report also found an increased risk of suicidal ideation/attempt associated with antidepressant treatment (RR = 1.8).

†From a regulatory perspective, the observed drug/placebo difference is the "gold standard"; albeit, a major problem with the FDA analysis was the lack of systematic and prospective data collection of the events of interest.

of life. In a third study,[71] an SSRI was detected in only 2 of 58 youths who committed suicide in New York City between 1993 and 1998.

Many reports from different countries have shown an association between SSRI use and *declining* suicide rates.[15,16,72–79] Collectively, global suicide rate reports show wide variation by country.[80,81] In the United States, the suicide rate for men and women aged 15 to 24 rose from the 1950s to the 1990s and then began to fall.[82] Since SSRIs were introduced in the United States in 1988, the subsequent decline in suicide rates in this age group has been attributed by some to the use of antidepressants during this period.[83] In 2004, there was an increase in the adolescent suicide rate,[84] which some researchers attributed to the early indications of FDA safety concerns about antidepressants in young populations that had surfaced in 2003. These concerns may have been associated with a decrease in the prescription of these drugs to children and adolescents[9,10] prior to the addition of the black box warning. Adolescent suicide rates declined in 2005,[85] returning to 2003 levels in 15–19 year olds in 2006 (A. Crosby, MD, MPH; electronic communication of Centers for Disease Control and Prevention data; December 2010).* It is unclear whether the suicide rate decrease in 2005 and 2006 was associated with an increase in antidepressant prescribing to adolescents or with other factors. Among elderly depressed patients, several studies are in agreement with the FDA data that found antidepressants to be protective against suicide in those 65 years and older.[86,87]

Identifying Drug-Related Treatment-Emergent Adverse Events (such as suicide and suicidal ideation/behavior) in the 21st Century

The current paradigm for assessing relative benefits and risks—which relies heavily on the acquisition and integration of information from premarketing studies and from spontaneous postmarketing reports of adverse events—needs to be updated.[88] A review of current practice should involve the recognition that (1) randomized controlled trials (RCTs) that serve as the basis for the approval of new therapies are relatively small, usually short-term, and confined to a highly selected group of patients whose results may not generalize to the broader clinical population; (2) although meta-analyses of data from clinical trials may increase the power to detect a safety problem, the application of this methodology for this purpose is confounded when the adverse event of gravest concern (eg, suicide) does not occur across the clinical trials and/or when the measured effect (eg, suicidal ideation) may bear little predictive power for the rare event in the population of interest (eg, adolescents) and/or (as in the case of suicidal ideation in major depression) may also be associated with the disorder being treated; (3) spontaneous reporting of postmarketing adverse events, in the absence of a large and systematic pharmacoepidemiologic database, is subject to underreporting, bias related to factors such as other unrelated side effects (ie, those receiving active drug may be more likely to have more side effects and communicate more with the clinical team), or erroneous interpretation; and (4) most postmarketing studies are voluntary and difficult to implement to assess treatment-emergent adverse events. While these problems are not new, they have become increasingly important over the last 2 decades with the introduction of new antidepressant, antipsychotic, and mood-stabilizing drugs and the exposure of many more patients to these drugs in primary care and psychiatric practice.

The state of the science related to assessing risk associated with drug use is vastly different than the well-established clinical trials methodology for evaluating benefits, ie, efficacy.[89] Clinical trials are not powered to assess safety related to rare events and are limited by the types of data that spontaneously emerge or are collected in the course of the trials. Although meta-analyses of RCTs are likely to have increased power to detect rare events, they have some of the same limitations as data generated from a single randomized trial, including restrictive study inclusion/exclusion criteria, narrowly focused questions, and limitations on generalizability.[90] To augment safety information, the FDA maintains the Adverse Event Reporting System (AERS) database, a voluntary program that constitutes a passive postmarketing surveillance system. The AERS data on all adverse events offer approximate incidence rates based on sales of the suspect drug in comparison to class-related products. The process has utility when the event is recognizable as drug-related (eg, Stevens-Johnson syndrome), especially if the event appears soon after the drug enters clinical practice. To assess the risk of rare events (such as suicide) or events that can be both drug-related and illness-related (such as suicidal ideation or behavior), the spontaneous and nonsystematic nature of the adverse event reports, coupled with the lack of a well-documented denominator of exposed individuals, limits the validity of the signal detection in the AERS.

Classical epidemiology addresses safety in terms of case-control studies. These studies are ideally suited for rare events, because detailed information on the validity of the definitions of cases and controls is generated with relatively small numbers. Most importantly, this study design permits validation of the temporal sequence of events, ie, that exposure precedes outcome.[91] Newer approaches to the case-control methodology involve a retrospective review of computerized records from large health systems to define a measurable outcome of risk in those defined as exposed to a drug (cases) compared with a comparison group (controls). Controls may be limited to individuals with the same condition, matched on critical correlates, and exposed to an alternative drug therapy.[92]† To obtain adequate statistical power, this model

*Crosby also noted that the suicide rate for 10- to 14-year-olds in 2006 was now below the level in 2003; while the rate for young adults aged 20 to 24 years was slightly higher in 2006 than in 2003. It is unclear whether the decline in prescribing rates for antidepressants was reversed in 2006, or whether other factors accounted for the decline to 2003 levels.

†Obviously, what it lacks is the power of random assignment and blinding. No one suggests that this should substitute for adverse event reporting in clinical trials as a source of information on treatment-emergent adverse events—only that both methodologies should be applied in considering drug safety issues.

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depends on the frequency of the exposure and outcome of interest, as well as the validity and reliability of the measures used to identify both exposure and outcome.

Synthesizing information from multiple data sources including randomized and nonrandomized studies, administrative databases, epidemiologic studies, and health-survey data can provide large amounts of information on many more patients in much broader settings than in a typical RCT. This "cross-design synthesis" approach to drug safety issues integrates results from efficacy, effectiveness, practice, and service-system research, which means combining data not just from different studies but from different kinds of studies.[93] By adjusting for selection and confounding effects,[94] advances in statistical methods can capture the diverse strengths of different study designs while minimizing their weaknesses and enabling a more inclusive synthesis paradigm.[93] This paradigm is consistent with public health approaches that have defined risk of exposure to a variety of environmental toxins, including the relationship between smoking and the full range of negative health outcomes.

Suicidal Ideation and Behavior as Primary Outcome Measures of Efficacy

The present practice of excluding patients who are deemed to be at risk of suicide from clinical trials raises both ethical and scientific issues. A number of studies have demonstrated the ethical and clinical feasibility of including such patients as participants in such studies, if research staff receive appropriate training to minimize risk to the subjects.[29,95] The InterSePT study established the feasibility and importance of clinical trials in patients with schizophrenia and a history of recent suicidal behavior and/or current suicidal ideation.[96] The study was notable for the large sample size (N = 980), the use of independent raters, the inclusion of high-risk patients, the comparison of a presumptively active drug (clozapine) and an active comparator (olanzapine), and the 2-year period of observation. Primary endpoints included suicide attempts, hospitalizations to prevent suicide, and a rating of "much worsening of suicidality." Clozapine-treated patients experienced 25% fewer serious suicide attempts or hospitalizations to prevent imminent suicide ("type 1 events") compared with patients receiving olanzapine. The FDA accepted these data and other data[97] and granted suicide risk reduction as an additional indication for the use of clozapine. A recent epidemiologic study[98] from Finland provided additional support for the efficacy of clozapine in suicide risk reduction for patients with schizophrenia.

Data from informative pharmacoepidemiologic case-control studies can suggest the possible efficacy of specifically marketed drugs for reducing suicide risk in high-risk patients and the potential value of future randomized controlled clinical trials to obtain the additional indication of suicide prevention or risk reduction. Goodwin et al[99] conducted a retrospective cohort study within the Kaiser Permanente system in California and at Group Health of Puget Sound in Washington of 20,638 health plan members age 14 years or older who had at least 1 outpatient diagnosis of bipolar disorder and at least 1 filled prescription for lithium, divalproex, or carbamazepine between January 1994 and December 2001. After adjustment for age, sex, health plan, year of diagnosis, comorbid medical and psychiatric conditions, and concomitant use of other psychotropic drugs, risk of suicide death was 2.7 times higher during treatment with divalproex than during treatment with lithium.* While of interest, this type of design cannot control for confounding by indication; that is, it is possible that clinicians shy away from prescribing lithium (deadly in overdose) to patients they deem to be at risk for suicidal behavior. Several other limitations, such as differences in clinical monitoring and blood level assessment, also confuse matters. Of note, a recently completed NIMH-funded study[101] of bipolar suicide attempters in an RCT of lithium and valproate found no difference between the two conditions in terms of suicide attempts or suicide events even though 35% of the 96 patients randomized had suicide events. Regrettably, no industry or government sponsor has stepped forward to design and implement a prospective study of suicidal behavior, suicidal ideation, or suicide in bipolar patients treated with lithium versus other mood-stabilizing drugs that might or might not lead to an approved FDA indication.

The pharmacoepidemiologic studies and clinical trials demonstrating drug efficacy in reducing suicide risk in patients with schizophrenia and bipolar disorder raise 2 interesting questions: (1) Do drugs that appear to reduce the risk of suicide for patients with one diagnosis (eg, clozapine in patients with schizophrenia) also lower suicidal risk for individuals with other diagnoses? (2) What is the relationship between treatment efficacy and reduction of suicide risk for patients with a specific disorder, if some drugs that are equally effective in relationship to other symptoms differ in their impact on emergent suicidal ideation and behavior? The questions highlight the importance of including patients with recent suicidal behavior and current suicidal ideation in scientifically and ethically sound clinical trials, with reduction in suicidal ideation, behavior, or risk as the primary endpoint. A full summary of recommendations related to the organization and management of such studies is included in the list of consensus recommendations coming out of the conference (see Consensus Findings and Recommendations).

RISK FACTORS AND MODERATING AND MEDIATING VARIABLES

A thorough evaluation of the effects of drugs that are suspected of increasing or decreasing the risk of suicidal

*A more recent study by Smith et al[100] was brought to our attention following the meeting. This paper suggests that anticonvulsants also have a protective effect in terms of suicide in Danish patients purchasing anticonvulsants, lithium, or antipsychotic drugs if they appeared to continue taking their medication. The study did not address psychiatric diagnosis or other covariates.

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ideation, suicidal behavior, and suicide might selectively address other factors associated with increased or decreased risk, as well as possible mediating and moderating variables. Apart from age, gender, and psychiatric diagnosis, these aspects (eg, demographics such as marital status, employment, and ethnicity; family history of suicide; substance abuse/dependence; feelings of hopelessness; "psychic anxiety"; and reasons for living) were not systematically examined in the FDA meta-analysis.* A brief review of some specific moderating and mediating variables and risk factors is given below.

Demographic Factors: Gender, Ethnicity, Occupation, and Relational Status

Reported suicide rates vary greatly among countries and regions[79] and, within countries, by gender,[102,103] occupation,[104,105] ethnicity,[106,107] and relational status. Men account for nearly 80% of all suicides in the United States, but rates of suicide attempts are higher in women.[102] Women choose less violent/lethal methods than men, and they are more likely to ask for help.[102] The higher rates of alcohol and drug abuse/dependence in men may contribute to the higher suicide rate. Unemployment increases suicide risk,[108] and divorce, separation, or widowhood increases risk 4- to 5-fold compared with that of married individuals.[109–111]

Age and Psychopathology

While suicide is the third leading cause of death for young people (aged 15–24 years),[112] it is a rare event. On the other hand, suicidal ideation and behavior are not uncommon among adolescents, and, because ideation in particular is relatively common and suicide is rare in this age group, ideation by itself is not a good indicator of level of suicide risk in this population. Obviously, the level of suicidal ideation must be taken into account in estimating risk. Someone with ideation that involves a wish to die or thoughts of killing oneself but has no plan or intent has a very different risk profile than someone with ideation who has an intent and plan to kill oneself.[21,22] Teen suicide attempts are often impulsive. The interval between a stressor and the onset of suicidal behavior is very brief—minutes, not hours or days. The impulsivity may not be a stable temperamental style, but rather an aspect of an abnormal mental state that takes hold during a suicidal moment. Behavioral contagion is a risk factor for suicide attempts and suicides in this age group. When asked directly about suicidal ideation or behavior, adolescents generally demur, but self-administered questionnaires, on either paper or computer, may be more successful in obtaining this information.[113,114]

Psychological autopsy studies of teenagers in the United States found that between 82% and 95% of individuals who committed suicide had a psychiatric disorder compared with between 23% and 48% of controls.[115–117]† The most common diagnoses were depression, antisocial personality disorder, substance abuse, and anxiety. Teenage females who commit suicide principally suffer from major depressive disorder, while male teens who commit suicide usually also have a previous history of antisocial behavior, conduct disorder, or substance abuse.[116,117] Substance use disorders are particularly common in adolescent and young adult suicides.[121–124] Combinations of disorders, such as depression and generalized anxiety disorder or depression and oppositional defiant disorder, increase the risk of suicide attempts in these age cohorts.[125,126]

In general, suicide rates are higher among adults 65 years and older than among any other age group.[127,128] Suicidal behavior is not usually impulsive in this age group, and suicidal ideation is one of the best predictors of suicide. Persistent suicidal ideation following a suicide attempt in the elderly is a very serious risk factor for suicide. Nonlethal suicide attempts are unusual in older patients.[128,129] In the recent IMPACT study, hopelessness was the leading predictor of late-life suicide.[87] Other prominent symptoms that may correlate with suicidal ideation and suicide in the elderly are persistent insomnia, weight loss, and hypochondriasis.[130,131] As is true in other age groups, the vast majority of older people who commit suicide are suffering from a diagnosable disorder at the time of death, especially major depression,[132–134] but also alcohol abuse/dependence and/or the presence of a narcissistic personality disorder.[135–137] Social factors, such as the loss of an intimate partner or friend and/or family discord, may be an additional risk factor in these individuals.[135,138] Late-life suicide can also be associated with serious, chronic, and painful medical illness, as well as the prospect of serious disability related to cardiopulmonary or cerebrovascular disorders.[135,139] Emerging dementia and a decline in cognition increase risk of suicide, but advanced dementia may be protective. Suicide rates in dementia patients are highest just after a diagnosis is made.[140,141]

Some of the conference participants believe that there is a consensus in the field that patients with severe major depression appear to present the greatest suicide risk[142–145]; others argued that bipolar disorder is associated with a greater risk of suicide.[146–151] Some of the participants believe that the lethality of depression is directly related to the severity of the illness, but others believe that this is controversial. Clinical predictors of suicide completion in patients with major depressive disorder include—in addition to comorbidity with substance use disorders—comorbidity with cluster B disorders, particularly borderline and antisocial personality disorders.[152,153] Symptoms more commonly present among depressed suicides compared with depressed controls include "psychic anxiety," insomnia, alcohol abuse, loss of interest or pleasure, weight or appetite loss, feelings of worthlessness or inappropriate guilt, and recurrent thoughts of death or

*From a regulatory perspective, these factors should be balanced between drug- and placebo-treated patients if true randomization has occurred across trials and sites. Because these variables can influence suicidal ideation, behavior, and risk, a determination of the balance of these factors across treatment groups should be a consideration in future studies.

†This is also true across all age groups.[118] Data from psychological autopsy studies indicate that approximately 90% of those who kill themselves are suffering from a major psychiatric disorder.[119,120]

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suicidal ideation.[154–156] Depressed patients with these specific symptoms who have a plan or have made preparations for a serious suicide attempt or have a recent history of hospitalization for depression are at particularly high acute risk of suicide.[157,158] Most suicides among those with a history of major depressive disorder occurred during their first depressive episode.[159] Similarly, suicidal acts in patients with major affective disorders are most frequent in the first year after onset of illness and decline in frequency over time, although there is a slight increase in suicidal behavior after patients have been ill for 25 years or longer.[159] Patients with polydrug abuse/dependence, schizophrenia, bipolar disorder, and alcohol abuse/dependence also have an elevated risk of suicide.[160] Primary or comorbid alcohol abuse or dependence is present in 25% to 50% of suicides.[161–163] A personal history of previous suicide attempts increases the risk of suicide 38-fold.[117] In one study, 25% of previous attempters made a second attempt, and 12% eventually died by suicide.[164]

Family History

Family history of suicide increases the risk of suicidal behavior 4- to 10-fold,[165,166] and familial transmission of suicidal behavior is independent of aggregation of psychopathology.[167–170] Recent studies also suggest that familial transmission of suicidal behavior is mediated by impulsive-aggressive behaviors.[171] Patients with a family history of suicide are more likely to attempt to kill themselves with more lethal methods.[172] A history of domestic abuse increases the risk of suicidal behavior 4- to 8-fold,[173,174] while a history of childhood physical or sexual abuse increases the risk up to 10-fold.[13,175,176]

Genetics

Using genes to predict medication responses, including side effects, is part of the rapidly growing field of pharmacogenetics. The methodology has some potential to predict individual responses to antidepressant and other psychotropic medications, and specifically treatment-emergent suicidal ideation and suicidal behavior and the efficacy of medications in reducing suicidal risk. Predictive genetic variation can be studied in candidate genes or using genome-wide screens to detect associations with good and bad outcomes. Extensive information on studies investigating genetic variation in suicidal behavior may be found in the Suicidal Behaviors: Genetic Association Studies Database.[177] Among the many associations conducted, genetic variants have been linked and/or associated with suicide independently of major depression.[178–183] Studies have identified some gene variants related to suicidal ideation in clinical treatment trials of SSRIs,[184–186] but none of these seem related to the genes expected to be primarily associated with suicidal behavior.

Consensus Findings and Recommendations

On the basis of a review of the history and current state of research on suicide and suicidal ideation and behavior, conference participants developed a set of recommendations to guide future research and practice. While meta-analysis of data from efficacy trials that were conducted before drug approval constitute one important source of information, the FDA should use its new postmarketing surveillance powers to access pharmacoepidemiologic databases from the United States and abroad to advance the type of cross-design synthesis that can more clearly delineate drug safety regarding suicide-associated risk. Although the meta-analyses conducted by the Agency clearly seemed to show age-related differences in risk of suicidal ideation and behavior, it is critical for the FDA's public health mission (and for clinical practice) to obtain a more granular definition of risk in this population through case-control studies and targeted clinical research studies that may delineate a possible causal pathway (eg, differential side effect profiles by age). This tripartite approach is consistent with other successful public health strategies that have led to more precise definitions of risk utilizing research from diverse data streams.[92]

Other recommendations focused on the following areas: definitions, assessment scales, risk factors and moderating and mediating variables, and ethical considerations in clinical trials involving high-risk individuals.

DEFINITIONS

1. *Suicidality* should be abandoned as a term.
2. *Suicidal ideation, suicidal behavior,* and *suicide* are preferable terms; operational definitions for these terms should be formulated and disseminated and should work in translation across languages and cultures.
3. The FDA endorsement of C-CASA offers a uniform standard for defining these terms.
4. Optimal nomenclature should be applied to clinical efficacy studies and the assessment of treatment-emergent suicidal ideation and behavior, population-based case-control studies, and postmarketing drug surveillance. It is not yet clear how the definition of terms in C-CASA will meet this broadly applicable standard.

Assessment Instruments

1. At this juncture, the most important criterion for international clinical trials with relevance to the United States would appear to be how well an instrument conforms to C-CASA. This is not currently a requirement of regulatory authorities outside of the United States. While the FDA has invited other instrument developers to match their assessments to the C-CASA definitions and requirements, the C-SSRS is the only method thus far endorsed by the FDA.

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2. Simplicity of licensing, cross-cultural and multilingual validity and equivalence for international studies, ease of administration by trained nonprofessional raters or computer, specified assessment intervals, and the costs of training and staff time related to the assessment instrument are additional criteria of particular interest to industry sponsors.
3. With respect to all of the available assessment instruments:
    a. Validate or abandon composite scale-derived measures of severity.
    b. Self-administered forms, including IVRS, should be validated against clinician ratings and judgment, and, although patients may be more forthcoming in disclosing information on suicidal ideation or behavior on a self-report instrument than to a live clinician, leaving the determination of intent up to the patient may complicate efforts at matching to C-CASA, which relies on rater assessment. At this juncture, the assessment scale should be clinician-administered, with information furnished by the patient and, wherever possible, augmented by other informants.
    c. It is best to measure suicidal ideation and behavior with different measurement strategies. The measurement of suicidal ideation involves different, but sometimes overlapping, considerations than the measurement of suicidal behavior in efficacy and safety studies. For example:
        i. Suicidal ideation can be assessed as a continuous measure; suicidal behavior is probably best evaluated as a definable endpoint or as a "time to event" measure of efficacy.
        ii. The individual's understanding of intent and potential lethality is important in assessing suicidal behavior.
        iii. Assessment of efficacy with respect to suicidal ideation requires longitudinal measures of improvement, worsening, and no change on measures of severity.
        iv. A Data and Safety Monitoring Board (which should include experts on suicide risk) should be included in efficacy assessments of suicidal behavior across the life cycle.
        v. Use of standard time intervals for the assessment of suicidal ideation is critical. This may vary by study (last day/last week/last month), but it must be consistent across the study.
        vi. Psychometric characteristics may vary by time interval selected, so measurement qualities need to be checked. The interval must be reasonable in terms of memory, or additional variance will be introduced. "Since last visit" is not a standard timeframe.
    d. Key psychometric criteria for treatment studies are validity, severity of ideation, test-retest reliability, sensitivity to change, predictive validity/specificity, and interrater reliability.
    e. Secondary psychometric criteria can be considered, including requirements for training, validity in both safety and efficacy applications, internal consistency, and sensitivity to reading ability (if computer administered).
    f. Semistructured interviews should have good anchor points.
4. Assessment approaches for relative benefits and risks need to be updated by drawing on broader data sources and capitalizing on more modern statistical and epidemiologic tools. Assessment approaches now rely heavily on the acquisition and integration of information from premarketing studies and from spontaneous postmarketing reports of adverse events. A new paradigm needs to be implemented based on new FDA authority to systematically monitor postmarketing events and on the development of a validated instrument for postmarketing surveillance. This should enable the Agency to utilize data from multiple sources including randomized and nonrandomized studies, administrative databases, epidemiologic studies, and US-based and non–US-based pharmacoepidemiologic resources; essentially, large amounts of information on many more patients in much broader settings than in a typical RCT. This broad-based paradigm would be consistent with public health approaches that have defined risk of exposure to a variety of environmental toxins, including the relationship between smoking and the full range of negative health outcomes.
5. Ultimately, the FDA, the clinical research community, and industry will need to obtain a better handle on the costs, risks, and benefits of the broad screening requirement for suicidal ideation, behavior, and risk across all CNS drugs in development; the impact on drug development in this therapeutic area; and the risks of failing to implement the new policy. For example, will the FDA require a therapeutic class–based black box warning on a new drug, with a novel mechanism of action, even if that drug fails to show a signal of increased suicidal ideation, suicidal behavior, or suicide across all premarketing studies?

RISK FACTORS AND MODERATING AND MEDIATING VARIABLES

Risk factors and moderating and mediating variables should be considered selectively in clinical trials. Because suicide assessment instruments by themselves do not necessarily provide a complete assessment of factors that may be associated with suicidal ideation, behavior, and risk, it will be important to consider how these issues may differentially affect these outcomes. These factors and variables include the following:

1. Age and other demographic information (to clarify the relationship between age and treatment-emergent suicidal ideation and behavior).

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2. Specific psychiatric and medical disorders, including substance abuse/dependence (including tobacco smoking).
    a. Psychiatric diagnosis using current criteria of the American Psychiatric Association, including past history and response to previous treatments.
    b. Urine drug screening at baseline and throughout a clinical trial involving patients with a current or recent history of drug abuse/dependence and systematic collection of self and significant other report of quantity/frequency/severity of alcohol use, validated by measures of plasma γ-glutamyl transpeptidase, mean corpuscular volume, and/or other indirect measures of heavy drinking in patients with a current or recent history of alcohol abuse/dependence.
3. Feelings of helplessness and hopelessness and other symptoms associated with suicidal risk in specific groups (such as poor sleep quality in the elderly).
4. Family history of suicidal behaviors, which should take into account the degree of familial loading (which should be used as an indicator of severity of risk) and method (including lethality and intent of the method).
5. Recent stressors related to work or relationship and the presence/absence of social support from friends, family members, coworkers, and/or coreligionists.
6. Blood drug level data or other markers of medication compliance.
7. DNA sampling, which should be included in informed consent protocols. Such sampling should be considered as an important domain for data collection in all clinical trials, and, because of the importance of familiality as a risk factor for suicide, the protocol should enable collection during the course of a clinical trial, including the analysis of deidentified data at a central location, with allowance for analysis long after the conclusion of the trial.

Additional Studies

To address questions about possible moderating or mediating factors that could account for age-related differences in antidepressant treatment–emergent suicidal ideation and behavior, additional hypothesis-testing studies should be encouraged. As an initial step, it would be useful to examine existing large data sets to determine whether younger patients have greater sensitivity to activating side effects, or side effects in general, compared with adults. If differences are identified, it would be useful to track self-report and behavioral measures of treatment-emergent hostility, agitation, and impulsivity during antidepressant clinical trials of adolescents in order to determine a relationship between these measures and the emergence of suicidal ideation and behavior. As a further step, it might be useful to conduct exploratory laboratory studies to determine whether SSRIs and serotonin-norepinephrine reuptake inhibitors produce differential activation in depressed adolescents (compared with depressed adults) utilizing behavioral measures during baseline and drug treatment.

Given the importance that clinical researchers assign to the presence of "psychic anxiety" in their assessment of suicidal risk, it will be important to clearly define the term, to try to differentiate the state from other anxiety states and disorders, to improve methods of assessment, and to determine the optimal frequency of measurement necessary to establish clear linkage to the emergence of suicidal ideation/behavior and risk of suicide. In particular, it is critical for clinicians to know whether failure to reach remission of the anxiety state is associated with a high risk of suicidal behavior. Clinicians will want to know how personality traits and/or a personal past history of child abuse and other potential moderators influence suicide risk in their patients and the risks and benefits of antidepressant drug treatment.

Finally, it is important for the NIMH to continue to invest in focused, hypothesis-testing research to identify potential biologic markers of suicidal behavior and suicide risk through selective brain scan studies, as well as additional research on hypothalamic-pituitary-adrenal axis function[157,187,188] and other potentially promising measures.[189–192]

ETHICAL CONSIDERATIONS IN CLINICAL TRIALS INVOLVING HIGH-RISK INDIVIDUALS

In light of studies that have demonstrated the ethical and clinical feasibility of including patients with suicidal ideation and/or recent suicidal behavior as participants in clinical trials,[80,81,193] it is difficult to argue in favor of the present practice that excludes patients who are deemed to be at risk of suicide from clinical trials, especially because many patients with these symptoms will be receiving these medications (after FDA approval) in the absence of systematic premarketing data on the associated risks and benefits related to suicidal ideation, suicidal behavior, and suicide in such individuals. The outcome of interest (whether a treatment-emergent serious adverse event or evidence of efficacy in a clinical treatment) should be suicide attempt or suicide-related event, such as hospitalization to prevent an attempt. A Data and Safety Monitoring Board should decide whether hospitalizations and/or self-harmful events that occur are events of interest. If patients are kept in the study after a first event, number of events can also be an outcome measure. Sample size will depend on the variables investigated and the characteristics of the sample, but large samples will be necessary given the relatively low frequency of suicidal behavior in clinical trials. This may require prioritization of collaborative strategies among multiple sites, similar to those used for other specialties such as cancer, cardiovascular, or diabetes. Although duration will depend on the base rate of suicidal behavior in the target population, the type of intervention investigated, clinical indications, and other study specific variables, 3 months is the minimum duration needed to be informative about changes in suicide risk, and 6 to 9 months would be preferable in studies of efficacy. Certain pharmacologic interventions may require longer periods of observation than others.

Consensus conference participants agreed with the following general principles regarding the inclusion of patients

with suicidal ideation and/or recent suicidal behavior in clinical trials:

1. Subjects may have evidence of a recent suicide attempt and some suicidal ideation at time of enrollment. Medically unstable patients should not be included.
2. All patients deemed at risk of suicide may not be eligible for participation in RCTs. There may need to be a "cutoff" of severity related to the seriousness and potential lethality of recent suicidal behavior, urgency of suicidal ideation, assessment of intent, and other variables, unless an inpatient lead-in is included, as was done by Oquendo et al.[193]
3. Patients deemed to be at serious and imminent risk to their own life should be excluded, even from studies that include suicidal patients, unless there is an inpatient lead-in phase.[194]
4. Inclusion and exclusion criteria should include an evaluation of risk by a mental health clinician, following initial screening on a scale to assess ideation and recent and past suicidal behavior. Such a well-defined procedure can allow for inclusion of patients with some level of "at risk" status.
5. Each investigator must understand that patients can be discontinued from the study at any time because of perceived imminent risk to self.
6. If suicide-related baseline exclusion criteria occur, the patient should be terminated from the study and offered urgent clinical care.
7. The following elements need to be addressed:
   a. Suicide prevention or risk reduction must be a legitimate outcome variable, not just a safety variable.
   b. Trials should not be placebo controlled, unless it is an add-on design. Comparisons could be to any active treatment, including treatment as usual, medication, or psychotherapy.
   c. Noninferiority studies are required if there are approved drugs with established efficacy in reducing risk of suicide for a disorder (eg, clozapine in schizophrenia).
   d. The consent process needs to inform that suicidal ideation and behavior are either possible treatment-related serious adverse events or targets of treatment and delineate what the limits of confidentiality will be if the patient becomes suicidal. Consent should also explain that if patients wish to withdraw from the study, they will be assessed for acute suicide risk and may be treated clinically.
   e. Staff must be trained in risk assessment and crisis management. The critical threshold for project approval at each site must include a vetted risk management protocol, validated staff training, and appropriate emergency and urgent care resources to implement a high-risk study. The latter includes round-the-clock availability of senior clinicians for evaluation and for hospitalization.
   f. A hierarchy of evidence-based, severity-based interventions should be available.
   g. The proper balance of research assessment and clinical care should be carefully calibrated. Although more frequent contact may suppress events, if both arms have the same frequency of contact, the data will be valid.
   h. Frequency of assessment should be consistent with standard treatment of the underlying condition and the requirements of the experimental treatments being evaluated, with the option of more contact as clinically indicated. More frequent monitoring of ideation, behavior, and intent via telephone or the Internet can be of value, especially in monitoring high risk–related ideation such as "psychic anxiety" and feelings of hopelessness, as well as the emergence of significant stressors and ongoing or emergent drug and alcohol use.
   i. A guide-based protocol for self-assessment and self-management of suicidal ideation should be utilized in clinical trials. One such plan that the consensus conference participants considered favorably, the manualized Safety Plan intervention developed by Stanley and Brown,[194] includes 6 levels of awareness and coping: (1) reduce the potential for use of lethal means, (2) recognize warning signs, (3) employ internal coping strategies without needing to contact another person, (4) socialize with family members or others who may offer support as well as distraction from the crisis, (5) contact family members or friends who may help to resolve a crisis, and (6) contact mental health professionals or agencies.

CONCLUSION

In the past decade, reports of increased "suicidality" associated with antidepressant and other CNS-active medications have made more urgent the need to accurately and consistently define terms associated with suicide, identify patients at risk, and measure the effects of treatment (both positive and negative) on suicidal ideation, behavior, and risk. This consensus statement is a snapshot of where things stand on this issue in 2009–2010. It is a broad review, and many experts from academia, government, and industry participated in its composition and execution, but it is still a document, and things will continue to evolve from here. It is not the last word, just the best that could be distilled from a consensus conference and postmeeting paper preparation by a large, complex group with diverse interests and perspectives. Participants in this consensus development conference agreed that the term *suicidality* is not as clinically useful as more specific terminology (*ideation, behavior, attempts,* and *suicide*) that can be defined more precisely across data sets from clinical trials and pharmacoepidemiology and can be more readily understood by clinicians and the public. Most participants applauded the FDA's effort to promote standard

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definitions and definable expectations for investigators and industry sponsors by endorsing the terminology in C-CASA. Currently, there is no consensus on the value or validity of composite scores of severity on any of the available assessment instruments. Their developers should continue their research to address the most important uncertainties (highlighted in Tables 3 and 4) regarding utility, reliability, and validity of the scales in identifying suicide-associated treatment-emergent effects and/or a signal of efficacy in suicide prevention trials. If the developers seek to gain FDA endorsement, they must meet the C-CASA matching threshold set by the Agency (Table 2). All assessment instruments should include a recommendation that would define the point at which a patient should be referred to an experienced mental health professional for a thorough assessment of suicide risk (eg, intent). No scale can, or should, replace clinical judgment where life-and-death issues are concerned.

The FDA needs to build upon its new authority to systematically monitor postmarketing events by encouraging the development of a validated instrument for postmarketing surveillance of suicidal ideation, behavior, and risk within informative large health care–related databases in the United States and abroad. By utilizing and synthesizing data from multiple sources, the Agency will be in a far stronger position to define drug-related risks and benefits in many more patients in much broader settings than in a typical RCT. This broad-based paradigm would be consistent with its public health mission. Over time, the FDA, industry, and clinical researchers should evaluate the impact of the current Agency requirement that all CNS clinical drug trials must include a C-CASA–compatible screening instrument for assessing and documenting the occurrence of treatment-emergent suicidal ideation and behavior. This evaluation should consider the costs and benefits of the broadly applicable mandate; the relevance of including specific risk, moderating, and mediating variables in the database; and the impact of the mandate and the associated data-gathering requirements on the development of CNS-active compounds and on the health and safety of the public.

Finally, patients at high risk for suicide can safely be included in clinical trials, if proper precautions are followed. They need to be included to enable premarket assessments of the risks and benefits of medications related to suicidal ideation, suicidal behavior, and suicide in such patients. Clinical trials in which suicide is the primary target of treatment will need to be large and of longer duration than the usual 8-week study. Informed consent must explain that suicidal ideation and behavior are the outcome measures, delineate the limits of confidentiality should a patient become suicidal, and describe the assessment and treatment patients will receive if they withdraw from the study. Each research participant should be provided with a suicide prevention plan with steps to follow if they recognize warning signs of imminent suicidal behavior. A balance between research assessment and clinical care can be established such that patients are safe and results are valid.

Drug names: carbamazepine (Carbatrol and others), clozapine (Clozaril, FazaClo, and others), divalproex (Depakote and others), fluoxetine (Prozac and others), lithium (Lithobid and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), valproate (Depacon and others).

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