CNS Clinical Trials: Suicidality and Data Collection: Workshop Summary

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CNS CLINICAL TRIALS

SUICIDALITY AND DATA COLLECTION

WORKSHOP SUMMARY

Sarah Hanson, Miriam Davis, and Bruce Altevogt, *Rapporteurs*

Forum on Neuroscience and Nervous System Disorders

Board on Health Sciences Policy

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Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the report before its release. The review of this report was overseen by **Dr. Charles F. Reynolds.** Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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Introduction[1]

The Institute of Medicine's Forum on Neuroscience and Nervous System Disorders planned and held a public workshop June 16, 2009, that brought together experts from industry, academia, government, and advocacy groups to discuss issues directly related to a recent Food and Drug Administration (FDA) policy that all clinical protocols for products developed in the Division of Psychiatry Products (of the FDA) include a prospective assessment for suicidality.[2] Given the focus of the Forum, participants were charged with examining and discussing currently available data, data analysis, and the future of potential partnerships that will be or are being impacted by this announcement as it relates to clinical trials involving the nervous system. Discussions centered on the critical areas of further examination and analysis needed.

[1] The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop.

[2] The definition of "suicidality" used for the purpose of the workshop is completed suicide, suicide attempt, or preparatory acts toward imminent suicidal behavior. Please refer to Box I-1 and the paragraphs before it for more information.

BACKGROUND ON THE ISSUES

Suicide is a serious, yet tragically underrecognized, public health problem that claims approximately 30,000 lives each year in the United States. Cast in its societal and historical context, the rate of suicide for the past century has been two to three times that of homicide. Worse yet, suicide is one of the foremost causes of death among children and young adults (IOM, 2002). Depression and other mood disorders confer the highest risk of suicide (Fawcett et al., 1991; Goodwin and Jamison, 2007; Harris and Barraclough, 1997). It has been estimated that 35 to 50 percent of depressed children make a suicide attempt, and 2 to 8 percent commit suicide over a 10-year period (Fombonne et al., 2001; Kovacs et al., 1993; Rao et al., 1993; Weissman et al., 1999).

Given the severity of the problem, the public health profession, after decades of effort, has developed successful programs to reduce suicide among high-risk groups (Brown et al., 2005; Guzzetta et al., 2007; Knox et al., 2003; Lauterbach et al., 2008; Rutz et al., 1989, 1992; Szanto et al., 2007). Meanwhile, the public health profession also has wrestled, since 1991, with the controversial possibility that the very medications given to combat depression and other mood disorders paradoxically *may contribute* to the risk of suicide ideation (i.e., suicidal thinking) and suicidality (i.e., suicidal attempts, preparatory behaviors, or suicide completions) in a minority of cases. Researchers and regulators began in earnest to examine the evidence systematically through randomized and controlled trials.

As more data and analysis came to light in 2004, the FDA issued its first set of warnings by calling attention to an increased risk of suicidality among children and adolescents taking antidepressants. The FDA required that labeling of specific antidepressants carry black box warnings, intended to alert physicians and patients to increase monitoring of troubling symptoms. One concern at the time was the surge in antidepressant prescriptions by primary care physicians with insufficient oversight of patients (IOM, 2002). The United Kingdom's drug regulatory agency, the Medicines and Healthcare Products Regulatory Agency (MHRA), used its Committee on Safety of Medicines to explore the issue in 1998 and eventually banned the use of antidepressants[3] for children and adolescents with mild cases of depression. In 2003, the MHRA stated that "on the basis of this review of the available clinical trial data, CSM has advised

[3] All antidepressants were banned in 2003, except for fluoxetine (Prozac), for use in children and adolescents by the Medicines and Healthcare Products Regulatory Agency.

that the balance of risks and benefits for the treatment of major depressive disorder (MDD) in under 18s is judged to be unfavourable for sertraline, citalopram and escitalopram and unassessable for fluvoxamine. Only fluoxetine (Prozac) has been shown in clinical trials to have a favourable balance of risks and benefits for the treatment of MDD in the under 18s" (MHRA, 2003).

At the time of FDA's regulatory actions, in 2004, many public health professionals feared that a black box warning would deter providers from prescribing antidepressants, which in turn could lead to more suicidality from untreated or undertreated depression. One study found a 20 percent reduction in physician prescribing in the United States from 2003 to 2005 and an increase in the youth suicide rate from 2003 to 2004 by 14 percent (Gibbons et al., 2007). New diagnoses of depression by primary care providers were reduced by 44 percent in pediatric populations, based on time series analysis (Libby et al., 2009).

Public health professionals agreed that the rarity of completed suicide presented a daunting methodological challenge: No single randomized clinical trial (RCT) of an antidepressant or any other medication, however well designed, has the power to detect such a rare event as completed suicide. This point was borne out by finding no completed suicides among nearly 4,600 pediatric subjects in clinical trials submitted to the FDA. The suicide rate among children and adolescents, ages 5 to 17 years, is approximately 1.8 per 100,000 (CDC, 2006). Another problem arose from confounding of variables, observed Robert Gibbons, University of Illinois at Chicago and workshop co-chair, who remarked that "depression is related both to suicide and to treatment for depression . . . suicide [also] can lead to treatment, the very same treatments that are suspected of potentially producing suicide." In addition, patients with suicidality are normally excluded from clinical trials. Gibbons questioned if, given all these methodological factors, plus others discussed subsequently, the study population is representative of the general population of patients being treated and whether an association exists that is free of bias and includes adequate control of confounding.

To help overcome methodological hurdles in measuring suicidality in central nervous system clinical trials, one obvious approach is to increase the number of patients under study by pooling each study's findings. Yet pooling is most methodologically rigorous when the outcome measures across studies are standardized, which was not the case—studies had varying definitions of outcome measures. Affirming the depth of the problem of measuring and tracking suicidality poses a significant challenge, given the low sample sizes and methodological

problems in pooling patients together, said William Potter of Merck Research Laboratories, co-chair of the workshop. He stressed that quality control, standardized measures, and training are essential for pooling studies. Age group is also a crucial issue. Studies in adults may be inapplicable to children and adolescents, who often manifest or express symptoms of a psychiatric disorder in ways that diverge from adults. Thus, diagnosis itself may be problematic.

Common definitions of suicidality are essential in clinical practice and in defining outcome measures in clinical trials, Potter commented. Referring simply to "suicidality" can become complicated because different researchers may exclude various behaviors in the definition. The FDA uses C-CASA (the Columbia Classification Algorithm for Suicide Assessment) terms to define "suicidality" as attempt or completion as well as thinking about suicide (suicidal ideation), or preparatory acts toward imminent suicidal behavior if intent is to die (Posner et al., 2007). Others exclude ideation, thereby defining suicidality more restrictively as an attempt, preparatory acts toward imminent suicidal behavior, or completion.

The following definition was used for the purpose of the workshop for consistency (Box I-1). One practical reason for excluding suicidal ideation in the definition of suicidality was that one of the key goals of the workshop was to determine whether suicidal ideation has predictive power as a surrogate measure for suicidality. When a speaker uses a different definition of suicidality, it is noted in the text.

BOX I-1
Definition of Terms Used During Workshop

Suicidal ideation refers to thoughts of suicide.

Suicidality, for the purpose of this workshop, refers to completed suicide, suicide attempt, or preparatory acts toward imminent suicidal behavior.

ABOUT THE FORUM AND WORKSHOP

As background, the Forum was expressly created by the IOM to bring together the public and private sectors, among other stakeholders, to discuss topics of critical and overarching importance, particularly ones that stimulate partnerships to accelerate understanding and treatment of nervous system disorders. The Forum has been convening stakeholders, sponsoring workshops, and producing short-turnaround workshop summaries since its inception in 2006. This summary of the workshop on measuring suicidality during clinical trials, which was held on June 16, 2009, offers guidance and insights from participants at the workshop. In accordance with IOM policy, the workshop is designed to seek different views but preclude participants from making explicit recommendations or reaching consensus.

The Forum planned and held the public workshop to identify effective methods to predict suicidality, in the near term,[4] during the conduct of clinical trials (seen Appendix B for full workshop agenda). Speakers and attendees included experts from industry, academia, government, and/or advocacy groups. They were asked to present data and stimulate discussion about the goals set by the steering committee as listed in Box I-2.

BOX I-2
Workshop Goals for "CNS Clinical Trials: Suicidality and Data Collection"

The overall purpose of the workshop on central nervous system (CNS) clinical trials is to examine what methods are best used to determine treatment-emergent suicidal behavior during the conduct of clinical trials. More specifically, attendees were asked to:

- Review available data on the extent to which emergent suicidal ideation predicts the occurrence, in the short term, of actual suicidal behavior;
- Identify promising methods of analysis to address whether suicidal ideation predicts the short-term occurrence of actual suicidal behavior; and
- Examine potential partnerships between the Food and Drug Administration, pharmaceutical industry, academia, and the National Institutes of Health that could be used to facilitate data sharing from randomized clinical trials.

[4] "Near term" in this context refers to 4 to 16 weeks, a typical duration of a clinical trial.

An important set of discussions grew from the workshop goals and was heavily emphasized at the meeting. Participants reviewed the classification instrument known as C-SSRS, the Columbia Suicide Severity Rating Scale, which does not have as its purpose the prediction of future suicide attempts or completed suicides but rather is used to systematically detect, or ascertain the occurrence of, and document events of suicidality as defined by C-CASA, which is discussed in Chapter 1. This subtly distinct focus allowed participants to emphasize the importance of capturing suicidal occurrence and non-suicidal occurrence. Elaborating on the specific goal of predicting suicidality, however, Gibbons asked whether suicidal ideation is an appropriate surrogate endpoint for suicidal behaviors and completion. "What information do we need," he asked, " . . . to determine whether or not suicidal thoughts, which are so ubiquitous among depressed people, are in fact good predictors of suicidal behavior and completion?"

Given the nature of the subject, it is important to remind readers that this workshop summary is a record of what occurred at the workshop. Many important discussions are needed in order to fully explore the statement of task, and while many of these issues were brought up and discussed, there are also a number that were not. This summary is by no means a complete review of the extent to which emergent suicidal ideation may or may not predict the occurrence of suicidal behavior. What is contained in this summary is a review of the presentations and discussions that took place during the workshop.

1

Perspectives from the FDA, Academia, and Patients

FDA PERSPECTIVE

Thomas Laughren, director of the Food and Drug Administration's (FDA's) Division of Psychiatry Products, explained the FDA's current policies and recommendations surrounding the relationship between suicidal ideation and suicidal behaviors and use of antidepressants. Laughren's presentation addressed the methodology and main findings of his division's meta-analysis of proprietary clinical trial data dealing with antidepressants and suicidality. His presentation also covered what Laughren characterized as the FDA's "evolving" policy on a requirement to assess suicidality prospectively in future clinical trials for *all* new psychiatric drugs. The details of that policy are due out in the form of a guidance document, which has not yet been released.

Acting on troubling case reports and some systematic data, the FDA issued a warning about suicidal risk and antidepressants in children. In 2004 the FDA required the addition of a "black box" warning on antidepressants regarding suicide risk to children and adolescents (see the Introduction for more information). Warnings of this kind do not preclude clinicians from prescribing antidepressants to these groups of patients, but they alert clinicians to monitor these patients more closely for signs of clinical worsening, suicidality, or unusual changes in

behavior. The FDA recognized the importance of a strong evidence base from randomized clinical trials (RCTs) on which to make policy. The FDA worked with researchers at Columbia University to develop an algorithm for classifying suicidality events from case narratives in previous clinical trials. The classification tool that emerged, with the assistance of Kelly Posner of Columbia University, was C-CASA, the Columbia Classification Algorithm for Suicide Assessment (Box 1-1). Four of the algorithm's major categories served, for the purpose of the meta-analysis, as primary outcome measures: completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, and suicidal ideation. The FDA sought to collect and further analyze additional data beyond what drug sponsors previously submitted to them from clinical trials. The FDA's solicitation covered all psychiatric drugs and all psychiatric indications. The FDA made a specific request for the case narratives, which would enhance the FDAs capacity to reclassify and pool the data into a meta-analysis, and used these C-CASA categories to classify trial-level and patient-level data that it required drug sponsors to submit.

BOX 1-1
C-CASA Domains

- Suicidal ideation
  - Passive (wish to be dead)
  - Active (four levels)
    - Non-specific (no method, intent, or plan)
    - Method, but no intent or plan
    - Method and intent, but no plan
    - Method, intent, and plan
- Suicidal behavior
  - Actual attempt (including completed suicide)
  - Preparatory actions toward imminent suicidal behavior
    - Interrupted
    - Aborted
    - Preparatory acts or behaviors
- Non-suicidal, self-injurious behavior

SOURCE: Laughren, 2009.

C-CASA domains were used to classify case narratives of more than 300 double blind, placebo-controlled RCTs involving 4,600 children and adolescents and more than 77,000 adults. It became clear, said Laughren, that the dataset was unlikely to be a direct source of evidence for the risk of *completed* suicide. The reason was the dearth of completed suicides. In the pediatric dataset (<18 years of age), there were no suicides. Among adults, there were a total of eight suicides. "[D]o these meta-analyses tell us anything about completed suicide? . . . The answer is no," said Laughren emphatically. However, Gail Griffith, patient representative to the FDA Psychopharmacological Drugs Advisory Committee, felt that the media, practitioners, and the public focused heavily on the risks despite the documented benefits of psychiatric drug treatments, leading to increased suspicion and alarm.

There are two main findings of the meta-analysis, according to the data in Laughren's presentation. First, the risk of suicidality is strongest among children and adolescents taking antidepressants versus placebo, OR = 2.2 (95% CI 1.4–3.6), followed by young adults (ages 18–24), OR = 1.55 (95% CI 0.91–2.7) and the risk appears to go down with age (e.g., ages 25–30, OR = 1.00; ages 31–64, OR = 0.77; ages 65+, OR = 0.39) (Figure 1-1). Second, the risk of suicidality is stronger for non-depressed psychiatric patients as compared to depressed ones. The last finding led the FDA to conclude that anyone treated with an antidepressant, *regardless of diagnosis,* is at risk for suicidality—not just depressed patients. The reasons behind the epidemiological associations are unknown. As more data came to light, the FDA revised its black box warnings, with the most recent changes occurring in 2007. It extended the age range to cover young adults and the diagnosis to cover any psychiatric disorder (Box 1-2).

Laughren addressed concerns about ascertainment bias (non-random sampling of patients) being responsible for erroneous results. Critics have raised two major arguments for ascertainment bias. One is that patients who take antidepressants are more likely to be less symptomatic and more talkative due to effective treatment than patients receiving placebo, and thus more likely to disclose their suicidality. The other is that suicidality is more likely to be detected because patients taking antidepressants, in contrast to patients taking placebo, might have other adverse events from the medication, which in turn might provoke more reporting of suicidal thoughts and behaviors. Laughren pointed out that even if patients were more talkative, that would not explain the age-relatedness of

BOX 1-2
Suicidality Black Box Warning Required by the Food and Drug Administration for Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Insert established name] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. *Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.*

SOURCE: FDA, 2007.

the finding because expressivity would act uniformly across age groups. Similarly, if ascertainment bias was responsible, he asked how the presence of treatment-emergent adverse events could explain the age-relatedness of the finding. Furthermore, how would ascertainment bias explain the other finding that the relationship is stronger in non-depressed psychiatric patients, usually those with anxiety disorders, rather than in depressed patients? How could ascertainment bias explain yet another finding that suicidality is stronger for behavior than for ideation? While recognizing legitimate disagreement over the FDA's findings, Laughren pointed out that a case-control study found that young adults (<19 years old) receiving antidepressant treatment were more likely to make a suicide attempt or completion than adults ages 19 or older (Olfson et al., 2006).

Finally, Laughren was unambiguous about the low predictive value of suicidal ideation as a surrogate endpoint for suicidality. The relationship between antidepressant use and suicidality was far stronger for suicidal behavior than for ideation, persuading him to conclude, "I think in subsequent meta-analyses we probably won't be looking at that broad endpoint [ideation]." Regarding the use of excluding suicidal patients from clinical trials, Laughren responded, "We do need to expand into more complicated, sicker patients. I think we will learn a lot more if we do that."

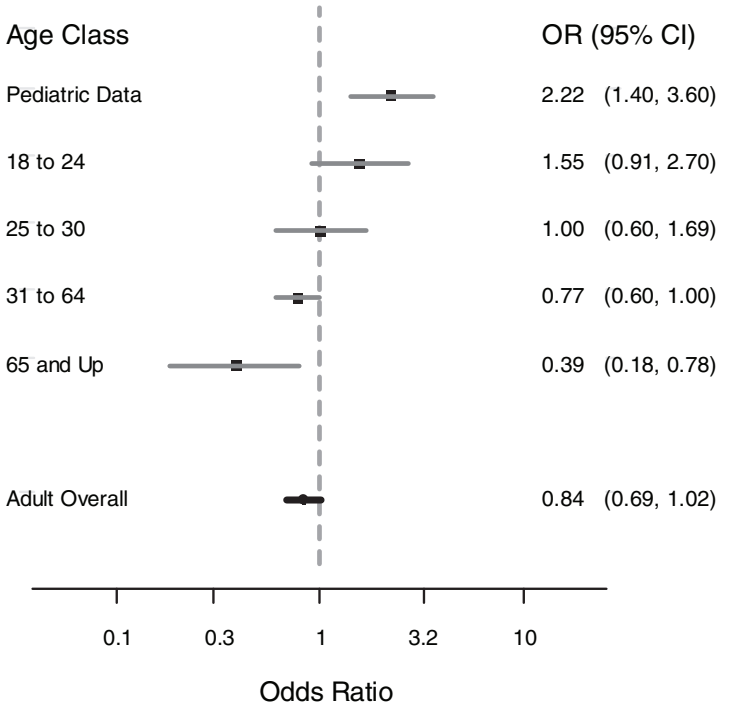

FIGURE 1-1 Suicidal behavior and ideation psychiatric indications, odds ratio.
NOTE: CI = confidence interval, OR = odds ratio.
SOURCES: Adapted from Hammad et al., 2006, and Stone et al., 2009.

PERSPECTIVE ON METHODOLOGY DEVELOPMENT AND IMPLEMENTATION

The development of C-CASA and C-SSRS, an instrument for use prospectively in RCTs intended to systematically ascertain and document the occurrence of events defined by C-CASA as suicidality events, was addressed by Kelly Posner of Columbia University, who worked closely with the FDA to analyze and classify its data. She opened her presentation with the observation that psychiatry as a field possesses neither the clarity on how to define suicidal occurrences nor the accompanying terminology, standardization, and training from which clarity would flow. Lack of clarity has tremendous implications because it limits confidence in epidemiological statistics, which can miss signals or amplify false signals.

Furthermore, clinical descriptions and patient management and treatment are also jeopardized.

Her team at Columbia University developed the classification and rating system C-CASA to overcome these problems for the purpose of distinguishing suicidal from non-suicidal events. C-CASA provides a common language to classify suicidality data derived from retrospective examination of clinical trials submitted to the FDA (Figure 1-2). It includes a set of operationalized guidelines to infer suicidal intent. C-CASA was found to have strong interrater reliability (Posner et al., 2007). The FDA recommends the use of a similar instrument in antidepressant clinical trials and many other trials for central nervous system disorders. The application of C-CASA to the FDA datasets revealed that a striking one-third of suicidality classifications from drug sponsors were misclassified, Posner noted. But she also acknowledged that C-CASA has its own limitations, especially from ascertainment bias. This bias might have occurred as a result of receiving an antidepressant versus a placebo because sometimes patients who are on a medication are more likely to report side effects of any kind. That gives the medication recipients more opportunities to report any adverse event, including a suicidal occurrence, said Posner.

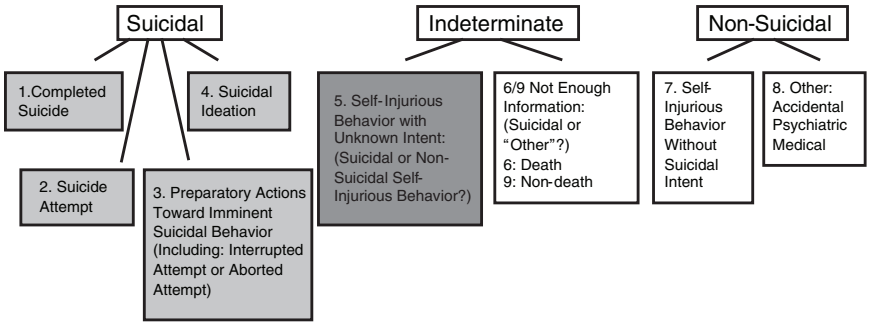

FIGURE 1-2 C-CASA classification scheme.
NOTE: Light gray boxes are Food and Drug Administration (FDA) "primary analysis" (includes events deemed suicidal); light and dark gray boxes are FDA "sensitivity analysis" (includes any event that could possibly be suicidal).
SOURCE: Posner, 2009.

C-CASA is the retrospective counterpart of the more detailed classification instrument C-SSRS. The C-SSRS tool was first developed for a prospective national study of treatment for adolescent suicide attempts. C-SSRS was developed by reliance on evidence stemming from two decades of research, noted Posner. It contains a 1-to-5 rating scale for suicidal ideation of increasing severity (from a "wish list to die" to an "active thought of killing oneself with plan and intent"), in contrast to C-CASA, which only has one ideation item. Further details are shown in Figure 1-3. Having been used in hundreds of studies worldwide, C-SSRS has long-standing feasibility.

C-SSRS has been translated into more than 90 languages, typically taking only a few minutes to administer. Psychiatric professionals are trained on this tool via a web-based DVD and more sophisticated means. It is used by national and international agencies, including the World Health Organization, Japanese National Institute, Centers for Disease Control and Prevention, and other Public Health Service agencies, as well as in primary care and schools and on college campuses, Posner said.

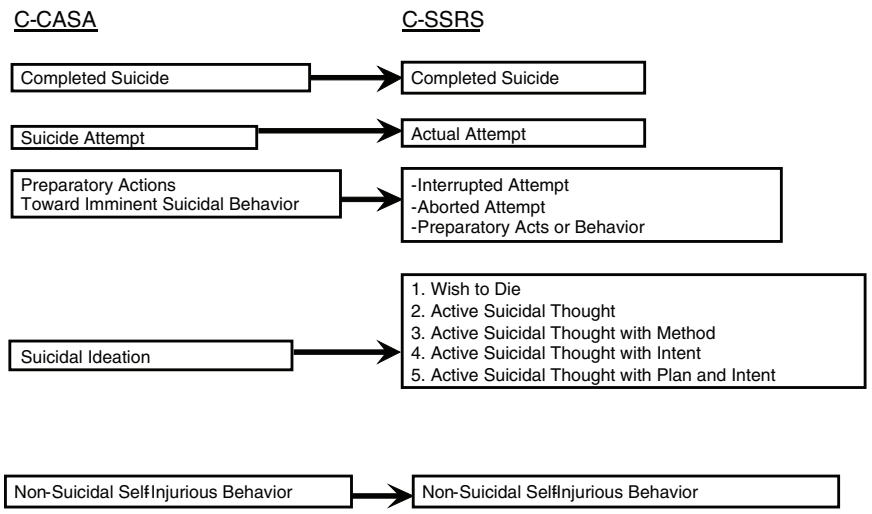

FIGURE 1-3 C-SSRS prospective C-CASA.
SOURCE: Posner, 2009.

PERSPECTIVE OF PATIENTS AND FAMILIES

As an informed parent and as patient representative to the FDA Psychopharmacological Drugs Advisory Committee, Gail Griffith offered her perspective. Feeling that her family was at the "nexus of the debate," she described her high school–aged son's initial response to antidepressants. Just as he began to feel well, he wrote four suicide notes and attempted suicide. Fortunately, his near-fatal attempt did not succeed, and he made a full recovery. The experience initially inspired Griffith to provide vigorous support in 2004 to an FDA-imposed black box warning. Yet, as she read more of the national news, she became troubled about misunderstanding by the media, which blurred the important distinctions among suicidal ideation, behaviors, and completed suicide. The media, in her opinion, unduly alarmed the public. Yet she still thought that the black box warning minimized the "somewhat cavalier approach we had seen in [physician] prescribing." As the FDA attempted to clarify and make transparent its concern about a possible relationship between antidepressants and suicidality, she believed the anxious public was so suspicious of psychiatry and psychiatric drugs that it was far more inclined to exaggerate the risks and ignore the potential benefits. At that point, she reached the conclusion that the black box warning "constituted a real setback in my mind for treatment and for the field of mental health."

In retrospect, Griffith said she regretted her support in 2004 in favor of the initial black box warning, despite the possible link between suicidality and antidepressants. Among her reasons was the difficulty of evaluating the risks versus benefits with respect to psychiatric drugs. She noted that mental illness is "treated as a suspect claim," carrying less legitimacy than does physical illness. The public, in her view, emphasized the risks and ignored the benefits around the time of the black box warning. More fundamentally, she asserted, our society does not know how to begin to engage in public discourse about suicidal thoughts and actions, much less completed suicide.

In contrast, she pointed to the way the epilepsy community tackled the possibility of a relationship between antiepileptic drugs and suicidality. An FDA meta-analysis found that antiepileptic drugs also were associated with increased suicidality (FDA, 2007). The epilepsy advocacy community, which she said garners far more legitimacy than the psychiatric community, argued that the treatments have great benefits. The possibility of undertreatment or treatment avoidance carried greater risks than did suicidal thoughts and actions, in that group's view. Being

squarely against a black box warning, epilepsy advocates succeeded in convincing the FDA not to proceed with one. Griffith said she believes that "until psychiatric illnesses are treated like physical illnesses, then all the efforts to end distortions and misperceptions about psychiatric medication benefits are for naught."

2

Data Collection and Optimization

NEW APPROACHES TO STUDYING THE PREDICTIVE POWER OF SUICIDAL IDEATION FOR SUICIDALITY

The relationship between suicidal ideation and behavior (e.g., attempts or completions) was the focus of several presentations. The first was by Matthew Nock of Harvard University, who spoke about his epidemiological findings. Similar to the clinical trial data presented by Thomas Laughren, Nock's epidemiological findings revealed that suicide ideation is not a strong predictor of a suicide attempt (Nock et al., 2009a). Still, most of those who make a suicide attempt do express ideation ahead of time. His presentation covered new methodologies to obtain greater specificity about the relationship between ideation and suicidality.

The types of studies Nock reported are epidemiological cohort studies, usually of previous ideation and attempts, and psychological autopsies for completed suicides. The latter analyze the cause(s) of death by examining the body *and* the circumstances that led or contributed to death. Such studies contain a set of structured questions, administered in face-to-face interviews of close friends and family, to infer the decedent's intent, risk factors, and related contributors. Psychological autopsy studies have found frequent expression of suicidal thoughts before completed suicide. Overall, about 50 to 66 percent of people who complete

suicide disclose their ideation or intent to those around them, according to one meta-analysis (Cavanagh et al., 2003). These studies have one critical limitation, however: The definitions of ideation and intent vary, leading to variations in prevalence. One of the most recent and thorough review articles found that 75 percent of those who subsequently die by suicide visited their primary care provider in the last year of life and 45 percent in the last month (Luoma et al., 2002).

An easy conclusion from these findings is that more attention should be given to suicidal ideation and threats. However, the major problem is that expressions of ideation or threats are highly common. A large, nationally representative survey of U.S. adults found that 15 percent of them report seriously considering suicide at some point in their life (Nock et al., 2009a). Approximately one-third of those who think about suicide at some point in their life later make a suicide attempt. Narrowing the time frame to the past 12 months, 15 percent of ideators proceed to make a suicide attempt (Nock et al., 2009a). What these findings suggest is that it is exceedingly difficult to identify from the large number of ideators the small percentage of those who will progress to a suicide attempt. While suicide has general risk factors, as well as chronic versus short-term risk factors, no combinations of risk factors currently have sufficient sensitivity and specificity to predict who among the groups at risk will make an attempt or completion, under what circumstances, and at what time (Goodwin and Jamison, 2007).

One surprising finding mentioned by Nock was that depressed people with suicidal ideation, although a risk group, were not the leading group at risk for progression to a suicide attempt. Ideators with anxiety disorders and disorders of impulse control, such as conduct disorder and posttraumatic stress disorder, exceeded depression in their predictive power for making suicide attempts, according to a large, nationally representative epidemiology study of U.S. adults, the National Comorbidity Survey Replication (Nock et al., 2009a, 2009b). Having an anxiety disorder is an independent risk factor for suicidal ideation and suicide attempts. Anxiety and mood disorders, when comorbid, heighten the risk as compared with a mood disorder alone, according to a prospective, population-based study of adults in the Netherlands (Sareen et al., 2005).

Two new alternatives to the general measure "suicidal ideation" show promise: real-time, electronic monitoring systems of suicidal thinking and behavior at different time points, and a new psychometric measure asking patients to rate suicidal intention "at its worst point in time."

REAL-TIME ELECTRONIC MONITORING SYSTEMS

Given the poor predictive power of current measures of suicidal ideation, it would be tempting to conclude that suicidal ideation should be discarded in favor of more robust measures. Instead, new techniques are being harnessed to study ideation and to understand the transition from ideation to suicidal behavior, especially with new methods investigated prospectively.

One novel methodological approach borrows techniques from the social sciences. It uses methods that do not rely on verbal and retrospective self-report, relying instead on systematic weekly monitoring of ideation, said Nock. The key is to collect data closer to these events using real-time methods and/or patients' daily assessment of self-injurious thoughts and behaviors. This methodology draws from a concept known as ecological momentary assessment, a collective term referring to detailed investigation of several mental health features in real-time, such as affect, mood, and interpersonal behavior. A study participant could be asked to report on these features around the same time that the experience occurs (Moskowitz and Young, 2006).

Nock reported on a preliminary study giving electronic diaries or Palm Pilots to a small sample of 30 adolescents. Over a period of 2 weeks, the subjects were asked to record evidence of self-injurious thoughts and behaviors. For example, the subjects recorded 100 episodes of non-suicidal, self-injurious behavior, such as cutting and burning, and 26 episodes of suicide ideation. Furthermore, these methods offer collection of data on the intensity, duration, and triggers of each episode. While Nock did not propose that every clinical trial collect such detailed measurements, he would like to see the methods used to understand the emergence of suicidal behaviors from suicidal ideation. One practical study, he noted, would be to equip adolescents with electronic diaries that beeped once or twice daily, prompting them to answer a range of questions about adverse effects, mood, and other data. The detailed information the subjects provide might shed light on the emergence of ideation over time.

Simply put, Nock noted, these new techniques offer the virtues of being prospective, being recorded near the time of each suicidal event, and being more informative about the meaning and severity of ideation. With that information, it may be possible to determine those features of suicidal ideation with better predictive power for suicidality.

THE PREDICTIVE VALIDITY OF SUICIDE IDEATION AT ITS WORST POINT IN TIME FOR SUICIDE ATTEMPTS

Evaluating the predictive validity of existing measures of suicide ideation was the focus of a presentation by Gregory Brown of the University of Pennsylvania. He and his colleagues sought to evaluate measure(s) of ideation for predicting suicide behavior and completed suicide with high sensitivity and specificity. Analyses relied on data from epidemiological studies and clinical trials. The investigators defined ideation as including suicide intent, the urge to kill oneself, or a specific plan to kill oneself.

Of several commonly used psychometric scales of suicide ideation in clinical trials, Brown's team began with the 20-year-old Scale of Suicide Ideation (SSI-C), a scale for measuring the severity or intensity of suicide ideation. The scale has excellent internal reliability, interrater reliability, current validity, and long-term predictive validity for completed suicide, noted Brown. The SSI-C is a 21-item, interviewer-administered rating scale that measures the current intensity of patients' specific attitudes, behaviors, and plans to commit suicide on the day of the interview. The ratings for the first 19 items are summed to yield a total score, ranging from 0 to 38. The SSI-C consists of five screening items. Three items assess the wish to live or the wish to die and two items assess the desire to attempt suicide. If the respondent reports any active or passive desire to commit suicide, then 14 additional items are administered. Individual items assess suicidal risk factors such as the duration and frequency of ideation, sense of control over making an attempt, number of deterrents, and amount of actual preparation for a contemplated attempt. Two additional items record incidence and frequency of previous suicide attempts. However, the SSI-C does not measure *previous* suicide ideation "at its worst point in the patient's life," which is the subject of a separate scale (SSI-W) (Beck et al., 1997, 1999).

Studying nearly 4,000 psychiatric outpatients, Beck and collaborators found that the SSI-W had the strongest odds ratio for outpatients later completing suicide, nearly 14 times higher (OR = 13.84, CI, 5.6–34) than for outpatients who subsequently did not complete suicide, using the National Death Index to verify deaths of subjects in the sample (Beck et al., 1999). The SSI-W surpassed the odds ratios for the SSI-C and the Beck Hopelessness Scale. To determine optimal cutoff points for maximizing the sensitivity and specificity of the SSI-W, Beck and colleagues compared its score against completed suicide by examining the Receiver Operating Characteristics (ROC) curves. The ROC is a graphical plot

that measures true positives versus false positives using a particular cut-off score. The results led the investigators to conclude that suicide ideation at its worst point identified a subset of patients at relatively high risk for completed suicide with high sensitivity and specificity. The mean time to completed suicide was about 4 years after participation in the study.

The investigators, seeking to evaluate the predictive validity of the SSI-C over a short-term period, studied individuals who had attempted suicide because this group has a high risk for subsequent attempts. Brown and his colleagues analyzed findings from their previously published clinical trial of a cognitive therapy intervention among suicide attempters seen at an emergency department (Brown et al., 2005). Because a high number of reattempters were found among the study group, the investigators were able to examine the short-term predictive capacity of current ideation versus ideation at its worst point. Participants in the study were evaluated at several follow-up visits (1 month, 3 months, 6 months, 1 year, and 18 months) and assessed for both current ideation and worst point ideation since the previous follow-up visit. Brown and collaborators found that the predictive validity of the SSI for current ideation on subsequent suicide attempts was poor. However, they also found that high scores on the SSI at the worst point in time since the participant's previous visit was a significant predictor of a repeat suicide attempt recorded at the 3-month visit. The investigators concluded that suicide ideation at its worst point was a significant predictor of a subsequent attempt over the near term and a better indicator for short-term risk than current ideation.

Regarding the broader question of current ideation over the course of a randomized clinical trial (RCT), several discussants expressed skepticism about its value as a predictor of suicidality. Robert Gibbons recommended another way to examine the nearly 400 RCTs analyzed by the Food and Drug Administration. He suggested examining the weekly Hamilton Depression Rating Scale—in particular, item 3 focusing on the *degree* of suicidal ideation and planning according to four levels of severity—plus overall Hamilton weekly ratings to determine treatment responsiveness and suicide attempts. That type of analysis would be more likely to improve suicidality measures, he remarked. He and Charles Beasley of Eli Lilly are conducting a reanalysis of the RCT data to determine whether this approach improves suicidal ideation as a predictor of suicidality.

NEUROBIOLOGICAL CONTRIBUTIONS TO PREDICTING SUICIDALITY

A biological marker would be a valuable and objective contributor to predicting suicidality. J. John Mann of Columbia University covered a constellation of potential biological markers for suicidality. At least one neurobiological defect, serotonin deficiency, is significantly associated with suicidality. That defect and other prominent defects might eventually be combined with measures of ideation and suicide attempts to predict suicidality with greater specificity and sensitivity, he said.

Several biological markers under study are low levels of the neurotransmitter serotonin, low norepinephrine levels, and hypothalamic-pituitary-adrenal (HPA) axis dysfunction. Their roles were at the core of Mann's presentation. But he was keen to point out that biology does not act alone. Biology is one of several key factors that contribute to suicidality, according to his model (Figure 2-1). Multifactorial models are commonly adopted to explain the origins of psychiatric disorders (Engel, 1978). Given the heritability of completed suicide, which stands at 21 to 50 percent (Currier and Mann, 2008), it becomes clear that multiple factors must be at play.

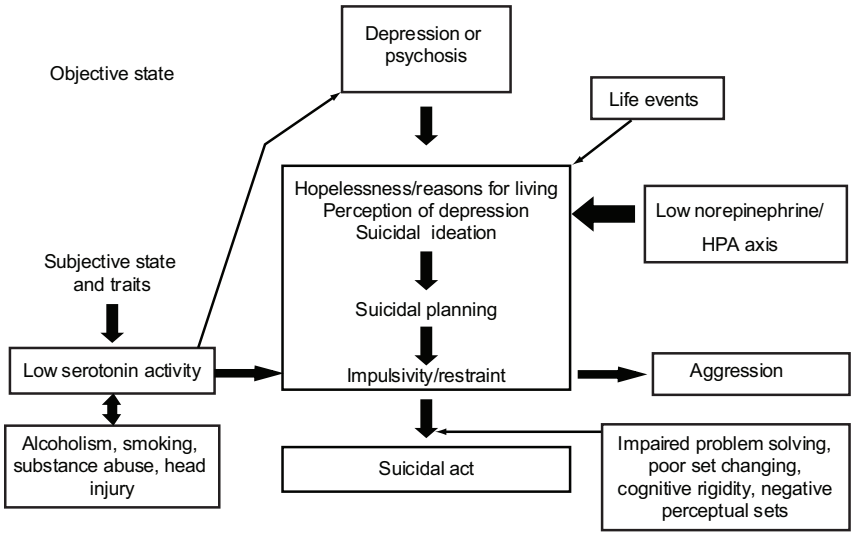

FIGURE 2-1 A model of suicidal behavior.
NOTE: HPA = hypothalamic-pituitary-adrenal, RFL = reason for living.
SOURCE: Mann, 2009.

For three decades we have known that low serotonin levels are associated with suicidality (Mann, 2003). The deficiency is so consistent across studies that Mann describes low serotonin as a long-standing trait. The method used to obtain these findings was by pharmacological challenge with the amphetamine derivative fenfluramine. Upon fenfluramine challenge, serotonin levels should normally rise. In suicidal groups, however, serotonin levels do not rise as highly as they do in control groups. The effect occurs in a matter of hours and is age dependent. Because most of the studies Mann described in his presentation were conducted in adults, he stressed that the findings may not apply to children and adolescents.

Low serotonin output has great significance for one of the brain areas to which serotonergic pathways project: the cerebral cortex's prefrontal cortex and its ventrolateral and dorsolateral regions. The ventral prefrontal cortex participates in rational decision making and regulates aggressive/impulsive behaviors (Damasio et al., 1994). This area of the cortex is altered in suicide and aggression (Mann, 2003). Positron emission tomography studies confirm that the prefrontal cortex is heavily involved in intent, planning, impulsivity, and lethality of suicidal behavior, said Mann. The odds of completed suicide are 4.5 times greater among those with low serotonin—as measured by its metabolite 5-hydroxy-in-doleacetic acid in the cerebrospinal fluid—than in those with high serotonin (Mann et al., 2006). The abnormalities in serotonin output may be traced to polymorphisms in several candidate genes for the serotonin transporter, serotonin receptors, and enzymes related to serotonin synthesis (Currier and Mann, 2008). Of these possibilities, the promoter region of the serotonin transporter has been the focus of numerous investigations. A meta-analysis of more than 20 studies found a significant association with one serotonin transporter allele and suicidality (Anguelova et al., 2003). Still, low serotonin is not the sole determinant of suicide, emphasized Mann.

Serotonin also is one of the regulators of the stress response, which is the central function of the HPA axis. A recent study by Mann's team prospectively followed several groups for a period of 2 years: depressed patients with previous suicide attempts, depression alone, and two other control groups (Keilp et al., 2008). The groups were compared in relation to fenfluramine challenge, on plasma prolactin, on cortisol (which is released by the adrenal gland during the stress response), and on psychometric measures of mood. The study found that blunting of cortisol and the worsening of mood, plus younger age, predicted *subsequent* suicide attempts in depressed patients with previous attempts. Lower prolactin

was also found after fenfluramine challenge, but the effects were not as statistically robust as those with cortisol.

The stress response also affects the structure and function of noradrenergic pathways. Fewer noradrenergic neurons in a nucleus found in the brain stem, the locus coeruleous, have been found postmortem in studies of depressed patients who completed suicide (Pandey and Dwivedi, 2007). The noradrenergic system is also a target of antidepressant treatments. Adults reporting past child abuse have excessive norepinephrine release after a laboratory stress test (Heim and Nemeroff, 2001). A noradrenaline metabolite in the cerebral spinal fluid predicts the lethality of a suicide attempt (Galfalvy et al., 2009). One key hypothesis, observed Mann, is whether excessive norepinephrine release related to the long-standing stress of severe major depression in those with childhood adversity or in genetically predisposed people eventually leads to hopelessness and pessimism. Those psychological traits, in turn, place these people at higher risk for suicidal behavior.

In summary, Mann believes that biological markers such as low serotonin levels predict future completed suicide. Biological findings, along with other psychological and social risk factors, may eventually be used in an integrative way to shed light on the emergence of suicidality in childhood, adolescence, and adulthood (Box 2-1).

BOX 2-1
Summary of Research Findings Reported by Presenters in This Session

- Epidemiological and clinical trial findings reveal that suicide ideation is not a strong predictor of a suicide attempt.
- New approaches show promise for strengthening the relationship between ideation and suicidality if more nuanced information about the nature of ideation is collected simultaneously.
- One approach seeks real-time electronic monitoring that prompts patients to report more about ideation at the time of its occurrence.
- Another approach shows that measuring "suicidal ideation at its worst point in time," through a questionnaire, is a significant predictor of suicide completion (Beck et al., 1999).
- Biological measures in response to serotonergic challenge also show promise if integrated with psychological and social measures. In a prospective study, blunting of cortisol response and the worsening of mood, plus younger age, predicted *subsequent* suicide attempts in depressed patients with a previous attempt (Keilp et al., 2008).

3

Data Analysis

ESTABLISHING CAUSAL RELATIONSHIPS IN MEDICINE FOR PUBLIC HEALTH POLICY

Statistician Joel Greenhouse of Carnegie Mellon University presented on how scientific evidence is best marshaled for public health policy decisions. The issue of what types of evidence are needed to establish a cause-and-effect relationship between antidepressants and suicidality faces the same steep hurdles as any other health policy issue. One overarching point is that regardless of the issue at hand, no single study is sufficient. The evidence must be synthesized and interpreted as a whole. To determine if there is a causal relationship, the landmark criteria often used as a guide are those developed by Hill (1965). These criteria remain in force today and are used routinely by numerous committees of the National Academy of Sciences when asked by Congress or any other public policy organization to evaluate the body of evidence to answer a public policy dilemma (Box 3-1). In the case of the meta-analysis supporting the Food and Drug Administration's (FDA's) black box warning, the foremost issues are related to the benefits and limitations of a meta-analysis. Several speakers in this session addressed the limitations. They focused primarily on the limitations of meta-analysis as a study design and the multiple alternative explanations for the apparent findings.

BOX 3-1
Evidence for Causal Relationships

- Strength of association
- Dose–response relationship
- Plausibility: plausible biological mechanism
- Consistency: replication in different settings using different methods
- Elimination of alternative explanations for the observed association

SOURCE: Hill, 1965.

BENEFITS AND LIMITATIONS OF META-ANALYSES

The evidence presented by the FDA to support a black box warning for the use of antidepressants in children and adolescents has several limitations, Greenhouse said. In its meta-analysis, the FDA relied on 24 randomized placebo-controlled trials with roughly 4,600 children and adolescents. None of the individual trials found completed suicides. The trials were designed to determine the efficacy of drugs for treating various disorders such as depression, anxiety, and attention deficit hyperactivity disorder. Greenhouse pointed out that the study populations consisted of young people with different disorders. The efficacy endpoints were different, as were the antidepressant medications and classes of medications, he said. The outcome of greatest interest to the FDA was suicidality, which in this case included suicide behavior and ideation. There were 87 cases reporting suicide behavior or ideation, assessed retrospectively. The graphic depiction used in the FDA's meta-analysis, the forest plot, revealed that only one study of antidepressants and suicidality found a significant relationship, the TADS (Treatment of Adolescents with Depression Study) (Figure 3-1). Nevertheless, the overall result of the meta-analysis was an odds ratio of about 2 (OR = 2.0, 95% CI 1.3–3.1) using a fixed-effect model. A random effects model generated a similar result.

The strength of using a meta-analysis is that it provides the means to pool data for study of a rare event. A randomized controlled trial (RCT) could never alone have enough subjects under study because of the rarity of suicidality, according to Greenhouse. Meta-analyses also provided an opportunity to look at heterogeneity across studies using study-level variables. That gave the FDA the opportunity to look at the relationship

between the risk of suicidality and age, which revealed itself to be an important finding for public health. Greenhouse reported being surprised that there was little heterogeneity across the different diagnostic categories and different classes of drugs. On the other hand, the use of meta-analyses also has limitations. By definition, meta-analyses are observational studies, a weaker type of study design, even if the individual studies being looked at are RCTs. Observational studies invite alternative explanations to explain their findings. Alternative explanations abound in the FDA data, according to presentations by Greenhouse and Robert Gibbons of the University of Illinois at Chicago.

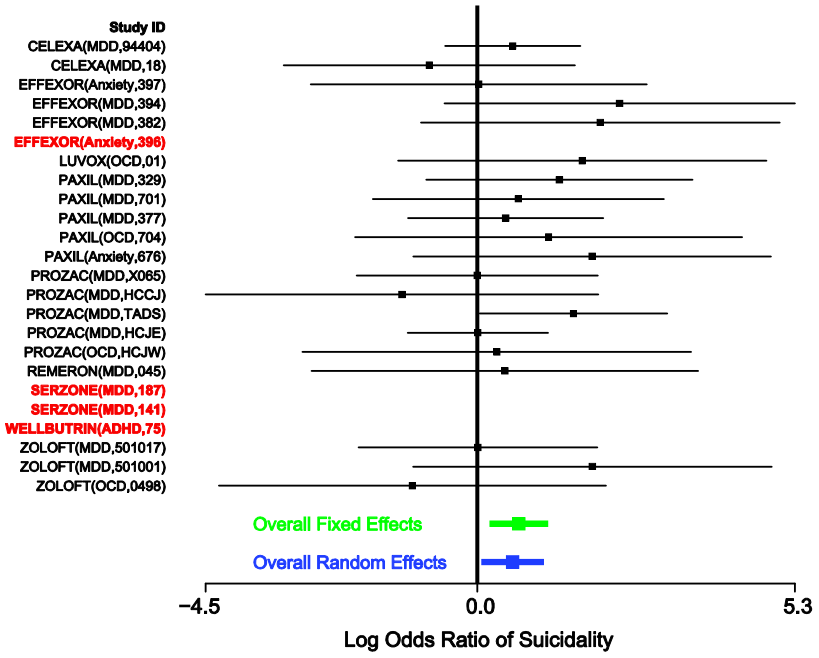

FIGURE 3-1 Forest plot of studies included in the Food and Drug Administration meta-analysis.
NOTE: Studies in red had no events in either the control or treatment arms. The horizontal axis is presented on a log scale. ADHD = attention deficit hyperactivity disorder, MDD = major depressive disorder, OCD = obsessive-compulsive disorder.
SOURCE: Adapted from Kaizar et al., 2006.

SOURCES OF BIAS IN ANTIDEPRESSANT CLINICAL TRIALS

A significant portion of the workshop covered methodological limitations stemming from bias. Several sources of bias were identified by a few speakers as potentially limiting the results of individual RCTs or their pooling through meta-analysis: selection bias (or selection effect), regression toward the mean, natural course of the disease, and confounding by indication. These sources of bias can compromise both the external and internal validity of clinical studies, according to presentations by Greenhouse, Gibbons, Marc Stone (FDA), and Robert Valuck (University of Colorado at Denver).

Selection Bias

Several types of selection bias may have threatened the validity of the results of antidepressant RCTs. Greenhouse agreed with an earlier suggestion from Kelly Posner, that one form of selection bias, ascertainment bias, could have occurred among the groups receiving antidepressants as opposed to the placebo groups. Posner said that antidepressant recipients may have been more likely than placebo patients to report suicidality because they were prompted to report any adverse effects.

Another source of bias, sampling bias, jeopardizes the generalizability or external validity of findings. This could have occurred because most RCT studies used for the meta-analysis had strict exclusion criteria specifying that subjects at high risk of suicide be prohibited from participating. Strict exclusion criteria usually leave the RCT population "healthier," that is, with less severe forms of illness. Said another way, the RCT population is healthier than other patients in the general population being treated with antidepressants and hence not representative of the population of interest.

To underscore problems with generalizability, Greenhouse compared the RCT population of adolescents to the population in a nationally representative database used in the Centers for Disease Control and Prevention's long-established "Youth Risk Behavior Surveillance System." He found that rates of suicidality were significantly higher in the nationally representative survey of youth than in the RCTs (Bridge et al., 2008; Greenhouse et al., 2008). Using statistical modeling techniques, another study of the selection effect in antidepressant trials found that more restrictive inclusion/exclusion criteria of an RCT generates greater

potential for inflation of the relative risk (Weisberg et al., 2009). The authors concluded that narrow study eligibility for cautionary reasons might, in the long run, harm "exactly those people whom the study is designed to help."

Building on that argument, Gibbons marshaled an analogous example of studying suicidality in thousands of bipolar patients treated with antiepileptic drugs as opposed to antidepressants. The suicide rate in the placebo group was lower than that in untreated bipolar patients in the general population, suggesting that placebo patients were healthier (Gibbons et al., 2009). That incurs higher likelihood of erroneously elevating the relative risk, assuming that the experimental group excludes patients more likely to be helped by the medications. Gibbons concluded that lack of generalizability presents the largest threat to RCT validity.

Regression Toward the Mean

Gibbons raised similar limitations of meta-analyses and other types of observational studies. He pointed out that meta-analysis is an observational study of other studies. In general, analysis of observational studies is fraught with difficulty. He also stressed the possibility of alternative explanations (i.e., confounders) of an apparent association between suicidality and antidepressants. One confounder was regression toward the mean, that is, the statistical term referring to the long-standing observation that if we initiate our observational period at a time of high risk, there is a natural tendency for the risk to decrease over time from the index episode (e.g., diagnosis of depression). Applying that alternative explanation here suggests that decreases in the risk of suicidality following initiation of treatment may at least in part be due to the natural decline in rate of suicidality over time and not a protective effect of the medication. To examine this possibility, he presented an illustrative example of a person-time logistic regression analysis of the relationship between antiepileptic drugs and suicide attempts in patients with bipolar illness. This permitted a comparison of suicide attempt rates in treated and untreated patients, adjusting for the natural decay in suicide rates over time from the index episode (Gibbons et al., 2009).

Natural Course of Illness

The natural course of the illness can also bias study findings, noted Gibbons. A suggestion is that the highest rates of suicide attempts happen before people initiate treatment (Gibbons and Mann, 2009). Thereafter, suicide attempts decrease exponentially with time. In longitudinal studies, for example, data may appear to show a protective effect of a medication, but instead the effect is an artifact of the natural course of the illness, that is, the effect would have occurred without any intervention.

Confounding by Indication

Confounding by indication refers to the bias introduced when the risk factor (e.g., antidepressant treatment) and the outcome (e.g., suicide) are both related to a third variable (e.g., depression) and therefore appear to be directly related. Depressed patients have increased risk of suicide and are more likely to take antidepressants as well, leading to the appearance that antidepressant use increases the risk of suicide. In this example, the relationship between antidepressants and suicide is confounded by the indication of depression. Similarly, in an observational study of depressed patients only, those patients who receive pharmacological treatment are generally sicker than those who do not receive such treatment. Therefore, they also would be expected to have a higher risk of suicide, if the antidepressant conveyed no protective effect. This is another example of confounding by indication, where the indication for treatment is increased severity, which is also directly related to the outcome—in this case, suicide.

Gibbons proceeded to discuss the pros and cons of a range of study designs (Box 3-2) that could be used to enhance understanding of the relationship between antidepressants and suicidality. He stressed that no current study design is ideal. The FDA's Adverse Event Reporting System, or AERS (events occurring after a drug's release into the market), is useful, but it is far from ideal because of heightened media reporting and the lack of a denominator (AERS only gives how many individuals receiving the drug report adverse events, not the total number of people receiving the drug). The design that most appealed to him was analysis of medical claims data, largely because of their huge sample size. The major detriments of this design are that while the data list prescriptions, they do not ensure that the patient actually took the drug.

BOX 3-2
Comparison of Study Designs

Method	Pros	Cons
RCTs	Randomized	Generalizability
AERS	Large samples	No denominator, media
Ecological	Large samples	Not person-level
Medical claims	Large samples	Prescriptions and DXs
Between subject	Person-level, drug vs. no drug	Confounding by indication
Within subject	Subject own control	Temporal effects
Person-time	Adjusts for time effects	Carry-over effects
Propensity score + time matching	Adjusts for confounds and time	May not eliminate baseline risk difference
Case-control	Adjusts for some confounds	Cases are still more severely ill

NOTE: AERS = Adverse Event Reporting System maintained by the Food and Drug Administration.
SOURCE: Gibbons, 2009.

Moreover, this design does not ensure that diagnoses are reliable or valid, among other problems.

Other Problems with Meta-Analyses

Marc Stone of the FDA offered his perspective in a presentation on meta-analysis and its broader problems when applied to rare events. He began by defining "suicidality" in a comprehensive way to include any suicide-related phenomena of interest. His first concern was with patient withdrawals from RCTs, because withdrawals related to treatment assignment have a high probability of confounding results. He asked the generic question of whether propensity to withdraw stemmed from susceptibility to drug-related adverse events (or lack of therapeutic effect in placebo subject), drug effect on tolerability of adverse events, and/or the

effect of drug on willingness to adhere to the protocol in the face of personality, lifestyle, and life events. All of these propensities can bias study outcome.

Non-random acts of withdrawal may be a prodrome for suicidality, he noted. It is also conceivable that they may be signs of remission with good prognosis. All of the use issues affect adherence to the protocol and desire to withdraw, which can differentially affect the drug and placebo groups. His overall point was that non-random acts of withdrawal from RCTs, affected by multiple factors, might reduce or negate the benefits of randomization. He was also concerned about whether the drug effect is constant over time. The length of the study is crucially important. If incidence rates vary over time, there can be significant effects on modeling and regression lines. He demonstrated how choice of statistical model could result in different estimates of comparative effect between drug and placebo groups. His bottom line was that both withdrawals from the RCT and statistical models affect meta-analysis findings, and the impact may be greater given the rarity of completed suicide.

During the workshop's discussion period devoted to methodological limitations of RCTs and their use in meta-analysis, FDA's Tom Laughren acknowledged that every method of study has its flaws. Still, he noted that an academic team using a case-control study produced results that were very similar to those of the FDA's, finding an association between antidepressants and suicidality in the pediatric population but none in the adult population (Olfson et al., 2006). Laughren asserted that he had not "heard anything that convinces me, with as much admitted weakness as there is in the data we have . . . [that we] reached the wrong conclusion." He also pointed out that a black box warning is "simply intended to alert clinicians to a potential risk that they need to pay attention to."

Additional studies and forms of analysis were also highlighted at the meeting that may offer equally important, albeit different, inferences. For example, a study of depressed adolescents receiving psychotherapy—as opposed to pharmacotherapy—showed risks of suicidality similar to that in the FDA trials (Bridge et al., 2005). This finding suggests that the suicidality in FDA trials is a treatment effect, not specifically a drug effect. Another study found that the benefits of antidepressants outweighed their risks (Bridge et al., 2007). However, several participants described the limitations of meta-analyses and examined potential opportunities in using other forms of analysis. Potter pointed out that this workshop would have been unnecessary had there been better methodologies available, especially prospective observational studies. However, Stone drew a distinction between the kinds of inferences that can be drawn from a clinical trial versus

observational data from a large dataset. The former allows inferences about causality, the latter about associations that may or may not be causal.

Observational Studies

Robert Valuck offered a different approach to study the effects of antidepressants, using epidemiology rather than RCTs. He described a newly linked network of health datasets consisting of nearly 500,000 patients (Pace et al., 2009). That large patient base readily lends itself to many types of observational epidemiological studies. Although such studies are almost universally deemed to be of lesser validity than RCTs, observational studies may be better suited to studying rare clinical outcomes in real-world settings, where patients are more ill and more complicated.

The foremost benefit of observational studies is the sample size and thus generalizability. Other benefits are their greater statistical power for studying rare outcomes and their capacity to compare the effectiveness of different treatments (considering that the FDA only requires treatments to be tested against placebos). The dataset also holds the potential for being undertaken as prospective cohort studies designed to measure and confirm outcome measures of interest. But these studies are not without disadvantages. Their pros and cons are summarized in Box 3-3.

BOX 3-3
Observational Studies

PROS

- Larger, heterogeneous populations can be studied
- More representative of real-world treatment
- Can give much greater power for rare/negative outcomes to be studied
- If prospective, can have very good measurement and validation of events

CONS

- Non-random allocation
  - Confounding by indication
  - Severity of illness
  - Other unmeasured covariates
- Complex statistical methods required to address residual confounding

SOURCE: Valuck, 2009.

Tapping into the dataset, Valuck described the Distributed Ambulatory Research in Therapeutics Network (DARTNet). DARTNet is a federally supported network of electronic health data created to promote comparative effectiveness research. The database already covers 500,000 individuals (without identifiers). Because of the nature of data acquisition, and lack of possibility of random allocation, it has limitations. But the dataset is highly useful because its patients represent the "real world" of treatment, rather than the exacting standards of treatment necessary for randomized controlled trials. It includes primary care, where, Valuck noted, 50 percent of depression care is rendered.

The database has not yet been used to study suicidality, but it does offer potential for such study, especially for conduct of prospective cohort studies. It also facilitates the conduct of retrospective and case-control studies. Within each of its more than 500 sites of clinical practice, it captures a broad mix of patient-level information (e.g., vital signs, social history, family history) from electronic health records, laboratory tests, imaging results, pharmacy use databases, and billing systems (e.g., Medicaid and Department of Veterans Affairs). The data can be used to determine if patients actually fill prescriptions, for example. The system does have drawbacks: lack of severity data, unmeasured covariates, and unvalidated outcomes, among others.

Valuck and colleagues, drawing from another dataset, conducted a large nested case-control study of suicide attempts using claims data from managed care organizations (Valuck et al., 2009). Although claims data are not ideal, the study examined 10,500 suicide attempters over the period 1999 to 2006 against nearly 42,000 controls. After controlling for confounders related to depression severity, antidepressants were shown to protect against a suicide attempt, while antidepressant discontinuation was a significant risk factor for having a suicide attempt. Nevertheless, the study did show that the highest risk of a suicide attempt was indeed associated with the initiation of treatment, which is a finding consistent with other studies.

4

Partnerships, Opportunities, Collaboration

CORE DATA TO OBTAIN FOR DATA SHARING

Data sharing and collaboration among experts is a time-tested guide to help practicing clinicians abide by the Food and Drug Administration's (FDA's) black box warning. Practicing clinicians, whether in primary care or specialty care, need guidance about what warning signals and adverse events to look for during the course of antidepressant treatment. The necessary guidance critically depends on two key issues for researchers and practitioners alike: deployment of common outcome measures and understanding of the evolution from suicidal ideation into suicidality. Addressing these issues is no small task. Measures and questionnaires used in randomized controlled trials (RCTs) are too lengthy and elaborate and thus do not readily lend themselves for use in everyday medicine. RCTs also typically exclude patients with suicidal ideation or suicidality. Furthermore, it is key to understand longitudinal trends and their predictive relationship to suicidality.

Madhukar Trivedi of the University of Texas Southwestern Medical Center at Dallas focused his presentation on the lessons learned from a 5-year depression trial, enrolling about 4,000 adults and sponsored by the National Institute of Mental Health (NIMH, 2009). This clinical trial had several unique features. It studied real-world depression treatments in everyday clinical practice, as opposed to the rarified circumstances of a

typical RCT with its strict inclusion and exclusion criteria. RCT patients are typically in better health and have fewer comorbidities than real-world patients. The study sought to find out how patients fared over the long term with depression treatment; its focus was on patients who are hard to treat, considering that the majority of depressed patients do not respond significantly enough to the first antidepressant they try (Little, 2009). It also sought to identify the comparative effectiveness of the several tiers of pharmacological therapies. The trial was conducted in a network of primary and specialty care settings across the country. Simply put, its goal was to help practicing clinicians sort out treatment recommendations in everyday practice. Until now, no studies have given guidance essential for patient management over the course of antidepressant treatments. With nearly 20 medications to choose from, this is no easy feat.

Formally known as Star*D, the Sequenced Treatment Alternatives to Relieve Depression trial used a common set of outcome measures, including one three-part question covering suicidal ideation and behavior, which was the centerpiece of Trivedi's presentation. The longitudinal nature of this study and its real-world setting helped his team discern the evolution of suicidal ideation into suicidality. That path rarely has been traced because such patients with ideation are normally excluded from clinical trials.

Suicidal ideation and suicidality were measured by a three-part question of the QIDS questionnaire (Quick Inventory of Depressive Symptomatology—Self-Report); (Zisook et al., 2009). The level of severity ranges from 0 to 3 (Box 4-1), with a score of 1 meeting the definition of mild suicidal ideation and 3 meeting the definition of a suicidal attempt. Designed as an open trial, there was no comparison group, so patients were assessed in relation to their baseline visit.

BOX 4-1
Question About Suicidal Ideation in the Quick Inventory of Depressive Symptomatology–Self-Report

Thoughts of death or suicide:

- I do not think of suicide or death.
- I feel that life is empty or wonder if it's worth living.
- I think of suicide or death several times a week for several minutes.
- I think of suicide or death several times a day in some detail or I have made specific plans for suicide or have actually tried to take my life.

SOURCE: Rush, 2009.

The study participants were treated with Citalopram, and nearly half of them had suicidal ideation at baseline. Of that half with suicidal ideation, 74 percent showed improvement at their first post-baseline visit 2 weeks later, 22 percent remained the same, and 4 percent worsened. Of the latter, 1 percent still had suicidal ideation by the last visit at 12 weeks from baseline. These patients would have been excluded from clinical trials. Trivedi said it is important to point out that the small percentage of patients who worsen take longer to respond to treatment. Among the other half of the sample, those *without* suicidal ideation at baseline, 7 percent experienced the emergence of suicidal ideation by their first post-baseline treatment visit, a small upsurge that the investigators attributed to early increases in energy, activation, and anxiety (Szanto et al., 2007). But the majority of that 7 percent, or 63 percent, did not report suicidal ideation by their final visit 12 to 14 weeks later. Fifteen of the total sample attempted suicide by the end of the trial, but there were no completed suicides.

The authors concluded that although there was an early increase in suicidal ideation in a small group of depressed patients, the majority of such cases were fleeting, suggesting that most cases of "emergent" suicidal ideation are more likely to be tied to natural fluctuations of suicidal ideation than to treatment. The major risk factors for developing treatment-emergent suicidal ideation were drug abuse, severe depression, and melancholic features. Demographic risk factors for suicide attempts were being less than 19 years old and being an African American. These findings suggest the importance of tracking suicidal ideation because a small percentage of patients do worsen and their risk factors are becoming clear.

THE FDA'S CRITICAL PATH INITIATIVE

Lack of progress in studying and treating suicidality is part of a broader trend in the United States. The country has undergone a decade-long decline in innovation of new medical products, according to ShaAvhree Buckman, acting director of the Office of Translational Sciences at the FDA. Innovation in the form of new product approvals has slowed strikingly, while pharmaceutical company research and development spending has progressively increased (Figure 4-1). This so-called innovation gap galvanized the FDA several years ago to spearhead collaborative efforts to facilitate and modernize product development.

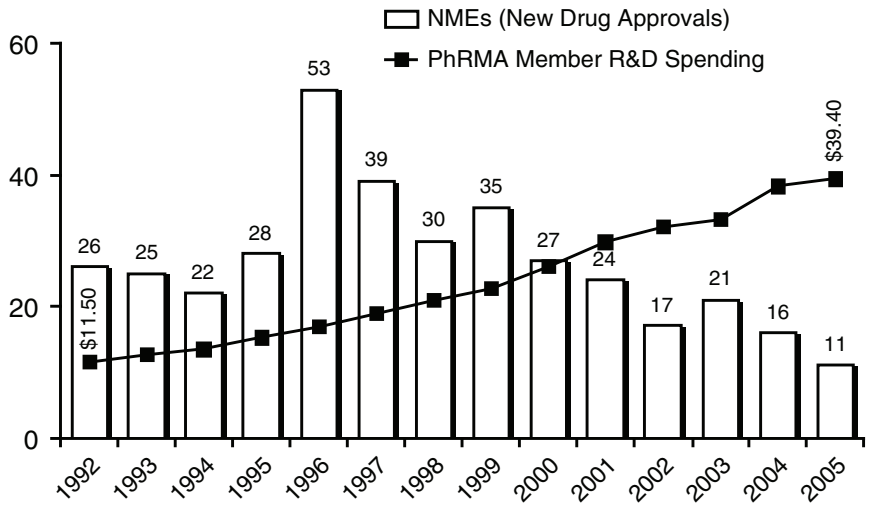

FIGURE 4-1 Innovation gap between new drug approvals and spending on research and development by year.
NOTE: NME = new molecular entitites; PhRMA = Pharmaceutical Research and Manufacturers of America; R&D = research and development.
SOURCE: Buckman, 2009.

Through the creation of its Critical Path Initiative,[1] the FDA has taken unprecedented steps to forge partnerships with the National Institutes of Health (NIH), industry, advocacy groups, and scientific societies, among others. Under the auspices of the Critical Path Initiative, the FDA is committed to promoting development of the infrastructure and furnishing tools to make product development more efficient and streamlined. It hopes to help sponsors predict early in the development process which products are most likely to be safe and effective, thereby avoiding expensive product failures in the later stages of development. Such failures in recent years have chilled the climate for investment.

The FDA's role, said Buckman, is carefully carved out to encourage development not of any single product or sponsor, but to encourage collaboration focused on overcoming widespread impediments to innovation, such as the lack of animal models or the lack of biomarkers. The purpose of fostering collaborations is to pool knowledge and resources and thereby help

[1] See http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm.

the FDA develop relevant data standards and regulations and build support for relevant academic science. The public–private partnerships and collaborations arising from the FDA's activities are focused on the "precompetitive" space, that is, areas of science and methodology that spur all partners rather than give any participating group a competitive edge.

The FDA has yet to start any specific initiatives in suicidality, although a new proposal is being developed by Charles Beasley of Eli Lilly (see the next section). Some of the FDA's previous and ongoing initiatives might serve as exemplars for the suicidality field. Some of the most prominent ongoing initiatives have been in the following areas: (1) Serious Adverse Events, the goal of which is to detect and validate DNA variants that are clinically useful in predicting patients' risk of experiencing drug-induced serious adverse events; (2) Clinical Trials Transformation, the goal of which is to focus on practices that, if adopted broadly, will increase the quality and efficiency of clinical trials; and (3) the Patient Reported Outcomes consortium, the goal of which is to develop and evaluate self-reported questionnaires (termed "patient-reported outcomes") to measure safety and/or efficacy in clinical trials. For the latter, the FDA has a liaison relationship with no voting rights or other fiduciary role. Submission of dossiers to the FDA does not automatically constitute "fit for purpose," the legal term for a method of measurement that satisfies the FDA's standards for appropriateness and quality.

Some common themes driving the Critical Path Initiative include identifying the public health need, determining whether partners are willing to share data precompetitively, identifying needed data standards, and sharing data in the public domain as quickly as appropriate. Although the FDA considers itself a catalyst in its initiatives and is committed to their success, the actual success of any single initiative requires partners to commit to collaboration and data sharing. Pinpointing the basis of success after 4 to 5 years since creation of the Critical Path Initiative, Buckman advised, "A lot of these efforts, they do take time. They take commitment. They take a champion."

A PROPOSAL FOR THE FDA'S CRITICAL PATH INITIATIVE UNDER DEVELOPMENT FOR SUICIDALITY

A novel proposal for the FDA's Critical Path Initiative was urged for suicidality studies by Charles Beasley, a distinguished scholar and chief scientific officer of Global Patient Safety at Eli Lilly. It would create a large database for safety purposes, among others. (Beasley stated clearly that the concept is his own, and represents official policy of neither Eli Lilly nor the Pharmaceutical Research and Manufacturers of America.) Beasley envisioned that the database would serve as a way of pooling RCT findings: It should include not only adverse events associated with antidepressants, but also those associated with many psychiatric and non-psychiatric medications. The imperative behind the formation of the warehouse, in his view, would be to answer many unresolved and thorny questions, such as whether and the extent to which suicidal ideation predicts suicidality, as well as many other research questions. The most immediate question of interest, from Beasley's perspective, is whether suicidal ideation as detected by an instrument such as the Columbia Suicide Severity Rating Scale (C-SSRS) is predictive of suicidal acts or completed suicide during the short-term, index acute treatment episode. The answer to this question has broad implications for the appropriateness of the FDA's labeling decisions. The warehouse would be open to academic, industry, and all other researchers.

Beasley predicated his idea on one of the current Critical Path Initiatives to assemble an electrocardiogram (ECG) data warehouse for studying cardiac toxicity. The warehouse is designed as a repository of more than 2 million ECGs, according to earlier remarks by Buckman. The ECG warehouse, which is mandatory under the *Food, Drug, and Cosmetic Act,* is intended to enable academic and industry researchers to find better biomarkers of cardiac toxicity. The purpose is to develop more efficient clinical trial outcome measures and improve patient safety, given that the utility of the Q-T interval, a measure of the heart's electrical cycle, has been seriously questioned. The ability to undertake suicidality studies rests on having an extremely large sample size because of the rarity of completed suicides.

Beasley foresees that at least 100 completed suicides would be a crucial component of the warehouse. To stimulate discussion, he explained that the overall patient size of the warehouse, patient demographics, placebo controls, and critical data elements are inchoate, as are administrative, procedural, and funding matters. Beasley stressed that uniformity of data collection is essential. The idea generated lively

discussion among participants. Most of the questions related to the most suitable outcome measures (e.g., Columbia Classification Algorithm for Suicide Assessment, C-CASA), the inclusion of biomarkers such as genetic data, the inclusion of comorbidities, longitudinal data, efficacy data, and the protection of corporate secrets.

Participants were intrigued by the proposal laid out by Beasley, although what is left to discuss is how best to move forward, who should be at the table, and under what auspices the discussions would be held and advanced. Many also agreed that any potential warehouse would need to incorporate other data elements—ideally in real time—to make the collection more robust and useful. This brings into question the issue of partnering with the proper stakeholders in order to realize such a robust warehouse. A number of participants believed that including several NIH institutes would be a good first step.

A

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B

Workshop Agenda

CNS Clinical Trials: Suicidality and Data Collection

Tuesday, June 16, 2009
National Academy of Sciences Main Building
Lecture Room
2101 Constitution Avenue, NW
Washington, DC

Workshop Objectives

The purpose of the workshop is to determine whether treatment-emergent suicidal ideation predicts suicidal behavior in the near term for conduct of clinical trials. It examines what methods are optimal and whether potential partnerships can facilitate data sharing among the Food and Drug Administration (FDA), pharmaceutical industry, academia, and the National Institutes of Health (NIH).

- Review available data on the extent to which emergent suicidal ideation predicts the occurrence of actual suicidal behavior, particularly in the short term.
- Ascertain optimal methods of analysis to address if suicidal ideation predicts the short-term occurrence of actual suicidal behavior.

- Examine potential partnerships among the FDA, pharmaceutical industry, academia, and the NIH that could be used to facilitate data sharing from randomized clinical trials.

9:00 a.m. Welcome, Introductions, and Workshop Objectives

WILLIAM POTTER, *Workshop Co-chair*
Vice President
Clinical Neuroscience
Merck Research Laboratories
Merck & Co., Inc.

ROBERT GIBBONS, *Workshop Co-chair*
Director, Center for Health Statistics
Professor of Biostatistics and Psychiatry
University of Illinois at Chicago

9:15 a.m. FDA Policies and Perspectives: Suicidality Studies in IND

THOMAS LAUGHREN
Director
Division of Psychiatry Products
Food and Drug Administration

9:35 a.m. C-CASA and C-SSRS in CNS Clinical Trials: Development and Implementation

KELLY POSNER
Director
Center for Suicide Risk Assessment
New York State Psychiatric Institute

9:55 a.m. Perspectives from the Patient Community

GAIL GRIFFITH
Consumer Representative
Food and Drug Administration's
Psychopharmacological Drug Advisory Committee

SESSION I: DATA COLLECTION AND OPTIMIZATION

Session Objective: Review available data on the extent to which emergent suicidal ideation predicts the occurrence of actual suicidal behavior, particularly in the short term (during an index of treatment period that typically lasts between 4 and 16 weeks). Discuss optimization of methods for data collection as well as if there is a need for additional data collection, in addition to C-SSRS data, to help address the question of this potential relationship.

10:10 a.m. Introduction to the Session

DAVID BRENT, *Session Chair*
Professor
Department of Psychiatry
University of Pittsburgh School of Medicine

10:15 a.m. Panel Discussion: Assessing the Risk Between Ideation and Action (Each presentation approximately 15 minutes)

Frequency with Which Suicide (or Serious Attempts) Is Preceded by Expressed Ideation: A Literature Review

MATTHEW NOCK
Associate Professor of Social Sciences
Department of Psychology
Harvard University

Measurement of Suicide Ideation

GREGORY BROWN
Research Associate Professor of Clinical Psychology in Psychiatry
Department of Psychiatry
University of Pennsylvania

Treatment Emergent Suicidal Events in Adolescents: Neurobiology and Clinical Significance

J. JOHN MANN
Professor of Translational Neuroscience, Psychiatry, and Radiology
Columbia University
Chief, Department of Neuroscience
New York State Psychiatric Institute

11:00 a.m. Moderated Discussion with Attendees

DAVID BRENT, *Session Chair*
Professor
Department of Psychiatry
University of Pittsburgh School of Medicine

Discussion Questions:

- Does the C-SSRS measure what it says it measures?
- Are there outcomes that should be assessed but are not?
- What conditions (type of interview, spontaneous vs. systematic) would optimize assessment?
- What are the public health implications of the events detected by the C-SSRS?

11:45 a.m. LUNCH

SESSION II: DATA ANALYSIS

Session Objective: Discuss optimal methods for meta-analyses for instances where the outcome of interest is very infrequent. In addition, ascertain optimal methods of analysis to address if suicidal ideation predicts the short-term occurrence of actual suicidal behavior.

12:45 p.m. Introduction to the Session

ROBERT GIBBONS, *Session Chair*
Director, Center for Health Statistics
Professor of Biostatistics and Psychiatry
University of Illinois at Chicago

12:50 p.m. Panel Discussion: Data Analysis Strategies
(Each presentation approximately 15 minutes)

Potential Drawbacks in Existing Methodologies

JOEL GREENHOUSE
Professor
Department of Statistics
Carnegie Mellon University

Design and Analytic Strategies for Modeling Suicidality

ROBERT GIBBONS
Director, Center for Health Statistics
Professor of Biostatistics and Psychiatry
University of Illinois at Chicago

Design and Analytic Strategies for Modeling Suicidality: An FDA Perspective

MARC STONE
Senior Medical Reviewer
Division of Psychiatry Products
Food and Drug Administration

Studying Suicidality: From RCTs to OCER

ROBERT VALUCK
Professor
Department of Clinical Pharmacy
University of Colorado at Denver

1:50 p.m. Moderated Discussion with Attendees

ROBERT GIBBONS, *Session Chair*
Director, Center for Health Statistics
Professor of Biostatistics and Psychiatry
University of Illinois at Chicago

Discussion Questions:

- What are the limitations of meta-analysis of RCT suicidality outcomes and how can they be solved?
- Are there other approaches to looking at rare adverse events that should replace or augment the traditional approaches?
- How do we insulate ourselves from bias?
  - (1) Ascertainment bias
  - (2) Regression toward the mean
  - (3) Natural course of the disease
  - (4) Confounding by indication
- What data should be used in screening new drugs for rare AEs?
  - (1) New sources of spontaneous reports
  - (2) Medical claims databases
  - (3) Large practice studies
  - (4) Linkage to NVDRS
- How can we determine if suicidal ideation is a valid predictor of suicide behavior and completion?

2:35 p.m. BREAK

SESSION III: PARTNERSHIPS: OPPORTUNITIES FOR COLLABORATION

Session Objective: Examine potential partnerships among the FDA, pharmaceutical industry, academia, and the NIH that could be used to facilitate data sharing from randomized clinical trials. Specifically, discuss optimal methods for collection of data by stakeholders in a common fashion and how best to share the data.

2:50 p.m. Introduction to the Session

HUSSEINI MANJI, *Session Co-chair*
Global Head, Neuroscience
Johnson & Johnson Pharmaceutical Research and Development, LLC

DAVID MICHELSON, *Session Co-chair*
Vice President, Clinical Neuroscience
Merck Research Laboratories
Merck & Co., Inc.

3:00 p.m. Panel Discussion: Current and Future Partnership Needs
(Each presentation approximately 15 minutes)

What Core Elements Should Be Included in Data Collection?

MADHUKAR H. TRIVEDI
Chair in Mental Health
Professor of Psychiatry
University of Texas Southwestern Medical Center at Dallas

Ways to Facilitate Collaborations: How and Who?

SHAAVHRÉE BUCKMAN
Acting Director, Office of Translational Sciences
Center for Drug Evaluation and Research
Food and Drug Administration

Are There Ways to Create Robust and Informative Datasets Through Pooling?

CHARLES BEASLEY
Chief Scientific Officer, Global Patient Safety
Lilly Research Laboratories
Eli Lilly and Company

3:45 p.m. Moderated Discussion with Attendees

HUSSEINI MANJI, *Session Co-chair*
Global Head, Neuroscience
Johnson & Johnson Pharmaceutical Research and Development, LLC

DAVID MICHELSON, *Session Co-chair*
Vice President, Clinical Neuroscience
Merck Research Laboratories
Merck & Co., Inc.

Discussion Questions:

- How can the FDA work with academic institutions, the NIH, and/or industry to provide better surveillance?
- How can all stakeholders conducting relevant clinical trials collect the needed information in a standard format?
- What is the most efficient way to share data across trials?

SESSION IV: FUTURE DIRECTIONS: DISCUSSION WITH WORKSHOP PARTICIPANTS AND ATTENDEES

Session Objective: Given the opportunities and constraints that exist to implementing the frameworks, methods, and partnerships discussed during the workshop, what resources are necessary to ensure that the most efficient and effective frameworks are in place for analysis of suicidality? What new ideas have surfaced in this meeting today that should be explored further?

4:30 p.m. Summary Remarks

WILLIAM POTTER, *Workshop Co-chair*
Vice President, Clinical Neuroscience
Merck Research Laboratories

ROBERT GIBBONS, *Workshop Co-chair*
Director, Center for Health Statistics
Professor of Biostatistics and Psychiatry
University of Illinois at Chicago

4:50 p.m. Open Discussion with Attendees

5:10 p.m. ADJOURN

C

Workshop Attendees

Omar Ali
i3 Statprobe

Larry Alphs
Ortho-McNeil Janssen Scientific Affairs, LLC

Mark Bangs
Eli Lilly and Company

Hendricks Brown
University of Miami

Pilar Cazorla

Kathryn Connor
Merck Research Laboratories

Vladimir Coric
Bristol-Myers Squibb

Brenda Crowe
Eli Lilly and Company

Rosina Dixon
Sanofi-Aventis

Sarah DuBrava
Pfizer

Amy Ellis
MedAvante

Reuven Ferziger

Regan Fong
GlaxoSmithKline

Richard Frank
GE Healthcare

Harry Gedney
National Park Service

Alan Gelenberg
Healthcare Technology Systems, Inc.

Paul Gilbert
MedAvante

Laurence Greenhill

Owen Hagino
Sanofi-Aventis

Richard Hodes
National Institutes of Health

Yiqun Hu
FRI

Joseph Hulihan
Ortho-McNeil Janssen Scientific Affairs

Neely Ivgy-May
Schering Plough Corp.

Thomas Konechnik
Eli Lilly and Company

Stephen H. Koslow
American Foundation for Suicide Prevention

Mary Kujawa
Hoffmann-LaRoche, Inc.

Deborah Lazzaretto
New York State Psychiatric Institute

Susi Lee
Merck & Co., Inc

Anne Libby
University of Colorado at Denver

Alan Lipschitz
GlaxoSmithKline

Clare Makumi
GlaxoSmithKline

Randall Marshall
Sepracor, Inc.

Roger Meyer
Best Practice Project Management, Inc.

Tanya Momtahen
Sanofi-Aventis

Sanjeer Pathak

Jane Pearson
National Institute of Mental Health

David Sheehan
University of South Florida College of Medicine

Peter Sorantin
MedAvante

Susanne Steinberg
Pfizer

Vani Vannappagari
GlaxoSmithKline

Lingfeng Yang
Wyeth Research

Kseniya Yershova
New York State Psychiatric
Institute/Columbia University

D

Biographical Sketches of Invited Speakers

Charles M. Beasley, Jr., M.D., F.F.P.M., is a distinguished Lilly Scholar and the chief scientific officer, Global Patient Safety, Lilly Research Laboratories, Eli Lilly and Company. Dr. Beasley's internship was in the Department of Psychiatry, Yale University, and he completed his training in psychiatry at the University of Cincinnati in 1987. He immediately joined Eli Lilly and Company in the area of clinical development of psychiatric medications. He was responsible for Prozac from the time of its U.S. launch through 1991, working extensively on the topic of the potential for SSRI medications to induce suicidality. During that period he was also responsible for the development program for atomoxetine as an antidepressant (program terminated). At that time he developed a particular interest in placebo response and trial design. From 1991 through 2001 he was responsible for the development of Zyprexa as a treatment for schizophrenia. From 2001 through 2002 he served as medical director for Cialis. Since 2003 he has served as a consultant across all therapeutic areas in both experimental design and safety, initially from a position in the neuroscience area and since 2004 in Global Patient Safety. He has a particular interest in three areas of safety: suicide, hepatic dysfunction, and delay in cardiac ventricular repolarization and the design of "Thorough QT Studies." He was first author of the first meta-analysis of the adult, major depression, controlled, fluoxetine database analyzing the

emergence of suicidal ideation and suicidal behavior. His interest in ventricular repolarization derives from work with academic collaborators on the characterization of multiple cardiac ion channel blockade by antipsychotics beginning in 1995 and the design of one of the first "Thorough QT Studies" required for regulatory approval of Cialis in 2000.

During his 21 years in industry with Lilly, he has authored over 80 peer-reviewed publications. He is an inventor on eight patents of Lilly products. He has extensive experience interacting with multiple divisions of the FDA, European regulatory authorities, and Japanese regulatory authorities. He is a member of the American Osteopathic Association, the American Psychiatric Association, the American Society for Clinical Psychopharmacology, the American College of Psychiatrists, the American College of Neuropsychopharmacology, and the American Federation for Clinical Research. He is also a fellow of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians of the United Kingdom and member of the American Academy of Pharmaceutical Physicians.

David Brent, M.D., was born in Rochester, New York, and grew up in the Philadelphia area. He received his undergraduate education at Pennsylvania State University and graduated from Jefferson Medical College of Thomas Jefferson University. Dr. Brent trained in pediatrics at the University of Colorado and in general and child psychiatry at Western Psychiatric Institute and Clinic and completed a master's degree in psychiatric epidemiology at the University of Pittsburgh School of Public Health. He is currently academic chief, child and adolescent psychiatry, at Western Psychiatric Institute and Clinic and professor of psychiatry, pediatrics and epidemiology, University of Pittsburgh School Medical Center. He cofounded and now directs Services for Teens at Risk (STAR), a commonwealth of Pennsylvania–funded program for suicide prevention, education of professionals, and the treatment of at-risk youth and their families. His work in the area of suicide has focused on the epidemiology of adolescent suicide and has helped to identify the role of firearms, substance abuse, and affective disorders as risk factors for youth suicide.

Consequently, he and colleagues at Western Psychiatric Institute and Clinic have helped to establish the role of cognitive therapy as a treatment for depressed adolescents in an NIMH-funded clinical trial. Dr. Brent has also focused on the familial and genetic aspects of suicide, having found that suicidal behavior clusters in families, and is currently, along with colleagues at New York State Psychiatric Institute, studying how suicidal behavior may be transmitted from parent to child. His work has been funded by the William T. Grant Foundation and the National

Institute of Mental Health, and he currently directs an NIMH-funded Advanced Center for Interventions and Services Research for Early-Onset Mood and Anxiety Disorders devoted to improving the life course of youth with mood and anxiety disorders and consequently at high risk for suicide.

Gregory Brown, Ph.D., is a research associate professor of clinical psychology in psychiatry at the University of Pennsylvania and serves as co-principal investigator of the NIMH-funded Center for the Treatment and Prevention of Suicide. His research has focused on targeted psychotherapy interventions for individuals who are at highest risk for suicide, and he has worked on developing suicide assessment and brief intervention strategies for suicide prevention in emergency departments. He is currently investigating the effectiveness of cognitive therapy for adult patients who recently attempted suicide and for suicidal older men. He is the winner of the 2007 Edwin Shneidman Award for outstanding contributions in suicide research from the American Association of Suicidology. He serves on the American Foundation for Suicide Prevention Scientific Advisory Board and Research Grants Committee.

ShaAvhrée Buckman, M.D., Ph.D., FAAP, is currently the director (acting) of the Office of Translational Sciences (OTS), Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration. OTS comprises the Office of Biostatistics, Office of Clinical Pharmacology, and provides oversight to CDER research involving human subjects as well as CDER regulatory science research. OTS is responsible for providing coordination for Critical Path Initiatives across CDER in partnership with individual CDER offices. Prior to joining OTS, Dr. Buckman served as a medical team leader in the Division of Pediatric Drug Development, Office of Counter Terrorism and Pediatric Drug Development, CDER. She received her M.D. and Ph.D. degrees with an emphasis on molecular cell biology from Washington University School of Medicine. She completed pediatric specialty training at Baylor College of Medicine.

Robert Gibbons, Ph.D., is the director of the Center for Health Statistics at the University of Illinois at Chicago (UIC) and professor of biostatistics and psychiatry, University of Illinois at Chicago. He is a fellow of the American Statistical Association and a member of the Institute of Medicine of the National Academy of Sciences. He is a recipient of the Youden Prize for Statistical Contributions to Chemistry and the Harvard Award for contributions to psychiatric epidemiology and biostatistics.

His research interests span many areas, including analysis of longitudinal data, environmental statistics, and statistical applications in health services research, mental health, fMRI, molecular genetics, chemistry, and organ transplantation.

Joel Greenhouse, Ph.D., is professor of statistics at Carnegie Mellon University and adjunct professor of psychiatry and epidemiology at the University of Pittsburgh. He is an elected fellow of the American Statistical Association, and the American Association for the Advancement of Science and an elected member of the International Statistical Institute. Professor Greenhouse is a recipient of Carnegie Mellon University's Ryan Teaching Award and the College of Humanities and Social Sciences' E. Dunlop Smith Award for distinguished teaching and educational service. He has been the director of an NIMH-funded training program in psychiatric statistics for pre and postdoctoral fellows; has served on data monitoring and safety boards and scientific advisory committees for a number of NIH and Veterans Administration studies; and has served on several National Academy of Sciences committees, including the Committee on National Statistics and the Institute of Medicine's Committee on the Assessment of Family Violence Interventions. He is an editor of *Statistics in Medicine* and is a past editor of the Institute of Mathematical Statistics' *Lecture Notes and Monograph Series*. His research interests include methods for the analysis of data from longitudinal and observational studies, including methods for clinical trials and meta-analysis. Professor Greenhouse is also interested in issues related to the use of research synthesis in practice, especially as it is used to synthesize evidence for making policy and for scientific discovery.

Gail Griffith worked for the campaign to ban landmines, which won the Nobel Peace Prize in 1997. As part of her efforts on behalf of the landmine campaign, she assembled renowned musical artists and produced concerts throughout the United States, Canada, and Europe to lobby for a landmine ban. She helped to craft rehabilitation programs on behalf of the Vietnam Veterans of America Foundation to address the needs of civilian victims of war in Southeast Asia and Africa and ran foreign policy-making and executive training programs for international leaders for Georgetown University's School of Foreign Service for over 15 years.

Since her adolescent son's near-lethal suicide attempt in 2001, Ms. Griffith has devoted herself to advocacy on behalf of people with mental illness and to writing about teen depression. She is a member of the Na-

tional Alliance on Mental Illness, Mental Health America, the International Association of Suicide Prevention and SPAN and served as a board member of the American Foundation for Suicide Prevention from 2005 to 2008, where she helped produce two instructional films on teen suicide prevention. In 2004 she was appointed to serve as the patient representative to the U.S. Food and Drug Administration's scientific advisory committee charged with investigating the possible link between antidepressant medication and suicidal thinking in young people. In 2005 she was invited to review the proposed research models on suicide and treatment options for the National Institute of Mental Health, and in 2007 she was named as the consumer representative to the FDA's Pharmacological Drugs Advisory Committee for a four-year term. In November 2008 she was invited to speak at the Institute of Medicine's Values in Health Care summit, and in January, 2010, she was a presenter at the Columbia University International Capstone Meeting on Suicidality. Ms. Griffith is listed in the 2005–2006 *National Register of Who's Who* in administrative and executive leaders.

Ms. Griffith is a graduate of the University of California at Berkeley and holds a graduate degree from Georgetown University. She lives in Washington, DC, with her husband, architect Jack Brady. She is the author of *Will's Choice: A Suicidal Teen, a Desperate Mother and a Chronicle of Recovery,* published by HarperCollins in May 2005. *Will's Choice* was a finalist for the 2005 Suze Orman First Book, "2005 Books for a Better Life Award." In June 2006 Ms. Griffith received the Tipper Gore: Remember the Children Award, bestowed by Mental Health America (formerly the National Mental Health Association).

Thomas Laughren, M.D., is currently division director for the Division of Psychiatry Products, Center for Drug Evaluation and Research at the FDA. Prior to coming to the FDA in September 1983, Dr. Laughren was affiliated with the VA Medical Center in Providence, Rhode Island, and was on the faculty of the Brown University Program in Medicine. He received his medical degree from the University of Wisconsin–Madison, and he also completed residency training in psychiatry at the University of Wisconsin. Dr. Laughren is board certified in general psychiatry. As division director for the Division of Psychiatry Products, he oversees the review of all psychiatric drug development activities conducted under INDs and the review of all NDAs and supplements for new psychiatric drug claims. He has authored or coauthored many papers on regulatory and methodological issues pertaining to the development of psychiatric drugs and is a frequent speaker at professional meetings on these same

topics. Dr. Laughren has received numerous awards from FDA for his regulatory accomplishments.

Husseini K. Manji, M.D., is global head, neuroscience at Johnson & Johnson Pharmaceutical Research and Development LLC. He was previously chief, Laboratory of Molecular Pathophysiology & Experimental Therapeutics, NIMH, and director of the NIMH Mood and Anxiety Disorders Program, the largest program of its kind. He is also a visiting professor in the Department of Psychiatry at Duke University. Dr. Manji received his B.S. (biochemistry) and M.D. from the University of British Columbia. Following psychiatry residency training, he completed fellowship training in psychopharmacology at the NIMH and obtained extensive additional training in cellular and molecular biology at the National Institute of Diabetes and Digestive and Kidney Diseseas. The major focus of his ongoing research is the investigation of disease- and treatment-induced changes in gene and protein expression profiles that regulate synaptic and neural plasticity in mood disorders. His work has helped to conceptualize these illnesses as genetically influenced disorders of synaptic and neural plasticity and has led to the investigation of novel therapeutics for refractory mood disorders. Additionally, he has worked extensively on the development of diagnostic and treatment response biomarkers. Dr. Manji is a recipient of numerous research awards, including the A. E. Bennett Award for Neuropsychiatric Research, the Ziskind-Somerfeld Award for Neuropsychiatric Research, the NARSAD Mood Disorders Prize (Falcone Prize), the Mogens Schou Distinguished Research Award, the American College of Neuropsychopharmacology's (ACNP's) Joel Elkes Award for Distinguished Research, the Canadian Association of Professors in Psychiatry Award, the Henry and Page Laughlin Distinguished Teacher Award, the Brown University School of Medicine Distinguished Researcher Award, the Depression and Bipolar Support Alliance Klerman Senior Distinguished Researcher Award, the NIMH Award for Excellence in Clinical Care and Research, and the NIMH Director's Career Research Award for significant scientific achievement.

In addition to his research endeavors, Dr. Manji is actively involved in medical and neuroscience education endeavors and has served as a member of the National Board of Medical Examiners (NBME) Behavioral Science Test Committee, the Howard Hughes Medical Institute Research Scholars Program Selection and Advisory Committee, and numerous national curriculum committees. He developed and codirects the NIH Foundation for the Advanced Education in the Sciences Graduate

Course in the Neurobiology of Mental Illness and has received both the NIMH Mentor of the Year and NIMH Supervisor of the Year awards. He has published extensively on the molecular and cellular neurobiology of severe mood disorders and their treatments, is editor of *Neuropsychopharmacology Reviews: The Next Generation of Progress,* deputy editor of *Biological Psychiatry,* associate editor of *Bipolar Disorders,* and a member of the editorial board of numerous journals. He is a councilor of the ACNP, chairs the ACNP's Task Force on New Medication Development, and is president of the Society of Biological Psychiatry.

J. John Mann, M.D., is The Paul Janssen Professor of Translational Neuroscience (in psychiatry and in radiology) at Columbia University and chief of the Department of Neuroscience at the New York State Psychiatric Institute. Dr. Mann is trained in Psychiatry and Internal Medicine and has also obtained a doctorate in neurochemistry. His research uses functional brain imaging, neurochemistry, and molecular genetics to probe the causes of depression and suicide. Dr. Mann is the director of the NIMH Conte Center for the Neuroscience of Mental Disorders, director of the Stanley Center for Applied Neuroscience of Bipolar Disorders, and president of the International Academy of Suicide Research. He has published 401 papers and edited 10 books on the subjects of the biology and treatment of mood disorders, suicidal behavior, and other psychiatric disorders. In private practice he specializes in the treatment of mood disorders.

David Michelson, M.D., received his B.A. in English from Wesleyan University. Following a period of service as a teacher in the Peace Corps, he received his M.D. from the Albert Einstein College of Medicine in New York. He completed his internship and residency in psychiatry at Yale University, where he was also a chief resident and faculty member prior to moving to the National Institute of Mental Health as a member of the Clinical Neuroendocrinology Branch. During his tenure at the National Institute of Mental Health, Dr. Michelson's research focused on the HPA axis, including development of investigative methodologies for assessing HPA axis regulation and elucidating the pathophysiology and clinical sequelae of HPA axis activation in depression and multiple sclerosis. His work in this area has been published in the *New England Journal of Medicine* and in the *Journal of Clinical Endocrinology & Metabolism.*

Dr. Michelson joined Eli Lilly and Company as a clinical research physician in 1996. In 1999 he became the medical director and later senior medical director for the atomoxetine product team (Strattera, a com-

pound for ADHD) and led its clinical development and regulatory submissions in the United States and globally. In 2003 he became the executive medical director of the Neuroscience Therapeutic Area, with overall responsibility for overseeing Lilly's early-phase neuroscience clinical development program, including compounds with psychiatric, neurologic, and pain/migraine indications. He also was a member of Eli Lilly's corporate governance team, managing the company's early-phase portfolio. In 2006 Dr. Michelson joined Merck in his current position as the vice president for neuroscience and ophthalmology clinical research.

Matthew K. Nock, Ph.D., is the John L. Loeb Associate Professor of the Social Sciences in the Department of Psychology at Harvard University. He received his M.S. (2000), M.Phil. (2001), and Ph.D. (2003) in psychology from Yale University. He completed his clinical internship at the NYU–Child Study Center and Bellevue Hospital Center (2003) and joined the faculty of the Department of Psychology at Harvard University the same year. His research interests focus primarily on the etiology, assessment, and treatment of self-injurious and aggressive behaviors, particularly among children and adolescents. Current projects include the development and evaluation of laboratory and ecological assessment methods for evaluating processes associated with self-injurious and aggressive behaviors. A related line of his research focuses on the evaluation of treatments for impulsive, aggressive, and self-injurious behaviors and on factors that mediate and moderate clinical change.

Kelly Posner, Ph.D., is the founder and principal investigator of the Center for Suicide Risk Assessment at Columbia University/New York State Psychiatric Institute and an associate clinical professor at Columbia University College of Physicians and Surgeons. Her expertise lies in the areas of suicidality and medication effects. Amidst the controversy over the relationship between antidepressants and suicidality, the FDA commissioned a study led by Dr. Posner as part of its antidepressant safety analyses to develop methods of suicidality assessment and foster interpretability of data. This methodology to better identify and categorize suicidal occurrences, the Columbia Classification Algorithm of Suicide Assessment (C-CASA), was subsequently mandated to clinical trials of numerous non-psychotropic drug classes and centrally acting agents, including anticonvulsants, Singulair, and cannabinoid 1 receptor (CB1R) inverse agonists and provided data for all FDA-mandated analyses. The FDA has characterized this work as "setting a standard in the field." The Columbia Suicide Severity Rating Scale (C-SSRS) is the prospective ver-

sion of the C-CASA and is being used broadly across the field of medicine in many clinical and research domains. It is frequently mandated or recommended by various international agencies such as the FDA and European Medicines Agency. The C-SSRS is used for the assessment of suicidality across a wide range of settings: NIMH- and foundation-supported research trials, emergency rooms, hospitals, clinical practice, surveillance efforts, VAs, and programs for college campuses.

Dr. Posner continues to work with the FDA, CDC, NIMH, VA, and other agencies on suicide assessment, surveillance, and prevention and publishes and speaks internationally on the risks, benefits, and public health implications encompassed by recent drug safety controversies. *New York* magazine named Dr. Posner and her colleagues among New York's most influential people for their work on the safety of antidepressants, and in 2007 she was recognized as the Most Distinguished Alumni of Yeshiva University in the past 50 years. Most recently, Dr. Posner gave the invited presentation on tackling depression and suicide at the first European Union high-level conference on mental health.

William Z. Potter, M.D., Ph.D., is vice president, Franchise Integrator Neuroscience at Merck Research Laboratories, Inc. Prior to joining Merck he served as the executive director and Lilly clinical research fellow of the Neuroscience Therapeutic Area at Lilly Research Laboratories. He developed a Lilly/Indiana University fellowship early in 1996 and was named professor of psychiatry at Indiana University Medical Center. Before being associated with Lilly Research Laboratories, he held the position of chief, Section on Clinical Pharmacology, Intramural Research Program, at the National Institute of Mental Health in Bethesda, Maryland. He had been with the Public Health Service and the National Institutes of Health since 1971. He has authored more than 200 publications in the field of preclinical and clinical pharmacology, mostly focused on drugs used in affective illnesses and methods for evaluating drug effects in humans. He has received many honors during his career, including the 1975–1977 Falk Fellow, American Psychiatric Association; 1986 Meritorious Service Medal, U.S. Public Health Service; and, in 1990, St. Elizabeth's Residency Program Alumnus of the Year Award.

Marc Stone, M.D., is a senior medical reviewer specializing in safety issues in the Division of Psychiatry Products at the U.S. Food and Drug Administration. Dr. Stone is board certified in internal medicine and has had fellowship training in general internal medicine and clinical epide-

miology. For the past 20 years he has applied economic and epidemiologic techniques to the evaluation of medical practices and technologies, the critique of research design, and the assessment and synthesis of research data. Before coming to FDA, Dr. Stone worked for the Centers for Medicare and Medicaid Services, the Agency for Health Care Policy and Research, the Institute of Medicine, and the U.S. Agency for International Development.

Madhukar Trivedi, M.D., is currently a professor and chief of the Division of Mood Disorders in the Department of Psychiatry at the University of Texas Southwestern Medical Center at Dallas. He holds the Betty Jo Hay Distinguished Chair in Mental Health. Dr. Trivedi is an established efficacy and effectiveness researcher in the treatment of depression. He has focused his research on pharmacological, psychosocial, and other nonpharmacological treatments for depression.

Dr. Trivedi has been a principal investigator in multiple clinical trials funded through NIMH and the Texas Department of Mental Health. He has been involved with evidence-based depression guideline development since 1990, when he joined the Depression Guideline Panel of the Agency for Health Care Policy and Research (AHCPR). He has been the director of the Depression Algorithm for Texas Medication Algorithm Project since its inception. He has served as the chair of the Depression Work Group of the International Psychopharmacology Algorithm Project and as the scientific content expert for the San Antonio Cochrane Center's evidence-based, AHCPR-funded efforts to update the Depression Guidelines. He spearheaded the rollout of best practices for the treatment of major depressive disorder in various mental health and mental retardation centers across the state of Texas. He is also studying the effectiveness of treatments of depression in primary care.

Dr. Trivedi is the principal investigator of the Depression Trials Network Combining Medications to Enhance Depression Outcomes (CO-MED) trial, which focuses on the use of specific antidepressant combinations to increase remission rates by treating a broader spectrum of depressed patients and by capitalizing on additive pharmacological effects. He is also principal investigator of three current NIMH grants entitled "CBASP Augmentation for Treatment of Chronic Depression (REVAMP)," "Treatment with Exercise Augmentation for Depression (TREAD)," and "Computerized Decision Support System for Depression (CDSS-D)." Dr. Trivedi is also the co-principal investigator of the Texas Node of the NIDA-funded Clinical Trials Network and was the co-principal investigator of the NIMH-

funded project entitled "Sequenced Treatment Alternatives to Relieve Depression (STAR*D)."

Dr. Trivedi has mentored many psychopharmacology postdoctoral fellows and research–track residents over the past many years in Mood and Anxiety Disorders and is the principal investigator of an NIMH-funded postdoctoral T32 training program. He has received numerous awards including the Gerald L. Klerman Award from the National Depressive and Manic-Depressive Association Scientific Advisory Board—NDMDA and the Psychiatric Excellence Award from the Texas Society of Psychiatric Physicians—TSPP. He is or has been a member of several institutional review groups of the NIMH. Dr. Trivedi has published over 286 articles and chapters related to the diagnosis and treatment of mood disorders.

Robert Valuck, Ph.D., is a professor in the Department of Clinical Pharmacy at the University of Colorado Denver School of Pharmacy. His training and education include a B.S. in pharmacy from the University of Colorado and an M.S. and a Ph.D. in pharmacy (with an emphasis in pharmacy administration) from the University of Illinois at Chicago. His clinical research interests are pharmacoepidemiology (emphasis on psychotropic medications); health services research (HSR); evaluation of drug-related policy; development, implementation, and evaluation of computerized decision support systems (DSS) for optimization of prescribed pharmacotherapy; drug utilization review (DUR); and drug formularies. Dr. Valuck has received numerous honors and awards, including the Distinguished Investigator Award from the American Foundation for Suicide Prevention in 2007.