National Initiative to Prevent Suicide: A new proposal to improve the understanding and prevention of suicide

LONNIE BUSCH

Sheldon H. Preskorn, MD
Professor
Department of Psychiatry
University of Kansas School of Medicine-Wichita
Wichita, Kansas
Research Professor
Laureate Institute for Brain Research
Tulsa, Oklahoma

Dr. Preskorn is a Section Editor on the Current Psychiatry Editorial Board

Analyzing biological samples from suicide victims could yield valuable data for researchers

Suicide is a staggering, tragic, and growing cause of death in the United States. One out of every 62 Americans will die from suicide, based on the national lifetime prevalence rate.[1] More than 42,000 Americans died from suicide in 2014, making suicide the second leading cause of death in individuals age 15 to 34, the fourth leading cause among those age 35 to 54, and the tenth leading cause of death in the country overall.[2] The incidence of suicide in the general population of the United States increased by 24% between 1999 and 2014.[3] This tragedy obviously is not solving itself.

The proposal

U.S. Centers for Disease Control and Prevention (CDC) publishes statistics about the number of suicides, as well as demographic information, collected from coroners and medical examiners across the country. However, these sources do not provide a biological sample that could be used to gather data concerning DNA, RNA, and other potential blood markers, including those reflecting inflammatory and epigenetic processes. However, such biological samples are commonly collected by the U.S. medicolegal death investigation system. In 2003, this system investigated 450,000 unnatural and/or

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The goal is to take the data that is currently being collected, systematize it, enter it into a database, and make it available to researchers

Box

History of governmental efforts to address suicide prevention

For 20 years, the U.S. government and worldwide health organizations have attempted to reduce the risk of death by suicide. This effort began in 1996 when the World Health Organization (WHO) formally acknowledged the worldwide problem of suicide—which is still growing—and urged member nations to address suicide in a document, *Prevention of suicide: guidelines for the formulation and implementation of national strategies.*[7] In response to this call from WHO, a public–private partnership was created in the United States with the goal to develop a national strategy for suicide prevention. That partnership included the Department of Health and Human Services, the Centers for Disease Control, the Health Resources and Services Administration, the Indian Health Service, the National Institute of Mental Health, the Office of the Surgeon General, the Substance Abuse and Mental Health Services Administration, as well as the Suicide Prevention Advocacy Network, a public grassroots advocacy organization made up of suicide survivors (persons close to someone who died from suicide).

The first step in this initiative was a joint conference involving representatives of these agencies and researchers, medical and mental health clinicians, policy makers, suicide survivors, and community activists and leaders to analyze what was known and unknown about suicide and consider a potential public health model emphasizing suicide prevention in the United States. In 1999, David Satcher, MD, PhD, the U.S. Surgeon General, issued the *Call to action to prevent suicide*,[8] which was followed by the publication of a National Strategy for Suicide Prevention in 2001.[9] Eleven years later, Regina M. Benjamin, MD, MBA, then U.S. Surgeon General, issued an updated plan.[10] These documents provide an excellent review of the tragic statistics concerning suicide.

Unfortunately, this approach has not yielded the intended result and a new direction is needed—the author therefore proposes that we implement a war on suicide following the paradigm used in the successful War on Cancer started in the mid 1970s.

unexplained deaths (ie, approximately 20% of the 2.4 million deaths in the United States that year).[4]

Each unnatural or unexplained death is examined, often extensively, by a coroner or medical examiner. This examination system costs more than $600 million annually. Yet the data that are collected are handled on a case-by-case and often county-by-county basis, rather than in aggregate. The essence of the proposal presented here is to take the information and biological samples collected in this process and put them into a National Suicide Database (NSD), which then can serve as a resource for scientists to increase our understanding of the genetic, epigenetic, and other factors underlying death due to suicide. This increased understanding will result in the development more effective tools to detect to those at risk for suicide (ie, risk factor tests), to monitor treatment, and to develop new treatments based on a better understanding of the underlying pathophysiology and pathogenesis of suicide. These tools will reduce:

- the number of lives lost to suicide
- the pain and suffering of loved ones
- lost productivity to society, especially when one considers that suicide disproportionately affects individuals during the most productive period of their lives (ie, age 15 to 54).

The NSD will be organized as a government–private partnership, with the government represented by the National Institutes of Health (NIH) and/or the CDC. The goal will be to take the information that is currently being collected by the nation's medicolegal death investigation system, including the biological samples, systematize it, enter it into a common database, and make it available to qualified researchers across the country. The administrative arm of the system will be responsible for ensuring systematic data collection, storage in a searchable and integrated database housed within the NIH and/or the CDC, and vetting researchers who will have access to the data, including those with expertise in genomics, molecular biology, suicide, epidemiology, and data-mining. (Currently, the CDC's National Violent Death Reporting System, which is a state-based surveillance system,

pools data on violent deaths from multiple sources into a usable, anonymous database. These sources include state and local medical examiners, coroners, law enforcement, crime labs, and vital statistics records, but they do not include any biological material even though it is collected [personal correspondence with the CDC, July 2016].)

Because information on suicides currently are handled primarily on a county-by-county basis, data concerning these deaths are not facilitating a better understanding of the causes and strategies for preventing suicide. Correcting this situation is the goal of this proposal, as modeled by the National Cancer Institute's War on Cancer, which has transformed the treatment and the outcomes of cancer. If this proposal is enacted, the same type of transformation will occur and result in a reduction in the suicide rate and better outcomes for the psychiatric illnesses that underlie most instances of suicide.

The proposed NSD will address a major and common problem for researchers in this area—small sample sizes. When considered from the perspective of the size of samples feasible for most independent research teams to collect and study, suicide on an annual basis is rare—however, that is not the case when the incidence of suicide in the nation as a whole is considered. In contrast to the data concerning suicides that individual research teams can collect, the proposed genomic database will grow by approximately 40,000 individuals every year, until a meaningful reduction in deaths due to suicide is achieved.

From a research perspective, suicide, although tragic, is one of the few binary outcomes in psychiatry—that is, life or death. Although there may be >1 genetic and/or epigenetic contributor to suicide, within a relatively short period of time, the proposed database will amass—and continue to amass on an ongoing basis—data from a large population of suicide victims. Researchers then can compare the findings from this database with the normative human genome, looking for variants that are over-represented in the population of those who have died by suicide.

Environmental factors undoubtedly also contribute to the risk of suicide, given that the incidence of suicide increases with age, particularly among white males, and with the addition of psychiatric and medical comorbidities. Inflammatory processes also have been implicated in the pathophysiology of a number of psychiatric disorders, including major depression, which is the primary psychiatric risk factor for suicide. Therefore, consideration should be given to collecting whole blood samples if the time between death and autopsy is within an appropriate limit to obtain interpretable data concerning RNA (ie, gene expression) and even biomarkers of inflammatory and other processes at the time of the suicide. This approach has been used by Niculescu et al[5,6] for whole blood gene expression. The rationale for using samples of whole blood is that this strategy could be more easily adapted to clinical practice in contrast to using samples from the target organ (ie, brain) or cerebrospinal fluid.

Roadblocks to progress. In the absence of this proposed NSD, progress in this area has been stymied despite concerted governmental efforts (***Box***[7-10]). One reason for the lack of progress has been that governmental efforts have focused on a public health model rather than also including a basic science model aimed at exploring the biological mechanisms underlying the risk of death from suicide. In the current decentralized system, individual researchers and even teams of researchers cannot easily collect data from a sufficiently large population of suicide victims to make inroads in gaining the needed understanding.

Because of the relatively small samples that individual research teams can collect in a reasonable period of time (ie, in terms of grant cycles), many investigators have studied suicide attempts as a surrogate for suicide itself, undoubtedly because suicide attempts are more numerous than suicides themselves, making it easier to collect data. However, there is evidence that these 2 populations—suicide attempters vs those who die by suicide—only partially overlap.

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Recent research also has demonstrated a role for epigenetic and inflammatory processes as contributors to suicide risk

First, the frequency of suicide attempts is 10 to 20 times higher than actual suicides. Second, suicide attempters are 3 times more likely to be female whereas those who die by suicide are 4 times more likely to be male. Third, most individuals who die by suicide do so on their first or second attempt, whereas individuals who have made ≥4 attempts have an increased risk of future attempts rather than for completed suicide compared with the general population. Fourth, certain psychiatric illnesses are more often associated with death by suicide (particularly major depressive disorder, bipolar disorder, and schizophrenia in the first 5 years of an illness) whereas multiple suicide attempts are more often associated with other psychiatric diagnoses such as antisocial and borderline personality disorders.

Finally, in a study in men with a psychiatric disorder, Niculescu et al[5] started with 412 candidate genes and found that 208 were associated with suicidal ideation but not suicide itself, whereas 76 genes were associated with both suicidal ideation and completion. Taken together, this evidence suggests that findings concerning suicide attempters, especially those who have made multiple (ie, >3) attempts, might not be extrapolatable to the population of actual suicides.

Is there evidence that this proposal could work?

Yes, research supports the potential utility of the proposed NSD, and this section highlights some of the major findings from these studies, although this review is not intended to be exhaustive.

First, considerable evidence exists for a biological basis for the risk of death due to suicide. The concordance rates for suicide are 10 times higher in monozygotic ("identical") vs dizygotic ("fraternal") twins (24.1% vs 2.8%) and 2 to 5 times higher in relatives of those who die by suicide than in the general population. Heritability estimates of fatal suicides and nonfatal suicide attempts in biological relatives of adoptees who die from suicide range from 17% to 45%.[11]

Second, studies using information from small samples that was arduously collected by individual research groups have yielded important positive data. Most recently, in 2015, a multidisciplinary group led by Niculescu et al[5] at Indiana University and other institutions described a test that could predict suicidality in men. This test was developed on the basis of a within-participant discovery approach to identify genes that change in expression between states of no suicidal ideation and high suicidal ideation, which was combined with clinical information assessed by 2 scales, the Convergent Functional Information for Suicidality and the Simplified Affective State Scale. Gene expression was measured in whole blood collected postmortem unless the method of suicide involved a medication overdose that could affect gene expression. These researchers identified 76 genes that likely were involved in suicidal ideation and suicide.

This report had a number of limitations.[5] All of the individuals in these studies were being treated for psychiatric illness, were being closely followed by the investigators, and all were male. In addition, as noted above, suicides by overdose were eliminated from the analysis.

In a subsequent study published in 2016, the Niculescu group[6] extended their work to women and identified 50 genes contributing to suicide risk in women. Underscoring the need for larger samples, only 3 of the top contributing genes were seen in both men and women, suggesting that there are likely significant sex differences in the biology of suicide completion. This important work needs to be replicated and extended.

In addition to these remarkable advances made in genetic understanding of the risk of suicide, recent research also has demonstrated a role for epigenetic and inflammatory processes as contributors to suicide risk.[12-15]

There are likely many contributors, including genetic, epigenetic, and environmental factors such as inflammatory processes, that increase the risk of suicide. The goal of this article is not to provide an exhaustive or integrative review of research in this area but rather to argue for the estab-

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lishment of a national initiative to study all of these factors and to begin that process by establishing the NSD.

What will be the foreseeable outcome of this initiative?

The establishment of the NSD is expected to lead to better identification of those who are genetically at increased risk of suicide as well as biological factors (eg, inflammatory or other processes) and environmental factors (eg, drug abuse), which can turn that genetic risk into reality. Using research results made possible by the implementation of this proposal, objective testing can be developed to monitor risk more effectively than is currently possible using clinical assessment alone.

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Furthermore, this work also can provide targets for developing new treatments. For example, there is convergence between the work of Niculescu et al,[5,6] who identified genetic biomarkers for mechanistic target of rapamycin (mTOR) signaling as a risk factor in individuals who died by suicide and the work of Li et al and other researchers,[16-18] whose findings have implicated mTOR-dependent synapse formation as a mechanism underlying the rapid (ie, within hours to a couple of days) antidepressant effects of *N*-methyl-D-aspartate antagonists, such as ketamine, CP-101,606, and esketamine. In fact, the authors of a study presented earlier this year reported that esketamine—an active enantiomer of ketamine—rapidly reduced suicidal ideation as well as other depressive symptoms in individuals admitted to the hospital for suicidal ideation.[19] (mTOR is a serine/threonine protein kinase that regulates a number of biological processes in addition to synaptogenesis, including cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and autophagy.[20,21])

In aggregate, establishment of this proposed database will facilitate identification of biological (and therefore pharmaceutical) mechanisms beyond those involving biogenic amines, which have been the exclusive biological targets for antidepressants for the past 50 years.[22] The likely consequences of the findings generated from research made possible by the proposed NSD will open completely new vistas for helping people at risk for suicide and psychiatric illnesses.

What foreseeable obstacles will need to be addressed?

Of course, obstacles and problems will arise but these will not exceed those encountered by the War on Cancer and they can similarly be overcome with sufficient public support and cooperation. Potential obstacles include:

- need for incremental funding
- obtaining the cooperation of the offices of each county medical examiner or coroner in a process that includes uniform systematic data collection
- determining the situations (eg, time after death and means of death) that will allow for meaningful collection of data such as RNA and inflammatory biomarkers
- establishing how data and particularly biological samples will be transported and stored
- issues related to privacy of health information particularly for relatives of suicide victims
- ensuring the reliability, validity, and comparability of the data received from different medical examiners and coroners.

With regard to the last issue, because stigma is associated with death by suicide, some true suicides could be missed, which would compromise sensitivity but simultaneously increase specificity. Other obstacles or problems may arise; however, I am certain that all such issues are surmountable and that the resulting NSD will be much better than what we have now and will propel our understanding of the biological underpinnings of the loss of life to suicide. (The author proposed a similar but even more ambitious plan 25 years ago,[23] but he believes that this is an idea whose time has come.)

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