Editorial

Primary Prevention Research in Suicide

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Challenge

At the American Association of Suicidology's (AAS) 46th Annual Conference in Austin, Texas (http://www.suicidology.org/web/guest/education-and-training/annual-conference), participants were challenged to address why there has not been more progress in reducing the rates of completed suicides (Berman, 2013). A draft of recommendations from the National Action Alliance for Suicide Prevention's Research Prioritization Task Force was presented at the meeting and subsequently published in this journal (National Action Alliance for Suicide Prevention [NAASP], 2013a, 2013b). The purpose of this commentary is to address this challenge by emphasizing the importance of employing a disease etiology strategy that integrates molecular data with clinical data, environmental data, and health outcomes in a dynamic, iterative fashion.

The recommendations of the Research Prioritization Task Force tackle important public health program issues and are embedded within seven key questions, summarized as:

1. Why do people become suicidal?
2. How do we better detect/predict risk?
3. What interventions prevent suicidal behavior?
4. What are the effective services for treating suicidal persons and preventing suicidal behavior?
5. How do we reduce stigma?
6. What are the suicide prevention interventions outside of health-care settings?
7. Which existing and new infrastructure needs are required to further reduce suicidal behavior? (NAASP, 2013b; Silverman et al., 2013)

These recommendations build on decades of rigorous research focusing on the outcomes of suicide ideation, suicide attempt, or death by suicide and note the ongoing need for standardized taxonomies and nomenclatures.

Historical Perspective

The quest for standardized research tools and terminology in suicidology has been documented in a number of publications and reports. In 1985, McIntosh pointed out that "the term *suicide* refers not to a single action but more broadly to a great many varied behaviors. … A standard set of terms and definitions are greatly needed to advance the science of suicidology and aid communication and understanding of the field."

By 1995–96, the National Institute of Mental Health (NIMH) and the AAS formed a nomenclature working group to clarify the terminology used in the field to describe suicidal ideations and suicidal behaviors. The group proposed a "nomenclature for suicide and self-injurious thoughts and behaviors" (O'Carroll, Berman, Maris, Santa Mina, & Gallop, 1996).

In 2000, Rudd suggested that "what is needed is an inclusive conceptual framework that allows for direct clinical application of empirical findings across specific areas of functioning (i.e., cognitive, emotional, biological, behavioral, and interpersonal domains). Such a model would address the broad range of factors empirically validated as relevant, incorporating Axis I and Axis II diagnostic components." He suggested that cognitive theory and therapy offer a unique foundation for such integrative efforts (e.g., Alford & Beck, 1997).

In 2002, the IOM report *Reducing Suicide* recommended efforts to improve the monitoring of suicide, to increase the recognition and consequently the treatment of the primary risk factors in primary care, and to expand multidisciplinary efforts in prevention (Goldsmith, Pellmar, Kleinman, & Bunney, 2002).

Silverman and colleagues pointed out in 2007 (Silverman, Berman, Sanddal, O'Carroll, & Joiner, 2007a) that "measures of suicide and nonfatal suicidal behavior continue to be hindered by the lack of: a standard nomenclature; clear operational definitions" (Berman, Shepherd, & Silverman, 2003; De Leo, Burgis, Bertolote, Kerkhof, & Bille-Brahe, 2004, 2006; Farberow, 1980; Garrison,

McKeown, Valois, & Vincent, 1993; McKeown et al., 1998; Moscicki, 1989, 1995; Rudd & Joiner, 1998; Silverman & Maris, 1995; Smith, Conroy, & Ehler, 1984). They emphasized that reliable statistics on the numbers, types, and methods of nonfatal, intentional self-inflicted injuries, in conjunction with national and regional suicide mortality data, are required for the development, targeting, and evaluation of national and regional strategies (Moscicki, 1995). In a second paper, Silverman et al. (Silverman, Berman, Sanddal, O'Carroll, & Joiner, 2007b) continued to present a revised version of the O'Carroll et al. (1996) nomenclature for suicide that focused on suicide-related ideations, communications, and behaviors. They hoped that the revised nomenclature would result in the development of operational definitions and suggested field testing of this nomenclature in clinical and research settings (Committee on a Framework for Developing a New Taxonomy of Disease, 2011; Silverman et al., 2007b).

Recently, the Veterans Administration (VA) and Centers for Disease Control (CDC) presented the *Self-Directed Violence Classification System* representing the ongoing work of a team of scientists and collaborators from VISN19, including Silverman (Matarazzo, Clemans, Silverman, & Brenner, 2012; Matarazzo, Gutierrez, & Silverman, 2012). The team recognized the lack of an accepted taxonomy for suicide and concluded that a shared understanding of self-directed violence (SDV) in its various forms is critical. The VA currently is adopting the CDC's Self-Directed Violence Classification System (SDVCS), which is a taxonomy of terms and corresponding definitions for thoughts and behaviors related to both suicidal and nonsuicidal SDV. The SDV focuses on the final pathway of clinical behaviors and outcomes rather than a taxonomy that includes etiology. *These programs primarily address secondary prevention rather than etiology and/or primary prevention.*

Several efforts to promote "upstream suicide prevention" are being developed and tested. The report of an expert panel held in April 2013 under the auspices of the AAS and the Society for the Prevention of Teen Suicide comprehensively addressed the lack of success in reducing suicide rates in youth over the last decade and also noted that the "narrow focus of current youth suicide prevention paradigm" in current programs mostly addresses secondary prevention. This panel recommended addressing *early* prevention by reducing risk factors for suicidal behavior, promoting more competent settings in which children develop, reducing triggering events and conditions, enhancing intergenerational protective processes, and promoting transmission of protective norms (Suicide Prevention Resource Center, 2012). Several of these programs presented might be construed as representing a model of universal prevention, because "all individuals, without screening, are provided with information and skills needed to prevent the problem" (Gordon, 1987). The theoretical underpinnings of these programs rely on the impact of environmental insults rather than intrinsic risks (Gordon, 1987; O'Carroll et al., 1996).

The science of suicidology is not unique in facing the challenges of discovering the etiologies of a complex disease. Both medicine and public health have faced similar challenges as science in a particular area has evolved. For example, fever is a symptom that has engaged the attention of researchers since the early Greeks. Finally, in the 19th century, tools were developed that allowed scientists to move beyond observation to determine that fever is produced by a nonspecific immune pathway that has multiple specific triggers – both intrinsic and extrinsic. The study of fever has provided important models in understanding the functioning of cells, chemical messengers, and anatomic structures that are involved in inflammation and thermoregulation; these models have added to our understanding of important physiologic processes that are informing newer studies in many areas including cardiovascular disease and exercise (Rowsey, 2013).

During a similar period of history, the work of John Snow illustrates the importance of understanding etiology in developing sustainable public health policy. Most researchers recognize that Snow temporarily halted the cholera epidemic in the Soho district of London in 1854 by removing the Broad Street pump. Many do not remember that Snow's conclusions were not accepted by the local health authorities and the pump handle was reattached in a relatively short period of time. It was only when *Vibrio cholerae* was isolated and findings correlated with the Broad Street outbreaks that water safety became an *ongoing* process with universal precautions (UCLA Department of Epidemiology, 2013).

Establishing Etiologies

The NIMH has already formally recognized the importance of establishing etiologies and recently commented that the "lesson from other areas of medicine is that a diagnosis that relies solely on manifest symptoms is not the best guide to choose the most effective treatment. Precision medicine for mental disorders could be even more transformative than for cancer. Will subdividing syndromes based on molecular signatures, neuroimaging patterns, inflammatory biomarkers, cognitive style, or histories give us subgroups that are more responsive to certain medications or psychosocial treatments?" (Insel et al., 2010).

Nascent research is already occurring in the fields of population epidemiology, genetics, functional imaging, physiology, and pharmacology and the following studies are exemplar rather than exhaustive.

The contribution of genomics to understanding the etiology of suicide is ongoing. Genetic studies have been undertaken because multiple epidemiologic studies suggest patterns of inheritance for suicide and neurologic studies indicate serotonergic dysfunction. The results of the search for serotonergic genes and suicidal genes have been mixed and are leading researchers to look for gene–environmental interactions that increase the risk of suicidal behaviors (Antypa, Serretti, & Rujescu, 2013). Autopsy studies that compare those who died by suicide and those who do not using GWAS (genome-wide association study) show that

a large amount of promoter DNA is differentially methylated in the subjects' hippocampal areas. It is believed that such changes in DNA promoter methylation can affect gene expression and possibly behavioral changes (Labonté et al., 2013). Additional research is addressing specific psychiatric disorders. For example, research looking at the interaction between borderline personality disorder and environmental stimuli revealed individual variation in the risk attributable to an insult such as maltreatment, with recent studies showing that these variations may be due to genetic neuroplasticity. Specific polymorphisms are being considered (Bresin, Sima Finey, & Verona, 2013).

Other studies take clinical findings and return them to translational research. Thus, a rat model of major depressive disorder is probing the proteomic bases for preclinical disease and has shown that energy and glutathione metabolism are the most commonly affected pathways in depression (Yang et al., 2013).

Finally, etiologic work is benefitting from newer imaging techniques. Low serotonergic transport binding has been implicated in completed suicide via autopsy studies. Positive emission tomography (PET) studies have documented similar problems in patients with major depressive disorders (MDD). In a recent work, Miller et al. (2013) studied three groups of patients by PET examination to quantify serotonin transporter binding: MDD patients with no history of suicide attempt, MDD patients with a recent history of suicide attempt, and healthy controls. Suicide attempters had significantly lower serotonergic transporter binding than either of the other groups, suggesting that the etiology for the low binding may be more predictive than depression alone as a risk factor for suicide. Similar PET technology is also being used to develop a tool to follow the results of treatment for specific diseases associated with a high risk of suicide. Lan et al. (2013) performed an uncontrolled pretest–posttest measuring brain serotonin 1 levels in patients with bipolar disease. These levels were correlated with remission after 3 months of treatment with a drug. Although the number of remissions was small (9/51), higher levels of serotonin receptor binding before treatment were associated with a higher rate of remission. The study suggests that additional prospective studies are indicated to validate this as a tool for predicting outcomes of treatment.

Recommendations

In 2011, the Institute of Medicine released the report *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease* (Committee on a Framework for Developing a New Taxonomy of Disease, 2011). The report notes that a new taxonomy would integrate multiple parameters and "describe and define diseases based on their intrinsic biology in addition to traditional physical signs and symptoms; go beyond description and be directly linked to a deeper understanding of disease mechanisms, pathogenesis, and treatments; be highly dynamic, at least when used as a research tool, continuously incorporating newly emerging disease information."

To move the field forward, we recommend the Research Prioritization Task Force propose research taxonomy, based on the current state of knowledge about the etiology of suicide, with the full understanding that this taxonomy and our understanding of etiology will improve with additional advances in research. A positive outcome of adopting etiologically based research taxonomy would be to establish testable objectives in suicide research and ultimately lead to significantly lower rates of death by suicide.

One incremental approach to developing suicide research taxonomy, based on our current state of knowledge about etiology, may be to base the taxonomy on thought patterns. In our current research (Geis & Edlavitch, 2013), we have identified eight thought patterns along with four facilitative/protective and four clinical mediators that relate to suicidology. Another approach might be to adopt the Interpersonal-Psychological Theory of Suicide proposed by Joiner (2005). According to the theory, when people hold two specific psychological states in their minds simultaneously, and when they do so long enough, they develop the desire for death. The two psychological states are *perceived burdensomeness* and *a sense of low belongingness or social alienation*. The process of repeatedly experiencing painful and otherwise provocative events (acquired capability) enhances the ability to die by suicide.

Eventually, well-designed and controlled longitudinal studies will be required to confirm the etiological theory and its utility in reducing the rates of suicides. A research program that includes longitudinal epidemiological studies and clinical trials can be envisioned. The impact of pharmaceutical and nonpharmaceutical therapies on outcomes, as well as the secondary prevention programs already underway, will need to be explored in order to have a maximal effect in protecting lives.

Thus, recommendations of the AAS Expert Panel may be enhanced if they include an aspirational goal to identify the mechanisms, pathways, and primary prevention strategies in suicide research. Clearly, the ultimate goal of this research is to significantly lower the rates of suicides and the burden of suicide on our society. The idea that it is critical to develop, validate, and adopt the best research taxonomy in an iterative fashion recognizes in a substantive way that symptoms or disease may arise from multiple etiologies, and that disease may require interactions of innate and extrinsic factors. This aspirational goal also recognizes that developing comprehensive models requires considerable research with collaborative, multi- and transdisciplinary teams.

Acknowledgments

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