Hard Outcomes: Clinical Trials to Reduce Suicide

Suicide accounts for nearly 12 in 100,000 deaths in the United States each year, making it the third leading cause of death among individuals ages 15–24 and fourth among those ages 25–44 (1). Individuals with mood disorders are around 20 times more likely than the general population to die by suicide—and this is likely an underestimate, as it misses misclassified accidents and deaths among people who do not live long enough to have their illness diagnosed (2).

Remarkably, psychiatry as a field knows little about how, or even if, this outcome may be prevented pharmacologically, even for patients who are already being treated for a psychiatric illness. Only one large randomized trial has addressed the comparative efficacy of two treatments—clozapine and olanzapine—for preventing suicide attempts (3). Imagine the cardiovascular medicine literature ignoring stroke and myocardial infarction and being preoccupied instead with hypertension and hyperlipidemia. Ironically, failed outcome studies in psychiatry are often explained away because of the particular challenges of working with "softer" outcomes, while the hardest of outcomes is neglected entirely.

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In this issue of the *Journal*, Oquendo and colleagues (4) ask whether two standard treatments for bipolar disorder have differential effects on suicide risk in bipolar disorder. They apply what is considered the gold standard in clinical trials, a randomized double-blind design. Disappointingly, they detect no significant differences between lithium, for which a body of nonrandomized studies suggests increased efficacy in reducing suicide, and valproate, for which even robust maintenance data are lacking. As the authors acknowledge, however, a study of this size has the statistical power to detect only an extremely large difference: roughly a fivefold difference in risk between treatments.

Indeed, perhaps the most remarkable aspect of this study is that it was done at all, given the ethical and logistical hurdles involved. Studies of high-risk individuals face particular scrutiny from institutional review boards, wary of even the appearance that an intervention could hasten death. The feasibility of such studies also poses a unique challenge: while suicide is all too common, in absolute terms it remains relatively rare, requiring large cohorts to observe enough suicide attempts to detect differences between treatment arms.

Attempts to study populations enriched for risk—those who are recent attempters, those who are severely depressed, and patients who are early in their illness course, for example—might improve statistical power but would draw even more scrutiny from reviewers. These challenges present a true dilemma—the population in which studies are most feasible and acceptable may be the one least likely to experience the outcome of interest. Conversely, the high-risk population may be deemed "too sick to study" and may be difficult to enroll even once identified. Notably, even with a relatively inclusive design, the Oquendo et al. study was unable to meet its enrollment targets, randomizing fewer than one in six patients screened.

In the face of these challenges, how can psychiatry address hard outcomes? Outside of psychiatry, very large collaborative studies are the norm; such large studies are necessary to definitively address meaningful questions about relatively uncommon outcomes. Absent an influx of resources from the National Institutes of Health, large foundations, or the pharmaceutical industry, such studies are unlikely in the near future.

One of the alternatives most generally pursued is to do the possible: focus solely on standard efficacy measures, reasoning that effective treatments should improve all outcomes—thus, in bipolar disorder, target acute depression and focus on prevention of recurrence, recognizing the centrality of depression to suicide. (Insert "hypertension and hyperlipidemia" for depression, and the parallel with myocardial infarction is apparent.) Another strategy is to aim for surrogate outcomes that may more closely approximate suicide risk—impulsivity or hopelessness, for example—but are more readily assessed in trials.

Yet another alternative is to make better use of large-scale medical records systems and pharmacovigilance approaches—the same ones that initially suggested lithium's antisuicide benefit (5). These designs make traditional statisticians highly anxious because of the challenges in addressing confounding factors, which present an important limitation. In particular, the problem of confounding by indication can be substantial: absent random treatment assignment, it is possible that clinicians might select treatment based on some clinical feature that also predicts suicide risk. Still, modern approaches allow multiple sophisticated and complementary methods for addressing these concerns (6).

Oquendo et al. instead attacked the problem directly, and while the statistical power ultimately does not permit us to reach a definitive conclusion about the difference between lithium and valproate, we can nonetheless value their attempt for what it shows us about the challenges in caring for sick patients. Even in a leading research center devoted to the study and treatment of suicide, one-third of the patients made a suicide attempt during the study. For the clinician, the work of Oquendo et al. should not meaningfully change the evidence-based pharmacotherapy of bipolar disorder. Compelling reasons remain for favoring lithium for long-term treatment of bipolar disorder. APA treatment guidelines and their international counterparts continue to highlight lithium as a first-line treatment (7, 8), based on over 40 years of accumulated understanding of its strengths and limitations. The suggestive, albeit indirect, evidence of additional antisuicide benefit was simply another reason to choose lithium, and the inability of the Oquendo et al. study to confirm a very large effect of lithium compared with valproate does not diminish either rationale.

By addressing a hard question about a hard outcome, Oquendo and colleagues crystallize a central problem in psychiatry: What are the outcomes that matter most, and can we study them directly? As the field moves toward new definitions of illness in an era of increasingly constrained resources, clinical researchers and those who allocate resources to support them face hard choices.

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