Existing and Novel Biological Therapeutics in Suicide Prevention

Joshua J. Griffiths, MD, Carlos A. Zarate Jr., MD, J. J. Rasimas, MD, PhD

We summarize outcomes for several pharmacologic and neurostimulatory approaches that have been considered potential treatments to reduce suicide risk, namely, by reducing suicide deaths, attempts, and ideation in various clinical populations. Available treatments include clozapine, lithium, antidepressants, antipsychotics, electroconvulsive therapy, and transcranial magnetic stimulation. The novel repurposing of ketamine as a potential suicide risk–mitigating agent in the acute setting is also discussed. Research pathways to better understand and treat suicidal ideation and behavior from a neurobiological perspective are proposed in light of this foundation of information and the limitations and challenges inherent in suicide research. Such pathways include trials of fast-acting medications, registry approaches to identify appropriate patients for trials, identification of biomarkers, neuropsychological vulnerabilities, and endophenotypes through the study of known suicide risk–mitigating agents in hope of determining mechanisms of pathophysiology and the action of protective biological interventions.

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Introduction

According to the WHO, suicide ranks among the top three causes of death worldwide for those aged 15–44 years.[1] In 2009, deaths from suicide surpassed deaths from motor vehicle crashes in the U.S.[2] According to the CDC, the overall rate of suicide for both male and female Americans has shown a slow but gradual increase since 2000.[3] Since the 1950s, suicide rates have not decreased, despite the fact that more than six decades of research have produced scores of medications and other interventions for diseases of the brain.

Aspirational Goal 5 of the National Action Alliance for Suicide Prevention's Research Prioritization Task Force petitions the medical community to "find better ways to use existing biological treatments and discover improved new ones to prevent suicide."

Historically, the biologic treatment of suicide attempts and suicidal ideation has been approached with a focus on treating underlying DSM diagnoses associated with suicide (e.g., major depression, substance abuse, bipolar disorder, schizophrenia), with less emphasis placed on addressing suicide risk directly. The logic behind this approach is that of those who die by suicide, an estimated 60%–90% have some form of mental illness.[4,5] However, more treatments for mental disorders in general have not decreased suicide rates, and risk factors for suicide have been found to cross diagnostic categories.[6]

Furthermore, despite multitudes of efficacy trials for biological agents designed around DSM diagnoses, there are very few adequately powered RCTs examining the efficacy of biological treatments in preventing suicide deaths, attempts, and ideation as independent outcomes, according to several recent systematic literature reviews.[7,8] Patients with suicidal ideation and prior suicide attempts have traditionally been excluded from studies of biological treatments for DSM diagnoses on both scientific and ethical grounds. Most evidence for biological intervention in suicide prevention comes from post hoc analyses.[9] There is even debate as to whether drugs developed to treat certain DSM diagnoses, such as selective serotonin reuptake inhibitors, may actually increase the risk of suicide acutely in certain groups of patients (e.g., youth).[10]

Thus, future research should seek to understand suicide as a phenomenon not entirely dependent on a particular mental disorder but as a separate construct that is a final common endpoint of many forms and paths of human suffering. The DSM-5 takes a step in this direction. Even though it continues to reference suicide

From the Department of Psychiatry (Griffiths), University of Colorado, Denver, Colorado; Experimental Therapeutics and Pathophysiology Branch (Zarate, Rasimas), Intramural Research Program, National Institute of Mental Health, NIH, Bethesda, Maryland; and Departments of Psychiatry and Emergency Medicine (Rasimas), Penn State College of Medicine, Hershey, Pennsylvania

Address correspondence to: Joseph J. Rasimas, MD, PhD, Psychiatry & Emergency Medicine, University of Minnesota & Penn State College of Medicine, Staff Psychiatrist & Medical Toxicologist, HealthPartners/Regions Hospital, 640 Jackson Street, Mailstop 12002A, Saint Paul MN 55101. E-mail: joseph.j.rasimas@healthpartners.com.

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as a symptom of its major disorders listed in section 2, it contains two new diagnoses—non-suicidal self-injury and suicidal behavior disorder—in section 3 for disorders requiring further research. These diagnoses refer to suicide and suicidal behavior independent of any major mental disorder classification.[11]

On the basis of the current limited state of clinical science, we provide an overview and present credible evidence for biological interventions that may be protective against suicidal ideation, suicide attempts, and ultimately suicide deaths. It is important to note that the three are not synonymous, despite the former often being used as proxy for the latter two because its study entails fewer ethical and practical concerns. It is still unclear whether reductions in suicidal ideation and suicide attempts will directly result in reduction of suicide deaths. Additionally, different forms of psychotherapy and other promising psychosocial interventions have roles in prevention of suicide,[12] but they are beyond the scope of this paper and are not discussed here.

Data exist for the use of lithium and clozapine for prophylaxis against suicide attempts in select populations. Additionally, some weaker evidence for antipsychotics, antidepressants, and neurostimulatory interventions such as transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT) are presented. The potential role of novel fast-acting anti-depressants such as ketamine as agents for further study in the mitigation of suicide risk is then discussed. Finally, a closer look is taken at the challenges facing suicide research and suggestions made as to how these challenges might be overcome with an eye toward suicide risk–mitigating medical interventions.

Clozapine

Clozapine is an atypical antipsychotic medication used primarily to treat patients with schizophrenia after other more conventional medications have failed. It acts on multiple neurotransmitter systems, including dopamine, acetylcholine, serotonin, histamine, epinephrine/norepinephrine, gamma aminobutyric acid, and glutamate. This wide array of actions is largely responsible for the drug's broad, and potentially dangerous, side effect profile. However, clozapine is relevant to the discussion of suicide prevention as it is the only medication with a specific U.S. Food and Drug Administration (FDA) indication for "reducing the risk of recurrent suicidal behavior"—namely, "in patients with schizophrenia or schizoaffective disorder who are judged to be at risk of re-experiencing suicidal behavior."

Though it is used relatively infrequently in the general psychiatric population because of its side effect profile and the need to have frequent monitoring of white blood cells for agranulocytosis,[13,14] clozapine remains an important treatment given evidence for its efficacy in select circumstances. The indication for the use of clozapine to decrease suicide risk in patients with schizophrenia is based on the InterSept trial, a large, multicenter, international RCT with 2-year follow-up and a total of 980 patients with schizophrenia and schizoaffective disorder.

In this trial, olanzapine (a more commonly prescribed atypical antipsychotic) was compared to clozapine. The clozapine group showed a significant reduction in suicide attempts compared to the olanzapine group (hazard ratio of suicide attempt or hospitalizations to prevent suicide attempt of 0.76, 95% CI=0.58, 0.97). However, the data are modest owing to the relative rarity of suicide even within such a large sample—there was no statistically significant difference between the two groups in suicide deaths (five in the clozapine group versus three in the olanzapine group).[15]

The mechanism for this decrease in suicide attempts is unclear, as it might be related to the closer follow-up of clozapine patients given the required biweekly blood counts to monitor for agranulocytosis, a rare (about 1%) but dangerous reaction unique to clozapine among antipsychotic medications. Another possible mechanism is better symptomatic control of the psychotic illnesses for which patients take the drug.

Considering clozapine's unique and complex pharmacology, however, it may bear some anti-suicidal mechanism that involves simultaneous modulation of multiple neurotransmitters (i.e., dopamine, norepinephrine, and serotonin)[16]; hormones (e.g., pregnenolone, cortisol)[17]; or intracellular systems (e.g., cyclic adenosine monophosphate–dependent modulation of *N*-methyl-D-aspartate [NMDA] receptor expression, brain-derived neurotrophic factor upregulation, and regulation of the arachidonic acid cascade)[18,19]—mechanisms independent of that which provides psychotic symptom relief. This possibility demands further study.

Despite being the first drug to demonstrate a reduction in suicidal behavior in a large RCT, clozapine's proven efficacy is limited to a very select subgroup of patients with increased suicidal risk, and its burdensome and potentially dangerous side effect profile limits the possibility for broader clinical applications. This notwithstanding, the drug's various modes of action may be potential targets for future therapeutics for suicide reduction in other groups of patients, as the pharmacologic mechanisms mentioned above are implicated in successful treatment of many DSM diagnoses, not merely schizophrenia and schizoaffective disorder. Additionally, the InterSept trial itself may be used as a model for future studies to evaluate the effectiveness of biological interventions in preventing suicide attempts and deaths.