Existing and Novel Biological Therapeutics in Suicide Prevention

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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

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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.

Lithium

Lithium is one of the oldest and most widely used medications in the modern era of psychiatry. Its efficacy in the treatment of bipolar disorder, although still not mechanistically well understood, is unquestioned in the psychiatric community. There is also a reliable body of evidence to support its use as an augmenting agent to traditional antidepressants in the treatment of unipolar depression.[20] Its role in preventing suicide in patients with affective disorder is not as well established, though a significant body of evidence for this claim exists. It is hypothesized that rather than decreasing suicidal ideation, lithium mitigates suicide "secondarily," by diminishing impulsivity in many who attempt suicide.[21] Lithium impacts inositol cycling and has some neuroprotective potential, but it also displays a low therapeutic index.

Adverse effects and issues of dosing adherence represent significant barriers to its effectiveness and widespread use, particularly in patients at risk for suicide, as its toxicity profile often deters physicians from prescribing. Problems such as thyroid dysfunction, kidney dysfunction, cardiac arrhythmia, neurologic symptoms, as well as the risk of serious neurotoxicity, delirium, and convulsions when overdosed, make the decision to use lithium a serious one.

Unlike clozapine and the InterSept trial, no large randomized placebo-controlled study examining the effect of lithium on suicide has been published. However, many smaller RCTs comparing lithium to a variety of other drugs (antidepressants and anticonvulsant mood stabilizers) and placebo have been conducted. Some such studies are detailed in Table 1. Many of these trials include data regarding suicide deaths and suicide attempts.

Most notable among these was a study conducted by Oquendo et al.[23] comparing lithium to valproate in 98 patients with either bipolar disorder I, II, or not otherwise specified. This study had many unique strengths including relatively large sample size, extensive follow-up (2.5 years), and examination of both suicidal ideation and behavior. Additionally it included only patients with prior suicide attempts who would thus be expected to have a greater risk for suicidal behavior. It further stratified these patients by proximity of attempt (<1 year versus >1 year). The weaknesses of the study were its high attrition rate (approximately 50%) and its lack of placebo control. An intent-to-treat analysis showed no significant difference between lithium and valproate groups mostly owing to insufficient statistical power. However, this study is relevant not only because of its results but also its unique design.

Another slightly larger RCT of lithium versus placebo was conducted by Lauterbach[26] in 2008 in 167 depressed patients. This study included patients at higher risk for suicide, enrolling only those with a recent suicide attempt (<3 months). However, this study also suffered from a high attrition rate (only 31% retained at the 13-month follow-up). Post hoc analysis indicated that all recorded suicide deaths occurred in the placebo group. This study should be interpreted with caution but does provide some evidence for the use of lithium to address the risk of suicide in other forms of affective illness, not just bipolar disorder.

A meta-analysis of the pooled data from smaller trials was conducted in 2005 by Cipriani and colleagues.[31] In the combined lithium group, there were 2 suicide deaths out of a total of 503 subjects, and in the combined placebo/comparator drug group, there were 11 suicide deaths among 611 subjects (OR=0.26, 95% CI=0.09, 0.77). The analysis also showed a decrease in all suicidal behavior (8 events among 670 subjects in the lithium groups vs 18 of 781 in the placebo/comparator drug groups, OR=0.21, 95% CI=0.08, 0.51). Finally, all-cause mortality was examined and found to be lower in the lithium group than the comparator/placebo group (9/696 vs 22/788, OR=0.42, 95% CI=0.21, 0.87), suggesting that the effect of lithium may be beneficial in preventing death despite the threat of toxicity.

An update to this analysis was published in 2013 and included data from 48 RCTs with a total of 6,674 subjects.[32] Examined outcomes were once again suicide deaths, suicidal behavior (renamed "deliberate self-harm"), and all-cause mortality. Again, lithium was more effective than placebo and comparator drugs in preventing suicide deaths (OR=0.13, 95% CI=0.03, 0.66), but unlike the 2005 analysis, it did not show a significant difference in reduction of deliberate self-harm (OR=0.60, 95% CI=0.27, 1.32). All-cause mortality was, again, found to be decreased (OR=0.38, 95% CI=0.15, 0.95). Given the pooled sample size and the size of the effect on suicide mortality, the findings of Cipriani et al give fairly compelling evidence for the use of lithium in preventing suicide deaths.

A meta-analysis of 45 mostly open-label, naturalistic studies conducted by Baldessarini and colleagues[33] in 2006 communicated a similar message; they found a suicide death or suicide attempt event prevalence of 0.435% per year on lithium, compared with 2.63% per year off lithium, a near seven-fold decrease in risk for the pooled drug treated group.[34] Other similarly conducted meta-analyses have yielded concordant results.[35,36] The case for lithium as a suicide prevention agent in patients with bipolar disorder who are at risk for suicide is a relatively strong one, based on limited RCTs and cohort studies. However, the magnitude of this protective effect, the generalizability of this effect to other mental

Table 1. Summary of randomized medication trials evaluating suicidal ideation/behavior as a primary outcome

Study	Diagnosis	History of suicide attempt	Design/sample	Primary measures	Results
Grunebaum et al. (2012)[22]	MDD	Yes	DB, RCT, N=74, paroxetine (max 50 mg/day) versus bupropion (max 450 mg/day), 16 weeks	Suicidal attempt classification by weekly consensus; suicidal events by Columbia Suicide History Form; SSI	Depressed patients with greater baseline SI treated with paroxetine compared to bupropion appeared to experience greater acute improvement in suicidal ideation, after adjusting for global depression
Oquendo et al. (2011)[23]	BD	Yes	DB, RCT, N=98, lithium versus valproate, 2.5 years	Time to suicide completion; time to suicide attempt; time to suicide event; SSI	Intent-to-treat analysis showed no differences between treatment groups in time to suicide attempt or to suicide event
Khan et al. (2011)[24]	MDD	No	DB, RCT, N=80, parallel group; citalopram (20 mg/day) + placebo versus citalopram + lithium (300 mg/day), 4 weeks	At screening and trial end: suicidal thoughts/behaviors; S-STS; MADRS; CSSRS	No significant differences in primary outcome measures at 4 weeks; post hoc analysis showed patients assigned to citalopram + lithium had significantly higher S-STS remission rates
Rucci et al. (2011)[25]	MDD	No	Two-site, RCT, N=29, allocated to IPT or SSRI, 4 months	SI; Suicidality items from HDRS and QIDS	Time to suicidal ideation was significantly longer in patients allocated to SSRI compared to those allocated to IPT, even after controlling for treatment augmentation, benzodiazepine use, and comorbid anxiety disorders
Lauterbach et al. (2008)[26]	Affective spectrum disorders	Yes	DB, RCT, N=167, recent suicide attempts (<3 months), treatment with lithium or placebo, 12 months	Suicide attempt; SSI	Survival analysis showed no significant difference of suicidal acts between lithium and placebo; post hoc analysis revealed that all suicide deaths had occurred in the placebo group, with significant difference in incidence rate
Reeves et al. (2008)[27]	MDD	No	DB, RCT, placebo-controlled, N=24, antidepressant + risperidone (0.25–2 mg/day) versus antidepressant + placebo, 8 weeks	Severity of suicidality; SSI	Risperidone significantly reduced SI in MDD patients; overall effect of risperidone superior to placebo; the onset of effect was within 2 weeks of treatment and sustained for the 8-week course
Lauterbach et al. (2005)[28]	Absence of MDD or BD	Yes	DB, RCT, N=70, placebo-controlled multi-center trial evaluating proposed suicide preventive effects of lithium in patients with suicidal behavior	Number of suicide attempts or suicide deaths; SIS; Medical Damage Scale; Risk-Rescue Scale; SSI	SUPLI study terminated because number of enrolled individuals after 5 years was still below necessary estimated sample size

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Table 1. Summary of randomized medication trials evaluating suicidal ideation/behavior as a primary outcome *(continued)*

Study	Diagnosis	History of suicide attempt	Design/sample	Primary measures	Results
Meltzer et al. (2003)[16]	Schizophrenia/ schizoaffective disorder	Yes	Multicenter, RCT, N=980, international, clozapine versus olanzapine, 2 years	Suicide attempts/ completion; hospitalizations to prevent suicide; rating of "much worsening of suicidality" from baseline; CGI-SS	Clozapine therapy was superior to olanzapine therapy in preventing suicide attempts in patients with schizophrenia and schizoaffective disorder at high risk for suicide
Verkes et al. (1998)[29]	No DSM diagnosis	Yes	DB, RCT, N=91, paroxetine (40 mg/ day) versus placebo in patients who recently attempted suicide for at least a second time, 1year	suicide attempt; self-rating scales for depressive symptoms, anger; Axis II diagnoses	With adjustment for the number of previous suicide attempts, paroxetine showed significant efficacy in the prevention of recurrent suicidal behavior

Adapted from Mathews et al.[30]
BD, bipolar disorder; CGI-SS, Clinical Global Impression of Suicide Severity; C-SSRS, Columbia Suicide Severity Rating Scale; DB, double blind; HDRS, Hamilton Rating Scale for Depression; IPT, interpersonal therapy; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; QIDS, Quick Inventory of Depressive Symptomatology; SI, suicidal ideation; SIS, Suicide Intent Scale; SSI, scale for suicide ideation; SSRI, selective serotonin reuptake inhibitor; S-STS, Sheehan-Suicidality Tracking Scale; SUPLI, Suicide Prevention by Lithium—the Lithium Intervention Study

disorders, and the risk–benefit profile of its widespread use primarily as a suicide risk–mitigating agent are all topics for further debate and study.

Antidepressants, Antipsychotics, and Neurostimulatory Techniques

There are a variety of other agents used to treat psychiatric disorders related to suicide. Antipsychotics, antidepressants, and neurostimulatory therapies, such as TMS and ECT, have all been proposed as possible biological treatments for the prevention of suicide and suicidal behavior. Perhaps with the exception of the newer and less-studied TMS, these therapeutic agents are widely accepted in the psychiatric community as treatments for discrete DSM-diagnosed mental disorders.

Additionally, untreated mental illness, particularly depression, has been shown in epidemiologic studies to be a significant risk factor for suicide attempts and deaths.[37,38] Therefore, much of the current rationale for the use of these agents in decreasing suicide risk is based on this indirect yet widely accepted logic. The symptomatic relief these agents provide is generally supported by literature that is beyond the scope of this paper. Nevertheless, direct evidence for the efficacy of these agents in suicide prevention is not as compelling as that for lithium and clozapine. Second-generation antipsychotics are widely prescribed, yet the class effect of these medications on suicide—aside from the protective effect of clozapine—has yet to be explored in much detail.

One study[27] of note in patients with major depressive disorder examined augmentation strategies by comparing the effect of antidepressant plus risperidone to antidepressant plus placebo on suicidal ideation. It used the scale of suicidal ideation as well as other "suicidality" measures as outcomes. For the risperidone group, a significant effect on suicidal ideation was seen at 2 weeks that continued until the end of follow-up at 8 weeks. This study, however, suffered from a short follow-up (8 weeks) and low statistical power (N=24), and it examined suicidal ideation only without any data on suicidal behavior.

A post hoc analysis[39] of pooled secondary outcomes data from two 6-week studies with a total of 737 patients where augmentation of antidepressants with aripiprazole was examined showed no difference in "suicide-related adverse events," although it did show significant decreases in suicidal ideation with aripiprazole augmentation on both the Montgomery–Åsberg Depression Rating Scale and the Inventory of Depressive Symptomatology. A retrospective database study has suggested that better medication compliance with antipsychotics is associated with a decreased risk of suicide.[40]

Several RCTs have been conducted in recent years examining effectiveness of antidepressants in reducing suicidal ideation and behavior. One trial[22] compared bupropion to paroxetine and evaluated suicide attempts, deaths, and ideation; it showed greater improvement in suicidal ideation for paroxetine over bupropion in patients with more severe baseline suicidal ideation. Another[29] compared paroxetine to placebo with 91 participants who

had all attempted suicide for at least the second time within the last year. With adjustment for the number of previous suicide attempts, paroxetine showed significant efficacy in the prevention of recurrent suicidal behavior. Both studies were relatively unique in that they included subjects at significant risk for suicide with active suicidal ideation.

Augmentation of the antidepressant citalopram with lithium has also been examined in a study[24] of 80 patients for 4 weeks. Although there was no difference in primary outcomes (suicidal thoughts and behaviors) at the 4-week point, a post hoc analysis showed that patients assigned to citalopram plus lithium had significantly higher Sheehan-Suicidality Tracking Scale remission rates—in these studies and several others summarized in Table 1. The observational studies also show a link between prescription rates of antidepressants and a decrease in the incidence of suicide, but the results of meta-analyses have been mixed.[41]

There is some evidence that the additional prescription of antidepressants or antipsychotics to an existing prescription of an anticonvulsant may actually increase the risk of suicide attempt in patients with bipolar disorder.[42] Additionally, for therapeutic efficacy, these interventions may take weeks to months to find the optimal blend of compounds and doses. During such times of trial and titration, a patient may remain at significant risk for suicide.

ECT is an intervention for which its role in suicide prevention is not based on any robust, formalized study, but rather relies on a long clinical history of successful use in the treatment of depression associated with suicidal thoughts and behaviors. Despite expert consensus that ECT is effective, it has a limited role in the general prevention of suicide given its cost, limited availability, and procedural logistics with associated stigma. Each treatment requires several hours for administration of anesthesia and recovery in a monitored medical setting, and it is generally given 3 times per week for 2–4 weeks, making it a very involved process for patients, clinicians, and family members. Unlike the pharmacotherapies discussed above, convulsive treatments can work rather quickly to reduce suicidal ideation, but their long-term impact is not as clear, and the potential for cognitive side effects can be limiting.

TMS is a newer neurostimulatory technique that is less invasive than ECT and does not require sedation. It utilizes alternating magnetic fields to induce neuronal firing in targeted brain regions. In a recent trial[43] that included some patients with a history of suicide attempt, TMS was shown to have an effect on depressive symptoms, including suicidal ideation, comparable to that of a 6-week course of standard antidepressant medications. One weakness of the study was it did not take into account the proximity of attempts to the treatment. Direct evaluation of this novel therapy with regard to suicide has not been conducted.

Ketamine or Ketamine-Like Compounds

Ketamine is an anesthetic agent that works on the glutamatergic system by specifically antagonizing NMDA receptors. Ketamine has been used and FDA approved as a general anesthetic agent since the 1970s, but it does sometimes precipitate transient psychotomimetic reactions, and these central nervous system (CNS) effects are related to its recreational use and abuse.

Until recently, its use had been largely limited to pediatric and veterinary populations, but utility for emergency procedures and management of chronic pain syndromes has been demonstrated. And in the past 10 years, evidence has emerged that ketamine has rapid-acting antidepressant properties, even at lower, subanesthetic doses. This effect is seen as early as 40 minutes after IV infusion and typically lasts 3–7 days, with some patients experiencing improved mood beyond 7 days.[44–46] The effect is thought to be mediated by molecular cascades that promote synaptic plasticity and dendritic spine maturation in key brain regions.[47]

Ketamine is generally well tolerated at low doses, with the most common side effects being transient and limited to the infusion period (generally 40–60 minutes), including transient increases in blood pressure and heart rate, mild dissociative symptoms such as dizziness, derealization, and depersonalization, and transient neurologic symptoms such as aphasia, diplopia, nystagmus, and paresthesias. These side effects only rarely are severe enough to lead to termination of infusion. One challenge of using ketamine as an antidepressant, though, is its potential for abuse and associated classification as a controlled substance. Efforts are being made to explore the efficacy of ketamine-like agents that act on the same brain systems but have a more favorable side-effect profile and lower addictive potential (e.g., GLYX-13 and AZD6765).[48,49]

Although no studies directly examining the effect of ketamine on suicide attempts and deaths have been completed, there is a significant body of evidence for its rapid effect on mood in patients with suicidal ideation. There have been several RCTs conducted in the last decade demonstrating the rapid antidepressant effect of ketamine in both bipolar and unipolar depression, even that refractory to other treatments.[44,45] Suicidal tendencies and thoughts that are conceptualized as part of these depressive conditions appear to remit just as rapidly as the overall syndrome.[50]

This may give a rapid-acting agent such as ketamine an advantage in the acute management of suicide risk

over traditional antidepressants with effects that may be more enduring with consistent daily dosing but take much longer to develop. There may be mechanistic grounds for this rapid effect, as new research connects inflammatory markers of depression with physiologic glutamate agonism in suicidal patients,[51] a clinical state that ketamine's NMDA antagonism rapidly reverses with potentially protective effects.

Because of the prolonged period between the initiation of treatment and the onset of action of most currently available antidepressant medications (often 2 weeks or more), there is little that can be done in the setting of acute and serious suicidal ideation aside from close monitoring or hospitalization. This could make ketamine and other potential rapid-acting antidepressant medications uniquely suited for acute biological intervention in suicide prevention. One open-label study in the emergency setting showed significant reductions of suicidal ideation on a standardized depression rating scale just 40 minutes after IV bolus administration of low-dose ketamine.[52] NMDA agents certainly warrant further investigation as part of strategies intended to reduce suicide deaths.

Conclusions and Future Research

Direct study of patients at high risk for suicide with particular attention to the acute precipitants and related opportunities for intervention will always be challenging. In such vulnerable populations who suffer rare but lethal events, it is particularly difficult to test single interventions the way that we expect in high-quality biomedical studies. To simultaneously monitor and ensure safety while controlling for therapeutic variables apart from a purported suicide risk–mitigating treatment itself is complicated, based upon what we know about the impact of psychosocial care, relatedness, and even the passage of time in a monitored environment.

Studies of suicidal ideation, though much easier to conduct from an ethical and logistic perspective, may not translate well to the more relevant outcomes of suicidal behavior and mortality. Sufficiently large, practical, multi-site studies using patient registries are needed so that larger-scale data can be gathered to assess treatment effects and track long-term outcomes. Many in the field are now advocating greater standardization of methodology and outcomes measures (e.g., suicidal ideation versus suicidal behavior versus suicidal mortality) to improve the shelf life and compatibility of data collected in smaller studies.[53]

For compounds that already appear to be beneficial, pharmacologic study coupled with neurobiological techniques such as functional neuroimaging, CNS spectroscopy, polysomnography, and genetic analysis may reveal what is vulnerable about patients and, correspondingly, what is protective about drugs like lithium and clozapine. Many psychological vulnerabilities place individuals at risk for suicide, including hopelessness, poor self-esteem, impulsivity, deficient problem-solving skills, disadvantageous decision making,[54] poor reality testing, and cognitive rigidity.

Yet, the neurobiological mechanisms of these vulnerabilities and their related constructs remain unexplicated; thus, it is difficult to discern how proposed biological agents could act to mitigate them at a neurophysiological level. Study of the nature of the neurobiological principles involved in suicidal vulnerability and resilience may lead to the tailoring of therapeutics to specific patient needs.

More sophisticated characterization of suicidal individuals should also be useful in its own right. Identifying DSM diagnostic entities and testing treatments designed to address them has not reduced rates of suicide. It is time for a shift in thinking about what a patient at risk for suicide is and what a suicide risk–mitigating drug would do. There are a number of different reasons why different types of individuals end their own lives. Assembling typologies of individuals based upon different factors of history, phenomenology, behavior, and advanced neurobiology together is likely to reveal certain therapies (both established and novel) that are helpful to different individuals.

Such research could reveal endophenotypes of suicidal individuals with new biological targets as well. Typological categorization of patients and of suicide risk itself would also serve as the foundation for detailed assessment of new therapies. One clinical reality supporting this mode of categorization is the tremendous comorbidity of psychiatric disorders and symptoms in those who attempt suicide. Diagnostic comorbidity has been shown to be one of the greatest predictors of suicide, though this finding has not yet put medical science closer to realistic prevention strategies.[55]

More sophisticated interventions should emerge from studies designed to understand suicide at the interface of biology with other factors—many of which are environmental—that impact risk. One recent study using an integrative approach to assess multiple variables demonstrated gender differences in suicide attempters related to a history of suffering abuse and markers of function (cortisol, dehydroepiandrosterone sulphate, and serotonin) in different neurobiological systems.[56] The findings of the study did not point to a simple chemical lesion or common CNS locus of self-destruction, but instead reflect the complex reality of factors that must be considered when targeting physiology for prevention.

Lastly, any assessments and innovations must account for the impact of time. Just as its passage is the ultimate arbiter of mortality for everyone, time also greatly impacts

the experience of and response to suicidal individuals. Some biological interventions may modulate traits, whereas others may be state-specific in their suicide risk–mitigating effects. Patients spend much more of their lives in non-clinical settings where trait-based treatments may be more effective, but many more variables and risk factors are at play at those times, making the systematic study and effective implementation of such treatments challenging. On the other hand, clinic- and hospital-based treatments of acute states, although more easily studied and systematized, may not provide lasting effects in the prevention of suicide.

Additionally, optimism about any intervention must be tempered by the realities of access and delivery. Though the prospect of discovering a rapidly acting biological agent to mitigate acute suicide risk may seem ideal for practice in the acute setting, one must also account for the daily existence that patients face outside the context of care—one that often still places them at high chronic risk for suicide.

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