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Preventing Suicide: A Multicausal Model Requires Multimodal Research and Intervention

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Suicide is devastating to individuals, families, institutions and communities. Suicidal behavior remains difficult to predict, as the underlying dynamics of suicidal behavior are inordinately complex and rely on biology, psychology and environmental factors. It is therefore unlikely that one theory or model can account for all suicidal behavior, even when limited to a single diagnosis.

In their review, Malhi and colleagues¹ perform essential work to synthesize multiple neurobiological, neurocognitive and psychological theories into one model of distal and proximal factors leading to suicidal thoughts and behaviors. Crucially, the authors have integrated neurobiological and psychological research out of their respective silos to examine how recent findings from each field may interact and support each other. Such an approach is vital for true progress in understanding suicidal behavior.

We argue that a similar approach is also required for the research in and treatment of suicidal thoughts and behavior. A suicide prevention strategy could be just as multifactorial and respectful of underlying biological, psychological and environmental influences on suicidal behavior. Just as there is no one simple explanation for all suicidal behavior, there is unlikely to be one monolithic “treatment” that will be useful for all patients.

As detailed in the integrated model, there is a wide range of distal and proximal risk factors for suicide. Risk factors for suicide begin at birth and early childhood, ranging from familial, genetic or epigenetic factors to adverse childhood experiences and abuse. As the individual ages, he or she may develop specific psychopathologies or cognitive biases that place them at long-term risk for suicidal behavior. At the end of this trajectory is the rapid tumult of the active suicidal crisis, in which the individual decides to act on suicidal thoughts. Much of the current treatments occur at this “middle phase” of suicide risk, but usually addresses only one or a few of multiple implicated factors. Traditional pharmacologic treatment including medications such as lithium, clozapine or SSRIs as well as psychotherapies such as CBT or DBT often target underlying psychopathology or cognitive appraisals and biases leading to

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Conflict of Interest:

Dr. Zarate is listed as a co-inventor on a patent application for the use of ketamine and its metabolites in major depression. Dr. Zarate has assigned his rights in the patent to the U.S. Government but will share a percentage of any royalties that may be received by the Government. The remaining authors have no conflicts of interest to disclose, financial or otherwise.

suicide risk. At the same time, these treatments are bound by timing limitations: 1.) they can only be initiated after the development of psychiatric symptoms (or suicidal thoughts or behaviors), 2.) as these treatments have a delayed onset of effects for weeks to months for full effect, they cannot treat a time-limited suicidal crisis, and 3) many do not benefit from them; in fact, there has been a significant rise in suicide² despite an armamentarium of treatment options. It is possible to imagine a range of interventions bookending these treatments, targeting the very distal and immediately proximal aspects of suicide risk. For the sake of example, we will describe two very different interventions: the Good Behavior Game (GBG) and the glutamatergic modulator, ketamine.

The GBG is representative of numerous early childhood interventions with long term effects. Specifically, the GBG is a classroom-based intervention, often implemented in the first few years of school. Students in this intervention are exposed to a prosocial classroom management strategy, in which positive behaviors are reinforced. The GBG has been associated with a number of later outcomes, including reduced aggressive behavior, substance dependence, criminal behavior as well as decreased suicidal ideation and behavior at 15 year follow-up.³ Therefore, a childhood intervention *which is implemented before the emergence of most psychiatric diagnoses and/or suicidal thoughts or behavior* can have impressive long-term impact. One could imagine comparable interventions for the prevention of child abuse or early intervention with children at high familial risk for suicidal behavior, evaluated for similar impact on long term suicide risk.

In distinct contrast to the long-term impact of the GBG, off-label use of ketamine is geared to proximal events, although not FDA approved for the treatment of suicide or depression. Originally used as an anesthetic, ketamine has an established literature as a rapid-acting antidepressant and a burgeoning interest in the relationship of the intervention to suicidal thoughts. A recent meta-analysis of the current literature demonstrated that ketamine has a rapid impact on suicidal thoughts, lasting up to one week.⁴ An evaluation of ketamine in a sample of bipolar patients with active suicidal thoughts found a reduction in suicidal thoughts at the trend level.⁵ Therefore, it is possible that interventions such as ketamine *could have a short-term, near-immediate impact on suicidal thoughts*, thereby decreasing suicide risk in the short-term before other longer term interventions take effect. Of course, such a perspective is not limited to ketamine and can include interventions with short-term impact such as ECT or psychotherapeutic approaches such as safety planning.

In summary, it is clear that a multicausal, multifactorial model for suicide risk is needed for bipolar disorder and all psychiatric diagnoses. Similarly, multimodal suicide prevention is also indicated, which includes both distal and proximal intervention as well as pharmacologic and psychotherapeutic treatment. In pursuit of personalized medicine for all patients, it is likely that our perspective and approaches will shift to consider early life intervention, traditional pharmacologic/psychotherapeutic treatment and rapid-acting emergency procedures across the continuum of suicide prevention for both research and intervention.

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References

1. Malhi GS, Outhred T, Das P, Morris G, Hamilton A, Mannie Z. Modeling suicide in bipolar disorders. *Bipolar Disord*. 2018; Available Online 19 Feb 2018. doi: 10.1111/bdi.12622
2. Curtin SCWM, Hedegaard H. Increase in suicide in the United States, 1999–2014. Hyattsville, MD: 2016.
3. Wilcox HC, Kellam SG, Brown CH, et al. The impact of two universal randomized first- and second-grade classroom interventions on young adult suicide ideation and attempts. *Drug Alcohol Depend*. 2008; 95(Suppl 1):S60–73. [PubMed: 18329189]
4. Wilkinson ST, Ballard ED, Bloch MH, et al. The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis. *Am J Psychiatry*. 2017 appiajp201717040472.
5. Grunebaum MF, Ellis SP, Keilp JG, et al. Ketamine versus midazolam in bipolar depression with suicidal thoughts: A pilot midazolam-controlled randomized clinical trial. *Bipolar Disord*. 2017; 19(3):176–183. [PubMed: 28452409]