

# Suicide Prevention and Emerging Interventions: Implications for Psychedelic Substances

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## Abstract:

Suicide rates in The United States have increased by 30% over the last two decades. Current risk stratification tools are overly broad and limit their clinical implementation and predictive capacity. Likewise, suicide prevention interventions are limited and most commonly proposed intervention lack sufficient evidence to support their widespread use. This paper sets out the 3-Ms model for suicide prevention utilizing mitigation, means restriction, and medication measures. It reviews the current supporting literature for each of these major groups. Finally, this article discuss the potential practice changing impact that psychedelics could have on effectively managing suicide, whether that is as a single administered compound or in combination with psychotherapy in the form of psychedelic assisted psychotherapy.

KEYWORDS: suicide, suicide prevention, psychedelics, psychedelic assisted psychotherapy

## INTRODUCTION

Suicide, or taking one's own life, is one of the most severe complications that can occur during a patient's treatment course. Suicide is an all-too-common occurrence and, as of 2020, was the 9th leading cause of death in the United States, claiming almost 46,000 lives which were more than two times more than the number of homicides that year [1]. Suicide is the second leading cause of death for individuals aged 10-14 and 25-34, respectively, and disproportionately afflicts males at a rate of 3.7 times higher than females [1]. Over the past two decades, there has been a 30% increase in the number of total suicides in the United States [1]. This increase has undoubtedly been due to difficult socioeconomic factors and the emerging opioid epidemic. As a result, suicides in this cohort have been labeled "deaths of despair." Poisoning or overdose ranks as the third most common method of suicide behind firearm use and suffocation but has been steadily increasing since 2008 [1]. The rising rate of suicide and associated psychiatric conditions

that often precede or accompany it has substantially impacted the United States. According to 2013 estimates, the total cost of suicide was 93.5 billion dollars, with 97% of that being due to lost productivity and only 3% due to medical expenses incurred by suicide or suicide attempts [2].

Suicide has been a persistent problem within Psychiatry and mental health for decades. While significant progress is being made regarding effective evaluation and risk stratification, little progress has occurred concerning interventions to prevent or reduce suicidal thoughts and behaviors. With the reemergence of psychedelics in clinical practice, it is crucial to determine their potential implications for suicide prevention and mitigation and how they compare to the current standards of care.

## SUICIDE EVALUATION

When evaluating a patient for suicidal tendencies, it is essential to differentiate between suicidal thoughts and suicidal behaviors. Suicidal thoughts can be broken down i

nto hopelessness, passive suicidal ideation, and active suicidal ideation. Hopelessness in the suicidal context is often described as "not wanting to live like this anymore." Patients also often state that they would not care if they did not wake up tomorrow. Notably, there are no thoughts of wanting to harm themselves but rather a totalizing sense of apathy devoid of purpose or sustaining meaning. Gradually hopelessness can evolve into suicidal thoughts. Passive suicidal ideation is the most common type of suicidal thought and is characterized by non-specific thoughts of wanting to end one's own life. However, patients with passive suicidal ideation have not devised a method for harming themselves and have no current intent or plan to do so. This is in sharp contrast to active suicidal ideation.

Active suicidal ideation ranges in severity from low to high. Low severity active suicidal ideation is characterized by thoughts of suicide with at least one accompanying potential method by which the suicidal act could be accomplished. However, a specific plan and intent are both absent. In moderate severity active suicidal ideation, a plan has been developed and sufficiently thought out, but the intent is still lacking. Finally, in high severity, suicidal ideation suicidal thoughts are present, and the patient has a specific plan and intent to harm themselves. It is typically during periods of active suicidal ideation when a patient moves from suicidal thoughts only and begins to engage in suicidal behaviors.

Suicidal behaviors, like active suicidal ideation, range in severity from low to high. Low severity suicidal behaviors include taking preparatory actions to carry out a suicide attempt. These actions can include but are not limited to purchasing a drug to overdose on, purchasing a firearm, giving away possessions, or writing a suicide note. In contrast, moderately severe suicidal behaviors are characterized by a patient who took steps to

attempt suicide but either stopped themselves or was stopped by someone or something else prior to engaging in the act. Examples of this type of behavior would be a patient walking to a high height but deciding not to jump or being talked out of it. Comparatively, high severity suicidal behaviors are defined as a potentially self-injurious act committed with at least some wish to die because of the act. Even if no injury occurs if there was any intent or desire to die, it should be considered a high severity suicidal behavior and suicide attempt.

A typical example would be a patient placing a firearm to their head and pulling the trigger and the gun not going off; this should be considered a suicide attempt regardless of the outcome. Behaviors of this kind are in contrast to non-suicidal self-injury, which is the deliberate, direct destruction or alteration of body tissue without conscious suicidal intent. Non-suicidal self-injury often results in an injury severe enough to damage underlying tissue. Given the wide variety of potential patient presentations, it can be challenging to extract a tangible set of symptoms that could be used to identify the patients in most need of help.

## **RISK STRATIFICATION**

Before diving into an in-depth analysis of the literature surrounding suicide-related risk factors, it is imperative to establish a common and shared vernacular to assess this literature. The process of risk stratification begins by identifying a potential correlation, which in its most basic form is a factor that appears to be associated with another factor. From this basic observation, a risk factor can be hypothesized and tested. For this article, a risk factor is a specialized type of correlation that precedes an outcome of interest, in this case, suicide, and is therefore used to partition a population into low and high-risk groups. More specific than general risk

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factors are causal risk factors, a more specialized subset of risk factors. The differentiating factor between a general risk factor and a causal risk factor is that causal risk factors precede suicide, and manipulation of the intensity or severity of the risk factor directly changes the probability of a suicide event occurring. General risk factors are considered an on-off switch, whereas causal risk factors are better analogized as a dimmer switch that modulates intensity. Insofar as the quality of the information goes, causal risk factors are both *predictive and valuable treatment targets*, risk factors are *predictive but less valuable treatment targets*, and correlations are likely *poor predictors and ineffective treatment targets*.

A complete analysis of the literature surrounding suicidal risk factors can be undertaken with all that information in mind. As of this writing, in 2022, the list of risk factors varies greatly across public health institutions. Looking at the Centers for Disease Control (CDC), National Institute of Mental Health (NIMH), and World Health Organization (WHO) yields a plethora of different results:

	Risk Factors
CDC [3]	Previous suicide attempt, Mental illness, such as depression Social isolation, Criminal problems, Financial problems, Impulsive or aggressive tendencies, Job problems or loss, Legal problems, Serious illness, Substance use disorder, Adverse childhood experiences such as child abuse and neglect, Bullying, Family history of suicide, Relationship problems such as a break-up, violence, or loss, Sexual violence, Barriers to health care, Cultural and religious beliefs such as a belief that suicide is noble resolution of a personal problem, Suicide cluster in the community, Stigma associated with mental illness or help-seeking, Easy access to lethal means among people at risk (e.g. firearms, medications), and Unsafe media portrayals of suicide
NIMH [4]	A history of suicide attempts, Depression, other mental disorders, or substance use disorder, Chronic pain, Family history of a mental disorder or substance use, Family history of suicide, Exposure to family violence, including physical or sexual abuse, Presence of guns or other firearms in the home, Having recently been released from prison or jail, Exposure, either directly or indirectly, to others' suicidal behavior, such as that of family members, peers, or celebrities
WHO [5]	Mental disorders (in particular, depression and alcohol use disorders), a breakdown in the ability to deal with life stresses, such as financial problems, relationship break-up or chronic pain and illness, experiencing conflict, disaster, violence, abuse, or loss and a sense of isolation are strongly associated with suicidal behaviour. Suicide rates are also high amongst vulnerable groups who experience discrimination, such as refugees and migrants; indigenous peoples; lesbian, gay, bisexual, transgender, intersex (LGBTI) persons; and prisoners. By far the strongest risk factor for suicide is a previous suicide attempt.

Additionally, the NIMH also describes a set of warning signs for potential suicide attempts:

	Warning Signs
NIMH [4]	Talking about wanting to die or wanting to kill themselves, Talking about feeling empty or hopeless or having no reason to live, Talking about feeling trapped or feeling that there are no solutions, Feeling unbearable emotional or physical pain, Talking about being a burden to others, Withdrawing from family and friends, Giving away important possessions, Saying goodbye to friends and family, Putting affairs in order, such as making a will, Taking great risks that could lead to death, such as driving extremely fast, Talking or thinking about death often, Displaying extreme mood swings, suddenly changing from very sad to very calm or happy, Making a plan or looking for ways to kill themselves, such as searching for lethal methods online, stockpiling pills, or buying a gun, Talking about feeling great guilt or shame, Using alcohol or drugs more often, Acting anxious or agitated, Changing eating or sleeping habits, Showing rage or talking about seeking revenge

The Werther and Papageno effects further complicate the discussion about suicide risk stratification. The Werther Effect, also known as copycat suicide, is a contagion effect that posits an increase in suicides attributed to increased reporting or attention of another suicide, typically of a celebrity. The name Werther comes from Goethe's 1774 novel *The Sorrows of Young Werther*, which details the trials and tribulations of a young man named Werther who was rejected by the love of his life commits suicide. Reportedly after the publication of this book, young men began to mimic Werther by dressing in similar attire, and there were also reports of

several young men taking their own lives in the same manner that Werther did in the book. Conversely, the Papageno Effect is the opposite of the Werther Effect. It states that there may well be a protective aspect when a suicide, especially of a prominent social figure, is discussed suitably and appropriately and provides an alternative solution instead of suicide. A 2018 article examined the role of media reporting on suicide rates and determined that there was evidence of both the Werther and Papageno Effects stating:

"The possibility of a suicide-protective effect of media items on positive coping in adverse circumstances, which has been discussed in the literature on a purely theoretical basis, was empirically supported by the present findings. Reporting of individual suicidal ideation (not accompanied by attempted or completed suicide) was associated with a decrease in suicide rates. ... By contrast, media items reporting public suicide myths and repetitive suicide-related reporting were associated with increases in suicide rates. Items with a high probability of containing expert opinions or epidemiological facts were identified as distinctive latent classes of media reports, which tended to be intertwined with unfavourable, sensationalist contents. These classes were associated with increases in suicide rates [6]."

Additionally, a 2021 literature review on the Werther and Papageno Effects concluded:

"While the media can be a double-edged sword and serve both as a risk and a protective factor, there is a growing amount of evidence showing that the relationship between media reporting and the actual suicide rates is causal and real. Consequently, the influence of media reporting on suicide is defined as an important risk factor affecting suicidality in the general

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population. At the same time, researchers suggest that both the quantity and the quality of media reporting may trigger additional suicides. Thus, suicide contagion is more likely to occur after extensive media coverage with a content rich in positive definitions of suicide. Moreover, especially non-fictional presentations of celebrity suicides can strongly influence the subsequent suicidal behavior. However, it should be acknowledged that because the negative reporting style can be modifiable and improved, the media can also have an educative or preventive effect and can reduce the risk of contagion [7]."

The vast number of potential factors potentially involved in a suicidal risk assessment is not conducive or readily applicable to standard clinical practice. Fortunately, a group of researchers in 2016 conducted a meta-analysis examining 365 articles spanning 50 years of research on risk factors for suicidal thoughts and behaviors and were able to synthesize all of this information into manageable and implementable items that fit well into the current clinical practice model [8]. Overall, the paper concluded:

"These broad analyses show that overall prediction of STBs is poor in terms of odds ratios, hazard ratios, and diagnostic accuracy statistics. Specifically, odds and hazard ratio analyses indicate that existing factors do not substantially increase the risk of STBs and diagnostic accuracy analyses suggest that existing factors rarely correctly identify people who go on to engage in suicidal behavior. Models that assumed and accounted for complete dependence among effect sizes produced virtually identical results."

The authors also determined that "[a]cross our 16 broad risk factor categories,

nearly 80% of risk factors fit into one of the top five most popular categories and nearly 95% of risk factors fit into one of the top nine most popular categories." As a result, they generated a list of the most common features of individuals at risk of suicidal ideation, suicide attempts, and suicide completion.

Based on weighted odds ratios, the top five predictors of developing suicidal ideation were in descending order: Prior suicidal ideation, Hopelessness, Depression, Abuse history of any kind, and diagnosis of an anxiety disorder. The weight odds ratios ranged from 3.55 on the high end for previous suicidal ideation to 1.50 on the low end for an anxiety disorder diagnosis. Regarding suicide attempts, the top five predictors were: Prior non-suicidal self-injury, prior suicide attempt, a history of multiple screenings for suicide attempts, any axis II disorder, and prior psychiatric hospitalization. The odds ratio spread was 4.15 for non-suicidal self-injury to 2.32 for previous psychiatric hospitalization. Finally, the top predictors of completed suicide were prior psychiatric hospitalization, prior suicide attempt, prior suicide ideation, low socioeconomic status, and stressful life events. The odds ratios ranged from 3.57 for prior psychiatric hospitalization to 2.18 for stressful life events. Unfortunately, as promising as the results may seem, when the researchers attempted to extrapolate these findings onto the general population, they found:

"In terms of clinical significance, assuming that these weighted odds ratio figures would apply on a population level, these combined risk factor effects would increase the 1-year odds of suicide death from 0.013 to 0.019 per 100 people; suicide attempt from 0.33 to 0.49 per 100 people; and suicide ideation from 2 to 3 per 100 people. These may not represent clinically significant effects, especially when considering clinicians often are tasked with determining STB risk over



the course of hours, days, or weeks rather than over an entire year."

Furthermore, the authors noted that "traditional risk factors are poor predictors of STBs within the narrow methodological constraints of the existing literature, but it is unknown how these risk factors perform outside of these narrow methodological limits." The authors also cautioned against a final common pathway or single variable approach to suicide and instead opted to pursue a multifactorial approach stating "it is likely that there are many different paths to STBs. This equifinality means that a single one-size-fits-all algorithm for STB prediction is unlikely; researchers will likely need to develop separate algorithms for different populations." Lastly, the authors noted that "[t]he present results show that single risk factors are inherently limited in their ability to accurately predict future STBs. We speculate that the additive or interactive effects of a small number of risk factors would also produce inaccurate prediction." Predicting suicidal thoughts and behaviors still poses challenges that necessitate further research, but as will be seen, so does the prevention aspect of suicide management.

### **SUICIDE PREVENTION AND INTERVENTIONS**

Suicide prevention can be broken down to a tripartite framework best remembered by the term "The 3 Ms of Suicide Interventions." The 3 Ms are Mitigation, Means Restriction, and Medications. Each of these intervention groups offers benefits, but, as with other areas of suicide management, much is still left to be desired. Combining all three of these groups currently provides the most comprehensive management plan for suicide prevention and is employed by most suicide prevention programs.

### *Mitigation*

Mitigation is defined as "[t]he action of reducing the severity, seriousness, or painfulness of something<sup>[9]</sup>." The most common examples of mitigation measures are Suicide Hotlines, Peer Support and Checking-in programs, multi-level ad and informational campaigns, and insomnia management. Mitigation efforts are the most expansive of suicide prevention efforts and tend to have the least amount of evidence supporting their use. The lack of data supporting their implementation is likely due to inadequate standardization techniques commonly utilized on Suicide Hotlines or Peer Support programs or generic and impersonal marketing campaigns often associated with suicide awareness. A 2016 systematic review of a post-suicide attempt telephone-based intervention<sup>[10]</sup> found "that telephone contact intervention did not significantly reduce further suicide attempts and completed suicides, and the crisis card did not significantly reduce further deliberate self-harm." Additionally, another 2016 systematic review that examined almost 1800 articles to determine the effectiveness of suicide prevention strategies over the previous 10-year period<sup>[11]</sup> stated, "[i]nsufficient evidence exists to assess the possible benefits for suicide prevention of screening in primary care, in general public education and media guidelines. Other approaches that need further investigation include gatekeeper training, education of physicians, and internet and helpline support."

The only mitigation intervention with significant evidence supporting its utilization is insomnia management. Insomnia is strongly associated with numerous adverse health outcomes, and suicide is no exception. A 2012 meta-analysis found an almost 2-3x increased risk of suicidal thoughts and behaviors in individuals with sleep disturbances<sup>[12]</sup>. A 2014 systematic review further quantified the impact of insomnia by examining the risk of

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suicidal behaviors in patients with a known psychiatric disorder and a diagnosis of a sleep disturbance [13]. Psychiatric patients suffering from sleep disturbances were almost twice as likely to report suicidal behaviors than those without sleep disturbances. This jarring statistic means that the management of insomnia and sleep-related disorders should be a priority in any suicide prevention system. Specifically, cognitive behavioral therapy for insomnia or CBT-I has been shown to improve insomnia and reduce the probability of developing suicidal thoughts and behaviors. A 2015 article examining the use of CBT-I in veterans with insomnia [14] found that "each 7-point decrease in Insomnia Severity Index score achieved during CBT-I treatment was associated with a 65% (odds ratio = 0.35; 95% confidence intervals = 0.24 to 0.52) reduction in odds of suicidal ideation." This effect was also independent of a change in depressive symptoms. Likewise, a 2011 article that looked at the use of CBT-I in patients categorized with high or low severity depression [15] found that 45% of the patients who reported suicidal ideation prior to CBT-I sessions no longer reported those thoughts after completing the treatment. While traditionally, CBT-I has been delivered through structured psychotherapeutic environments, recently, phone apps like *CBT-I Coach* or online programs like the Cleveland Clinic's *Go To Sleep* program offer more access to patients who might otherwise be unable to benefit from them.

### *Means Restriction*

Regarding suicide prevention, means restriction is commonly thought of as a community or societal action that, ideally, does not depend on an individual's intention or volition. Reducing access to heights from which to jump, gun safety measures, inpatient hospitalization, and pill packs are all typical examples of this aspect of suicide prevention.

There is a large body of evidence to support pill packs and limiting access to heights. The previously mentioned 2016 article reviewing the previous 10-years of suicide prevention noted a 43% reduction in suicides due to analgesics, primarily due to pill packs. Additionally, they noted an 86% reduction in suicides by reducing access to "hot spots" for jumping [11].

Similarly, when looked at through the lens of means reductions, psychiatric hospitalization achieves its intended effect of reducing suicide, but only for as long as the patient remains admitted. As was noted previously, psychiatric hospitalizations are the fifth highest risk factor for suicidal behaviors and the highest risk factor for completed suicide. The relationship between psychiatric hospitalization and future suicidal thoughts and behaviors was further investigated by a 2017 systematic review [16] that concluded "[t]he immediate post discharge period is a time of marked risk, but rates of suicide remain high for many years after discharge. Patients admitted because of suicidal ideas or behaviors and those in the first months after discharge should be a particular focus of concern." With this information in mind, inpatient psychiatric stabilization should be viewed as a time buying intervention during which other interventions and strategies should be implemented to help reduce the post-discharge risk of suicidal thoughts and behaviors.

A common area of focus is reducing access to lethal means such as firearms. The discussion surrounding firearms and suicide is a trade-off that is often complicated by passion and politics. The objective and dispassionate data regarding firearms and suicide are complicated. Firearms are the preferred method of suicide among males and are one of, if not the most lethal method available, and given this information, it is understandable why gun safety would seem to be a prominent area to center a suicide prevention

intervention. Several studies, including a 2016 article on firearm availability and gun regulations' impact on suicides <sup>[17]</sup> and a 2002 article on the association between household handgun ownership and suicides <sup>[18]</sup>, reach similar conclusions of increased suicide rates in homes with firearms, especially in those with unsafe storage practices. However, mandatory safe storage laws do impose a potentially serious trade-off, as a 2001 paper notes:

"It is frequently assumed that safe-storage gun laws reduce accidental gun deaths and total suicides, while the possible impact on crime rates is ignored. We find no support that safe-storage laws reduce either juvenile accidental gun deaths or suicides. Instead, these storage requirements appear to impair people's ability to use guns defensively. Because accidental shooters also tend to be the ones most likely to violate the new law, safe-storage laws increase violent and property crimes against law-abiding citizens with no observable offsetting benefit in terms of reduced accidents or suicides <sup>[19]</sup>."

In 2019 a research team conducted a systematic review <sup>[20]</sup> on all of the available data surrounding the effects of firearm prevalence on suicide rates. The results of this paper attempted to consider all of the significant trade-offs and reached the following conclusions:

"Prior macro-level research is afflicted by the use of small samples of large heterogeneous units, invalid measures of gun prevalence, and few controls for confounders. The methodologically soundest prior research indicates that gun prevalence affects rates of gun suicides, but not total suicides. The new analysis likewise finds no significant effect of gun prevalence on total suicide rates."

To further explain their bottom-line conclusion, the researchers contrasted the proposed benefits that reducing firearms might provide with the likelihood that an individual would elect to use another method to achieve their goal of suicide. This is a critical point that should not be overlooked in suicide prevention strategies, as the goal should not be to single-mindedly focus on one particular method to the exclusion of all others. As the article notes:

"Strictly speaking, reducing firearms suicides is not, in and of itself, a public benefit. If a gun law caused the number of firearms suicides to decline by 50, but also caused the number of suicides committed by other lethal methods to increase by 50, there would be no net savings in lives. And unless one were willing to argue that there is public benefit in getting people to kill themselves by hanging (or other nonshooting methods) instead of shooting, there would be no suicide-related benefit from this law. Thus, it is inconsequential by itself if more guns cause more gun suicides, but very important if more guns cause more total suicides."

With this idea in mind, means restrictions are likely the least implementable aspect of the 3-Ms model. Given that there are almost infinite ways to attempt or complete suicide, means restriction can become a never-ending game of whack a mole if taken to its logical extreme. For this reason, only those interventions that both provide a statistically significant impact in reducing suicides and can be practically adopted without a burdensome cost being imposed are selected as targets. In contrast to medications which work in the opposite direction as means restriction. While means restriction attempts to impose a primarily one size fits all model across all environments, medications that can reliably reduce suicide can be introduced at the



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individual level. They can be selected and tailored to a patient's specific needs based on their clinical presentation.

### *Medications and Other Interventions*

It is essential to remember that medications are not a panacea from the outset. While certain medications can reduce the likelihood of suicide in specific populations, few show generalizability to larger populations. For this reason, the correct medication should be selected for the proper indication based on a patient's specific risk factors and medical history.

As of 2005 <sup>[21]</sup>, antidepressants were the most prescribed medication in the United States. Given the wide range of indications for which they can be prescribed, including but not limited to mood disorders, anxiety disorder, trauma disorders, and obsessive-compulsive disorders, and combined with their relatively favorable safety profile, it is also not difficult to see how they gained their place at the top of the prescription pyramid. As most prescribers are aware, though, antidepressants carry a black box warning for the possibility of increasing suicidal thoughts in individuals under 24 years old. However, this black box warning says nothing of the impact on suicide risk for adults older than 24. A 2009 systematic review <sup>[22]</sup> sought to answer this question and found that Selective Serotonin Reuptake Inhibitors (SSRIs) nearly doubled the risk of suicidal thoughts and behaviors and completed suicides in adolescents. However, SSRIs appeared to reduce the risk of all those outcomes in the adult population by almost 50%. For adults over the age of 65, SSRIs did reduce the risk of suicidal thoughts and behaviors and completed suicides by more than 50%. More research on other antidepressants medications such as Serotonin Norepinephrine Reuptake Inhibitors, Tricyclic Antidepressants, Monoamine Oxidase Inhibitors, and other atypical antidepressants

is needed to determine if the reported findings for SSRIs apply to them as well.

In contrast to antidepressants, antipsychotic medications are routinely used in patient populations with severe and persistent mental illnesses such as schizophrenia, psychotic disorders, and bipolar disorders. However, their impact on suicide rates in these populations has largely been underwhelming, except for clozapine. A recent 2019 systematic review <sup>[23]</sup> on clozapine's anti-suicidal effects in individuals with schizophrenia found that "Long-term, crude mortality rate ratios were not significantly lower in patients ever treated with clozapine during follow-up, but significantly lower in patients continuously treated with clozapine compared to patients with other antipsychotics." This is in sharp contrast to all other antipsychotics; a 2021 study <sup>[24]</sup> compared the effects of all available antipsychotics versus no antipsychotics in reducing suicidal thoughts and behaviors in individuals with schizophrenia. Again, the results supported using clozapine for this purpose, noting, "Compared with no use of antipsychotics, clozapine use was the only antipsychotic consistently associated with a decreased risk of suicidal outcomes. ... No other antipsychotic was associated with a reduced risk of attempted and/or completed suicide."

It has been speculated that the reason why clozapine produces these anti-suicidal effects has less to do with the pharmacologic receptor profile of clozapine and more with the REMS monitoring program associated with the drug. The strict monitoring program maintains compliance with clozapine dosages, a feat unable to be obtained with other oral antipsychotics. However, that is not the case with long-acting injectable (LAI) antipsychotics that provide continuous amounts of the antipsychotic medication to the patient over prolonged periods from weeks to months, depending on the formulation. A 2021 study <sup>[25]</sup> comparing the anti-suicidal

effects of an LAI versus the same antipsychotic given orally favored the LAI group, which saw lower mortality rates and fewer suicide attempts. The next step will undoubtedly be to compare LAI formulations against clozapine to determine if a difference exists.

Like clozapine, lithium has a well-established role as an anti-suicidal agent in treating mood disorders. A 2013 systematic review and meta-analysis <sup>[26]</sup> found that lithium effectively reduced suicidal behaviors across 48 randomized controlled trials. A more recent systematic review in 2020 <sup>[27]</sup> noted that lithium produced a "reduction in suicide in patients with mood disorders." The authors said, "[a]ll studies about lithium treatment's duration reported that long-term lithium give more benefits than short-term lithium in suicide risk. The evidence seems to attribute an intrinsic anti-suicidal property of lithium, independent of its proven efficacy as a mood stabilizer." Unlike clozapine's anti-suicidal effects, which, based on current data, only apply to schizophrenia, lithium's effects appear to be more generalizable to the population at large. A 2020 systematic review <sup>[28]</sup> examining 15 ecological studies found that lithium in drinking water exerted a dose-dependent protective effect in reducing suicide rates in those specific areas.

Compared to lithium, other mood stabilizers do not exert anti-suicidal properties to the same degree, if at all. A 2014 systematic review and meta-analysis <sup>[29]</sup> examined the impact of antiepileptic drugs (AEDs), commonly prescribed mood stabilizers for psychiatric patients, on suicide rates. This study found mixed results with conflicting data on whether AEDs had a protective or harmful effect on patients at risk of suicidal thoughts and behaviors. Even after excluding epilepsy patients and singly out bipolar patients for analysis, these conflicting results remained present. This finding was corroborated by a 2019 study <sup>[30]</sup> investigating valproic acid's impact on reducing suicide in patients with

bipolar disorder. This systematic review and meta-analysis looked at six studies and found no difference between valproic acid and placebo or between valproic acid and carbamazepine concerning anti-suicidal effects. Of more concern was a 2008 FDA statical review and evaluation article <sup>[31]</sup> looking at AEDs found:

"Overall, patients who received an antiepileptic drug had statistically significant increased risk of Suicidal Behavior or Ideation relative to placebo patients. The estimated overall odds ratio (OR) of a drug patient experiencing a Suicidal Behavior or Ideation event versus a placebo patient was 1.80 (95% CI: 1.24, 2.66). The results for individual drugs were generally consistent with the overall result. Suicidal Behavior had a larger estimated odds ratio [2.92 (95% CI: 1.44, 6.47)] than Suicidal Ideation [1.45 (95% CI: 0.93, 2.30)]. Sensitivity analyses showed that the results were robust to statistical methods and differences in the treatment durations between the treatment groups."

The epilepsy cohort had more than twice the risk of developing suicidal thoughts and behaviors while on AEDs compared to the psychiatric diagnosis cohort. However, when comparing AEDs to placebos, the results were flipped, and the psychiatric diagnosis cohort carried a higher risk of suicidal thoughts and behaviors. Given the, at best equivocal anti-suicidal effects of AEDs, they should have a limited to no role in treating suicidal thoughts and behaviors.

There are some patients for whom medications are ineffective for various reasons. Typically, more aggressive and invasive avenues are considered in these patients, such as transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT). TMS is a treatment commonly reserved for treatment-resistant depression patients who have failed

to respond to oral antidepressant therapy with or without augmentation adequately. Unilateral repetitive TMS (rTMS) has yielded conflicting results on whether it reduces suicidal thoughts, but bilateral rTMS has been shown to reduce suicidal thoughts more than unilateral rTMS and substantially more than sham TMS [32]. ECT appears to be even more effective at reducing suicidal thoughts than TMS in head-to-head comparisons [33]. ECT was shown in the 2014 Consortium for Research in ECT (CORE) study [34] to reduce suicidal thoughts and behaviors significantly. "Overall, 63.2% of the high suicide risk patients had complete resolution of suicide thoughts with ECT. Only 10 (4.0%) patients of the two cohorts with high baseline score remained at high risk after the ECT course." While ECT is commonly used as a last-line treatment option due to its inherent procedural risks, it should be strongly considered an earlier potential intervention for those patients with significant suicidal thoughts or behaviors.

### **PSYCHEDELICS**

The relatively mild success of the aforementioned interventions in managing patients with suicidal thoughts and behaviors has sparked renewed interest in potentially using psychedelics and psychedelic-like compounds as a treatment option. The most widely available substance of this kind is ketamine and its intranasal formulation, esketamine. The anti-suicidal effects of ketamine have been widely reported in the literature [35, 36]. Most systematic reviews and meta-analyses have concluded that at least in the acute period of a few days, ketamine significantly reduces suicidal thoughts and behaviors [37]. When esketamine received final FDA approval, it joined clozapine as the only medications to have an indication for specific patient populations, depression and schizophrenia, respectively, who were suffering from suicidal ideation. The clinical trials submitted

to the FDA showed that chronic esketamine had a rapid and persistent effect on reducing depressive symptoms and suicidal thoughts and behaviors that were not dissimilar to intravenous ketamine. However, a 2021 systematic review [38] comparing esketamine to intravenous ketamine came to a different conclusion: "[r]esults from esketamine trials did not demonstrate anti-suicidal effects, as between-group differences were not found. Intravenous ketamine appeared to rapidly decrease the severity of suicidal ideation and depressive symptoms in individuals with baseline suicidal ideation, though retrospective studies suggest that these effects may be short-lasting." While ketamine and esketamine are the first psychedelic-like compounds available to treat suicidal thoughts and behaviors, they are unlikely to be the last or best options.

The classical psychedelics, psilocybin, LSD, and DMT, are currently being studied for a plethora of psychiatric conditions ranging from treatment-resistant depression to PTSD to substance use disorders. However, one area of limited study is the impact these substances have on suicidal thoughts and behaviors. It is reasonable to hypothesize that given their profound effects in treating patients with treatment-resistant depression, psychedelic substances could exert more anti-suicidal effects than any of the other medications discussed thus far. No clinical trials have been conducted with the primary endpoint of examining the impact of classical psychedelics on suicidal thoughts and behaviors. However, a 2015 article [39] found that any lifetime use of these substances was associated with "a significantly reduced odds of past month psychological distress (weighted odds ratio (OR)=0.81 (0.72–0.91)), past year suicidal thinking (weighted OR=0.86 (0.78–0.94)), past year suicidal planning (weighted OR=0.71 (0.54–0.94)), and past year suicide attempt." These findings were further corroborated in a 2019 article [40] that examined

classical psychedelics and novel compounds such as phenylethylamines. This study found that “Lifetime classic tryptamine use was associated with a decreased odds of past month psychological distress [aOR = 0.76; (0.69–0.83)] and past year suicidal thinking [aOR = 0.79; (0.72–0.87)].” In contrast, phenylethylamine compounds caused increased risks of both distress and suicidal thinking. Finally, a 2021 systematic review<sup>[41]</sup> looking at the totality of the articles discussing the use of classical psychedelics and their impact on suicidal thoughts and behaviors found mixed results regarding the benefits of any lifetime use. However, in “recent psychedelic therapy clinical trials, we found no reports of increased suicidality and preliminary evidence for acute and sustained decreases in suicidality following treatment.” While anti-suicidal effects of classical psychedelics require more research to determine their specific efficacy, combining these compounds with psychotherapy will likely produce the most robust results.

Psychedelic Assisted Psychotherapy (PAP) is the current standard of care utilized when administering psychedelic compounds to patients. It is a comprehensive program that involves preparatory sessions prior to a psychedelic experience, psychological support during the experience, and integration sessions after the experience. It is through psychotherapy that the maximal benefits of psychedelics are cemented. While psychedelics cultivate the psychological soil, psychotherapy allows patients to plant, grow, and harvest new skills to overcome their previous trauma and suffering. Specifically, regarding suicidal thoughts and behaviors, psychotherapy effectively reduces these events. A 2019 systematic review<sup>[42]</sup> examining the effect of dialectal behavior therapy (DBT) and cognitive behavior therapy (CBT) found that when these therapies were used in patients with borderline and personality and depression, respectively, they reduced the chances of

suicidal ideation by 55% and suicide attempts by 37.5%. A separate 2019 systematic review<sup>[43]</sup> examining psychoanalytic and psychodynamic psychotherapy also found a reduction in attempted suicides in patients participating in therapy. It is reasonable to hypothesize that the combination of classical psychedelics and psychotherapy would produce a more significant reduction in suicidal thoughts and behaviors. However, this area of research is lacking. With the increase in psychedelic clinical trials, the need for studies comparing PAP vs. classical psychedelics, PAP vs. psychotherapy, and PAP vs. placebo, all with the primary outcome of a reduction in suicidal thoughts and behaviors, is imperative. PAP has the potential to permanently alter how psychiatrists and other mental health providers approach patients at high risk of suicide and thereby possibly begin to stem the tide of increasing suicides in society today.

## CONCLUSION

The rate of suicides has been steadily increasing over the last decade due to many factors. Our current predictive abilities for identifying at-risk individuals are overly broad, preventing wide-scale adoption. Unfortunately, the currently available interventions also have proved insufficient to reverse this trend. The 3-Ms model provides a framework to try and implement evidence-based interventions across three major domains: mitigation, means restriction, and medications. Most mitigation measures do not have any substantial evidence supporting them. The one exception is insomnia management. Reducing insomnia has been conclusively shown to reduce the risk of suicidal thoughts and behaviors.

Similarly, most means restriction methods have not been well validated and impose significant trade-offs that limit implementation. Blister pill packs and reducing access to heights are two interventions that

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significantly reduce suicide attempts and completed suicide rates. Finally, Lithium and Clozapine are medications with well-established data supporting their use in specific patient populations to reduce suicidal thoughts and behaviors. SSRIs may also be of increasing benefit in adults as they age, producing a more protective effect over time. Interventions like ECT show substantial impacts on reducing suicidal thoughts and behaviors. Ketamine derivatives appear to offer at least short-term protection for acutely suicidal patients. Emerging therapies include classical psychedelics, which have shown significant promise in reducing suicidal thoughts and behaviors. Their effects may be increased by combining them with psychotherapy in a Psychedelic Assisted Psychotherapy based intervention. However, more research is needed to completely elucidate the degree of this impact. If substantial, PAP has the potential to bring about a foundational shift in how psychiatrists and the mental health field engage with and treat patients at risk for suicidal thoughts and behaviors.

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Kjorvestad, T.; (2022, March). Suicide Prevention and Emerging Interventions: Implications for Psychedelic Substances. *The Journal of Psychedelic Psychiatry*, 4(1).

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