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Suicidal behavior-advances in clinical and neurobiological research and improvement of prevention strategies

Sobanski T *et al.* Suicidal behavior-improvement of prevention strategies

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Abstract

22 Suicide is the 14th leading cause of death worldwide. It is responsible for 1%-5% of all mortality. This article highlights the latest developments in universal, selective, and indicated prevention strategies. Concerning universal suicide prevention, current research has shown that strategies such as restricting access to lethal means (e.g., control of analgesics and hot-spots for suicide by jumping) and school-based awareness programs are most efficacious. Concerning selective prevention, substantial progress can be expected in psychological screening methods for suicidal behavior. 27 The measurement of implicit cognition proved to be more valid in predicting future suicide attempts than classic clinical assessment. Latest developments are smartphone-based interventions and real-time monitoring of suicidal behavior. Great effort has been made to establish valid neurobiological screening methods (e.g., genetic and epigenetic risk factors for suicide, hypothalamic-pituitary-adrenal axis) without yielding a major breakthrough. Potentially, multiple biomarkers rather than a single one are necessary to identify individuals at risk. With regard to indicated prevention in form of psychopharmacological treatment, recent pharmacoepidemiological meta-analyses have supported a protective role of antidepressants, lithium, and clozapine. However, the data concerning a specific anti-suicidal effect of these drugs are currently not consistent. Promising results exist for ketamine in reducing suicidal ideation, independently of its antidepressant effect. Concerning psychotherapy, recent findings suggest that psychotherapeutic interventions specifically designed to prevent suicide re-attempts are most efficacious. Specifically, cognitive-behavioral therapy and psychodynamic therapy approaches proved to decrease the number of suicide re-attempts significantly.

Key Words: Antidepressants; Biomarkers; Cognitive behavioral therapy; Ketamine; Prevention; Suicide

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Core Tip: This Editorial highlights recent developments concerning suicide prevention. According to current research, measures such as restricting access to lethal means and school-based awareness programs are the most efficacious universal prevention strategies. Novel psychological screening methods for suicidal behavior (implicit cognition, smartphone-based interventions, and real-time monitoring) have improved suicide risk assessment. Pharmacoepidemiological studies and meta-analyses support a protective role of antidepressants, lithium, and clozapine. Promising results exist for ketamine in reducing suicidal ideation. However, its suicide-preventive effect is under debate. Specific psychotherapeutic approaches for suicide attempters that focus on suicidal episodes proved to be efficacious for reducing suicide re-attempts.

³⁷ **INTRODUCTION**

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Suicide and suicidal behavior are major public health concerns. Around 700000 people commit suicide each year. Suicide was the fourth leading cause of death among 15 to 29 year-old individuals globally in 2019^[1]. According to the United Nations, more people die by suicide every year than by both homicide and war^[2]. In developed countries, more than 90 percent of all suicide victims suffered from mental illnesses, most frequently from mood disorders^[3]. In the developing countries, on the other hand, the reasons for suicidal behavior are likely to be similar but the number of suicides is significantly higher there potentially due to a lack of access to medical and especially psychiatric care^[4-7]. Mood disorders are regarded as a proximal factor for developing of an increased suicide risk^[8]. The risk of suicide is 17 times higher in people with mood disorders than in the general population^[9]. Follow-up studies documented that ten to fifteen percent of the patients with major

depressive disorder (MDD) die by suicide during the course of the disease^[10]. Despite this remarkably high association, however, it remains unclear why most people with mood disorders do not attempt suicide. This suggests that there may be a predisposition to suicidal behavior that is, to some extent, independent of the psychiatric disorder itself^[8,11,12]. Although suicidal behavior often occurs in association with affective disorders, there is evidence from genetic, familial and neurobiological studies that it might represent a separate diagnostic entity^[13]. In the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5)^[14], “suicidal behavior disorder” is therefore included as a “condition for further study”. It is characterized by “attempted suicide within the past two years” and does not include suicidal ideation or non-suicidal self-injurious behavior. A key feature of this definition is the intent to die, which distinguishes suicidal behavior from suicidal ideation and non-suicidal self-injury (NSSI).

There is still too little knowledge about the risk factors that facilitate the transition from suicidal ideation to suicidal action. The majority of people considering suicide do not go as far as attempting suicide. Therefore, the central concern is to understand the differences between suicide ideators and suicide attempters and to identify which ideators are at the greatest risk of suicide attempts^[15]. This information could significantly improve risk assessment and theoretical models of suicide. In the subsequent sections we will highlight some recent developments in clinical and neurobiological research that have the potential to significantly improve future suicide prevention strategies. It is likely that these advances will primarily concern selective and indicated prevention measures (*i.e.*, screening methods and therapy).

At this point, we would like to briefly address the existing controversy regarding the classification of preventive measures for mental disorders. First of all, Caplan (1964) introduced his concept of primary, secondary, and tertiary prevention which had a strong influence on the development of early prevention models^[16,17]. In 1983, Gordon^[18] developed another three-tiered model, in which a division into universal, selective, and indicated preventive interventions was made, depending on the targeted population group. With the 1994 Institute of Medicine (IOM) Framework [IOM, *i.e.*, Institute of Medicine; the IOM changed its name to National Academy of Medicine (NAM) in 2015], the Caplan model was abandoned in favor of an adapted

Gordon approach. At the same time, prevention measures were strictly separated from therapy and maintenance interventions. The term “prevention” was now reserved for interventions designed to reduce the occurrence of new cases (NAM, 2007)^[19]. However, only a few years later the National Advisory Mental Health Council (NAMHC) Workgroup on Mental Disorders Prevention Research stated that the IOM definition was too narrow because it excluded all individuals with full-blown disorders^[20]. Other authors have also claimed that benefits could be gained from closer integration of prevention and treatment research without separating both from each other, thus sharing methodological advances in the corresponding field^[21].

In the present work, we refer to the classification according to the 1994 IOM Framework. On the other hand, we use a unified approach with the inclusion of therapeutic measures, as it was also applied in the most relevant systematic reviews^[22,23].

It has already been implicitly mentioned that we are referring here to suicidal behavior and not to NSSI, which has a different etiological background and requires other prevention strategies.

UNIVERSAL PREVENTION STRATEGIES

Universal prevention refers to strategies designed for an entire population regardless of the presence of individual risk factors. Since the 1960s, several developed countries have implemented national suicide prevention plans. According to the WHO^[24], universal prevention programs include, inter alia: (1) Limitation of access to lethal means, (2) school-based awareness programs, (3) initiatives with regard to public education and awareness, (4) responsible media reporting, (5) access to health care, and (6) policies to reduce harmful use of alcohol or other substances (Table 1). As one of the first, Mann *et al*^[22] performed an exhaustive review on the effectiveness of suicide prevention strategies. Experts from 15 countries evaluated all eligible studies published between 1966 and 2005. Only articles were included that used completed suicide, suicide attempts or suicidal ideations as outcome criteria. The main results were that restricting access to lethal means and the education of physicians (selective prevention; please see the following section) have the potential to prevent suicide. Other measures like public education and media education

needed more evaluation. More recently, Zalsman *et al*^[23] performed a systematic review using a similar methodology to assess the progress in suicide prevention research between 2005 and 2014. The authors assessed several universal prevention measures: public education, media strategies, and restricting access to suicide means. Moreover, they included studies on selective prevention measures like screening procedures, crisis helplines, and education of physicians, as well as on indicated prevention approaches like treatment methods and community support. Eighteen suicide prevention experts from 13 European countries reviewed all relevant articles and rated the strength of evidence. According to the authors, restricted access to lethal means has been further shown to be an effective suicide preventive measure, especially relating to control of analgesics (overall decrease by 43 percent) and to securing hot-spots for suicide by jumping (reduction by 86 percent). School-based awareness programs have proved to have a protective effect on suicide attempts and suicidal ideation. Other approaches that still needed further investigation included gatekeeper training and education of physicians. These results substantiate that several components of prevention programs as many countries realize them prove to be effective. In the quest for effective suicide prevention programs, no single strategy clearly stands above the others. The lacking efficacy proof of some measures might be due to a paucity of randomized controlled trials (RCTs) which is a major limitation in the evaluation of preventive interventions.

Furthermore, despite implementing various prevention approaches, an increasing trend in the number of suicides over the last two decades is detectable in the United States (Centers for Disease Control and Prevention, CDC), Web-Based Injury Statistics Query and Reporting System (WISQARS) Fatal Injury Reports^[25]. Thus, further improvement in specific suicide prevention programs will be necessary to enhance our understanding of these complex and heterogeneous behaviors at the individual level in order to develop more personalized preventive strategies.

SELECTIVE PREVENTION STRATEGIES

Selective prevention refers to strategies designed for one or more subgroups of a population being at risk for suicidal behavior, like patients suffering from an affective disorder. Typical selective prevention strategies are the education of

physicians, gatekeeper training, as well as psychological and neurobiological screening methods (Table 1).

Long-established risk factors for suicidal behavior

In suicidology, an important individual-level approach is characterized by searching for valid screening methods or markers of suicidal behavior. Broadly accepted clinical risk factors are, for instance, prior suicide attempts^[26], mental disorders (particularly depression and other mood disorders)^[9], abuse of alcohol^[27] and other drugs^[28], access to lethal means^[22], social isolation, gender, and age^[13]. However, a careful examination of the suicide literature reveals a considerable gap in knowledge. In particular, commonly known risk factors for suicidal behaviors are, in fact, more likely risk factors for suicidal ideas, and not for the transition from ideas to attempts^[15].

For example, hopelessness has long been deemed to be a central risk factor for suicidal behavior^[29]. However, several studies have indicated that, while elevated among suicide ideators relative to non-suicidal controls, hopelessness fails to discriminate between suicide ideators and attempters^[15]. For example, a study investigating 102 psychiatric patients with bipolar disorder demonstrated that the level of hopelessness was higher among both suicide ideators and attempters compared to healthy controls, but comparable between ideators and attempters^[30]. A similar finding that hopelessness is not different between attempters and ideators has been observed in psychiatric patients with Major Depression^[31] and adolescents undergoing psychiatric treatment^[32]. The same pattern can be seen even when comparing hopelessness between “severe attempters” and suicide ideators^[33].

Interestingly, the same also applies for the role of impulsivity, which has been considered as a significant risk factor for suicidal behavior. Furthermore, it has been postulated that this is a key factor in the transition from suicidal ideas to suicide attempts^[15]. For example, individuals with high impulsivity scores have been described as being “more likely to act on suicidal feelings”^[34]. Similarly, impulsivity has been suggested as “a more significant indicator of suicide attempt than the presence of a specific suicide plan”^[15]. An implication of these theoretical perspectives is that impulsivity should be higher in suicide attempters than in

ideators. Remarkably, empirical findings do not support the theory that impulsivity is higher in attempters than in ideators. In a large military sample, impulsivity was higher among attempters and ideators compared with non-suicidal individuals, but equivalent between attempters and ideators^[15].

The differences between ideators and attempters obviously need further evaluation. Regardless of this, it is important to note that suicide attempters themselves seem to represent a heterogeneous group regarding demographic features, histories of suicide attempts, and the assumed clinical factors, e.g., hopelessness or impulsivity. The authors recently conducted a study on this issue and compared single and multiple suicide attempters for this purpose^[35]. A sample of patients with a recent suicide attempt ($n = 252$) was recruited. Statistical analyses revealed that the re-attempters had more severe psychopathology with significantly higher levels of suicidal ideation and hopelessness. Furthermore, re-attempters had more often first-degree relatives with suicidal behavior and emotional abuse during childhood. They also exhibited a higher degree of specific personality traits, i.e., higher excitability and higher self-aggressiveness^[35]. Multivariate discriminant analysis discriminated the re-attempters from single attempters by higher levels of self-aggressiveness^[35]. Although suicidal behavior is a complex and multifaceted phenomenon, in the future individual factors such as self-aggressiveness could be suitable as an indicator in order to identify patients who are particularly at risk and to provide them with suitable therapeutic measures.

Psychological screening methods for suicidal behavior

Another major challenge to scientific and clinical research in this area is that most assessment methods rely on the patients' self-report about suicidal thoughts and intent. This makes the evaluation of suicidal behavior especially difficult because patients often are motivated to deny suicidal thoughts for fear of undesired measures (e.g., involuntary hospitalization)^[36]. Moreover, suicidal thoughts are transient in nature and may not be present upon assessment but can return shortly thereafter and some people may lack conscious awareness of their current level of risk^[37]. Indeed, nearly 80% of people who die by suicide in hospital wards explicitly deny suicidal thoughts or intent in their last communication before dying^[38]. Recently, Woodford et

al^[26] explicitly investigated in a meta-analysis the accuracy of unassisted clinician predictions of future suicidal behavior. Based on 22499 predictions, this meta-analysis revealed a pooled sensitivity of 0.31 (95%CI: 0.18-0.50), indicating that nearly 70% of patients with repeated suicidal behavior were considered being at low risk. The reported pooled negative predictive value (NPV) of 0.89 (0.86-0.92) shows that nearly 10% of patients classified as low-risk cases will show future suicidal behavior.

Thus, there is an enormous need for standardized methods of assessing suicide risk that do not rely on explicit self-report and unassisted clinicians' decisions. In the last decades, psychological methods were developed to assess people's implicit cognition (*i.e.*, unconscious mental processes that can influence behavior) which could have a significant influence on suicide prediction. For instance, the Suicide Implicit Association Test (IAT) is a brief psychological test that measures reaction times of patients when viewing suicide-related and other stimuli. Previous studies demonstrated that it significantly predicted future suicidal behavior better than other factors like the presence of a mental disorder or a clinicians' prediction of a future suicide attempt^[36]. Glenn *et al*^[39] replicated these results in a large sample of participants ($n = 7015$) demonstrating that implicit associations related to suicidal behavior were stronger among individuals with a history of suicide attempt. The results also showed that these implicit associations were robust and sensitive to recency and severity of a given history of suicidal behavior. Associations turned out to be stronger for more recent and more lethal prior suicide attempts^[39].

Recent studies have shown that even brief, smartphone-based interventions that aimed to increase aversion to self-harm, can significantly reduce such behavior^[40]. Another promising approach is the real-time monitoring of suicidal thoughts and behaviors. Real-time monitoring has provided important information about several essential characteristics of suicidal thinking. Some of these studies have revealed that the severity of suicidal ideation varies significantly over a short period of time^[41]. Two studies have shown that the occurrence of suicidal ideas varies from hour to hour almost as much as from person to person^[42,43]. Moreover, episodes of suicidal ideation have a quick onset with nearly one third of all observations in one study differing by a standard deviation or more from the prior rating just a few hours earlier^[42]. In the same sense, episodes of suicidal ideation tend to be brief, with

participants reporting that most episodes are shorter than an hour^[37]. Furthermore, suicidal ideation can be differentiated from thoughts of NSSI using real-time assessment. Thus, it turned out that thoughts of suicide⁴⁶ co-occur less than half the time with thoughts of NSSI^[37].

Prior suicide prevention studies have failed to provide sufficient evidence for the benefits of screening individuals in primary care and of establishing internet and helpline support^[24]. Hopefully, this is going to change due to the development of improved screening methods as well as the use of multiple screening and assessment tools.

In this context, the Zero Suicide (ZS) model also represents a remarkable advance. In this prevention⁴⁹ approach all persons receiving care for a mental disorder¹⁵ are screened for suicidal thoughts and behaviors at intake. Whenever a patient screens positive for suicide risk, a full risk formulation is completed for the client^[44]. The core features of this prevention strategy are the targeted detection and support of people at risk by trained specialist staff, but also by gatekeepers and family members, as well as the development and implementation of specific interventions^[44]. Layman *et al*^[45] were able to demonstrate in a current study that less suicidal behavior occurred in clinics that had introduced and used ZS organizational best practices.

Neurobiological screening methods for suicidal behavior

Previous biological studies on suicidal behavior have consistently revealed that biological factors underpin this condition in terms of a predisposing diathesis^[46]. This diathesis rests on the known genetic risk factors for suicide^[47], but also on epigenetic mechanisms, which represent changes in gene expression and activity due to environmental factors^[48]. One such factor discussed for suicidal behavior and producing pronounced effect on the epigenome, is early life adversity (ELA), *e.g.*,⁴⁴ physical or sexual abuse during childhood^[46,49]. A significant number of subjects with suicidal behavior have a history of early life adversities, which is therefore considered as a risk factor for future suicide attempts^[50]. In our recent work (see above) we were able to show that especially patients with multiple suicide attempts had higher levels of early life adversities compared to single attempters^[35].

Animal studies^[51] have shown that epigenetic alterations following early life adversities may affect the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, a key system for cortisol release and stress response. A dysregulated HPA axis has also been often reported in subjects with suicidal behavior. For example, a lack of decrease in cortisol levels in the dexamethasone suppression test (DST) was associated with an increased risk of a future suicide death^[52]. Postmortem studies in suicide victims indicated that early life adversities may lead to increased methylation of the promoter region of the glucocorticoid receptor and decreased expression of its mRNA in the hippocampus^[53]. Recently, Jokinen *et al*^[54] showed reduced methylation of several HPA-related genes in individuals at high-risk of suicide. Thus, dysregulation of this major stress system is an important component of diathesis to suicide.

Moreover, markers of neuroinflammation influencing the stress response by modulation of the HPA axis, have been recently investigated in suicide. Altered levels of cytokines, such as IL-1, IL-6, and tumor necrosis factor alpha (TNF- α) have been detected in the frontopolar cortex of suicide victims^[55]. Additionally, microgliosis was observed in prefrontal, anterior cingulate, and thalamic regions in suicide victims^[56]. Due to the putative role of cytokines in neuroplasticity and neurotoxicity, the authors related the detected microglial activation to pre-suicidal stress.

Recently, growing attention was paid to the polyamine system, also important for stress-response, and its relation to suicide risk^[57]. Studies investigating postmortem suicide brains show that expression levels of gene products associated with the polyamine stress response system are dysregulated^[46,58]. Expression of the enzyme spermine N1-acetyltransferase (SAT1) was found to be altered in the brain of suicide victims, which has been therefore recognized as a potential biomarker for suicide^[59].

Thus, all these studies suggest a complex stress-diathesis interaction between genetic, epigenetic factors, and early traumatic experiences, which alter the response of stress systems to proximal stressors and accompanied response of the immune system, thus increasing the risk for suicidal acts.

Furthermore, the serotonergic system was extensively studied in subjects with suicidal behavior. Low levels of the main metabolite of serotonin (5-

hydroxyindoleacetic acid, ⁴³ 5-HIAA) were detected in suicide attempters^[60] and predicted future suicide deaths^[52]. Postmortem studies additionally showed alterations in serotonin (5-HT) markers^[61]. Blunted prolactin response to fenfluramine challenge ¹⁹ was found in high vs low lethality suicide attempters. High lethality suicide attempters had significantly lower prolactin response than low lethality suicide attempters^[62]. Recently, PET studies showed greater raphe 5-HT_{1A} receptor binding potential ¹⁹ in high compared to low lethality suicide attempters^[63]. Variants in several 5-HT genes have also been associated with the risk of suicide^[64,65]. While persisting 5-HT deficits are robustly associated with suicide, the causal mechanisms remain to be clarified.

Finally, based on recent clinical studies suggesting an “anti-suicidal effect” of ketamine^[66], the role of the glutamatergic system in suicidal behavior received growing attention. However, previous findings on glutamatergic alterations in suicidal behavior are inconsistent and need further examinations. For example, N-methyl-D-aspartate (NMDA) binding in the prefrontal cortex in suicide has been shown to be decreased^[67] or unaffected^[68].

To sum up, a number of biological alterations in different systems have been detected in subjects with suicidal behavior. However, currently, there are no biomarkers with a positive predictive value for suicide. A deeper understanding of the biological foundation of suicidal behavior and thus identification of stable and clinically useful biomarkers for suicide would equip clinicians with additional valuable information to properly address suicidal behavior in those most at risk. In light of the number of biological findings in suicidal behavior, Oquendo *et al*^[69] state in their review on biomarkers for suicide that potentially multiple biomarkers, rather than a single one, are necessary to identify individuals at risk.

INDICATED PREVENTION STRATEGIES

Indicated prevention strategies target individuals showing suicidal ideations and/or having past suicidal behavior. Psychopharmacological and psychotherapeutic treatment approaches are used for this (Table 1).

Psychopharmacological and psychotherapeutic treatment approaches

Regarding psychopharmacological treatment approaches, the role of antidepressants has been discussed controversially. Indeed, meta-analyses indicate a slightly increased risk for suicidal behavior in pediatric patients and young adults^[70,71]. In contrast, there seems to be a protective effect in older adults^[71]. Pharmacoepidemiological studies, however, show a protective effect across the whole life span^[72]. In the same sense, Simon *et al*^[73] reported in a population-based study that the rate of suicide attempts subsequently to the initiation of an antidepressant was much lower than the rate before the initiation. From a methodological point of view, the question arises as to why the results of RCTs and pharmacoepidemiological studies differ so remarkably. From our point of view, three decisive factors are involved in this discrepancy: (1) Suicidal patients are not usually included in RCTs and the design of RCTs is therefore poorly suited for assessing the influence of antidepressants on suicidal behavior; (2) the duration of the majority of RCTs is too short to detect the possible beneficial long-term effects of antidepressants on suicidal behavior; on the contrary, during the earlier stages of treatment antidepressants may act as an additional stress factor for the patients, due to adverse drug reactions, unfulfilled expectations or dissociated states during partial remission (*e.g.*, willpower improved, mood still depressed); and (3) additionally, the sample size of pharmacoepidemiological studies is much larger, and the time frame much longer compared with RCTs. Thus, although pharmacoepidemiological studies still have some challenges regarding standards in conducting and reporting, they have the strengths to have sufficient statistical power to measure differences in the actual frequency of rare events like suicides (instead of “suicidal events” as is usual in RCTs)^[72].

The important role of effective pharmacological treatment of depression for suicide prevention was also emphasized in an influential systematic review by Zalsman *et al*^[23]. In addition, the authors were in favor of suicide-protective effects of lithium and clozapine. Several RCTs have supported the assumption that lithium reduces the risk of suicide in patients with mood disorders^[74-77]. A specific anti-suicidal effect of lithium was suggested in a controlled treatment study on suicide attempters, although the number of suicides was very small (three suicides in the control group *vs* no suicides on lithium)^[77]. Clozapine is the only drug that has been approved by

the United States Food and Drug Administration (FDA) for reduction of the suicide risk in psychosis. A meta-analysis of the effects of clozapine in comparison with other dopamine and serotonin-receptor antagonists (e.g., olanzapine and risperidone) supports its anti-suicidal effects in schizophrenia^[78]. Nevertheless, a recent review has called into question, whether certain drugs that improve the underlying disease also have an independent anti-suicidal effect^[79].

Other promising drugs for the treatment of suicidal behavior are ketamine and esketamine. Ketamine (a racemic mixture of S- and R-ketamine) is a drug with dissociative properties. It was approved by the FDA in 1970 for anesthetic use^[66]. The mechanism of action of ketamine has not yet been fully elucidated, but it is known that ketamine antagonizes glutamatergic NMDA receptors in the central nervous system^[80]. Moreover, several studies have implied a role for opioid neurotransmission, as ketamine also appears to activate the mu, kappa, and delta-opioid receptors^[81-84]. In recent years, it became a target of research for its antidepressant effects, which occur within hours at subanesthetic doses^[80]. Grunebaum *et al*^[66] reported the acute effect of intravenous ketamine on suicidal ideation in patients with MDD. Ketamine therapy resulted in a clinically significant reduction of suicidal ideation in depressed patients within 24 h. Adverse drug reactions (ADRs) were transitory, and clinical improvement was maintained for several weeks. Abbar *et al*^[85] investigated the anti-suicidal efficacy of intravenous infusions of ketamine in a placebo-controlled RCT. The primary outcome was that at day 3 of the study more participants in the ketamine group reached full remission of suicidal ideas than in the placebo arm (63.0% vs 31.6%)^[85]. This effect persisted at follow-up after 6 wk^[85].

To avoid the distress of intravenous ketamine therapy, alternative formulations and routes of application were sought^[86]. Esketamine has four times higher affinity for the NMDA receptor than ketamine and thus allows for a lower dosage with a corresponding decrease in dissociative symptoms^[87]. Moreover, esketamine is available through an intranasal delivery system^[88]. Ultimately, esketamine was approved by FDA in 2019 as a nasal spray for treatment-resistant depression in adults and in conjunction with an oral antidepressant for treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior. Because of

⁹ the potential risks associated with this drug, including sedation, dissociation, and abuse or misuse, its label contains boxed warnings, and esketamine is subject to strict safety controls on administration under a safety program called Risk Evaluation and Mitigation Strategy (REMS)^[89]. In 2019, esketamine was also approved by the European Medicines Agency (EMA) for the same indication. Because of the risk of abuse, the approval applies only to inpatient treatment^[90].

Unfortunately, recent studies on ketamine and esketamine have been less conclusive with regard to their anti-suicidal effects^[91-93]. In their current review, Witt *et al*^[92] came to the conclusion that the reduction of suicidal ideations might be stronger after intravenous ketamine than after esketamine administration. However, there was still no evidence of a long-lasting effect beyond 3 d^[92]. Siegel *et al*^[93] performed a review of trials on patients with high level of baseline suicidal ideations. In this work, esketamine was not superior to placebo regarding the effect on suicidal ideations. Intravenous ketamine appeared to immediately and significantly ameliorate suicidal ideation, but was not superior to placebo regarding long-lasting effects^[93]. Finally, it should be noted that esketamine seems to be inferior to intravenous ketamine in the treatment of depression as Bahji *et al*^[91] reported in their meta-analysis.

In previous sections we pointed out that suicidal ideation represents only a comparatively unspecific parameter that only provides limited information about imminent suicide attempts. Therefore, the validity of studies that only refer to suicidal ideation as an outcome criterion is limited. To date there are no prospective RCTs, which investigated the effect of ketamine/esketamine treatment on future suicidal behavior and suicides as outcome parameter. Thus, the evidence for the efficacy of ketamine/esketamine therapy as a suicide preventive treatment measure has yet to be determined.

Regarding psychotherapeutic treatment, it has to be noted that results differ considerably and even the adequate targets of suicide interventions are still a matter of debate. For instance, Franklin *et al*^[94] point out that the majority of applied intervention targets are derived from untested theoretical assertions, moderate correlates, or weak risk factors of suicidal thoughts and behaviors. None of these forms of evidence would allow somebody to draw conclusions regarding causal

inferences. For cutting this Gordian knot, we first of all recommend to make a strict distinction between suicidal ideation and suicidal behavior^[conf.95]. Suicidal ideation refers to any thoughts, imaginations, beliefs, or other cognitions associated with ending one's life. Previous studies demonstrated a consistent reduction in suicidal ideations during psychotherapeutic or antidepressant treatment of affective disorders, very likely resulting from the general effect on depression^[96,97]. Furthermore, the predictive value of suicidal ideation for suicidal behavior has been shown to be low^[29]. There is also some evidence for the notion that the genetic transmission of suicidal ideation may follow a different pathway than suicidal behavior^[95]. Suicidal behavior, on the other hand, is a strong predictor for suicide re-attempts^[98]. This fact underscores the need for development of specific psychotherapeutic approaches for individuals with suicidal behavior to reduce the risk of suicide re-attempts. In a most recent meta-analysis on psychotherapeutic interventions only RCTs were included that referred directly to suicide attempts and used the number of re-attempts as an outcome variable^[99]. By this procedure, 18 studies were identified. Statistical comparison of all studies showed that psychotherapeutic interventions in general reduced the risk of future suicidal behaviour nearly by a third^[99]. Separate analyses revealed that cognitive-behavioral therapy (CBT) as well as two different psychodynamic therapy approaches was significantly more efficacious than control conditions. Dialectical behavior therapy (DBT) and elementary problem-solving therapy (PST) were not superior to control conditions in reducing the number of suicide re-attempts^[99]. Based on the results of this meta-analysis, it appears as a key recommendation for future psychotherapeutic approaches to focus the intervention directly on the episodes of suicidal behavior.

CONCLUSION

In this work we have pointed out significant advances in the field of scientific suicidology. We would like to add that, from our point of view, it already represents a progress that suicidal behavior disorder was included in the DSM-5 as a disorder for further consideration. This decision has sharpened the focus on suicidal behavior and both, screening methods and therapeutic approaches can be developed in a more targeted manner. As an example, we would like to point out the advances in

screening methods, *e.g.*, using implicit cognition, smartphone-based interventions, and real-time monitoring. These methods should be further developed and much more involved in the patient care. The same applies to the development of a valid biomarker set. On the other hand, existing psychotherapy approaches should be further developed. In our view, the greatest opportunities arise for procedures that are aimed directly at suicidal behavior. Concerning pharmacotherapy, a specific anti-suicidal effect of antidepressants, lithium, and clozapine is likely but not yet proven. Ketamine is a promising new drug with promising results for reducing suicidal ideation. However, more evidence is needed to demonstrate sustained and specific anti-suicidal efficacy. The advances such as highlighted in this editorial make us optimistic. Since each of the methods shown has its strengths and weaknesses, we believe that far-reaching future progress can only be achieved with a multifaceted approach using appropriate ¹⁰ universal, selective and indicated prevention strategies.

Table 1 Allocation of single preventive measures to the overarching strategies of ⁴⁵ universal, selective, and indicated prevention

Type of prevention strategy	Prevention measures ¹⁰
Universal prevention strategies	Limitation of ¹⁰ access to lethal means (<i>e.g.</i> , control of analgesics, and hot-spots for suicide by jumping) School-based awareness programs Initiatives with regard to public education and awareness Media education Access to health care Policies to reduce ³¹ harmful use of alcohol or other substances
Selective prevention strategies	Education of physicians Gatekeeper training Psychological screening methods (<i>e.g.</i> , measurement of implicit cognition by the IAT, smartphone-based interventions, real-time

monitoring of suicidal thoughts and behaviors)

ZS model

Neurobiological screening methods

Crisis helplines

Indicated prevention strategies Assessment and management of suicidal behavior
Psychopharmacologic treatment approaches
[antidepressants (caveat), ketamine, lithium, clozapine]
Psychotherapeutic treatment approaches (recent methods, specifically focusing on suicidal behavior)
Assessment and management of substance abuse and other mental disorders
Psychopharmacologic treatment approaches
[antidepressants (caveat), ketamine, lithium, clozapine]
Psychotherapeutic treatment approaches (recent methods, specifically focusing on suicidal behavior)
Assessment and management of substance abuse and other mental disorders
Community support

IAT: Implicit association test; ZS: Zero Suicide.

28%

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