ISSN 2220-3206 (online)

# World Journal of *Psychiatry*

*World J Psychiatry* 2022 September 19; 12(9): 1115-1267

Published by Baishideng Publishing Group Inc

World Journal of Psychiatry

Contents

Monthly Volume 12 Number 9 September 19, 2022

*World Journal of Psychiatry*

**Monthly Volume 12 Number 9 September 19, 2022**

## Contents

### LETTER TO THE EDITOR

*World Journal of Psychiatry*

**Monthly Volume 12 Number 9 September 19, 2022**

# Contents

## ABOUT COVER

Editorial Board Member of *World Journal of Psychiatry*, Giampaolo Perna, MD, PhD, Chairman, Professor, Department of Biomedical Sciences, Humanitas University, Milan 20090, Italy. giampaolo.perna@hunimed.eu

## AIMS AND SCOPE

The primary aim of *World Journal of Psychiatry* (*WJP*, *World J Psychiatry*) is to provide scholars and readers from various fields of psychiatry with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJP* mainly publishes articles reporting research results and findings obtained in the field of psychiatry and covering a wide range of topics including adolescent psychiatry, biological psychiatry, child psychiatry, community psychiatry, ethnopsychology, psychoanalysis, psychosomatic medicine, *etc.*

## INDEXING/ABSTRACTING

The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJP* as 3.500; IF without journal self cites: 3.313; 5-year IF: 7.380; Journal Citation Indicator: 0.62; Ranking: 89 among 155 journals in psychiatry; and Quartile category: Q3.

## RESPONSIBLE EDITORS FOR THIS ISSUE



**NAME OF JOURNAL**
*World Journal of Psychiatry*

**ISSN**
ISSN 2220-3206 (online)

**LAUNCH DATE**
December 31, 2011

**FREQUENCY**
Monthly

**EDITORS-IN-CHIEF**
Rajesh R Tampi, Ting-Shao Zhu, Panteleimon Giannakopoulos

**EDITORIAL BOARD MEMBERS**
https://www.wjgnet.com/2220-3206/editorialboard.htm

**PUBLICATION DATE**
September 19, 2022



**INSTRUCTIONS TO AUTHORS**
https://www.wjgnet.com/bpg/gerinfo/204

**GUIDELINES FOR ETHICS DOCUMENTS**
https://www.wjgnet.com/bpg/GerInfo/287

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**
https://www.wjgnet.com/bpg/gerinfo/240

**PUBLICATION ETHICS**
https://www.wjgnet.com/bpg/GerInfo/288

**PUBLICATION MISCONDUCT**
https://www.wjgnet.com/bpg/gerinfo/208

**ARTICLE PROCESSING CHARGE**
https://www.wjgnet.com/bpg/gerinfo/242

**STEPS FOR SUBMITTING MANUSCRIPTS**
https://www.wjgnet.com/bpg/GerInfo/239

**ONLINE SUBMISSION**
https://www.f6publishing.com

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

*World J Psychiatry* 2022 September 19; 12(9): 1115-1126

DOI: 10.5498/wjp.v12.i9.1115

ISSN 2220-3206 (online)

EDITORIAL

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

Thomas Sobanski, Gregor Peikert, Ulrich W Kastner, Gerd Wagner

**Specialty type:** Psychiatry

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Mikellides G, Netherlands; Yanagi M, United States

**Received:** April 13, 2022
**Peer-review started:** April 13, 2022
**First decision:** June 11, 2022
**Revised:** June 26, 2022
**Accepted:** August 15, 2022
**Article in press:** August 15, 2022
**Published online:** September 19, 2022

**Thomas Sobanski,** Department of Psychiatry, Psychotherapy, and Psychosomatic Medicine, THUERINGEN-Kliniken GmbH, Saalfeld 07318, Germany

**Thomas Sobanski, Ulrich W Kastner, Gerd Wagner,** Network for Suicide Prevention in Thuringia (NeST), Jena 07743, Germany

**Gregor Peikert, Gerd Wagner,** Department of Psychiatry and Psychotherapy, University Hospital Jena, Jena 07743, Germany

**Ulrich W Kastner,** Department of Psychiatry and Psychotherapy, Helios Fachkliniken Hildburghausen, Hildburghausen 98646, Germany

**Corresponding author:** Thomas Sobanski, MD, Chief Doctor, Senior Lecturer, Senior Research Fellow, Department of Psychiatry, Psychotherapy, and Psychosomatic Medicine, THUERINGEN-Kliniken GmbH, 68 Rainweg, Saalfeld 07318, Germany.
tsobanski@thueringen-kliniken.de

## Abstract

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. Regarding selective prevention, substantial progress can be expected in psychological screening methods for suicidal behavior. 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 studies and 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



**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.

**Citation:** Sobanski T, Peikert G, Kastner UW, Wagner G. Suicidal behavior-advances in clinical and neurobiological research and improvement of prevention strategies. *World J Psychiatry* 2022; 12(9): 1115-1126
**URL:** https://www.wjgnet.com/2220-3206/full/v12/i9/1115.htm
**DOI:** https://dx.doi.org/10.5498/wjp.v12.i9.1115

## INTRODUCTION

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 suicidal behavior[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

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

| Type of prevention strategy | Prevention measures |
|---|---|
| Universal prevention strategies | Limitation of access to lethal means (*e.g.*, 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 harmful use of alcohol or other substances |
| Selective prevention strategies | Education of physicians |
| | Gatekeeper training |
| | Psychological screening methods (*e.g.*, 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 |
| | Community support |

IAT: Implicit Association Test; ZS: Zero Suicide.

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 22.499 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 ($n$=7.015) 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 suicide 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 regard, the Zero Suicide (ZS) model also represents a remarkable advance. In this prevention approach all persons receiving care for a mental disorder 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.*, 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, 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 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-HT1A receptor binding potential 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 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 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.

### *Psychotherapeutic treatment approaches*

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[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 behavior nearly by a third[99]. Separate analyses revealed that cognitive behavioral therapy (CBT) as well as two different psychodynamic therapy approaches were 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 universal, selective and indicated prevention strategies.

## FOOTNOTES

**Author contributions:** Sobanski T, Peikert G, Kastner UW, and Wagner G contributed to this paper with conception, literature review and analysis, drafting and critical revision and editing, and approval of the final version.

**Conflict-of-interest statement:** Thomas Sobanski, Gregor Peikert, and Gerd Wagner have nothing to disclose. Ulrich W. Kastner owns shares in a healthcare company (Fresenius LTIP 2018, long-term incentive plan). However, this company is not active in the field of psychiatry or neuroscience. Thus, there is no content or technical reference.



**Country/Territory of origin:** Germany

**ORCID number:** Thomas Sobanski 0000-0002-0647-8924; Gregor Peikert 0000-0002-9718-1412; Ulrich W Kastner 0000-0002-2504-6107; Gerd Wagner 0000-0003-2296-0259.

**Corresponding Author's Membership in Professional Societies:** Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Neurologie, No. DGPPN, 102012; Deutsche Gesellschaft für Biologische Psychiatrie, No. DGBP, 7020171; Deutsche Gesellschaft für Klinische Neurophysiologie, No. DGKN, 1-D36002-494; Deutsche Gesellschaft für Schlafforschung und Schlafmedizin, No. DGSM, 950078; Deutsche Gesellschaft Zwangserkrankungen, No. DGZ, 1451; Deutsches Bündnis gegen Depression, No. M0085; Verband der Leitenden Krankenhausärzte Deutschlands, No. 11682.

**S-Editor:** Chen YL

**L-Editor:** A

**P-Editor:** Chen YL

## REFERENCES

1 **World Health Organisation**. Suicide. June 17, 2021. [cited 1 April 2022]. Available from: https://www.who.int/news-room/fact-sheets/detail/suicide
2 **United Nations**. World Population Prospects: The 2008 Revision. New York: United Nations Publications, 2009
3 **Arsenault-Lapierre G**, Kim C, Turecki G. Psychiatric diagnoses in 3275 suicides: a meta-analysis. *BMC Psychiatry* 2004; **4**: 37 [PMID: 15527502 DOI: 10.1186/1471-244X-4-37]
4 **Phillips MR**, Yang G, Zhang Y, Wang L, Ji H, Zhou M. Risk factors for suicide in China: a national case-control psychological autopsy study. *Lancet* 2002; **360**: 1728-1736 [PMID: 12480425 DOI: 10.1016/S0140-6736(02)11681-3]
5 **Liu Y**, Lan Z, Yin Y, Liu NH, Tong Y. Trends in suicide rates and the case-fatality of pesticide self-poisoning in an agricultural county in china, 2009 to 2014. *J Affect Disord* 2021; **283**: 52-59 [PMID: 33517228 DOI: 10.1016/j.jad.2021.01.024]
6 **Thippaiah SM**, Nanjappa MS, Math SB. Suicide in India: A preventable epidemic. *Indian J Med Res* 2019; **150**: 324-327 [PMID: 31823913 DOI: 10.4103/ijmr.IJMR_1805_19]
7 **Bonvoisin T**, Utyasheva L, Knipe D, Gunnell D, Eddleston M. Suicide by pesticide poisoning in India: a review of pesticide regulations and their impact on suicide trends. *BMC Public Health* 2020; **20**: 251 [PMID: 32075613 DOI: 10.1186/s12889-020-8339-z]
8 **Mann JJ**. Neurobiology of suicidal behaviour. *Nat Rev Neurosci* 2003; **4**: 819-828 [PMID: 14523381 DOI: 10.1038/nrn1220]
9 **Bostwick JM**, Pankratz VS. Affective disorders and suicide risk: a reexamination. *Am J Psychiatry* 2000; **157**: 1925-1932 [PMID: 11097952 DOI: 10.1176/appi.ajp.157.12.1925]
10 **Angst J**, Angst F, Gerber-Werder R, Gamma A. Suicide in 406 mood-disorder patients with and without long-term medication: a 40 to 44 years' follow-up. *Arch Suicide Res* 2005; **9**: 279-300 [PMID: 16020171 DOI: 10.1080/13811110590929488]
11 **Ernst C**, Mechawar N, Turecki G. Suicide neurobiology. *Prog Neurobiol* 2009; **89**: 315-333 [PMID: 19766697 DOI: 10.1016/j.pneurobio.2009.09.001]
12 **Sobanski T**, Bär K-J, Wagner G. Neural, cognitive, and neuroimaging markers of the suicidal brain. *Rep in Med Imaging* 2015; **8**: 71-81 [DOI: 10.2147/RMI.S55532]
13 **Turecki G**, Brent DA. Suicide and suicidal behaviour. *Lancet* 2016; **387**: 1227-1239 [PMID: 26385066 DOI: 10.1016/S0140-6736(15)00234-2]
14 **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA, USA: American Psychiatric Publishing, 2013
15 **Klonsky ED**, May AM. Differentiating suicide attempters from suicide ideators: a critical frontier for suicidology research. *Suicide Life Threat Behav* 2014; **44**: 1-5 [PMID: 24313594 DOI: 10.1111/sltb.12068]
16 **Caplan G**. Principles of Preventive Psychiatry. New York, USA: Basic Books, 1964
17 **Cowen EL**. The wooing of primary prevention. *Am J Community Psychol* 1980; **8**: 258-284 [PMID: 7416089]
18 **Gordon RS Jr**. An operational classification of disease prevention. *Public Health Rep* 1983; **98**: 107-109 [PMID: 6856733]
19 **Springer FJ**, Phillips J. National Academy of Medicine: The Institute of Medicine Framework and its implication for the advancement of prevention policy, programs and practice. 2007. [cited 1 April 2022]. Available from: http//ca-sdfsc.org › docs › SDFSC_IOM_Policy
20 **Heller K**. Prevention research priorities: Forward movement and backward steps in the NAMHC workgroup recommendations. *Prevention & Treatment* 2001; **4**: 22C [DOI: 10.1037/1522-3736.4.1.422c]
21 **Pearson JL**, Koretz DS. Opportunities in prevention research at NIMH: Integrating prevention with treatment research. *Prevention & Treatment* 2001; **4**: 18C [DOI: 10.1037/1522-3736.4.1.418c]
22 **Mann JJ**, Apter A, Bertolote J, Beautrais A, Currier D, Haas A, Hegerl U, Lonnqvist J, Malone K, Marusic A, Mehlum L, Patton G, Phillips M, Rutz W, Rihmer Z, Schmidtke A, Shaffer D, Silverman M, Takahashi Y, Varnik A, Wasserman D, Yip P, Hendin H. Suicide prevention strategies: a systematic review. *JAMA* 2005; **294**: 2064-2074 [PMID: 16249421 DOI: 10.1001/jama.294.16.2064]
23 **Zalsman G**, Hawton K, Wasserman D, van Heeringen K, Arensman E, Sarchiapone M, Carli V, Höschl C, Barzilay R, Balazs J, Purebl G, Kahn JP, Sáiz PA, Lipsicas CB, Bobes J, Cozman D, Hegerl U, Zohar J. Suicide prevention strategies revisited: 10-year systematic review. *Lancet Psychiatry* 2016; **3**: 646-659 [PMID: 27289303 DOI: 10.1016/S2215-0366(16)30030-X]

24 **World Health Organisation**. Preventing Suicide: A global imperative. 2014. [cited 1 April 2022]. Available from: http://www.who.int/mental_health/suicide-prevention/world_report_2014/en/

25 **Centers for Disease Control and Prevention (CDC)**. Fatal Injury Reports, National, Regional, and State, 1981-2020, Webbased Injury Statistics Query and Reporting System (WISQARS). 2022. [cited 1 April 2022]. Available from: https://webappa.cdc.gov/sasweb/ncipc/mortrate.html

26 **Woodford R**, Spittal MJ, Milner A, McGill K, Kapur N, Pirkis J, Mitchell A, Carter G. Accuracy of Clinician Predictions of Future Self-Harm: A Systematic Review and Meta-Analysis of Predictive Studies. *Suicide Life Threat Behav* 2019; **49**: 23-40 [PMID: 28972271 DOI: 10.1111/sltb.12395]

27 **Borges G**, Bagge CL, Cherpitel CJ, Conner KR, Orozco R, Rossow I. A meta-analysis of acute use of alcohol and the risk of suicide attempt. *Psychol Med* 2017; **47**: 949-957 [PMID: 27928972 DOI: 10.1017/S0033291716002841]

28 **Ferrari AJ**, Norman RE, Freedman G, Baxter AJ, Pirkis JE, Harris MG, Page A, Carnahan E, Degenhardt L, Vos T, Whiteford HA. The burden attributable to mental and substance use disorders as risk factors for suicide: findings from the Global Burden of Disease Study 2010. *PLoS One* 2014; **9**: e91936 [PMID: 24694747 DOI: 10.1371/journal.pone.0091936]

29 **Beck AT**, Steer RA, Kovacs M, Garrison B. Hopelessness and eventual suicide: a 10-year prospective study of patients hospitalized with suicidal ideation. *Am J Psychiatry* 1985; **142**: 559-563 [PMID: 3985195 DOI: 10.1176/ajp.142.5.559]

30 **Acosta FJ**, Vega D, Torralba L, Navarro S, Ramallo-Fariña Y, Fiuza D, Hernández JL, Siris SG. Hopelessness and suicidal risk in bipolar disorder. A study in clinically nonsyndromal patients. *Compr Psychiatry* 2012; **53**: 1103-1109 [PMID: 22503379 DOI: 10.1016/j.comppsych.2012.03.013]

31 **Vuorilehto MS**, Melartin TK, Isometsä ET. Suicidal behaviour among primary-care patients with depressive disorders. *Psychol Med* 2006; **36**: 203-210 [PMID: 16420714 DOI: 10.1017/S0033291705006550]

32 **Rudd MD**, Joiner T, Rajab MH. Relationships among suicide ideators, attempters, and multiple attempters in a young-adult sample. *J Abnorm Psychol* 1996; **105**: 541-550 [PMID: 8952187 DOI: 10.1037//0021-843x.105.4.541]

33 **Apter A**, Horesh N, Gothelf D, Graffi H, Lepkifker E. Relationship between self-disclosure and serious suicidal behavior. *Compr Psychiatry* 2001; **42**: 70-75 [PMID: 11154719 DOI: 10.1053/comp.2001.19748]

34 **Mann JJ**, Waternaux C, Haas GL, Malone KM. Toward a clinical model of suicidal behavior in psychiatric patients. *Am J Psychiatry* 1999; **156**: 181-189 [PMID: 9989552 DOI: 10.1176/ajp.156.2.181]

35 **Lübbert M**, Bahlmann L, Josfeld S, Bürger J, Schulz A, Bär KJ, Polzer U, Walter M, Kastner UW, Sobanski T, Wagner G. Identifying Distinguishable Clinical Profiles Between Single Suicide Attempters and Re-Attempters. *Front Psychiatry* 2021; **12**: 754402 [PMID: 34646179 DOI: 10.3389/fpsyt.2021.754402]

36 **Nock MK**, Park JM, Finn CT, Deliberto TL, Dour HJ, Banaji MR. Measuring the suicidal mind: implicit cognition predicts suicidal behavior. *Psychol Sci* 2010; **21**: 511-517 [PMID: 20424092 DOI: 10.1177/0956797610364762]

37 **Nock MK**, Prinstein MJ, Sterba SK. Revealing the form and function of self-injurious thoughts and behaviors: A real-time ecological assessment study among adolescents and young adults. *J Abnorm Psychol* 2009; **118**: 816-827 [PMID: 19899851 DOI: 10.1037/a0016948]

38 **Busch KA**, Fawcett J, Jacobs DG. Clinical correlates of inpatient suicide. *J Clin Psychiatry* 2003; **64**: 14-19 [PMID: 12590618 DOI: 10.4088/jcp.v64n0105]

39 **Glenn JJ**, Werntz AJ, Slama SJ, Steinman SA, Teachman BA, Nock MK. Suicide and self-injury-related implicit cognition: A large-scale examination and replication. *J Abnorm Psychol* 2017; **126**: 199-211 [PMID: 27991808 DOI: 10.1037/abn0000230]

40 **Franklin JC**, Fox KR, Franklin CR, Kleiman EM, Ribeiro JD, Jaroszewski AC, Hooley JM, Nock MK. A brief mobile app reduces nonsuicidal and suicidal self-injury: Evidence from three randomized controlled trials. *J Consult Clin Psychol* 2016; **84**: 544-557 [PMID: 27018530 DOI: 10.1037/ccp0000093]

41 **Kleiman EM**, Turner BJ, Fedor S, Beale EE, Picard RW, Huffman JC, Nock MK. Digital phenotyping of suicidal thoughts. *Depress Anxiety* 2018; **35**: 601-608 [PMID: 29637663 DOI: 10.1002/da.22730]

42 **Kleiman EM**, Turner BJ, Fedor S, Beale EE, Huffman JC, Nock MK. Examination of real-time fluctuations in suicidal ideation and its risk factors: Results from two ecological momentary assessment studies. *J Abnorm Psychol* 2017; **126**: 726-738 [PMID: 28481571 DOI: 10.1037/abn0000273]

43 **Hallensleben N**, Spangenberg L, Forkmann T, Rath D, Hegerl U, Kersting A, Kallert TW, Glaesmer H. Investigating the Dynamics of Suicidal Ideation. *Crisis* 2018; **39**: 65-69 [PMID: 28468557 DOI: 10.1027/0227-5910/a000464]

44 **Zero Suicide (ZS)**. Your guide to understanding the Zero Suicide mission and framework, as well as a road map toward implementation. 2022. [cited 1 April 2022]. Available from: https://zerosuicide.edc.org

45 **Layman DM**, Kammer J, Leckman-Westin E, Hogan M, Goldstein Grumet J, Labouliere CD, Stanley B, Carruthers J, Finnerty M. The Relationship Between Suicidal Behaviors and Zero Suicide Organizational Best Practices in Outpatient Mental Health Clinics. *Psychiatr Serv* 2021; **72**: 1118-1125 [PMID: 33730886 DOI: 10.1176/appi.ps.202000525]

46 **Lutz PE**, Mechawar N, Turecki G. Neuropathology of suicide: recent findings and future directions. *Mol Psychiatry* 2017; **22**: 1395-1412 [PMID: 28696430 DOI: 10.1038/mp.2017.141]

47 **Brent DA**, Melhem N. Familial transmission of suicidal behavior. *Psychiatr Clin North Am* 2008; **31**: 157-177 [PMID: 18439442 DOI: 10.1016/j.psc.2008.02.001]

48 **Turecki G**, Ota VK, Belangero SI, Jackowski A, Kaufman J. Early life adversity, genomic plasticity, and psychopathology. *Lancet Psychiatry* 2014; **1**: 461-466 [PMID: 26361201 DOI: 10.1016/S2215-0366(14)00022-4]

49 **Brezo J**, Paris J, Vitaro F, Hébert M, Tremblay RE, Turecki G. Predicting suicide attempts in young adults with histories of childhood abuse. *Br J Psychiatry* 2008; **193**: 134-139 [PMID: 18669998 DOI: 10.1192/bjp.bp.107.037994]

50 **Johnson JG**, Cohen P, Gould MS, Kasen S, Brown J, Brook JS. Childhood adversities, interpersonal difficulties, and risk for suicide attempts during late adolescence and early adulthood. *Arch Gen Psychiatry* 2002; **59**: 741-749 [PMID: 12150651 DOI: 10.1001/archpsyc.59.8.741]

51 **Francis D**, Diorio J, Liu D, Meaney MJ. Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science* 1999; **286**: 1155-1158 [PMID: 10550053 DOI: 10.1126/science.286.5442.1155]

52 **Mann JJ**, Currier D. A review of prospective studies of biologic predictors of suicidal behavior in mood disorders. *Arch*

*Suicide Res* 2007; **11**: 3-16 [PMID: 17178639 DOI: 10.1080/13811110600993124]
53 **McGowan PO**, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, Turecki G, Meaney MJ. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 2009; **12**: 342-348 [PMID: 19234457 DOI: 10.1038/nn.2270]
54 **Jokinen J**, Boström AE, Dadfar A, Ciuculete DM, Chatzittofis A, Åsberg M, Schiöth HB. Epigenetic Changes in the CRH Gene are Related to Severity of Suicide Attempt and a General Psychiatric Risk Score in Adolescents. *EBioMedicine* 2018; **27**: 123-133 [PMID: 29277323 DOI: 10.1016/j.ebiom.2017.12.018]
55 **Pandey GN**, Rizavi HS, Ren X, Fareed J, Hoppensteadt DA, Roberts RC, Conley RR, Dwivedi Y. Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. *J Psychiatr Res* 2012; **46**: 57-63 [PMID: 21906753 DOI: 10.1016/j.jpsychires.2011.08.006]
56 **Steiner J**, Bielau H, Brisch R, Danos P, Ullrich O, Mawrin C, Bernstein HG, Bogerts B. Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide. *J Psychiatr Res* 2008; **42**: 151-157 [PMID: 17174336 DOI: 10.1016/j.jpsychires.2006.10.013]
57 **Gross JA**, Turecki G. Suicide and the polyamine system. *CNS Neurol Disord Drug Targets* 2013; **12**: 980-988 [PMID: 24040803 DOI: 10.2174/18715273113129990095]
58 **Sequeira A**, Gwadry FG, Ffrench-Mullen JM, Canetti L, Gingras Y, Casero RA Jr, Rouleau G, Benkelfat C, Turecki G. Implication of SSAT by gene expression and genetic variation in suicide and major depression. *Arch Gen Psychiatry* 2006; **63**: 35-48 [PMID: 16389195 DOI: 10.1001/archpsyc.63.1.35]
59 **Le-Niculescu H**, Levey DF, Ayalew M, Palmer L, Gavrin LM, Jain N, Winiger E, Bhosrekar S, Shankar G, Radel M, Bellanger E, Duckworth H, Olesek K, Vergo J, Schweitzer R, Yard M, Ballew A, Shekhar A, Sandusky GE, Schork NJ, Kurian SM, Salomon DR, Niculescu AB 3rd. Discovery and validation of blood biomarkers for suicidality. *Mol Psychiatry* 2013; **18**: 1249-1264 [PMID: 23958961 DOI: 10.1038/mp.2013.95]
60 **Asberg M**, Träskman L, Thorén P. 5-HIAA in the cerebrospinal fluid. A biochemical suicide predictor? *Arch Gen Psychiatry* 1976; **33**: 1193-1197 [PMID: 971028 DOI: 10.1001/archpsyc.1976.01770100055005]
61 **Mann JJ**, Huang YY, Underwood MD, Kassir SA, Oppenheim S, Kelly TM, Dwork AJ, Arango V. A serotonin transporter gene promoter polymorphism (5-HTTLPR) and prefrontal cortical binding in major depression and suicide. *Arch Gen Psychiatry* 2000; **57**: 729-738 [PMID: 10920459 DOI: 10.1001/archpsyc.57.8.729]
62 **Malone KM**, Corbitt EM, Li S, Mann JJ. Prolactin response to fenfluramine and suicide attempt lethality in major depression. *Br J Psychiatry* 1996; **168**: 324-329 [PMID: 8833686 DOI: 10.1192/bjp.168.3.324]
63 **Sullivan GM**, Oquendo MA, Milak M, Miller JM, Burke A, Ogden RT, Parsey RV, Mann JJ. Positron emission tomography quantification of serotonin(1A) receptor binding in suicide attempters with major depressive disorder. *JAMA Psychiatry* 2015; **72**: 169-178 [PMID: 25549105 DOI: 10.1001/jamapsychiatry.2014.2406]
64 **Lin PY**, Hung CF, Hung TH, Lung FW, Chong MY, Wu CK, Wen JK. Association between Serotonin Transporter Gene Promotor Polymorphism and Male Suicide Attempt in Han Chinese. *Biol Psychiatry* 2009; **65**: 215s-216s
65 **Lin PY**, Tsai G. Association between serotonin transporter gene promoter polymorphism and suicide: results of a meta-analysis. *Biol Psychiatry* 2004; **55**: 1023-1030 [PMID: 15121487 DOI: 10.1016/j.biopsych.2004.02.006]
66 **Grunebaum MF**, Galfalvy HC, Choo TH, Keilp JG, Moitra VK, Parris MS, Marver JE, Burke AK, Milak MS, Sublette ME, Oquendo MA, Mann JJ. Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial. *Am J Psychiatry* 2018; **175**: 327-335 [PMID: 29202655 DOI: 10.1176/appi.ajp.2017.17060647]
67 **Nowak G**, Ordway GA, Paul IA. Alterations in the N-methyl-D-aspartate (NMDA) receptor complex in the frontal cortex of suicide victims. *Brain Res* 1995; **675**: 157-164 [PMID: 7796124 DOI: 10.1016/0006-8993(95)00057-w]
68 **Holemans S**, De Paermentier F, Horton RW, Crompton MR, Katona CL, Maloteaux JM. NMDA glutamatergic receptors, labelled with [3H]MK-801, in brain samples from drug-free depressed suicides. *Brain Res* 1993; **616**: 138-143 [PMID: 8358605 DOI: 10.1016/0006-8993(93)90202-x]
69 **Oquendo MA**, Sullivan GM, Sudol K, Baca-Garcia E, Stanley BH, Sublette ME, Mann JJ. Toward a biosignature for suicide. *Am J Psychiatry* 2014; **171**: 1259-1277 [PMID: 25263730 DOI: 10.1176/appi.ajp.2014.14020194]
70 **Hammad TA**, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry* 2006; **63**: 332-339 [PMID: 16520440 DOI: 10.1001/archpsyc.63.3.332]
71 **Stone M**, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A, Hammad TA, Temple R, Rochester G. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ* 2009; **339**: b2880 [PMID: 19671933 DOI: 10.1136/bmj.b2880]
72 **Brent DA**. Antidepressants and Suicidality. *Psychiatr Clin North Am* 2016; **39**: 503-512 [PMID: 27514302 DOI: 10.1016/j.psc.2016.04.002]
73 **Simon GE**, Savarino J, Operskalski B, Wang PS. Suicide risk during antidepressant treatment. *Am J Psychiatry* 2006; **163**: 41-47 [PMID: 16390887 DOI: 10.1176/appi.ajp.163.1.41]
74 **Cipriani A**, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ* 2013; **346**: f3646 [PMID: 23814104 DOI: 10.1136/bmj.f3646]
75 **Baldessarini RJ**, Pompili M, Tondo L. Suicidal risk in antidepressant drug trials. *Arch Gen Psychiatry* 2006; **63**: 246-248 [PMID: 16520428 DOI: 10.1001/archpsyc.63.3.246]
76 **Kessing LV**, Søndergård L, Kvist K, Andersen PK. Suicide risk in patients treated with lithium. *Arch Gen Psychiatry* 2005; **62**: 860-866 [PMID: 16061763 DOI: 10.1001/archpsyc.62.8.860]
77 **Lauterbach E**, Felber W, Müller-Oerlinghausen B, Ahrens B, Bronisch T, Meyer T, Kilb B, Lewitzka U, Hawellek B, Quante A, Richter K, Broocks A, Hohagen F. Adjunctive lithium treatment in the prevention of suicidal behaviour in depressive disorders: a randomised, placebo-controlled, 1-year trial. *Acta Psychiatr Scand* 2008; **118**: 469-479 [PMID: 18808400 DOI: 10.1111/j.1600-0447.2008.01266.x]
78 **Asenjo Lobos C**, Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Leucht S. Clozapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev* 2010; CD006633 [PMID: 21069690 DOI: 10.1002/14651858.CD006633.pub2]

79 **D'Anci KE**, Uhl S, Giradi G, Martin C. Treatments for the Prevention and Management of Suicide: A Systematic Review. *Ann Intern Med* 2019; **171**: 334-342 [PMID: 31450239 DOI: 10.7326/M19-0869]

80 **Newport DJ**, Carpenter LL, McDonald WM, Potash JB, Tohen M, Nemeroff CB; APA Council of Research Task Force on Novel Biomarkers and Treatments. Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression. *Am J Psychiatry* 2015; **172**: 950-966 [PMID: 26423481 DOI: 10.1176/appi.ajp.2015.15040465]

81 **Finck AD**, Ngai SH. Opiate receptor mediation of ketamine analgesia. *Anesthesiology* 1982; **56**: 291-297 [PMID: 6278991 DOI: 10.1097/00000542-198204000-00011]

82 **Freye E**, Latasch L, Schmidhammer H, Portoghese P. [Interaction of S-(+)-ketamine with opiate receptors. Effects on EEG, evoked potentials and respiration in awake dogs]. *Anaesthesist* 1994; **43** Suppl 2: S52-S58 [PMID: 7840415]

83 **Jonkman K**, van Rijnsoever E, Olofsen E, Aarts L, Sarton E, van Velzen M, Niesters M, Dahan A. Esketamine counters opioid-induced respiratory depression. *Br J Anaesth* 2018; **120**: 1117-1127 [PMID: 29661389 DOI: 10.1016/j.bja.2018.02.021]

84 **Sarton E**, Teppema LJ, Olievier C, Nieuwenhuijs D, Matthes HW, Kieffer BL, Dahan A. The involvement of the mu-opioid receptor in ketamine-induced respiratory depression and antinociception. *Anesth Analg* 2001; **93**: 1495-1500, table of contents [PMID: 11726430 DOI: 10.1097/00000539-200112000-00031]

85 **Abbar M**, Demattei C, El-Hage W, Llorca PM, Samalin L, Demaricourt P, Gaillard R, Courtet P, Vaiva G, Gorwood P, Fabbro P, Jollant F. Ketamine for the acute treatment of severe suicidal ideation: double blind, randomised placebo controlled trial. *BMJ* 2022; **376**: e067194 [PMID: 35110300 DOI: 10.1136/bmj-2021-067194]

86 **Jelen LA**, King S, Stone JM. Alternatives to ketamine in depression: state-of-the-art and future perspectives. *Ther Adv Psychopharmacol* 2018; **8**: 95-98 [PMID: 29492257 DOI: 10.1177/2045125317749456]

87 **Correia-Melo FS**, Leal GC, Vieira F, Jesus-Nunes AP, Mello RP, Magnavita G, Caliman-Fontes AT, Echegaray MVF, Bandeira ID, Silva SS, Cavalcanti DE, Araújo-de-Freitas L, Sarin LM, Tuena MA, Nakahira C, Sampaio AS, Del-Porto JA, Turecki G, Loo C, Lacerda ALT, Quarantini LC. Efficacy and safety of adjunctive therapy using esketamine or racemic ketamine for adult treatment-resistant depression: A randomized, double-blind, non-inferiority study. *J Affect Disord* 2020; **264**: 527-534 [PMID: 31786030 DOI: 10.1016/j.jad.2019.11.086]

88 **Schatzberg AF**. A Word to the Wise About Intranasal Esketamine. *Am J Psychiatry* 2019; **176**: 422-424 [PMID: 31109197 DOI: 10.1176/appi.ajp.2019.19040423]

89 **Food and Drug Administration (FDA)**. FDA alerts health care professionals of potential risks associated with compounded ketamine nasal spray. 2022. [cited 1 April 2022]. Available from: https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-professionals-potential-risks-associated-compounded-ketamine-nasal-spray

90 **Wei Y**, Chang L, Hashimoto K. A historical review of antidepressant effects of ketamine and its enantiomers. *Pharmacol Biochem Behav* 2020; **190**: 172870 [PMID: 32035078 DOI: 10.1016/j.pbb.2020.172870]

91 **Bahji A**, Vazquez GH, Zarate CA Jr. Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis. *J Affect Disord* 2021; **278**: 542-555 [PMID: 33022440 DOI: 10.1016/j.jad.2020.09.071]

92 **Witt K**, Potts J, Hubers A, Grunebaum MF, Murrough JW, Loo C, Cipriani A, Hawton K. Ketamine for suicidal ideation in adults with psychiatric disorders: A systematic review and meta-analysis of treatment trials. *Aust N Z J Psychiatry* 2020; **54**: 29-45 [PMID: 31729893 DOI: 10.1177/0004867419883341]

93 **Siegel AN**, Di Vincenzo JD, Brietzke E, Gill H, Rodrigues NB, Lui LMW, Teopiz KM, Ng J, Ho R, McIntyre RS, Rosenblat JD. Antisuicidal and antidepressant effects of ketamine and esketamine in patients with baseline suicidality: A systematic review. *J Psychiatr Res* 2021; **137**: 426-436 [PMID: 33774537 DOI: 10.1016/j.jpsychires.2021.03.009]

94 **Franklin JC**, Huang X, Fox KR, Ribeiro JD. What suicide interventions should target. *Curr Opin Psychol* 2018; **22**: 50-53 [PMID: 30122278 DOI: 10.1016/j.copsyc.2017.08.002]

95 **Brent DA**, Bridge J, Johnson BA, Connolly J. Suicidal behavior runs in families. A controlled family study of adolescent suicide victims. *Arch Gen Psychiatry* 1996; **53**: 1145-1152 [PMID: 8956681 DOI: 10.1001/archpsyc.1996.01830120085015]

96 **Cuijpers P**, de Beurs DP, van Spijker BA, Berking M, Andersson G, Kerkhof AJ. The effects of psychotherapy for adult depression on suicidality and hopelessness: a systematic review and meta-analysis. *J Affect Disord* 2013; **144**: 183-190 [PMID: 22832172 DOI: 10.1016/j.jad.2012.06.025]

97 **Weitz E**, Hollon SD, Kerkhof A, Cuijpers P. Do depression treatments reduce suicidal ideation? *J Affect Disord* 2014; **167**: 98-103 [PMID: 24953481 DOI: 10.1016/j.jad.2014.05.036]

98 **Beautrais AL**. Subsequent mortality in medically serious suicide attempts: a 5 year follow-up. *Aust N Z J Psychiatry* 2003; **37**: 595-599 [PMID: 14511088 DOI: 10.1046/j.1440-1614.2003.01236.x]

99 **Sobanski T**, Josfeld S, Peikert G, Wagner G. Psychotherapeutic interventions for the prevention of suicide re-attempts: a systematic review. *Psychol Med* 2021; 1-16 [PMID: 34608856 DOI: 10.1017/S0033291721003081]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
**Telephone:** +1-925-3991568
**E-mail:** bpgoffice@wjgnet.com
**Help Desk:** https://www.f6publishing.com/helpdesk
https://www.wjgnet.com