

Point-by-Point Response Letter

We would like to thank both reviewers for their positive and helpful comments.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This manuscript highlights the recent research for suicide prevention. Although the manuscript focuses well on the current issues about it, minor revisions as specified below are required prior to publication.

1. In this manuscript, the term “suicidal behavior” and the abbreviations “SB” and “SBD” are used interchangeably. I recommend using “suicidal behavior” without the abbreviations.

Reply: As suggested by reviewer #1, we have amended the manuscript accordingly and refrained from using the abbreviations "SB" and "SBD".

2. It would be helpful for the readers to provide a brief explanation for the following terms: “universal,” “selective,” and “indicated prevention strategies.”

Reply: In the present manuscript, 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. On pages 8 and 9 of the manuscript we address the existing controversy regarding the classification of preventive measures for mental disorders. For better understanding, we have provided a table (Table 1; available at the end of this Point-by-Point Response Letter) that shows the classification according to the 1994 IOM Framework with the categories "universal," "selective," and "indicated prevention strategies" more clearly. Additionally, we inserted the following sentences:

On page 9

“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 (2014) ^[1], 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, as well as (6) policies to reduce harmful use of alcohol or other substances (see Table 1).”

On page 10

"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."

On page 11

"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 (see Table 1)."

On page 18

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

3. In the following sentence on page 7, "The situation differs in the developing countries in this regard; here oppression, poverty and aporia are important factors in the emergence of suicidal behavior." I think these factors could also be the risk for mood disorders. Therefore, the dissimilarity between developed and developing countries might only be due to a lack of access to a medical facility for diagnosis in a developing country. If so, there may be no significant difference in the risk factors for suicide between the two types of countries.

Reply: We fully agree with reviewer #1 and have modified the sentence as follows:

"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 due to a lack of access to medical and especially psychiatric care."

4. Please revise the following section to clarify the context. Page 17–18 "Some of the association between antidepressant use and suicide attempt in cross-sectional studies may be due to confounding of indication and treatment. Thus, a suicide attempt is a common reason to initiate treatment with antidepressants. Therefore, a positive correlation between suicidal behavior and therapy by antidepressants does not allow for the conclusion of a causal relationship."

Reply: We thank reviewer #1 for his suggestion. As we re-read this section, we realized that the meaning is somewhat misleading. We therefore decided to delete these sentences entirely, and instead go into more detail about the methodological reasons for the different results of RCT studies and pharmacoepidemiological studies. For reasons of context and comprehensibility, the new section was inserted after the Simon quote ^[2] (one sentence later). The newly added paragraphs are as follows:

On page 18

"From a methodological point of view, the question arises as to why the results of randomized controlled trials (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). (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)." [3]

5. The following sentence can be excluded to improve the clarity of context. Page 10 "We will go into more detail about the individual-level strategies in the following sections."

Reply: We have removed that sentence from the text.

6. I recommend elaborating on the following sentences: Page 15 "For example, a lack of decrease in cortisol levels was associated with an increased risk of a future suicide death" Is this a lack of decrease in cortisol level in dexamethasone suppression test?

Reply: We thank reviewer #1 for the careful reading of the manuscript. We modified this sentence, accordingly.

"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".

Page 16 "Blunted prolactin response to fenfluramine challenge was found in high vs low lethality suicide attempters" Was the blunted response seen in high lethality suicide attempters?

Reply: Thank you for this remark. We modified this sentence, accordingly.

"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."

Page 16 "Recently, PET studies showed higher raphe 5-HT_{1A} receptor binding in high vs low lethality suicide attempters" Was the binding higher in high lethality suicide attempters?

Reply: Thank you for this remark. We modified this sentence, accordingly.

"Recently, PET studies showed greater raphe 5-HT_{1A} receptor binding potential in high compared to low lethality suicide attempters".

7. Please specify the appropriate information for references, such as the one stated below:
Page 18 "(e.g.,79)"

Reply: We thank reviewer #1 for the careful reading of the manuscript. We modified this sentence and this reference, accordingly.

"Nevertheless, a recent review has called into question, whether certain drugs that improve the underlying disease also have an independent anti-suicidal effect." [4]

8. Please correct the inappropriate usage of comma in the following sentence. Page 20
"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."

Reply: Thank you for this remark. We modified this sentence, accordingly.

Page 20 "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."

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Its important to clarify the studies done with ketamine and esketamine as is not the same thing. A number of studies have used ketamine and not esketamine and it seems that esketamine is more promoted in this article, where following a systematic review and meta-analysis , esketamine was found to be less effective, compared to racemic IV ketamine, in treating depression. 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) 278:542–55. doi: 10.1016/j.jad.2020.09.071 So it would need to be clarified accordingly. Also its important to highlight if the Information in this editorial is somehow any different from already published literature?

Reply: We thank reviewer #2 for his suggestion. As we re-read this section, we realized that the statements in some passages were somewhat misleading. We therefore decided to restructure the whole section and we also did an extensive literature search on ketamin and esketamin. It was shown that the data clearly support ketamine, both in terms of antidepressant efficacy and the reduction in suicidal ideation. The newly inserted paragraphs are as follows:

On page 19

"The mechanism of action of ketamine has not yet been fully elucidated, but it is known that ketamine antagonizes glutamatergic N-methyl-D-aspartate (NMDA) receptors in the central nervous system. [5] Moreover, several studies have implied a role for opioid neurotransmission, as ketamine also appears to activate the mu, kappa, and delta-opioid receptors." [6-9]

On page 20 (top)

"To avoid the distress of intravenous ketamine therapy, alternative formulations and routes of application were sought. ^[10] 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. ^[11] Moreover, esketamine is available through an intranasal delivery system." ^[12]

On page 20 (below)

"In 2019, esketamine was also approved by the EMA (European Medicines Agency) for the same indication. Because of the risk of abuse, the approval applies only to inpatient treatment." ^[13]

On pages 20/21

"In their current review, Witt et al ^[14] 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 days. ^[14] Siegel et al ^[15] 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. ^[15] Esketamine was also found to be inferior to intravenous ketamine in the treatment of depression, as Bahji et al were able to show in their meta-analysis." ^[16]

On page 21

"Thus, the evidence for the efficacy of ketamine/esketamine therapy as a suicide preventive treatment measure has yet to be determined."

We have revised our manuscript very carefully and made it more precise in several passages. We hope the reviewers and the editor will appreciate the updated version. Again, we sincerely thank the reviewers for their thorough examination of the manuscript and their helpful comments.

Thomas Sobanski
MD

Ulrich Kästner
MD

Gregor Peikert
PhD

Gerd Wagner
PhD

References:

- 1 World-Health-Organisation, *Preventing Suicide: A global imperative*. 2014: http://www.who.int/mental_health/suicide-prevention/world_report_2014/en/.
- 2 Simon GE, Savarino J, Operskalski B, and Wang PS, Suicide risk during antidepressant treatment. *Am J Psychiatry* 2006; **163**: p. 41-7 [PMID: 16390887 DOI: 10.1176/appi.ajp.163.1.41]
- 3 Brent DA, Antidepressants and Suicidality. *Psychiatr Clin North Am* 2016; **39**: p. 503-12 [PMID: 27514302 DOI: 10.1016/j.psc.2016.04.002]
- 4 D'Anci KE, Uhl S, Giradi G, and Martin C, Treatments for the Prevention and Management of Suicide: A Systematic Review. *Ann Intern Med* 2019; **171**: p. 334-342 [PMID: 31450239 DOI: 10.7326/M19-0869]
- 5 Newport DJ, Carpenter LL, McDonald WM, Potash JB, Tohen M, Nemeroff CB, Biomarkers APACoRTFoN, and Treatments, Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression. *Am J Psychiatry* 2015; **172**: p. 950-66 [PMID: 26423481 DOI: 10.1176/appi.ajp.2015.15040465]
- 6 Finck AD and Ngai SH, Opiate receptor mediation of ketamine analgesia. *Anesthesiology* 1982; **56**: p. 291-7 [PMID: 6278991 DOI: 10.1097/0000542-198204000-00011]
- 7 Freye E, Latasch L, Schmidhammer H, and Portoghesi P, [Interaction of S-(+)-ketamine with opiate receptors. Effects on EEG, evoked potentials and respiration in awake dogs]. *Anaesthesist* 1994; **43 Suppl 2**: p. S52-8 [PMID: 7840415, <https://www.ncbi.nlm.nih.gov/pubmed/7840415>]
- 8 Jonkman K, van Rijnsoever E, Olofsen E, Aarts L, Sarton E, van Velzen M, Niesters M, and Dahan A, Esketamine counters opioid-induced respiratory depression. *Br J Anaesth* 2018; **120**: p. 1117-1127 [PMID: 29661389 DOI: 10.1016/j.bja.2018.02.021]
- 9 Sarton E, Teppema LJ, Olievier C, Nieuwenhuijs D, Matthes HW, Kieffer BL, and Dahan A, The involvement of the mu-opioid receptor in ketamine-induced respiratory depression and antinociception. *Anesth Analg* 2001; **93**: p. 1495-500, table of contents [PMID: 11726430 DOI: 10.1097/00000539-200112000-00031]
- 10 Jelen LA, King S, and Stone JM, Alternatives to ketamine in depression: state-of-the-art and future perspectives. *Ther Adv Psychopharmacol* 2018; **8**: p. 95-98 [PMID: 29492257 DOI: 10.1177/2045125317749456]
- 11 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, Araujo-de-Freitas L, Sarin LM, Tuena MA, Nakahira C, Sampaio AS, Del-Porto JA, Turecki G, Loo C, Lacerda ALT, and 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**: p. 527-534 [PMID: 31786030 DOI: 10.1016/j.jad.2019.11.086]
- 12 Schatzberg AF, A Word to the Wise About Intranasal Esketamine. *Am J Psychiatry* 2019; **176**: p. 422-424 [PMID: 31109197 DOI: 10.1176/appi.ajp.2019.19040423]
- 13 Wei Y, Chang L, and Hashimoto K, A historical review of antidepressant effects of ketamine and its enantiomers. *Pharmacol Biochem Behav* 2020; **190**: p. 172870 [PMID: 32035078 DOI: 10.1016/j.pbb.2020.172870]
- 14 Witt K, Potts J, Hubers A, Grunebaum MF, Murrough JW, Loo C, Cipriani A, and 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**: p. 29-45 [PMID: 31729893 DOI: 10.1177/0004867419883341]
- 15 Siegel AN, Di Vincenzo JD, Brietzke E, Gill H, Rodrigues NB, Lui LMW, Teopiz KM, Ng J, Ho R, McIntyre RS, and Rosenblatt JD, Antisuicidal and antidepressant effects of ketamine and esketamine in patients with baseline suicidality: A systematic review. *J Psychiatr Res* 2021; **137**: p. 426-436 [PMID: 33774537 DOI: 10.1016/j.jpsychires.2021.03.009]

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

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 Implicit Association Test [IAT], smartphone-based interventions, real-time monitoring of suicidal thoughts and behaviors) Zero Suicide (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 |



seit 1558

Friedrich-Schiller-Universität Jena

Friedrich-Schiller-Universität Jena

Lian-Sheng Ma
President and Company Editor-in-Chief
Baishideng Publishing Group Inc
8226 Regency Drive
Pleasanton, CA 94588
USA

Universitätsklinikum Jena

Hans-Berger-Kliniken

Klinik für Psychiatrie

Direktor:
Prof. Dr. Martin Walter

Zentrum für Neuroimaging

**Present Address of
Corresponding Author:**

Thomas Sobanski, MD, Chief
Department of Psychiatry, Psychothera-
py, and Psychosomatic Medicine
Thüringen-Kliniken GmbH
Rainweg 68
D-07318 Saalfeld
Telefon: +49 3671 / 54-1750
FAX: +49 3671 / 54-1759

E-Mail: sobanski@aol.com
tsobanski@thueringen-kliniken.de

2022-06-24

Re-Submission of invited manuscript to the “World Journal of Psychiatry”

(Revision ID: 77052)

Sobanski, Peikert, Kastner, and Wagner:

**"Suicidal Behavior – Advances in Clinical and Neurobiological Research and
Improvement of Prevention Strategies"**

Dear Professor Ma,

Dear Professor Giannakopoulos,

Dear Professor Tampi,

Dear Professor Zhu,

Dear ladies and gentlemen,

Thank you very much for your invitation to write an Editorial for publication in the World Journal of Psychiatry. Please find electronically submitted our revised manuscript mentioned above, that we would kindly like to ask you to consider for publication in the “World Journal of Psychiatry”.

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 laying the focus on suicidal episodes proved to be efficacious for reducing suicide re-attempts.

Today we are sending you a thoroughly revised and updated version of the editorial, which addresses all of the reviewers' criticisms in detail. In addition, at your suggestion, we have created a table showing the assignment of single preventive measures to the strategies of universal, selective, and indicated prevention. We have also thoroughly revised the Core tip section so that the innovations are even more clearly visible.

Five years ago we have founded the Network for Suicide Prevention in Thuringia (NeST). This is one of the largest prevention projects in Germany and the associated scientific studies have been funded by the Federal Ministry of Health with over EUR 600,000. A number of works have already been published. Recently, our working group developed a psychotherapy manual for the treatment of patients after a suicide attempt. This approach (called RISE= Relapse Prevention Intervention after Suicidal Event) has already been used successfully and the manual is currently being published.

We hope you find our revised manuscript interesting and worthwhile publishing in your journal and we are looking forward to a favourable reply.

Yours sincerely,

Thomas Sobanski, M.D.

Corresponding Author

Department of Psychiatry, Psychotherapy,

and Psychosomatic Medicine

Thüringen-Kliniken GmbH

Rainweg 68

07318 Saalfeld

Germany

T +49 3671 54 1750

FAX +49 3671 54 1759

Email: sobanski@aol.com

tsobanski@thueringen-kliniken.de

PS: Please send all correspondence to both email addresses because emails from China are regularly deleted by our clinic's firewall. I can't even find these emails in the SPAM folder.