It is illegal to post this copyrighted PDF on any website.

Clinical Trials With Suicidal Individuals Can Be Conducted Safely

To the Editor: We applaud the recent report from Iltis and colleagues[1] addressing the issue of exclusion of suicidal patients from clinical trials for depression. Suicide rates in the United States have increased 33% since 1999,[2] partly due to the lack of appropriate treatments for suicidal individuals; clozapine is the only medication approved for suicidal behavior, and, as of the writing of this letter, no medications have been approved to treat suicidal thoughts. In addition, as Iltis and colleagues highlight, suicidal individuals are typically excluded from clinical trials for depression, so it is unclear which of our current medications are effective for treating these most vulnerable patients. Furthermore, suicidal patients are often excluded from non-depression clinical trials, including those for substance dependence, anxiety, or schizophrenia, further compounding health inequities. Consequently, clinicians have few evidence-based treatments for the 9 million Americans who consider suicide each year.

We agree that it is possible to safely perform clinical trials with suicidal participants and, furthermore, that such clinical trials are essential in efforts to stabilize, and potentially decrease, the suicide rate. In our work with the *N*-methyl-D-aspartate receptor antagonist ketamine[3] as well as studies focused on the neurobiology of suicide, we have experienced challenges in recruiting, consenting, and monitoring suicidal patients in clinical research. While a number of specific considerations exist for research groups considering the ethics of research with suicidal individuals,[4,5] we recommend the following general guidelines as particularly important:

- Engage in proactive discussions within the research group regarding areas of particular risk before study implementation. Models such as Failure Modes and Effects Analysis have been adapted for hospital settings, in which all involved parties (including clinicians, nurses, research staff, and hospital administrators) proactively identify areas of concern. In addition to identifying scenarios that may be overlooked, such discussions can moderate anxiety and stigma around working with suicidal participants. It is preferable to identify unsafe situations ahead of time rather than after an adverse event or root cause analysis.
- Consider additional supports around the informed consent process—including study monitors, quizzes, and multiple consents—to ensure adequate comprehension by study participants.
- Create clear guidelines for regularly assessing, monitoring, and referring suicidal individuals while they are enrolled in the clinical trial. Study staff should understand what level of suicidal thoughts will exclude the patient from further participation.
- Train all involved staff in the principles of treating suicidal patients, including standards for appropriate suicide risk assessment and potential warning signs for suicide.[6] Administrative or technical staff without mental health training may require safety-specific education, including the importance of closing doors or ensuring that potentially lethal means are not left in research environments.

We urge researchers, clinicians, and regulators to view the inclusion of suicidal participants into psychiatric clinical trials as critical to efforts to reduce suicide rates. Such an approach would improve quality of care and clinical outcomes for suicidal patients as well as inspire research into the neurobiology of suicide. The 9 million Americans who consider suicide each year deserve better.

REFERENCES

1. Iltis AS, McCall WV, Deria R. Suicidality, depression, and the FDA: health inequities and the ethical conduct of research. *J Clin Psychiatry*. 2020;81(2):19m13050.
2. Hedegaard H, Curtin SC, Warner M. Suicide mortality in the United States, 1999–2017. *NCHS Data Brief*. 2018;(330):1–8.
3. Wilkinson ST, Ballard ED, Bloch MH, et al. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *Am J Psychiatry*. 2018;175(2):150–158.
4. Ballard ED, Waldman L, Yarrington JS, et al. Neurobiological research with suicidal participants: a framework for investigators. *Gen Hosp Psychiatry*. 2020;62:43–48.
5. Nugent AC, Ballard ED, Park LT, et al. Research on the pathophysiology, treatment, and prevention of suicide: practical and ethical issues. *BMC Psychiatry*. 2019;19(1):332.
6. Rudd MD, Berman AL, Joiner TE Jr, et al. Warning signs for suicide: theory, research, and clinical applications. *Suicide Life Threat Behav*. 2006;36(3):255–262.

Elizabeth D. Ballard, PhD[a]
elizabeth.ballard@nih.gov
Lawrence T. Park, MD[a]
Maryland Pao, MD[b]
Carlos A. Zarate, Jr, MD[a]

[a]Section on the Neurobiology and Treatment of Mood Disorders, Intramural Research Program, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland

[b]Office of the Clinical Director, Intramural Research Program, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland

Published online: August 4, 2020.

Potential conflicts of interest: **Dr Zarate** is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation; as a co-inventor on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (*S*)-dehydronorketamine, and other stereoisomeric dehydro and hydroxylated metabolites of (*R*,*S*)-ketamine metabolites in the treatment of depression and neuropathic pain; and as a co-inventor on a patent application for the use of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and posttraumatic stress disorders. He has assigned his patent rights to the US government but will share a percentage of any royalties that may be received by the government. All other authors have no conflict of interest to disclose, financial or otherwise.

Funding/support: Funding for this work was supported by the Intramural Research Program at the National Institute of Mental Health (NIMH), National Institutes of Health (IRP-NIMH-NIH; ZIAMH002857; NCT02543983); by a NARSAD Independent Investigator Award to Dr Zarate; and by a Brain and Behavior Mood Disorders Research Award to Dr Zarate.

Role of the sponsor: These organizations had no further role in study design; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the letter for publication.

Acknowledgment: The authors thank the 7SE research unit and staff for their support. Ioline Henter (NIMH) provided excellent editorial assistance. Ms Henter reports no conflict of interest with regard to this letter.

J Clin Psychiatry 2020;81(5):20l13353

To cite: Ballard ED, Park LT, Pao M, et al. Clinical trials with suicidal individuals can be conducted safely. *J Clin Psychiatry*. 2020;81(5):20l13353.

To share: https://doi.org/10.4088/JCP.20l13353

© Copyright 2020 Physicians Postgraduate Press, Inc.

You are prohibited from making this PDF publicly available.