See article by Iltis et al

Inclusion of Suicidal Individuals in Research Studies

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It is important to thank Dr Iltis and collaborators for tackling, in their recent article,[1] a crucial issue: the almost systematic exclusion of suicidal patients from clinical trials on antidepressants. The exclusion of these individuals is particularly critical given that suicidal behavior is a leading cause of death (about 800,000 deaths by suicide per year worldwide) with very few specific treatments.[2]

Until recently, suicidal patients were forgotten in research. Moreover, for a long time, suicidal behavior was considered just a symptom of another psychiatric pathology (mainly depression) and not a specific pathology.[3] On the basis of the hypothesis that suicide occurs more frequently in patients with depression, suicidal patients are mostly treated with antidepressants. However, antidepressants were neither developed for nor tested in this specific population. As noted by the authors "The exclusion of persons with suicidality from antidepressant trials is common, creating uncertainty about medication safety and efficacy in parts of the target population."[1(p1)] In fact, antidepressant treatments seem to be less efficient in suicidal patients, as highlighted by recent studies showing that these patients respond less well to antidepressant treatment and are less likely to achieve remission.[4]

As most trials on antidepressants excluded suicidal patients and did not assess suicidal ideation and behavior systematically, data on this topic are very limited.[5] One strategy could be to investigate the frequency of actual suicides and suicide attempts in patients who received antidepressants or placebo in these trials. However, the interpretation of these kinds of data is difficult because of the rarity of the relevant events, which is logical because patients were not suicidal at inclusion. This strategy might also lead to deleterious consequences for patients, as exemplified by the decrease in antidepressant prescriptions followed by an increase of suicide after the addition of the black box warning by the US Food and Drug Administration (FDA) in 2006.[6,7] Furthermore, there is evidence that the emergence or worsening of suicidal ideation during treatment concerns a small group of depressed patients with a specific (clinical and genetic) profile and that it could depend on the antidepressant molecule.[8] These patients mainly do not respond to antidepressant treatment.[9] Due to their exclusion from clinical trials, suicidal patients are "treated with inadequate or unproven interventions"[1(p2)] that could lead to dramatic issues.

In their article, Iltis and collaborators addressed the issue of excluding suicidal patients from clinical trials in a pertinent way and as a continuation of the study by Khan et al,[10] who hypothesized that the decline of suicide rates in antidepressant clinical trials after 2000 was probably explained mainly by restrictions on the inclusion of patients with suicidality. This hypothesis seems to be validated by the present study showing that, after 2000, all clinical trials excluded suicidal patients. Iltis and colleagues also found that suicidality was not mentioned in about 72% of clinical trials before 2000 and in only 14% after 2000. Furthermore, after 2000, 39% of clinical trials explicitly excluded suicidal patients, but did not specify the suicidality measure used and how it was defined. These results raise another question concerning the lack of definition of the vague term *suicidality* and consequently on how to identify patients who respond to antidepressant treatments.

Iltis and collaborators also explained why it is important and necessary to include these patients in clinical trials. Particularly, this is an ethical issue because suicidal patients represent a large part of the population treated with antidepressants (eg, 45% to 70% of patients with depression experience suicidal ideation[11]). By being excluded, they cannot profit from the accumulated knowledge and resources that result from research study. Moreover, as Iltis and colleagues note, "the potential benefits of improved generalizability could help to justify the increased risk associated with exposing more people to research risks."[1(p2)] It might also be possible to create alternative designs to include these patients in clinical trials.

Iltis and collaborators identified 4 main barriers (ie, participant safety and research risks, decisional capacity and voluntary informed consent, difficult study population that increases liability, and statistical considerations) that limit the inclusion of suicidal patients in clinical trials, and proposed key steps to overcome them. Two of them are particularly interesting. Concerning participant safety, they proposed the following: "Investigators should develop a plan to maintain contact with participants, monitor and assess suicide risks, and establish a plan for responding to changes, including when and how hospitalization will be managed." [1(p4)] It is important to note that some studies have already adapted their design to investigate the therapeutic response of suicidal

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patients to specific pharmacologic strategies. For instance, Khan et al[12] investigated the combination of lithium and citalopram in severely suicidal outpatients with depression. To this aim, they designed and conducted an exploratory proof-of-concept trial in these patients. They identified several safety factors, such as assessing whether patients had enough family and social networks and prepared emergency plans with them, and they put in place several strategies to avoid patient loss to follow-up (eg, frequent telephone calls, use of Facebook to keep in touch and follow them, calling their families if they had no news and no response). At the end of the follow-up, no suicidal act was reported. The study by Khan et al demonstrated that it is possible to include suicidal patients and minimize the risks (eg, by using close clinical monitoring and psychosocial interventions, as recommended by Oquendo and colleagues[13]).

Another barrier to inclusion of suicidal patients in clinical trials concerns their decisional capacity and informed consent. Iltis and colleagues state that, instead of systematically excluding suicidal patients on the basis of a supposed decisional capacity disability, investigators could evaluate decisional capacity using validated instruments such as Evaluation to Sign Consent instead of automatically excluding suicidal individuals and note that "third party advocates and authorized representatives can help protect against changes in capacity."[1(p5)] All possible barriers to including suicidal patients in clinical trials can be overcome.

The inclusion of suicidal behavior disorder in *DSM-5* as a pathology that needs to be studied is proof that today we must find therapeutic strategies to manage this population.[14] Thanks to the entry of suicidal behavior disorder in *DSM-5* and to the change in attitudes regarding it, research on these patients is increasing and new clinical trials on this population have been started (ie, ketamine).[15,16] Nevertheless, research on suicidal behavior must continue, and it is urgent to better understand its physiopathology and to find new therapeutic targets. As noted by Iltis and collaborators, reaching and helping suicidal patients is an ethical issue. Nevertheless, some questions on the design of clinical trials must be clarified. One of them is about the definition of the term *suicidality*. The study by Iltis and colleagues confirms that the term is not clearly defined in many clinical trials, and when it is defined, most of the time, the used scales and cutoffs vary according to the study. The same problem concerns the definition of emergence or worsening of suicidal ideation after treatment onset. A consensus should be established because this definition affects, among other factors, a study's reproducibility.

In conclusion, although attitudes concerning suicidal behavior are changing, much remains to be done. As the authors state: "Increasing the generalizability of research to persons with mental health disorders, including persons with suicidality, is important for reducing health inequities and improving the ethical quality of research."[1(p4)]

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