American College of Neuropsychopharmacology

www.nature.com/npp

CORRESPONDENCE

Learning about the course of suicidal behavior but not about the effects of SSRIs

Neuropsychopharmacology (2022) 47:803; https://doi.org/10.1038/s41386-021-01224-x

Lagerberg et al. [1] reported on the risk of suicidal behavior before and after the initiation of SSRIs, based on the national Swedish register. This allowed a precise estimation of the course of suicide risk, which was highest before SSRI prescription and declined afterwards. However, because there was no control group, the effect of SSRIs remains unknown. There could be the same or even a better course without treatment or a different treatment. Suicidality, just like depression, is an episodic condition, so risk reduction over time could be fully explained by regression to the mean and spontaneous remission. Lagerberg et al. correctly state that there are "no strong grounds to claim that the risk reduction immediately following SSRI initiation is causal". However, some parts of the text may be read as a causal interpretation, for example, "This suggests that, in the first year of treatment, SSRI medication does not bring the risk of suicidal behavior to baseline". "Another statement that might be interpreted as causal claim is in the conclusion: The results suggest that, overall, clinicians should be reassured that SSRI initiation is not associated with an increased risk of suicidal behaviour". Moreover, they point out problems with the representativeness of randomized controlled trials (RCT) and confounding in observational studies, thereby suggesting that their design is better to assess the effect of SSRIs on suicide risk.

Lagerberg et al. also did not discuss important research opposing the assumption that SSRIs reduce suicide risk, including a study by Björkenstam et al. which used the same Swedish register data, but with a case-crossover control design [2]. Björkenstam et al. found an increased risk for suicide at initiation of SSRI, especially in the second week after initiation. Lagerberg et al. dismissed this study because of confounding by indication, but according to Björkenstam et al.: "the descriptive question on whether there is an increased risk of suicide in the early phase of treatment, which is of great clinical relevance, is not confounded by indication". In light of the increased risk especially in the second week, Lagerberg et al. should have reported their results week-wise, at least for the first month.

Finally, it is important to acknowledge that suicidal behavior was increased with SSRI treatment in studies that are more appropriate in design because they have a control group, for example well-controlled observational studies [3]. Admittedly, observational studies also have limitations due to possible residual confounding; therefore, RCT remain the gold standard. A meta-analysis of clinical trials on second generation antidepressants submitted to the FDA again confirmed an increased risk for suicide attempts and likely also suicides [4]. Despite remaining uncertainties if and how strongly SSRIs increase risk for suicidal behavior, it can safely be said that SSRI's do not reduce the risk of suicidal behavior [5]. In conclusion, data from clinical trials and well-controlled observational studies (even with the same register data) are at odds with the assumption that SSRIs reduce the risk of suicidal behavior and the study by Lagerberg et al. is hardly informative in this regard.

Martin Plöderl[1]✉ and Michael P. Hengartner[2]

[1]*Department for Crisis Intervention and Suicide Prevention and Department for Clinical Psychology, University Clinic for Psychiatry, Psychotherapy, and Psychosomatics, Paracelsus Medical University, Salzburg, Austria.* [2]*Department of Applied Psychology, Zurich University of Applied Sciences, Zurich, Switzerland.*

✉*email: m.ploederl@salk.at*

REFERENCES

1. Lagerberg T, Fazel S, Sjolander A, Hellner C, Lichtenstein P, Chang Z. Selective serotonin reuptake inhibitors and suicidal behaviour: a population-based cohort study. Neuropsychopharmacology. 2021. [Epub ahead of print].
2. Bjorkenstam C, Moller J, Ringback G, Salmi P, Hallqvist J, Ljung R. An Association between initiation of selective serotonin reuptake inhibitors and suicide—a nationwide register-based case-crossover study. PLoS ONE. 2013;8:e73973.
3. Hengartner MP, Amendola S, Kaminski JA, Kindler S, Bschor T, Ploderl M. Suicide risk with selective serotonin reuptake inhibitors and other new-generation antidepressants in adults: a systematic review and meta-analysis of observational studies. J Epidemiol Community Health. 2021. [Epub ahead of print].
4. Hengartner MP, Plöderl M. Newer-generation antidepressants and suicide risk in randomized controlled trials: a re-analysis of the FDA database. Psychother Psychosom. 2019;88:247–8.
5. Ploderl M, Hengartner MP, Bschor T, Kaminski JA. Commentary to "antidepressants and suicidality: a re-analysis of the re-analysis". J Affect Disord. 2020;273:252–3.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to the conception, drafting, and revision of this commentary and both approve the published version.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Martin Plöderl.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 1 October 2021 Revised: 12 October 2021 Accepted: 21 October 2021
Published online: 8 November 2021