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CORRESPONDENCE

Reply to Ploderl and Hengartner: learning about the course of suicidal behavior but not about the effects of SSRIs

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Plöderl and Hengartner raise questions [1] regarding our study [2], which we address below in the context of previous research. Our study, employing a self-controlled design, found that incidence rates of suicidal behavior were highest in the month before treatment start, and then declined over treatment time. However, rates remained elevated throughout treatment compared with the month 1 year before treatment initiation.

Plöderl and Hengartner state that our findings are different to those of a previous Swedish study using a self-controlled design [3]. This is not entirely accurate. First, this 2013 study considered only death by suicide, whereas our work examines suicide attempts and death by suicide in more recent data. Second, both studies found that the risk of suicide outcomes was elevated after SSRI treatment initiation when compared to a reference period a year before the index date (date of death or date of SSRI initiation, respectively). Third, our study additionally showed that, when considering suicide attempts, the risk was highest in the month prior to treatment initiation. This is consistent with the well-replicated observation that individuals are prescribed SSRIs when most mentally unwell, and a recent review has highlighted that existing observational studies of antidepressant safety insufficiently account for confounding by indication [4].

The presence of unmeasured time-varying confounding limits the extent to which we can interpret the difference between the months before and after initiation, which we discuss in the paper. Even in studies where an external control group is used, individuals who initiate SSRIs will be different from individuals who do not based on both unmeasured static and time-varying factors, notably changes in depression severity over time. A clear strength of our study is that it accounts for all time-stable confounding.

We agree that RCTs remain the gold standard in medical research. However, RCTs apply extensive exclusion criteria, notably of individuals with a history of suicidal behavior, which limits their generalizability to clinical populations [5]. The rarity of suicidal outcomes also means individual RCTs are under-powered to detect associations in adults, and that the findings of meta-analyses are sensitive to sometimes subtle decisions regarding study inclusion and meta-analytic method. Observational studies can therefore be an important complement to RCTs.

What type of observational design would best help triangulate ours? Possibly an emulated target trial design [6], e.g., where individuals with a diagnosis of the indication of interest (say, depression) are selected, and suicide risk over time is compared between those who initiate SSRIs and those who do not. Of course, this design is also liable to unmeasured time-varying confounding by indication if there are insufficient measures of depression severity over time. It is also expected to be biased by other types of static between-individual confounding, making our self-controlled study an informative comparison. Our work assists in contextualizing previous observational studies, and adds to the understanding of the risk of suicidal behavior associated with SSRI initiation in real-world settings.

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REFERENCES

1. Plöderl M, Hengartner MP. Learning about the course of suicidal behavior but not about the effects of SSRIs. Neuropsychopharmacology. 2021. https://doi.org/10.1038/s41386-021-01224-x.
2. Lagerberg T, Fazel S, Sjölander A, Hellner C, Lichtenstein P, Chang Z. Selective serotonin reuptake inhibitors and suicidal behaviour: a population-based cohort study. Neuropsychopharmacology. 2021. https://doi.org/10.1038/s41386-021-01179-z.
3. Björkenstam C, Möller J, Ringbäck 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.
4. Dragioti E, Solmi M, Favaro A, Fusar-Poli P, Dazzan P, Thompson T, et al. Association of Antidepressant Use With Adverse Health Outcomes: a Systematic Umbrella Review. JAMA Psychiatry. 2019;76:1241–55. https://doi.org/10.1001/jamapsychiatry.2019.2859.
5. Zimmerman M, Balling C, Chelminski I, Dalrymple K. Have treatment studies of depression become even less generalizable? Applying the inclusion and exclusion criteria in placebo-controlled antidepressant efficacy trials published over 20 years to a clinical sample. Psychother Psychosom. 2019;88:165–70.
6. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol. 2016;183:758–64.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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