Int. j. adv. multidisc. res. stud. 2022; 2(3):400-401

Received: 28-05-2022
Accepted: 04-06-2022

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Letter to the Editor

Before attributing depression to SARS-CoV-2 vaccination alternative triggers should be ruled out

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We read with interest the article by Hoffman *et al*. about an online survey on the association between the number of side effects after the first dose of the Biontech Pfizer vaccine (BPV) and the level of depression in 939 Israeli participants [1]. The mean latency period between vaccination and survey was 28 days, half had an academic education, about half were female, and the mean age was 69 years [1]. It was concluded that self-reported side effects may be useful in identifying depression in older adults and to informing them about the link between vaccination and depression, and that psycho-educational intervention, emphasising that side effects of vaccination neither challenge vaccine safety nor efficacy, may help reduce depression [1]. The study is appealing but raises concerns that need to be discussed.

A limitation of the study is that the level of depression prior to vaccination was not known. Therefore, it remains unclear whether there is really a link between vaccination and the depression. Only a change in the results of the depression score using PHQ-9 or other scores could show whether side effects of the vaccination had a modifying effect on depression.

A second limitation is that patients with severe side effects may not be able to complete the questionnaire. This may be due to acute impairment requiring hospitalisation or due to long-term side effects of vaccination. Therefore, it would be interesting to know how many of those invited did not respond and for what reasons they did not participate.

We disagree with the statement that "vaccination side effects do not challenge vaccine safety". On the contrary, adverse reactions from a vaccine show that it is unsafe, at least for those who develop side effects.

Another shortcoming is that the current medication that the included patients regularly take was not included in the evaluation. Therefore, we should be told how many vaccinees were taking antidepressants, anxiolytics, neuroleptics, or other compounds prior to vaccination and how many had side effects to these drugs that could be responsible for their depression.

We disagree that quantifying and qualifying a vaccine's side effects is the tool for identifying depression, as outlined in the conclusions [1]. Although side effects can trigger depression, depression should not be diagnosed based on side effects alone, as depression is often a multicausal condition.

Another disadvantage of the study is that it is not certain that the vaccinee himself responded to the questions, that the answers given represent the truth, and that the level of cognitive performance was checked if the vaccinee was able to capture the dimensions of the questions.

The question is also if those with depression already prior to vaccination developed more severe and higher number of side effects than those without pre-existing depression. Missing in this respect is the history about previous depressive episodes in the investigated cohort.

Overall, the interesting study has limitations and inconsistencies that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could enhance the study. The design of the study is not really suitable to answer the question to which degree BPVs influence a pre-existing depression or trigger a de novo depression. To answer this question an approach should be chosen that takes more variables potentially influencing depression into account.

Declarations
Funding sources: no funding was received.

Conflicts of interest: the author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.'

Acknowledgement: none

Ethics approval: was in accordance with ethical guidelines. The study was approved by the institutional review board.

Consent to participate: was obtained from the patient.

Consent for publication: was obtained from the patient.

Availability of data: all data are available from the corresponding author.

Code availability: not applicable.

Author contribution: JF: design, literature search, discussion, first draft, critical comments, final approval, DM: literature search, discussion, critical comments, final approval.

Keywords: Depression, SARS-CoV-2, Vaccination, COVID-19, Side Effects, Adverse Reactions

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