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Nocebo affects after COVID-19 vaccination

Professor Peter Sever

National Heart and Lung Institute, Imperial College London, United Kingdom

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Amanzio and colleagues are to be congratulated for their review of adverse events associated with vaccinations against corona virus-SARS-CoV-2 [1]. Adverse events claimed to be caused by modern medicines be they tablets or injections, are the commonest reason given by patients for not accepting medication or for failing to adhere to prescribed drugs.

This has serious implications not only for the individual who refuses potentially life-saving medication, but for the community in the case of vaccinations against infectious agents in the context of a pandemic. This is particularly frustrating when in many cases the perceived adverse reactions are not causally related to the administered drug or vaccine.

In the systematic review reported in this issue of the journal, [1] the authors have identified 3 studies of SARS-CoV-2 vaccines-two mRNA based and one adenovirus type- involving approximately 45,000 subjects, and compared the rates of solicited adverse events, classified by the Medical Dictionary for Regulatory Activities, in patients assigned placebo and active vaccination. The key findings were high rates of commonly encountered adverse events in both placebo and active arms of the trials.

Fatigue was reported by 21–29% of patients in the placebo arms and 38–42% in the active treatment arms. For headache the proportions were 24–27% and 33–39% for placebo and active arms respectively, and for muscle aches and pains 10–14% and 18–33% respectively.

Injection site reactions were also common-12–17% in placebo and 48–84% following active vaccination. Other adverse events were reported less frequently but also in both placebo and active treatment arms. Generally younger subjects were more likely to report adverse events. Whilst there is clearly an excess incidence of these adverse events with the vaccination, with the exception of local injection site inflammation, it is evident that most of these events are not due to the vaccine and the authors have correctly attributed the nocebo reaction as the cause of most of these symptoms.

The nocebo response is less well described compared with its the opposite -the placebo response. It is a negative reaction characterised by the expression of adverse symptoms largely driven by the expectation of the individual that some untoward events will occur following the administration of a drug, vaccine or other medical intervention [2].

The phenomenon has been highlighted recently in relation to statin treatment where the majority of adverse events have been demonstrated not to be due to the statin but to the anticipation of adverse symptoms based on prior information provided by a variety of sources [3,4]. The nocebo response is extremely common in medical practice. Drug packaging inserts highlighting possible side effects of drugs, the internet, uncritical widespread media reports of adverse reactions attributed to (but not caused by) drugs and ill-informed comments from friends and relatives all contribute to the high incidence of adverse responses to various treatments.

Are there limitations to the current report? The authors have restricted their survey to trials registered with the European Medicines Agency and the Federal Drug Administration, but it is unfortunate that no information has been provided on the AZD 1222 trials. In the case of the latter, the reasoning provided was that most of these trials had meningococcal vaccination as the control arm instead of placebo. Of 171 studies, 3 were finally selected as meeting the inclusion criteria for the survey, [5,6,7] thereby potentially introducing bias. However, whilst the actual number of adverse events will vary from trial to trial depending on the population studied and factors including the various methods of assessment and symptom retrieval, it is highly likely that a wider review, including the AZ trials, would confirm the high incidence of adverse events in the placebo arm and the importance of the nocebo phenomenon.

Highlighting the importance of the nocebo response associated with current vaccination against SARS-CoV-2 is timely. Not only in the UK, but in many countries where the vaccine has been made available there is a significant minority who refuse to be vaccinated. Amongst ethnic minority groups in the UK, there remains a high proportion of unvaccinated individuals. Most are poorly informed about the vaccine's safety, its ability to protect against severe SARS-CoV-2 infection and the importance of community immunity. The current paper adds importantly to the information on adverse reactions to the vaccine and it is hoped that physicians will use this knowledge in educating their patients on the need to accept vaccination against SARS-CoV-2.

E-mail address: p.sever@imperial.ac.uk

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Declaration of Competing Interest

The author has no interests to declare.

Contributors

As a sole author PS contributed to all aspects of this Commentary.

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