Noisy Nocebo Harms: A Two-Part Problem for Active Drug Surveillance

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Abstract

Post-market pharmaceutical surveillance or 'pharmacovigilance' relies on the reporting of suspected adverse drug reactions to regulatory databases. Recently, more 'active' methods that directly involve patients in identifying and reporting suspected adverse drug reactions have been suggested. This is different than traditional 'passive' methods, e.g., using databases without contacting patients directly. Though there are benefits to active pharmacovigilance, it is not without its potential risks. Here I highlight one of those risks – the nocebo effect. Nocebo effects are harms that are thought to arise by conditioning or negative expectation. If a patient engaged in active pharmacovigilance is improperly motivated to seek out and report suspected adverse drug reactions, nocebo harms can occur. Not only is this a bioethical concern about harm, but it is also an epistemic or data-quality problem. Since nocebo effects are not due to the pharmacological properties of the drugs under investigation, nocebo effects reported as suspected adverse drug reactions constitute false positives in these databases.

Introduction

The aim of post-market pharmaceutical surveillance or 'pharmacovigilance' is to support effective pharmacotherapy through the understanding and preventing of drug-related harms. This aim is hindered by a lack of reported suspected adverse drug reactions (SADRs) to regulatory databases. Various reasons are given for this paucity of SADR reports, including practitioner attitudes about reporting (García-Abeijon et al., 2023) and institutional barriers (Hohl et al., 2018). To overcome this paucity, suggestions to engage patients more 'actively' as SADR sources have been recently proposed (e.g., Kant, 2024; Yoong et al., 2024). This follows a more general recent trend in medicine towards greater patient involvement in research (Harrison et al., 2019). However, this new 'active' surveillance is not without its potential risks. One challenge for active pharmacovigilance is the nocebo effect, i.e., the negative counterpart to the placebo effect. Nocebo effects are harms that are thought to arise because of conditioning or negative patient expectations (Friesen, 2020; Howick, 2021), and are not due to the pharmacological properties of a drug (Due, 2023). For 'active' surveillance, how are patients motivated to be vigilant for SADRs without bringing about nocebo harms by conditioning or expectation? Though these harms are not caused by the pharmacological properties of drugs, they are harms nonetheless and ought to be prevented if possible. However, nocebo effects are problematic for active surveillance beyond this normative bioethical concern. When nocebo harms occur and are reported as SADRs, this contributes 'noise' to SADR databases. 'Noise' here is contrasted with 'signal,' with the latter being about data from a phenomenon of interest and the former being data not

relevantly about that phenomenon that was collected in the measurement or gathering process. The higher proportion of 'signal' to 'noise' in databases makes discovering the relevant properties of some phenomenon – like the effects of drugs – easier. Thus, nocebo effects are doubly nefarious for active surveillance. This more robust understanding of nocebo effects in active surveillance bolsters the need for thoughtful risk communication in such research.

Discussion

Nocebo effects are often identified as bioethical problems across medicine and are frequently discussed in the context of informed consent. When patients are told that taking a medication might cause adverse reactions, worried patients might expect these to occur and thereby cause their occurrence. In these cases where harms are brought about via negative expectations and not by the pharmacological properties of the drug, this is a nocebo effect. Since nocebo effects are still genuinely harmful, mitigating these is essential in medicine. There are ongoing discussions on how this can be done, including 'positive framing' (Howick, 2021) among others. We might imagine the case to be similar with active surveillance. While some active methods emphasize procuring health records, some focus on engaging with patients directly. We can foresee that directly telling patients to be vigilant for SADRs might cause patients to expect SADRs, possibly then causing nocebo effects. This has been recognized to some degree in scholarly articles about active methods (e.g., Kant, 2024) with a broad acknowledgement that awareness ought to be created without also creating concern. But, this is only half of the problem that nocebo effects constitute for active surveillance.

As above, nocebo effects are also data-quality problems, i.e., 'noise' in this context. Imagine a patient agrees to participate in some active surveillance project. Say that the patient's expectation that a SADR will happen increases, followed by the patient experiencing and reporting a SADR. That report is either (1) an adverse reaction caused by the drug, (2) a nocebo effect, or (3) some unrelated symptom. If (1), this is data about our phenomenon of interest – the pharmacological effects of a drug. This is (and is often called such by pharmacovigilance researchers) our 'signal' data, and it is crucial for the aims of pharmacovigilance. If (2), this report is not about the phenomenon of interest – the pharmacological effects of the drug – it is 'noise.' While the experienced SADR is in fact a SADR, reporting a nocebo-caused-SADR to researchers whose aims are determining the pharmacological properties of drugs is something similar to a false positive. SADRs caused by nocebo effects are by definition not data potentially about the pharmacological properties of drugs. Thus, mitigating nocebo

effects in active surveillance is compelled not only by the reduction of harm, but also by having good, relevant data. How ought this mitigation occur? Likely in step with suggestions made to mitigate nocebo effects in other contexts in medicine, e.g., 'positive framing' mentioned above.

Conclusion

Nocebo effects are a two-part problem for active surveillance. Firstly, they constitute bioethical concerns about harm, and secondly, they are 'noise' in SADR databases that aim to uncover the pharmacological properties of our drugs. Either problem suffices to motivate mitigating nocebo effects, though the latter has been underemphasized in recent discussions about active surveillance. A more robust understanding of how nocebo effects can negatively impact active practices bolsters thoughtful risk communication with participants. Moreover, a more robust understanding of the nocebo effect's impact may benefit those developing novel active methods in pharmacovigilance.

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