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Response to "The Self-Controlled Case Series Design as a Viable Alternative to Studying Clinically-Relevant Drug Interactions"

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Keywords

drug-drug interactions; design; bias

We thank Zhou and colleagues for their thoughtful comments on our paper "A Case-Crossover-Based Screening Approach to Identifying Clinically Relevant Drug-Drug Interactions in Electronic Healthcare Data".[1] Although our study did not compare the case-crossover design to the self-controlled case series (SCCS), we agree with Zhou et al. that the designs have a lot in common. Zhou et al. drew analogies between the SCCS and a cohort design and between the case-crossover and a case-control design. In extending these analogies, just as a case-control study can be conceptualized as sampling of person-time from an underlying cohort study,[2] a case-crossover design can be viewed as utilizing a sample of the person-time that contributes to the SCCS analysis. However, whereas a case-control study requires the assumptions of a corresponding cohort study plus additional assumptions related to control selection, the case-crossover and the SCCS designs each require at least one distinct assumption when studying outcomes of drug exposures, including drug-drug interactions (DDIs).

On the one hand, in contrast to cohort, case-control, and case-crossover studies, which can validly censor patients at the time of an outcome event, the standard implementation of the SCCS design follows patients after an outcome occurs and requires the assumption that the outcome does not influence censoring or subsequent exposure.[3] When a drug is likely to be discontinued following an event (e.g., dabigatran and bleeding), the SCCS approach may produce biased results.[4] On the other hand and as mentioned by Zhou et al., the case-crossover design requires an assumption of no time trends in exposure under the null hypothesis, which may not hold when precipitant drugs are life-long treatments, leading to upward bias.[4]

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As we continue to evaluate these designs and their adaptations aimed at addressing violations of these assumptions, we might consider a complementary approach to post-approval DDI screening that involves both designs. For example, given the differences in assumptions, DDI signals that persist through application of both designs may be more robust and worthy of subsequent investigation. Alternatively, design selection may be tailored to specific drugs and outcomes of interest. If drugs are not likely to be discontinued following the occurrence of the outcome of interest, the SCCS might be preferred. In other situations, the case-crossover design might be preferred, especially if potential precipitant drugs of interest are not life-long therapies. We appreciate the discussion of these issues and look forward to further research and developments in this area.

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