

### Drs Azouley and Bérard Reply

**To the Editor:** We would like to thank Thakrar and Robinson for their interest in our article.<sup>1</sup> We would like to respond in detail to the methodological concerns described in their letter.

Thakrar and Robinson suggested that our study design was not appropriate to study depression. In fact, although case-crossover designs have been originally used to study short-duration exposures and abrupt outcomes, Wang and colleagues<sup>2</sup> have shown that it is equally powerful to study exposures with prolonged effects and outcomes with insidious onsets such as the ones we used in our study. In addition, given the time span of our study (1983–2002), the case-crossover design was best suited to inherently adjust for trends in acne management over the years and guideline changes, as is discussed in length in our article.<sup>1</sup>

Thakrar and Robinson claimed that our criterion of requiring *at least* 1 acne diagnosis in the year prior to the index date might have introduced a bias. That is, patients with a first diagnosis with acne in the risk period had no opportunity of being exposed to isotretinoin in the control period (since they did not have acne), thereby biasing the point estimates away from unity under the null hypothesis. However, this concern is unfounded for the following reasons. First, acne is a slowly progressing, chronic condition. Thus, even under the situation where cases were “diagnosed” with

acne in the risk and not the control period, these cases most likely had acne prior to their clinical diagnosis. As such, the absence of an acne diagnosis in the control period does not necessarily indicate the absence of the condition, especially within the 12-month time frame of the observation period. Second, the absence of an acne diagnosis in the Régie de l'Assurance Maladie du Québec (RAMQ) administrative databases does not necessarily translate into meaning that patients were not being treated for acne. The entry of clinical diagnoses is optional in the RAMQ, whereas the entry of prescription data is absolutely required for copayment purposes. Finally, within the context of a sensitivity analysis<sup>3</sup> that was not published with our article, we determined the risk of depression associated with the use of minocycline, a systemic antibiotic used to treat moderate-to-severe acne, and whose use was never associated with depression. The objective of this analysis was to determine whether the observed association between isotretinoin and depression was, in fact, genuine, or an artifact of our case selection. Using exactly the same time windows and related methodology described in our article, the use of minocycline did not increase the risk of depression, with all point estimates around unity. Thus, these results, taken together with the reasons described above, do not indicate the presence of a bias in our case selection. In fact, requiring at least 1 acne diagnosis in the year prior to index date was deemed necessary to ensure that cases had acne and, therefore, an opportunity to be exposed to an anti-acne agent.

Isotretinoin is primarily indicated for patients with severe, recalcitrant acne who have not responded to conventional therapy. Thakrar and Robinson hypothesized that it is possible that patients who failed with conventional therapy initiated their isotretinoin treatment weeks or months later, making them less likely to be exposed in the control period. While this may be a legitimate concern, it seems that patients whose treatments have failed are more likely to be diagnosed with depression at that point (ie, after treatment failure), rather than after initiating an isotretinoin treatment, with the latter being the most effective drug against severe acne currently on the market.<sup>4</sup> Another concern was that patients initiating isotretinoin treatment might be at an increased risk of depression because of a history of previous treatment failures and not because of the drug itself. However, we previously found that over 60% of patients with a first isotretinoin prescription did not receive an anti-acne agent prior to their treatment,<sup>5</sup> as is recommended by product guidelines. Thus, isotretinoin is either used as a first-line agent or in patients with mild or moderate acne. This should dispel any concerns related to the impact of previous treatment failures on the incidence of depression in this population.

Thakrar and Robinson have also miscalculated the annual risk of depression in our study. Although it is true that our base cohort included 30,496 isotretinoin users, due to the fact that our case definition was specific, the number of cases cannot be used to calculate risk estimate. Indeed, we wanted to validate our depression diagnoses with an antidepressant prescription and, thus, excluded nontreated cases of depression as is stated in our article. This exclusion increases internal validity, but, as a consequence, limits the use of the number of cases for annual risk calculation purposes. The specificity of our case definition decreased the number of eligible cases. This specificity is offset by the use of the case-crossover design, which further increased the internal validity of the study (because the 'cases' and 'controls' are the same).

Finally, Thakrar and Robinson compared our results to those of previous observational studies.<sup>6,7</sup> However, as discussed in detail in our article, there are important methodological limitations in these studies. In fact, the methodological limitations embedded in these studies have only fueled the controversy, which was part of the rationale for conducting our study. Our case-crossover design was specifically designed to address many of these limitations, including case ascertainment and confounding. While

the association between isotretinoin and depression may still be uncertain, it is our hope that future studies properly address the complexities of this controversial question. In the meantime, we still believe that close monitoring of depressive symptoms among isotretinoin users is warranted.

## REFERENCES

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