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Comment on Osler et al: Misinterpretation of pre-post-differences invalidate the authors' conclusions

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Osler and colleagues published a cohort study investigating antidepressant medication and suicidal behaviour and violent crime in patients and conscripts (1). They report an increased incidence rate for both events before and after treatment initiation when compared to the follow-up period. They conclude that there is likely no causal effect of antidepressants on either of the two endpoints, because the rates between treated and untreated individuals did not differ substantially at each time-point and the rates of both events did not increase in the antidepressant group after treatment initiation as compared to the pre-treatment time period.

The authors write in their conclusion: “the similar incidence of suicide attempts and violence before and after start of antidepressants argues against a causal relation between suicidal and aggressive behavior and initiation of antidepressants.” This reasoning, however, is flawed. It is not possible to examine causal effects of an intervention by comparing different time-points, as other sources of variation and different pathomechanisms are not taken into account. Baseline rates are not counterfactuals. That the absolute risk is higher before starting treatment does not exclude the possibility that antidepressants may cause suicidal or violent behaviour. Severe affective disorders and critical life events are major predictors of suicides (2), so it is not surprising that the suicide rate is highest before people start treatment. However, once antidepressants have been initiated, adverse drug effects such as severe agitation or akathisia may be important mediating factors (3, 4). The curves of untreated patients in Figure 1 clearly demonstrate a strong time-effect on both suicides and violent crimes, so changes in incidence rates over time cannot be attributed specifically to the initiation of antidepressants. The very same misinterpretation of pre-post differences in incidence rates misled some people to claim that vaccines cause autism. To infer causality, researchers estimate the pharmacologic treatment effect via drug-placebo differences at end of treatment, and not via pre-post differences in a single drug arm.

The comparison of the crude incidence rates (Fig.1) actually suggests an increased risk of both (attempted) suicide and violent crimes over time in the treated group, since the slopes are steeper in the untreated group (which indicates larger risk reduction). This is particularly evident with respect to suicide attempts and, even more pronounced, violent crimes (1). However, as the two groups are not randomized and differ in important aspects, this result cannot be interpreted in a meaningful manner.

When comparing the treated versus the untreated in the more appropriate Cox-regression model in supplementary Table 11, a significant increase in suicides is seen after 1 year (HR = 1.76) and an increase in suicide attempts is already visible 1 month after treatment initiation. For conscripts,

the increase in suicides and suicide attempts is even more prominent and already visible in the first month of treatment.

Similarly, the authors conclude that “The incidence of conviction for a violent crime was independent of time since treatment initiation in both patients and conscripts, arguing against a causal association between treatment initiation and acts of violence.” This, again, is flawed reasoning. We have to compare the incidence rates in treated versus untreated to draw such conclusions. The more appropriate Cox-regression model in supplementary Table 11 actually shows an increase in violent crimes for conscripts ranging from 1.31 to 1.66 in the treated group.

However, as the authors state correctly, residual confounding cannot be ruled out completely. Even the adjustment for confounding by indication is not necessarily sufficient, as compliers may differ from non-compliers in important aspects. Deriving causality from observational data requires a careful analysis with a robust causal model. Such an analysis would require a careful control for potential confounders by applying, for example, propensity-score matching. The authors did not provide a detailed rationale for their choice of confounders and did not report details about their applied regression model.

Furthermore, the authors write that the difference in event rates between the first month and the rate after one year “is likely explained by disease severity and a delay in mood response rather than increase in aggressive behaviour.” While this may be true, the statement is misleading, as this does not rule out an increase in aggressive behaviour caused by antidepressant medication.

Another major limitation in the study by Osler et al. (1) is that antidepressants prescribed in hospitals were not recorded. Presumably, a substantial fraction of people who attempted suicide in hospital or shortly after discharge was treated with antidepressants during hospital stay. These attempters were then erroneously classified as not having initiated antidepressant treatment, which might have inflated the rate of pre-treatment suicide attempts among the «untreated» group.

In summary, contrary to the authors’ conclusion, this study does not argue against the possibility that antidepressants lead to an increase in suicidal behaviour and violent crimes. It actually suggests that antidepressants increase suicidal behaviour and violent crime in both conscripts and patients with affective disorders.

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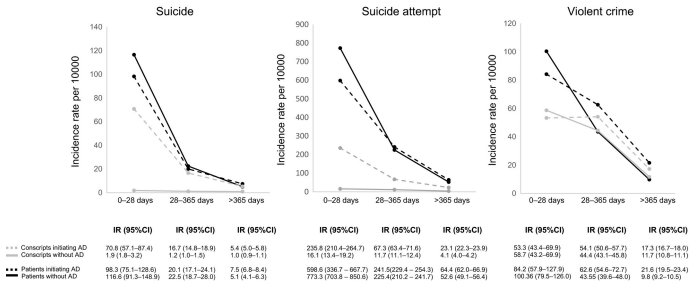

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