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## Invited Letter Rejoinder

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**Author for correspondence:**
Robert B. Whitaker,
E-mail: rwhitaker@madinamerica.com

# Rejoinder to commentary

Robert B. Whitaker

Mad in America Foundation, 763 Massachusetts Avenue, Cambridge, MA 02139, USA

I appreciate this response by Tiihonen, Taipale, and Correll, as it helps promote a much-needed discussion about this issue. Four points:

(1) A meta-analysis of studies beset with methodological issues and limitations is similarly beset with those same issues. After reviewing the research on this topic, Vermuelen and colleagues concluded that the 'true relationship between the adverse effects of antipsychotic medication and the consequence of this for long-term mortality risk in patients with schizophrenia remained unrevealed.'

(2) The Crump study, which assessed early death in Swedish patients with schizophrenia, found that they had an 'elevated risk of death from ischemic heart disease, stroke, diabetes, influenza/pneumonia, COPD, and cancer.' Except for cancer, all of these illnesses are well-known to be risks associated with the adverse effects of antipsychotics. As for the higher mortality rate for the small percentage of patients said to be 'non-users' of antipsychotics during the study period, there is no information about the makeup of this group: their average age, their medication use prior to the start of the study period, whether they received any sort of medical treatment during the study, and so forth. As such, it is impossible to assess the methodological issues or flaws that may be present in this comparison.

(3) Khan's study of mortality rates in the RCTs of antipsychotics approved by the FDA from 1990 to 2011 illustrates how the use of 'person years' can produce a misleading result. In the trials, 9 of 3419 randomized to placebo died (1 in 379), compared with 115 of 26 648 randomized to an antipsychotic (1 in 231).

However, after the six-week trials, no placebo patients were entered into the extension phase of the trials. Thus, the maximum 'person-years' that a single patient could account for was 6/52 of a year. In total, the 3419 placebo patients only rang up a total of 313 person-years, or little more than a month per patient.

In contrast, those randomized to an antipsychotic who completed the six-week trials were then entered into the extension studies. As a result, the 26 648 patients in the antipsychotic category racked up 9618 person-years, or roughly four months per individual. Thanks to that person-year differential, the mortality rate for placebo became 1 per 34 person-years, compared with 1 per 83 person-years for the medicated group. That calculation produced a 'finding' that in clinical trials antipsychotics were shown to reduce mortality, even though the absolute death rate was higher for the antipsychotic group.

The big-picture question for the field is this: SMRs for schizophrenia patients have steadily risen in the past 40-plus years. Indeed, the very studies that conclude that antipsychotics reduce mortality, such as the studies cited by Tiihonen, Taipale, and Correll, report high SMRs for the entire cohort. That is 'big-picture' data that tells of a paradigm of care that needs to be rethought.

In addition, long-term recovery rates for schizophrenia patients have steadily declined in the antipsychotic era, with a recovery rate of 6% since the second-generation antipsychotics were introduced in the mid-1990s. That is down from a recovery rate of 18% in the period from 1941 to 1955 (Jääskeläinen et al., 2013). Together, these two findings – a rise in SMRs and a drop in recovery rates – tell of a pressing need for the field to re-examine its long-term use of these medications.

## Reference

Jääskeläinen, E., Juola, P., Hirvonen, N., McGrath, J. J., Saha, S., Isohanni, M., … Miettunen, J. (2013). A systematic review and meta-analysis of recovery in schizophrenia. *Schizophrenia Bulletin*, *39*(6), 1296–1306. doi: 10.1093/schbul/sbs130.



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