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Invited Commentary

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Author for correspondence:
Jari Tiihonen, E-mail: jari.tiihonen@ki.se

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Commentary on Robert Whitaker's viewpoint

Jari Tiihonen[1,2,3], Heidi Taipale[1,2,4] and Christoph U. Correll[5,6,7,8]

[1]Department of Forensic Psychiatry, Niuvanniemi Hospital, University of Eastern Finland, Niuvankuja 65, FI-70240 Kuopio, Finland; [2]Department of Clinical Neuroscience, Karolinska Institutet, Tomtebodavägen 18A, 5th floor, SE-171 77 Stockholm, Sweden; [3]Stockholm County Council, Stockholm Health Care Services, Norra Stationsgatan 69, SE-113 64 Stockholm, Sweden; [4]School of Pharmacy, University of Eastern Finland, PO Box 1627, SE-70211 Kuopio, Finland; [5]Division of Psychiatry Research, The Zucker Hillside Hospital, 75-59 263rd St, Glen Oaks, NY 11004, USA; [6]Department of Psychiatry and Molecular Medicine, Hofstra Northwell School of Medicine, Hempstead, NY 11550, USA; [7]The Feinstein Institute for Medical Research, Manhasset, NY 11030, USA and [8]Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany

We read with interest the article by Whitaker (2020) that concerns a relevant topic of potential benefits and harms of long-term antipsychotic use in schizophrenia, particularly focusing on effects on mortality.

In medicine, a single study is insufficient to guide clinical practice, and meta-analyses are considered the highest level of evidence. Studying the association between mortality and long-term antipsychotic treatment among patients with schizophrenia is practically impossible in randomized controlled trials (RCTs) and, therefore, the issue has been investigated in observational studies. A recent systematic review and meta-analysis including studies with adequate methodology concluded that mortality during antipsychotic use was 43% lower [95% confidence interval (CI) 24–54%] compared with no use (Vermeulen et al., 2017). The meta-analysis did not include a Swedish nation-wide study with 8277 patients reporting that mortality was 45% (95% CI 20–76%) higher during no use *v.* use of antipsychotics (Crump, Winkleby, Sundquist, & Sundquist, 2013). The reason for omission of this large study may have been the fact that this numeric result was mentioned only in a result section (p. 328), and not in the abstract – possibly because the authors considered the result self-evident. To our knowledge, all nine large studies investigating this issue have observed that among patients with schizophrenia antipsychotic treatment *v.* no treatment is associated with lower mortality (references available from the authors).

Short-term mortality can be studied in RCTs and, this far, there are two meta-analyses examining this issue. Khan, Faucett, Morrison, and Brown (2013) reported that patients randomized to antipsychotics had about 50% lower risk of death compared with patients randomized to placebo. A more recent meta-analysis (Schneider-Thoma et al., 2018) reported that mortality was 31% lower among patients with schizophrenia if they had been randomized to antipsychotics rather than placebo. However, among patients with dementia, the mortality was higher among those randomized to antipsychotics *v.* placebo, which emphasizes that these medications should be used only for the right indication, and off-label use should be avoided if possible. In conclusion, meta-analyses on both observational and randomized studies show that mortality is about 30–50% lower with *v.* without antipsychotic use among patients with schizophrenia.

Whitaker's main argument questioning the beneficial effects of antipsychotics for the reduction of mortality in people with schizophrenia is that mortality has been studied within a drug-centered paradigm in which patients switch their medication back and forth and on and off and, that those patients never exposed to antipsychotics might have the best outcome. While this may be possible among patients with non-schizophrenia disorders, such as drug-induced psychosis, this is not the case among patients with schizophrenia, as already alluded to above. In particular, a Swedish nationwide cohort, the highest mortality, by far (hazard ratio = 3.60, 95% CI 1.40–9.23 compared with moderate antipsychotic exposure), was observed among those first-episode patients with schizophrenia who did not use any antipsychotic in outpatient care during a 5-year follow-up (Torniainen et al., 2015). These results are mirrored by Finnish first-episode data, as well as Swedish and Finnish data in nationwide, representative schizophrenia patient cohorts not restricted to first-episode patients, each demonstrating statistically significant and clinically relevant mortality disadvantages for patients not treated with antipsychotics.

We strongly believe that both medication and psychosocial treatment are important, and that providing a balanced view on pros and cons is more useful than polarization of different treatment approaches. While antipsychotics and, especially, second-generation antipsychotics are associated with decreased mortality, certain types of drug treatments can be harmful, such as the old antipsychotic levomepromazine (Kiviniemi et al., 2013; Taipale et al., 2020) and long-term, high-dose benzodiazepine treatment (Tiihonen, Mittendorfer-Rutz, Torniainen, Alexanderson, & Tanskanen, 2016). The results from nationwide cohorts have shown that compared with no use of benzodiazepines, benzodiazepine treatment among patients with

schizophrenia is associated with 91% higher all-cause mortality in Finland (Tiihonen, Suokas, Suvisaari, Haukka, & Korhonen, 2012), up to 74% higher all-cause mortality in Sweden (Tiihonen et al., 2016), and 78% higher natural cause mortality in Denmark (Baandrup et al., 2010). While short-term benzodiazepine treatment can be effective and useful, the available evidence indicates that long-term treatment conflicting with guidelines is a major problem for patients' well-being and survival. In contrast, the overwhelming evidence suggests that in people with schizophrenia, antipsychotics protect against/delay mortality compared to not taking antipsychotics.

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