Psychological Medicine

cambridge.org/psm

Invited Letter Rejoinder

Cite this article: Tiihonen J, Taipale H, Correll CU (2020). Rejoinder to rejoinder to commentary. *Psychological Medicine* **50**, 2812–2813. https://doi.org/10.1017/S003329172000433X

Received: 19 October 2020
Accepted: 27 October 2020
First published online: 21 December 2020

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

CAMBRIDGE UNIVERSITY PRESS

Rejoinder to rejoinder to commentary

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

First, we agree that the mortality gap is observed in people with severe mental illness, including schizophrenia, and driven in large part by cardiovascular deaths (Correll et al., 2017), and needs to be reduced, including by use of the least cardiometabolically problematic medications possible (Pillinger et al., 2020). Similarly, the insufficient recovery rates in schizophrenia (Jääskeläinen et al., 2013) need to be increased, and the treatment paradigm that focuses mostly on pharmacologic management needs to be expanded to include sufficient medical and psychosocial care. In fact, integrating psychosocial with pharmacological management was found to increase recovery rates by as much as 24% in early phase patients compared to usual care (Correll et al., 2018). However, while clearly remaining far too low, it is not true that recovery rates have dropped significantly over the past 50 years. Instead, they have remained unchanged (likely affected also by higher demands on people in education and at work), as indicated in the meta-analysis cited by Whitaker (Jääskeläinen et al., 2013) which reported an overall median recovery rate of 13.5%, without finding a significant time effect ($p = 0.70$). Moreover, a recent study following 98 first-episode patients treated with long-acting injectable antipsychotics for 24 months reported a recovery rate defined by concurrent symptomatic and functional remission of 44%, dropping to 29% when good overall quality of life was also required (Phahladira et al., 2020).

Concerning the detailed discussion on the meta-analysis of randomized trials by Khan, Faucett, Morrison, and Brown (2013), it is incorrect that raw mortality rates are more accurate than those adjusted for follow up since discounting duration of follow up obviously inflates raw mortality events in the group followed for a longer period of time during which more events can occur. Moreover, a more recent meta-analysis focusing only on the short-term treatment phase (excluding open extension phase data in antipsychotic treated patients, thereby, eliminating the use of person-years criticized by Whitaker) confirmed that there was no increased mortality risk with antipsychotics, reporting a non-significantly 31% lower mortality risk among patients with schizophrenia randomized to antipsychotics *v.* placebo (Schneider-Thoma et al., 2018).

Concerning the big-picture question, a recent nation-wide cohort study showed a large reduction in the standardized mortality (SMR) rate for suicide and a slight increase in the SMRs for cardiovascular illness and cancer. Overall, the all-cause SMR of patients with schizophrenia remained similar during the last 30 years (i.e. from 1984 to 2014), and both patients with schizophrenia and the general population live nowadays about 10 years longer (Tanskanen, Tiihonen, & Taipale, 2018). Nevertheless, we agree with Whitaker that much remains to be done to decrease the mortality gap and increase recovery rates, yet, we believe that the data indicate that antipsychotic maintenance treatment should be part of these efforts and is not counterproductive.

Acknowledgement. We thank Whitaker for his rebuttal (Whitaker, 2020) to our Commentary that we wish to also comment on.

Conflict of interest. JT reports personal fees from the Finnish Medicines Agency (Fimea), European Medicines Agency (EMA), Eli Lilly, Janssen-Cilag, Lundbeck, and Otsuka; and is a member of the advisory board for Lundbeck. JT and HT have participated in research projects funded by grants from Janssen-Cilag and Eli Lilly to their employing institution. HT reports personal fees from Janssen-Cilag. CC reports personal fees as a consultant and/or advisor to or have received honoraria from: Acadia, Alkermes, Allergan, Angelini, Axsome, Gedeon Richter, Gerson Lehrman Group, Indivior, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Medscape, Merck, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He is also a stock option holder of LB Pharma.

References

Correll, C. U., Galling, B., Pawar, A., Krivko, A., Bonetto, C., Ruggeri, M., … Kane, J. M. (2018). Comparison of early intervention services vs treatment as usual for early-phase psychosis: A systematic review, meta-analysis, and mmeta-regression. *JAMA Psychiatry*, *75*(6), 555–565. doi: 10.1001/jamapsychiatry.2018.0623

Correll, C. U., Solmi, M., Veronese, N., Bortolato, B., Rosson, S., Santonastaso, P., … Stubbs, B. (2017). Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: A large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry*, *16*(2), 163–180. doi: 10.1002/wps.20420

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. *Schizophr Bull*, *39*(6), 1296–1306. doi: 10.1093/schbul/sbs130

Khan, A., Faucett, J., Morrison, S., & Brown, W. A. (2013). Comparative mortality risk in adult patients with schizophrenia, depression, bipolar disorder, anxiety disorders, and attention-deficit/hyperactivity disorder participating in psychopharmacology clinical trials. *JAMA Psychiatry*, *70*(10), 1091–1099. doi: 10.1001/jamapsychiatry.2013.149

Phahladira, L., Luckhoff, H. K., Asmal, L., Kilian, S., Scheffler, F., Plessis, S. D., … Emsley, R. (2020). Early recovery in the first 24 months of treatment in first-episode schizophrenia-spectrum disorders. *NPJ Schizophr*, *6*(1), 2. doi: 10.1038/s41537-019-0091-y

Pillinger, T., McCutcheon, R. A., Vano, L., Mizuno, Y., Arumuham, A., Hindley, G., … Howes, O. D. (2020). Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: A systematic review and network meta-analysis. *Lancet Psychiatry*, *7*(1), 64–77. doi: 10.1016/S2215-0366(19)30416-X

Schneider-Thoma, J., Efthimiou, O., Huhn, M., Krause, M., Reichelt, L., Röder, H., … Leucht, S. (2018). Second-generation antipsychotic drugs and short-term mortality: A systematic review and meta-analysis of placebo-controlled randomised controlled trials. *Lancet Psychiatry*, *5*(8), 653–663. doi: 10.1016/S2215-0366(18)30177-9

Tanskanen, A., Tiihonen, J., & Taipale, H. (2018). Mortality in schizophrenia: 30-year nationwide follow-up study. *Acta Psychiatr Scand*, *138*(6), 492–499. doi: 10.1111/acps.12913

Whitaker, R. B. (2020) Rebuttal. *Psychological Medicine*, xxxx.

https://doi.org/10.1017/S003329172000433X Published online by Cambridge University Press