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T. Kishi and N. Iwata: Varenicline for smoking cessation in people with schizophrenia: systematic review meta-analysis

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Dear Prof. Dr. Falkai,

The meta-analysis of efficacy of varenicline for smoking cessation in schizophrenia by Kishi and Iwata published in *European Archives of Psychiatry and Clinical Neuroscience* inappropriately included two trials which were not smoking cessation trials, conducted in patients with schizophrenia with no intention to quit smoking, which caused the authors to erroneously conclude that varenicline is ineffective for smoking cessation in this important population of smokers [1]. The meta-analysis appropriately included the two randomized, controlled smoking cessation trials in smokers with schizophrenia that demonstrate efficacy for varenicline when added to behavioral smoking cessation support in this population at the end of the treatment [2, 3], but inappropriately included two randomized, controlled trials of varenicline as a putative cognitive enhancing agent in smokers and non-smokers with schizophrenia, who expressed no desire to quit smoking prior to enrollment, received no additional behavioral smoking cessation treatment, and set no cessation date as part of the trials [4, 5]. The meta-analysis also inappropriately included a third trial in its analysis of efficacy of varenicline for smoking cessation for those with schizophrenia, a relapse prevention trial in which randomization occurred when all participants were abstinent [6].

A meta-analysis of efficacy of a smoking cessation treatment must be drawn from smoking cessation trials. It is inappropriate to include trials intended to test the effect of varenicline on cognitive performance and other important biomarkers of schizophrenia in a meta-analysis of efficacy of varenicline for smoking cessation. Further, Table 1 in the meta-analysis erroneously reports that all participants in the Shim study reported a desire to quit smoking and drinking. Participants in this trial were not required to express desire or

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Conflict of interest: Dr. Evins reports receiving study product and unrestricted research funding support to her institution from EnVivo Pharmaceuticals, GSK and Pfizer. Pfizer is the manufacturer of varenicline. Dr. Hong has received unrestricted research funding from Mitsubishi, Your Energy Systems LLC, and Pfizer. Pfizer is the manufacturer of varenicline. Dr. Kelly reports no potential conflicts.

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intention to try to quit smoking to be enrolled and were excluded from participation if they had an alcohol use disorder [4].

Importantly, if only studies of varenicline added to smoking cessation interventions in smokers with schizophrenia who wanted to quit smoking had been included in the meta-analysis, the conclusion would be that varenicline is both effective for smoking cessation at the end of the treatment and well tolerated. Thus, the published literature, when appropriately compiled, does not support the conclusions drawn in this paper. This is of high importance, as recent reports have found that varenicline is underused in smokers with psychotic disorders [7], despite the continued epidemic of smoking in people with psychotic disorders, with disastrous public health consequences [8]. The erroneous conclusions of this meta-analysis, that varenicline is ineffective but well tolerated in smokers with schizophrenia, will likely contribute to under use of this medication.

On the other hand, a meta-analysis on the potential adverse effects of varenicline that would demonstrate the lack of a substantially different side effect profile in schizophrenia patients as compared to those in the general population and, within those with schizophrenia, the lack of a signal for greater neuropsychiatric adverse events between those assigned to drug and those assigned to placebo, would be entirely relevant and could use all of these double-blind, placebo-controlled trials included in this paper. Unfortunately, that was not how the data from these studies were used.

In our opinion, the authors' conclusion that 'although varenicline adjuvant therapy is well tolerated, varenicline is not superior to placebo for smoking cessation in people with schizophrenia.' is inappropriately drawn from the data, and the paper has the potential to cause harm. We respectfully advise the journal to take further action on the paper. A more appropriate meta-analysis, including only smoking cessation studies to judge smoking cessation outcomes, has already been published by the Cochrane group [9].

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