Antidepressants and Risk of Dementia: Methodology Is Essential

To the Editor: Having read with great interest the recent *JCP* article by Lee et al[1] that examined the association between antidepressant treatment and risk of dementia, I would like to make some remarks on this important topic.

First, in relation to patient selection, the first group that was selected from the Catastrophic Illnesses Patient Database (of the Taiwan National Health Insurance Research Database) was treated for depression in 1997–2004 and newly diagnosed with dementia in 2005–2011. The control group was not selected from the same database and did not have a catastrophic illness certificate. However, they were newly diagnosed with major depression in 2005–2011 and did not have dementia. This comparison of the 2 groups is not suitable and leads to bias. The use of antidepressants would be expected more in the first group than in the second group. The control group should also have been selected from the Catastrophic Illnesses Patient Database (from those without a diagnosis of dementia).

Second, regarding the cumulative antidepressant dose, antidepressant dose ranges even in the same class differ from each other. For example, one selective serotonin reuptake inhibitor (SSRI), fluvoxamine, has a 50–300 mg/d dose range, while another SSRI, escitalopram, has a dose range of 10–20 mg/d. Calculating the cumulative dose of each drug separately (sertraline, paroxetine…) rather than as a group (SSRI, TCAs…) would be more appropriate.

Because of these two methodological limitations, it would not be absolutely right to claim that antidepressant use is associated with a (reduced *or* increased) risk of dementia on the basis of this study.

Reference

1. Lee CW, Lin CL, Sung FC, et al. Antidepressant treatment and risk of dementia: a population-based, retrospective case-control study. *J Clin Psychiatry*. 2016;77(1):117–122.

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Dr Kao Replies

To the Editor: My colleagues and I appreciate the critique of our study by Dr Doruk and would like to clarify the issues he raised about its design.

First, we identified patients newly diagnosed with dementia from the Registry of Catastrophic Illnesses Patient Database (CIPD) of the Taiwan National Health Insurance Research Database (NHIRD) as the case group to confirm the accuracy of the dementia diagnosis, because the approval of a catastrophic illness certificate is a rigorous process. Since patients without a dementia diagnosis in CIPD usually have other severe diseases that may confound the analysis, our control group comprised patients without dementia selected from the Longitudinal Health Insurance Database 2000 of NHIRD, a sampling file of 1 million people with almost identical distributions of sex, age, and health care cost as the total population of 23 million in Taiwan. Each dementia patient was matched with a nondementia patient on age, sex, year of major depression diagnosis, and year of index date, ie, the date at first diagnosis of dementia. Therefore, the duration of antidepressant use is the same in both groups. Yet, we do agree with Dr Doruk's comment that selecting cases and controls from different subsets of NHIRD may introduce some unknown bias.

Second, the antidepressants included in our study are tricyclic antidepressants (amitriptyline, clomipramine, desipramine, doxepin, imipramine, and nortriptyline), selective serotonin reuptake inhibitors (SSRIs; fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram), monoamine oxidase inhibitors (MAOIs; tranylcypromine, phenelzine, selegiline, and isocarboxazid), heterocyclic antidepressants (nefazodone and trazodone), and others (bupropion, venlafaxine, and mirtazapine). We decided not to show cumulative doses of individual drugs, but to list only the partition of quartile or median doses of each group of antidepressants, in order to improve the readability of the article. Indeed, this may obscure specific pharmacologic properties of individual drugs, and the results should be interpreted carefully.

In conclusion, we found an association between antidepressant use and the risk of dementia in our population-based study. As mentioned in our article, the quality of evidence derived from retrospective case-control studies is generally lower than that from randomized trials, so large-scale randomized clinical trials are required any definitive conclusions can be drawn.

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