See article by Bartels et al

Why Do Some Older Adults Treated With Antidepressants Progress to Dementia?

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The relationship between a history of depression and incident dementia is well established, yet incompletely understood. A history of remote or recent depression is associated with about a 2-fold higher risk of incident dementia.[1] Despite large studies designed to elucidate the mechanism underlying this epidemiologic relationship, it is still not clear whether depression is a causal contributor to dementia, a disorder with common risk factors, or a symptom of an underlying neurodegenerative process and a prodrome of dementia.[2–4] This uncertainty is due in large part to the complexity of these two clinical syndromes, each with heterogeneous etiologies, pathophysiologies, and treatments, all of which can interact with biopsychosocial factors across individuals and populations. Thus, a given individual with depression may progress from depression to dementia due to one, all, or none of the above mechanisms.

Because antidepressant medications are effective (although not when dementia is already present),[5] their use may help to understand the dementia-depression relationship. If depressive episodes causally contribute to the development of dementia, their successful treatment should lower the risk of dementia compared to untreated episodes. However, antidepressants are heterogeneous, with broad biological effects. They can directly or indirectly impact the overlapping physiologic changes observed in depression and dementia, including neuroinflammation, neurovascular factors, neurotrophic factors, or the metabolism of amyloid-β and tau protein.[1] Thus, antidepressants could increase or decrease the risk of dementia, independent of their effect on depression.

In their article, Bartels et al[6] report on a study of the relationship between antidepressant use and risk of incident dementia conducted in the context of preexisting conflicting studies. While most studies published to date have grouped antidepressants by class, and few have addressed the issue of treatment duration, their study addresses both of these potentially important factors. They used an observational, case-control design to retrospectively analyze data from a representative sample of 1,203 (3%) of the primary care practices in Germany. They identified 62,317 patients 65 years of age or older who received an incident diagnosis of dementia in 2013–2017. Dementia patients were matched with 62,317 control patients based on age, sex, individual primary care physician, and index year. Dementia patients and controls were compared based on whether they were prescribed 1 of 14 antidepressant pharmacotherapies at the index date: 5 selective serotonin reuptake inhibitors (SSRIs)—citalopram, escitalopram, fluoxetine, paroxetine, or sertraline; 2 serotonin-norepinephrine reuptake inhibitors (SNRIs)—duloxetine or venlafaxine; 4 tricyclic antidepressants (TCAs)—amitriptyline, doxepin, opipramol, or trimipramine; the herbal *Hypericum perforatum*; lithium; or mirtazapine. Regression models assessed the association between incident dementia and either prescription of antidepressants or duration of treatment. Covariates included a diagnosis of depression (to control for the association between a diagnosis of depression and receiving an antidepressant), severity of depression, diagnoses of other common medical disorders associated with dementia or antidepressant use (eg, diabetes or anxiety), and health insurance.

Depression was associated with incident dementia: 31% of patients had depression versus 24% of controls. Odds of incident dementia varied by medications classes: it was increased with SSRIs and SNRIs and decreased with TCAs. Citalopram was the most prescribed SSRI, and it was the only SSRI statistically associated with increased odds of dementia, as was mirtazapine. All TCAs and *Hypericum perforatum* independently decreased the odds of dementia. Duration of treatment was dichotomized as short- or long-term based on a median split of 710 days. Typically, long-term use was associated with a lower risk of incident dementia than short-term use. This was striking for escitalopram, for which short-term use was associated with an increased risk and long-term use with a decreased risk.

Bartels et al state that their covariates address confounding by indication because they include diagnoses and severity of depression (when available). However, their analysis does not account for some other important potential confounds. and we do not believe that confounding by indication has been ruled out. For example, physicians often choose

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antidepressants based on their perceived side effects,[7,8] including cognitive effects. In patients who are at risk for cognitive impairment, antidepressants associated with cognitive impairment (like TCAs) are avoided and SSRIs are favored. Since these factors are not captured by the covariates, SSRIs may spuriously appear to increase the risk of dementia and TCAs to decrease it.

Depression severity was recorded for only a quarter of study patients. Thus, it may also contribute to confounding by indication because more severe or treatment-resistant depression is associated with a higher risk of dementia,[1] and it may affect prescribing: patients with complex depression are more likely to be treated with medications rather than herbal remedies. Severe or treatment-resistant depression may also be associated with cognitive impairment, obscuring a diagnosis of dementia.[9]

The most important finding of Bartels et al may be the differential risks of short- versus long-term antidepressant use. However, in an observational study, we do not know whether treatment duration was short because the depression was limited (due to effective treatment or natural course) or whether a medication was discontinued due to its lack of efficacy or poor tolerability. Similarly, we do not know whether treatment was long-term because it was thought to be effective and needed to prevent relapses, or ineffective but not discontinued. If many remissions are due to the natural history of depression but are attributed to antidepressants that are continued, long-term treatment may be a marker of lower risk of dementia independent of any biological effect of the drug. Further, the short-term medication subgroup represents more recent prescriptions. As acknowledged by the authors, if antidepressants are initiated in patients presenting with prodromal symptoms of dementia that are interpreted as target symptoms of depression (eg, apathy, weight loss, anxiety, or agitation), these antidepressants will spuriously appear to be associated with an increased risk of dementia. For example, over the past 20 years, a series of studies have reported on the efficacy for citalopram to treat agitation associated with Alzheimer's dementia. Thus, the preferential use of citalopram or escitalopram in older patients suspected of having an incipient dementia may explain the observed association between the use of citalopram or the short-term use of escitalopram and incidence of dementia, both of which account for most of the reported class effect of SSRIs. By contrast, long-term use may be capturing early-onset depression, which may have a lower risk of dementia. Future studies will need to account for the age at onset and total duration of depression, which both may mediate dementia risk.[1]

Regardless, the lower odds of dementia associated with longer-term use of 17 of 18 antidepressant treatments studied (all except lithium) are evidence against a harmful effect of antidepressants on dementia. These associations also suggest that unadjusted confounds are contributing to the results: we would not expect to observe associations in opposite directions depending on duration, as was observed with escitalopram.

Complex and interacting factors alter risk of dementia in older patients. The extent to which antidepressants alter dementia risk remains an important question that can best be answered by prospective studies, ideally well-designed, large randomized controlled trials (RCTs). Future RCTs investigating current and new antidepressant treatments in older patients should include longer follow-up and cognitive outcomes. Absent large RCTs, meta-analyses, including network meta-analyses, may help to assess the differential risk of dementia associated with specific medications. A large open-label observation study with adequate follow-up may strike the right balance between feasibility and scientific merit; it could accomplish for depression what the Framingham study[10] did for cardiovascular diseases.

If the findings of the study by Bartels et al are confirmed in future prospective trials, they should change practice. All else being equal, clinicians should choose antidepressants associated with a protective rather than harmful effects on dementia risk. However, even if on average certain antidepressants alter the risk of future dementia, older patients with depression are not "all equal": as reported by Bartels et al, most have comorbid medical disorders and underlying pathologies that interact with this risk. Future studies will need to incorporate available and emerging biomarkers of depression and neurodegenerative disorders[11] to tease out the heterogeneity of the association between depression and incident dementia.

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