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# Adverse Cognitive Effects of Medications:

## Turning Attention to Reversibility

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**In this issue** of *JAMA Internal Medicine*, Gray and colleagues[1] present findings from an observational analysis that show a higher risk for dementia with the increasing dose and duration of exposure to medications with strong anticholinergic activity. The risk for dementia was consistent when comparing participants with recent and past heavy use of such medications with nonusers, suggesting that the adverse cognitive effects are permanent. Other studies[2–4] have consistently shown similar results. However, the question of reversibility of the adverse cognitive effects of medications and the safety risks of discontinuing the use of such medications remain untested in randomized clinical trials (RCTs).

Gray and colleagues[1] paid special attention to reducing several sources of bias, including recall bias, by defining medication exposure through dispensing records. They also addressed protopathic bias and confounding by indication by excluding anticholinergic exposure in the year before the outcome assessment and by adjusting for prodromal symptoms of dementia. Finally, the investigators used the clinical diagnosis of dementia derived from a consensus panel of experts as the dependent cognitive variable of interest. The clinical diagnosis of dementia has become the preferred method of identifying cognitive impairment in pharmacoepidemiologic studies because it represents cognitive decline that affects daily activities and is not owing to an otherwise reversible cause.[2,3]

In addition to anticholinergics, the American Geriatrics Society has also recognized benzodiazepines and histamine receptor$_2$ antagonists as potentially inappropriate for older adults owing to their adverse cognitive effects.[5,6] Gray and colleagues[1] report that 78.3% of their cohort were dispensed at least 1 strong anticholinergic in the 10-year study period. Castelino and colleagues[7] have also reported that as many as 60% of ambulatory older adults use at least 1 medication with adverse cognitive effects. The methods used by Gray



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and colleagues should be repeated to determine the risk for cognitive impairment conferred by all medications with adverse cognitive effects, not only anticholinergics, within healthy older adults and older adults with multiple chronic conditions.

Our group[2,3] previously found an association between exposure to anticholinergics and the clinical diagnosis of cognitive impairment (mild cognitive impairment or dementia). The investigators used 1 year of dispensing data as the independent variable and found results similar to those of Gray and colleagues,[1] suggesting a 2-fold increased risk for a clinical diagnosis of mild cognitive impairment or dementia among those using strong anticholinergics for at least 60 days in a 1-year period.[3] Those findings showed a stronger association with the diagnosis of mild cognitive impairment than dementia, suggesting the possibility of a reversible effect. The findings by Gray and colleagues provide the alternative hypothesis that the adverse cognitive effect of anticholinergics may be permanent.

The question of reversibility of the adverse cognitive effects of medications is of significant importance for the aging population and the health care system.The current burden of dementia (5 million people in the United States in 2013) represents an estimated $214 billion in costs of care.[8] With the growth of the aging population, the anticipated number of older adults with dementia is expected to be 16 million by 2050, with $1.2 trillion expected in costs of care.[8] Although a number of pharmacologic agents are being investigated to reduce the burden of or to prevent dementia, no medication-based intervention is currently available to prevent dementia.

Therefore, reversing the adverse cognitive effects of medications such as anticholinergics is an important intervention that may attenuate the expected increasing burden of dementia. It makes clinical sense to minimize exposure to these medications among older adults; however, no evidence from RCTs supports the hypothesis that discontinuing these medication therapies improves cognition. Although studies have shown that reducing exposure to medications with adverse cognitive effects can be accomplished successfully in ambulatory older adults, the effect on cognition remains insufficiently studied.

Such an RCT must be conducted not only to determine the effect on cognition but also to determine the safety and unintended consequences of discontinuing medication therapies among older adults. Because the approach to discontinuing such a wide array of medication therapies depends on the dose, duration, and indication (eg, meclizine for dizziness, amitriptyline for depression or neuropathy, and lorazepam for insomnia), the intervention must be designed with the ability to tailor the deprescribing and monitoring approach to each individual to optimize safe and effective medication changes. Only with results from such RCTs will we be able to translate findings from observational cohort studies into interventions to minimize the adverse cognitive effects of medications. Last, although an RCT would require a few years to be conducted, a successful intervention would be available for clinical use in a significantly shorter period than the 17 years required for the development, testing, and approval of a novel pharmacologic agent.

We therefore applaud the work by Gray and colleagues[1] for the novel approach of describing the cumulative risk for dementia among users of medications with adverse

cognitive effects; however, we emphasize that translation of these findings into clinical interventions is an important next step with the potential for a meaningful effect on the quality of care of older adults and the global burden of dementia. Results from observational studies heighten the need to develop interventions to identify and attenuate potentially reversible risk factors for dementia among older adults.

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