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COMMENTARY

Balancing risks and benefits: nuisance medication and cognitive decline in late-life

Commentary on "Benzodiazepine use and risk of incident MCI and dementia in a community sample" by Teverovsky *et al.*

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In this issue of the journal, Teverovsky and colleagues describe the incident rates of mild cognitive impairment (MCI) and dementia in a large and comprehensively characterized population-based cohort ($n = 1959$) of cognitively normal adults 65 years of age and older as a function of benzodiazepine use (Teverovsky *et al.*, 2023). The median length of follow-up was 5.1 years, and 7.7% of the cohort reported taking benzodiazepines. Relevant covariates (age, sex, education, sleep, anxiety, and depression) and an interaction between benzodiazepine use and APOE*4 status were included in the model. The results suggest that use of benzodiazepines is associated with developing MCI but not dementia. APOE*4 genotype status did not moderate the effect for either MCI or dementia, meaning that the use of benzodiazepines and risk for cognitive decline were not different between participants with and without this non-modifiable risk for dementia neuropathology and clinical presentation.

The authors meticulously place their observations in the context of other peer-reviewed publications. However, replication of previous findings is not a slam dunk. As Teverovsky and colleagues describe, in two earlier studies of benzodiazepine use and cognitive decline, one study described a relationship between benzodiazepine use and cognitive impairment, not dementia (CIND) but not with dementia (Nafti *et al.*, 2020), and one observed a relationship between benzodiazepine use and developing dementia but not with CIND (Gallacher *et al.*, 2012). Teverovsky describes similarly varied results for the relationship between benzodiazepines and dementia in community-based samples. As late-life psychiatrists who pledge *primum non nocere*, what is the best clinical approach to reduce the risk of MCI and dementia in our patients who by the nature of their psychiatric illnesses are enriched for neurodegenerative diseases (Jang *et al.*, 2020)?

To begin to answer this question, we must first consider the importance of prevention efforts in addressing the tsunami of incident dementia. According to the Alzheimer's Association, an estimated 6.7 million Americans age 65 and older (11%) are living with Alzheimer's dementia in 2023 (Alzheimer's Association Report, 2023; Rajan *et al.*, 2021), and a systematic review of over 30 studies reported that about 17% of people age 65 and older have MCI (Petersen *et al.*, 2018). While there is evidence that the prevalence and incidence of Alzheimer's Disease and Related Dementias (ADRDs) may have decreased over the past 25 years in high-income countries, by 2025, the number of people age 65 and older with Alzheimer's dementia is projected to reach 7.2 million – a 7% increase (Rajan *et al.*, 2021). With an estimated 13.8 million people 65 and older projected to have Alzheimer's dementia by 2060, and without the rapid development of scalable and cost-effective medications to "prevent, slow, or cure Alzheimer's disease," (Rajan *et al.*, 2021) it is only through global prevention efforts – not expensive and potentially risky disease modifying drugs – that a meaningful reduction in incidence and prevalence will be accomplished. This includes (1) preventing and treating cardiovascular and metabolic diseases, in particular hypertension and diabetes; (2) encouraging healthy behaviors, such as exercise, intellectual stimulation, and adhering to DASH and Mediterranean diets; (3) treating mental illness, in particular depression; (4) preventing head trauma by reducing falls and utilizing seatbelts; and (5) smoking prevention and cessation, prevention of excessive alcohol use, using hearing protection or aides, promoting education across the lifespan, and

accounting for air pollution. All of these interventions have evidence for their efficacy in reducing the risk for and delaying the development of cognitive impairment (Livingston *et al.*, 2020).

Preventing clinically significant cognitive decline and promoting brain health also requires attending to nuisance medications that may have brain toxicity and impair cognitive function. Other examples of potentially iatrogenic medications include the recently published observation that opioid exposure during the ages of 75–80 is linked with a 1.39-fold increased risk of dementia (Levine *et al.*, 2023), and a population-based cohort study describing that higher cumulative anticholinergic use (e.g., tricyclics, first-generation antihistamines, and bladder antimuscarinics) is associated with an increased risk for dementia (Gray *et al.*, 2015). While the mechanisms by which opioids, benzodiazepines, and medications with high anticholinergic burden contribute to impaired cognitive function, MCI, and dementia are unclear and likely multifactorial (and Alzheimer's disease biomarker progression (amyloid, tau, neurodegeneration) associated with these medications is not established), minimizing unnecessary exposure to these drugs is part of the pledge of *primum non nocere*.

However, these potentially inappropriate medications must not be demonized or thoughtlessly tossed onto the rubbish heap without simultaneously considering how to best help these patients suffering from anxiety, insomnia, depression, pain, and incontinence. To provide personalized, patient-centered care, we must weigh the potential risks (hastening cognitive decline and conversion to MCI and dementia) versus benefits (reducing depression, pain, anxiety, insomnia, incontinence). The American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults has become more nuanced than previous versions and suggests that when a potentially inappropriate medication is chosen, "it is done so through shared decision-making that includes recognition of its potential harms and consideration of the older person's preferences and goals of care" (2023 American Geriatrics Society Beers Criteria® Update Expert Panel, 2023). This is prudent because untreated or undertreated depression (Gallagher *et al.*, 2018), pain (Zhao *et al.*, 2023), anxiety (Gulpers *et al.*, 2016), and insomnia (de Almondes *et al.*, 2016) are all associated with cognitive decline and brain dysfunction. The holy grail medications to address these common conditions in late-life are those which reduce neuropsychiatric symptoms, stabilize or improve cognition, and do not contribute to amyloid, tau, neurodegeneration, or other measures of brain toxicity.

Conflict of interest

Within the past five years, Dr. Karp has received compensation for development and presentation of a (disease-state, not product-focused) webinar for Otsuka. He has served as scientific advisor (paid) to NightWare and Biogen and Dr. Karp has options for shares in Aifred Health. He receives compensation from *Journal of Clinical Psychiatry* and *American Journal of Geriatric Psychiatry* for editorial board service.

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