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COMMENTARY

The Long and the Short of Benzodiazepines and Sleep Medications: Short-Term Benefits, Long-Term Harms?

Steven T. DeKosky[1,2] · John B. Williamson[3,4,5]

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In the movie, "Starting Over," there is a scene in a crowded department store in which an anxious Burt Reynolds cries out, "Does anyone have a Valium?" When he looked up to see if anyone had responded, all of the shoppers in the busy aisle were in frozen postures and holding out prescription vials of Valium. While it was a funny comment on the ubiquitous presence of benzodiazepines in modern society in 1979, the widespread use of diazepam and similar drugs led, in addition to their therapeutic benefits, to addiction, altered judgment, medical morbidity, and deaths from overdose. Warnings were subsequently issued to the public and to physicians to decrease prescribing benzodiazepines for the everyday stressors of life, and these warnings stimulated successful efforts to develop benzodiazepines with shorter half-lives. The hope was to decrease the dangers associated with their use, while achieving similar reductions in stress and improvements in sleep. While use may be less prevalent today than in the latter part of the previous century (perhaps due to the emergence of selective serotonin reuptake inhibitors), the overuse and inappropriate use of benzodiazepines continue to be associated with significant adverse events including addiction. Medical and psychiatric comorbidities complicate the use case determination for these medications. Further, these issues are compounded in the elderly, in whom cognitive and brain frailty may provide increased vulnerability to the manifestation of dementia with benzodiazepines and in whom neurodegenerative processes may be facilitated. Ultimately, an important consideration is the potential for irreversible loss of functional independence that may be sparked through (as-yet) unknown mechanistic effects of this class of medications on the progression of neurodegenerative disease or even through neurological toxicity. Indeed, impairment of alertness, postural unsteadiness, and falls resulting in fractures and other traumatic injuries are common, especially when benzodiazepines are used by the elderly to aid sleep.

Similarly, the sedative-hypnotic "z-drugs"—zaleplon, zolpidem, and zopiclone—were developed as soporifics with better pharmacodynamics that theoretically allow a lower risk of causing cognitive and attentional impairment, with minimal effects on alertness during the day. These drugs have been advertised and used widely and have unfortunately had similar complications, especially among the elderly, and particularly when used alone or in combination with benzodiazepines and medications with anticholinergic effects [1].

There may be other contributions from these medications to the development and progression of neurodegenerative diseases, such as Alzheimer's disease (AD). Progress has been made in identifying the pathological cascades that lead to AD and other late-life neurodegenerative dementias, but a full understanding of how environmental risk factors, genetics, other abnormal protein aggregates, and comorbid diseases (especially vascular pathology) contribute to the manifestation and progression of these catastrophic conditions remains elusive. Doses of benzodiazepines high enough to cause adverse symptoms may also predispose to or facilitate neurodegenerative processes, possibly via its effects on $GABA_A$ receptors or global cortical activity suppression.

In this issue, Tseng and colleagues [2] utilized a very large, well-characterized national hospital dataset from Taiwan to assess the relationship of benzodiazepines and z-drugs to the

✉ Steven T. DeKosky
DeKosky@UFL.edu

John B. Williamson
john.williamson@UFL.edu

[1] McKnight Brain Institute, University of Florida, Gainesville, USA

[2] Department of Neurology, UF College of Medicine, Gainesville, USA

[3] Center for OCD and Anxiety-Related Disorders, Gainesville, USA

[4] Department of Psychiatry, College of Medicine, University of Florida, Gainesville, USA

[5] Brain Research and Rehabilitation Center, North Florida/South Georgia Department of Veterans Affairs, Malcom Randall VAMC, Gainesville, USA

occurrence of dementia. They found significantly increased risk of a diagnosis of dementia in people who took these medications, a risk that was even more pronounced if patients were taking drugs from both categories simultaneously. This is an alarming finding and one that merits additional scrutiny and identification of both prescribing habits and susceptibility to neurodegenerative changes.

Sleep problems are very common among the elderly, and treatment solutions are badly needed. Though the article of Tseng et al. [2] highlights a relationship between the studied medications and dementia risk, it remains to be seen if this relationship is causal and to what extent providers should consider modifying their prescription approaches.

While there have been consistent epidemiological suggestions of increased risk of dementia with the use of soporifics, as well as meta-analyses of benzodiazepines and dementia showing a significant relationship [3], a mechanism whereby they could be a causal contributor to dementia onset or progression is not known. People who are prescribed multiple medications (e.g., Tseng et al. [2]) had the highest risk and likely have more difficulty sleeping than people who receive fewer medications. Further, the most at-risk group may also have other conditions contributing to sleep disturbances.

Though it is possible that these medications exacerbate neurodegeneration, cause unwanted side effects, or are related to comorbidities that lead to polypharmacy, the paper of Tseng et al. [2] does not explore the mechanisms that might facilitate neurodegenerative processes; there is also an apparent paradox that the shorter-acting z-drugs appear to have a stronger relationship to dementia. These findings will require prospective controlled studies of the possible mechanisms whereby the medications might foment cognitive decline [4].

Benzodiazepines have a variety of clinical uses. Psychiatric diseases, such as anxiety spectrum disorders, may contribute to brain aging (e.g., [5]) and are often associated with insomnia. Further, sleep disruption is associated, even in mild stages, with AD trajectory neurodegeneration [6]. There appears to be a reciprocal relationship between amyloid and tau accumulation in the brain and sleep [7]. Poor sleep may also be a contributor to the progression of AD via impaired beta-amyloid clearance [8], though the causation is complicated to parse, as deterioration of slow-wave sleep tracks with the progression of beta-amyloid and tau pathology in AD [9].

Further, poorer sleep is associated with worse cognitive performance, regardless of presence of AD. Patients on benzodiazepines may also have had a longer standing sleep problem, preceding any AD-associated sleep disruption, but insomnia may be increased if AD-related sleep disruption worsens even in the face of a prior effective dose, leading not uncommonly to increased dosage.

GABA agonists have a known relationship to cognition in aging; decreasing concentrations of GABA and metabolites in human forebrain in aging correlates with cognitive function [10]. It is here that other options for controlling sleep must be employed, certainly prior to use of these medications or the anticholinergic medications which are not uncommonly employed for sleep but are also associated with increased dementia in late life [1].

Experimental work and cross-sectional studies on sleep quality in older people with similar symptoms should be followed by prospective studies to determine the effectiveness of nonpharmacologic interventions and other less problematic medications, with the knowledge that giving sedating medications at night will need high vigilance to assure that such patients do not get up and move around while slowed cognitively and having an unsteady gait.

The apparent adverse effects of these medications in older patients (e.g., falls, cognitive effects) suggest that clinicians should be very cautious in their use in older patients. In addition to developing safer pharmacotherapeutics that will decrease the risks associated with these medications, good sleep hygiene should be pursued both to alleviate the discomfort of anxiety or insomnia that calls for treatment and to minimize, to the extent possible, the facilitation of neurodegenerative changes in the brain. This strategy includes minimal caffeinated beverages, especially in the evening, regular exercise, maintaining a regular sleep routine, and other strategies [11, 12]. The increased risk of dementia and the associated morbidities of the use of benzodiazepines [13] calls for careful consideration when using them, and should motivate a change in prescriptive practice while the search for other strategies continues.

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