Benzodiazepines and the Risk of Alzheimer’s Disease: Association or Protopathic Bias?

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Benzodiazepines are widely used and effective for the short-term treatment of anxiety symptoms and anxiety disorders (with some controversy about long-term treatment in selected populations). Yet, because they have been implicated as increasing the risk of Alzheimer’s disease, the overall risk-benefit ratio has been questioned by clinicians, patients, and the media. (After reading a newspaper article, one of my patients who has fully benefited from long-term treatment of anxiety in the context of treatment-resistant depression and comorbid generalized anxiety disorder called me in a panic about whether or not she should stop her benzodiazepine.) At best, the evidence has been interpreted as a possible association and at worst as causal. Should, then, clinicians avoid prescribing benzodiazepines and should patients reject them as options because of this possible risk? And if it is a risk, how much of a risk is it?

Before examining the link between benzodiazepines and Alzheimer’s disease, it is necessary to consider the idea of protopathic bias. As defined by Horwitz and Feinstein, “Protopathic bias occurs when a pharmaceutical or other therapeutic agent is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnostically detected.” For example, if back pain occurs due to a metastasis before a diagnosis of metastatic cancer is established and patients are treated with nonsteroidal anti-inflammatory drugs (NSAIDs), it could falsely appear that the NSAIDs caused the cancer once the diagnosis is made. Instead, of course, the NSAIDs were prescribed for an early (”proto”) manifestation of the cancer.

The evidence for the association between benzodiazepines and Alzheimer’s disease is, not surprisingly, mixed. Several studies confirm and others refute the association. The evidence for the association between benzodiazepines and Alzheimer’s disease is, not surprisingly, mixed. Several studies confirm and others refute the association.4-8

With regard to the association of benzodiazepines and Alzheimer’s disease, the question is whether mild neuropsychiatric impairment (anxiety, irritability, insomnia, or agitation) can precede the diagnosis of dementia (and provoke treatment with a benzodiazepine) and if so, what is the time lag from the onset of these symptoms to fully diagnosable Alzheimer’s disease? The evidence is substantial for mild neuropsychiatric impairment as a prodrome of dementia. Additionally, anxiety can be an independent risk factor for developing Alzheimer’s disease when combined with mild amnestic cognitive impairment.9 How early these symptoms can occur before Alzheimer’s disease becomes apparent is unclear.

Overall, if benzodiazepines increase the risk of Alzheimer’s disease, protopathic bias makes it difficult to study.10 As with all psychiatric medications, clinicians should carefully assess benefits and risks of benzodiazepines, especially their long-term use.

REFERENCES
2. Tapiainen V, Taipale H, Tanskanen A, Tiitinen J, Hartikainen S, Tolppanen AM.


