AFP Journal Club

The Story Behind the Study

Benzodiazepines and Alzheimer Disease

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Purpose

In *AFP* Journal Club, three presenters review an interesting journal article in a conversational manner. These articles involve hot topics that affect family physicians or "bust" commonly held medical myths. The presenters give their opinions about the clinical value of the individual study discussed. The opinions reflect the views of the presenters, not those of *AFP* or the AAFP.

Article

Billioti de Gage S, Moride Y, Ducruet T, et al. Benzodiazepine use and risk of Alzheimer's disease: case-control study. *BMJ.* 2014;349:g5205.

For more information on evidence-based medicine (EBM) terms, see the EBM Toolkit at http://www.aafp.org/afp/ebmtoolkit.

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Does chronic benzodiazepine use cause Alzheimer dementia?

Jill: A handful of past studies have suggested a link between dementia and benzodiazepine use. Because it is not possible to do randomized controlled trials to evaluate this, researchers are working to answer this important public health question by accumulating evidence in many different populations and settings to assess whether the relationship is causative or merely an association with other mediating factors.

What does this article say?

Jill: In this case-control study, researchers used RAMQ (a Quebec health insurance program database) to identify a random sample of 1,796 community-dwelling adults older than 66 years who had an initial diagnosis of Alzheimer dementia or were first prescribed drugs to treat dementia (i.e., memantine [Namenda] or cholinesterase inhibitors) between 2000 and 2009, at least six years before the study started. From the same database, 7,184 age- and sex-matched control patients (four per case patient) without these conditions were randomly selected. Prior benzodiazepine exposure was categorized through dispensation claims by ever vs. never use, by cumulative prescribed daily doses (1 to 90, 91 to 180, more than 180), and by drug half-life (short [less than 20 hours] vs. long [20 hours or more]).

Multivariate logistic regression evaluated the relationship between exposure (benzodiazepine use) and the dependent variable (Alzheimer disease), and adjusted for covariates including hypertension, stroke, diabetes mellitus, hypercholesterolemia, depression, anxiety, insomnia, and other comorbidities. The adjusted odds ratio (OR) for Alzheimer disease in those who had ever used benzodiazepines was 1.51 (95% confidence interval [CI], 1.36 to 1.69). The odds of Alzheimer disease increased with more cumulative benzodiazepine exposure: no significant association (OR = 1.09; 95% CI, 0.92 to 1.28) with fewer than 90 prescribed daily doses, OR = 1.32 (95% CI, 1.01 to 1.74) with 91 to 180 prescribed daily doses, and OR = 1.84 (95% CI, 1.62 to 2.08) with more than 180 prescribed daily doses. A longer drug half-life also had a stronger association: OR = 1.43 (95% CI, 1.27 to 1.61) for short-acting benzodiazepines, and OR = 1.70 (95% CI, 1.46 to 1.98) for longer-acting benzodiazepines. There was no significant interaction for anxiety, depression, or insomnia.

Should we believe this study?

Mark: The Canadians have a robust database for the population in this study, with more than 98% of adults in this age group participating in the Quebec health insurance plan. This minimizes the risk of sampling bias as much as possible. They also controlled for the delay of diagnosis in the database with a minimum follow-up of six years. This helps to demonstrate a temporality, with the exposure to benzodiazepines clearly occurring before

the initial diagnosis or treatment of Alzheimer disease. It also addresses the possibility of reverse causality, which is always a concern in case-control studies.

Bob: So what is reverse causality? It is essentially the age-old question: Which came first … the chicken or the egg? In this case, did the early symptoms of Alzheimer disease prompt the prescription of benzodiazepines? As Mark said, the authors did a very smart thing to try to get around this—they assessed benzodiazepine use six to 10 years prior to the diagnosis of Alzheimer disease, thus limiting the potential for reverse causality.

Jill: A case-control study isn't the best study to establish causation, however. The best we can do with this type of study is to illustrate associations and support our hypotheses about causality by demonstrating some of the criteria of causality. Hill's criteria for causation are a broadly accepted set of nine criteria to establish causality between an exposure or incidence and an effect or consequence. In general, the more criteria that are met, the more likely the relationship is causal.[1]

In this study, the authors do a nice job of displaying some of these criteria. They suggest, for example, a dose-response gradient, both through the prescribed daily doses and the drug half-lives. The strength of the association is also demonstrated nicely. The ORs are not only statistically significant, but large enough to be clinically significant as well. And, as Mark said, the temporal association seems likely with the drug exposure occurring well before the disease is diagnosed.

Mark: The absence of other causes for dementia in this study (specificity) is also implied by eliminating many of the potential confounding variables in the logistic regression analysis. Certainly, there might be a mediating factor, such as a prodromal symptom of dementia or coexisting condition, that prompts benzodiazepine use. The authors attempted to address this to some extent by including the diagnoses of anxiety, depression, and insomnia in their regression analysis.

Bob: Right. We've discussed the problems associated with using coding data before. In this case, we may be missing some symptoms that may be important to consider in analysis simply because they aren't listed as diagnoses in the coding database.

What should the family physician do?

Mark: There are many reasons to question the chronic use of benzodiazepines in practice. Effectiveness is questionable (even for those disorders for which they are indicated), there is potential for addiction, and the immediate adverse effects could be dangerous. Possible long-term adverse effects, such as increased risk of dementia, should give us even more pause.

Main Points

- Benzodiazepine exposure over the preceding five years seems to be associated with an increased likelihood of an Alzheimer disease diagnosis.
- A dose-response gradient also seems to exist, with more prolonged dosing and a longer half-life associated with higher likelihood of disease.

EBM Points

- An association does not confer causation. But, when multiple criteria are met (e.g., strength of association, consistency, specificity, temporality, dose-response relationship, biologic plausibility, coherence, experimental evidence, analogy), the likelihood of a causal relationship increases.
- Case-control studies are not interventional studies and are retrospective, so we use odds ratio rather than relative risk as a measure of the association. Odds ratio is calculated by dividing the odds of disease given exposure by the odds of disease given nonexposure.
- A reverse causality error occurs when the outcome, or some component of it, causes the intervention or exposure in question.
- Hill's criteria for causation are a broadly accepted set of nine criteria to establish causality between an exposure or incidence and an effect or consequence. In general, the more criteria that are met, the more likely the relationship is causal. See the EBM Glossary at http://www.aafp.org/afp/ebmtoolkit for more information.

Jill: It's often difficult to counsel patients about the risks of benzodiazepines, especially when they specifically request the medications. If further research continues to support a causal relationship between the use of these drugs and such a feared diagnosis, patients and physicians may be persuaded to use other, safer treatments for common symptoms of anxiety and insomnia, such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, exercise, meditation, or cognitive behavior therapy.

Bob: As the population ages, answers to these questions become even more crucial. Dementia is a major public health concern, with no effective treatment and a huge disease burden. Anything we can do to mitigate the risk would be important.

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REFERENCE

1. Hill AB. The environment and disease: association or causation? *Proc R Soc Med.* 1965;58(5):295-300. ■