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Benzodiazepines and Dementia Risk: An Overview of Recent Evidence

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Abstract | **Review Article**

***Objective*:** To review recent epidemiological and mechanistic data on the association between benzodiazepine (BZD) use and dementia risk, discuss methodological biases, and propose adapted clinical recommendations, including for the Moroccan context. ***Methods*:** A targeted narrative review of literature (published up to July 2024), including cohort studies, case-control studies, recent meta-analyses, neuroimaging studies, and animal mechanistic studies. Databases consulted: PubMed/PMC, Embase, BMJ/BMC, *J Clin Neurol*, *Int Psychogeriatr*. Priority was given to meta-analyses and large prospective cohorts. ***Results*:** Studies remain discordant. Some prospective and case-control studies report an increased risk (e.g., Billioti de Gage *et al*., 2012; meta-analyses 2018–2019), while other large cohorts with better temporal controls find no clear overall effect (e.g., Gray *et al*., 2016; vom Hofe *et al*., 2024). Recent mechanistic work in mice shows that prolonged diazepam treatment can promote synaptic loss via the TSPO receptor and impair plasticity, providing biological plausibility for persistent cognitive effects. The role of protopathic bias (prescription for prodromal dementia symptoms: anxiety, insomnia) and confounding by indication largely explain the heterogeneity of results. In some analyses, cumulative duration, drug half-life, and dose appear to modulate the observed signal. Moroccan data show significant consumption and reported cases of intoxication, suggesting an important local public health issue. ***Conclusion*:** There is currently no definitive proof of an unambiguous causal link between BZDs and dementia for all populations. However, the body of evidence (epidemiology + experimental mechanisms + imaging) argues for caution, especially in the elderly. Practical recommendations should aim to: limit prescriptions, favor non-pharmacological alternatives, and implement structured deprescribing when indicated.

Keywords: Benzodiazepines, Dementia, Protopathic Bias, Deprescribing, Morocco, TSPO, Neuroimaging.

1. INTRODUCTION

Benzodiazepines remain widely prescribed for anxiety and sleep disorders. For about a decade, epidemiological studies have suggested an association between prolonged BZD use and an increased risk of dementia, sparking scientific debate and revisions of best practices [1–3]. However, studies vary greatly in design and control for temporal biases—particularly protopathic bias (prescription for precursor symptoms of dementia)—and some well-controlled cohorts observe no net increase in risk [4, 5]. Simultaneously, recent experimental data provide biological plausibility (synaptic loss linked to microglial activation via TSPO after prolonged diazepam exposure) [6]. This review synthesizes recent epidemiological and mechanistic data, discusses sources of divergence, and proposes concrete clinical recommendations—with a practical focus for prescribers in Morocco.

2. REVIEW METHODOLOGY

- **Type:** Systematized narrative review (targeted selection).
- **Search period:** Publications from 1990 to July 2024 (priority to 2010–2024).
- **Databases:** PubMed/PMC, Embase, BMJ/BMC, *J Clin Neurol*, *Int Psychogeriatr*, *Nature/Science* (mechanistic).
- **Inclusion criteria:** Epidemiological studies (prospective, retrospective, case-control), meta-analyses, neuroimaging studies, and animal mechanistic studies focusing on BZDs and cognition/dementia.
- **Exclusion criteria:** Isolated anecdotal reports without analytical data.
- **Selection:** Priority was given to large prospective cohorts and recent meta-analyses (see tables).

3. RESULTS

To provide a clear and critical overview of the evidence, we have synthesized the findings from major epidemiological studies and key mechanistic research in Table 1. The selected studies were prioritized based on their sample size, prospective design, control for confounding factors (particularly protopathic bias), and their influence on the current debate. This synthesis highlights the methodological heterogeneity and the contrasting conclusions that characterize this field of research. The table is followed by a narrative summary of the main trends and mechanistic insights.

Table 1: Major Studies and Meta-Analyses

Study (Year)	Design	Population	Key Finding	Interpretation
Billioti de Gage *et al*., (2012) [1]	Prospective (PAQUID)	Elderly (France), ~15 y FU	New BZD prescription associated with increased dementia risk (HR ~1.6)	Association found; possible confounding/protopathic bias
Gray *et al*., (2016) [4]	Prospective cohort (ACT)	N = 3,434, ≥65 y, cumulative exposure	Slightly increased risk at low exposure but no dose-response; no clear support for causality	Weak association, likely explained by biases
Penninkilampi & Eslick (2018) [2]	Meta-analysis	Various, after protopathic bias control	Overall positive association after specific adjustments	Highlights importance of protopathic bias and methodological heterogeneity
He *et al*., (2019) [3]	Meta-analysis (10 studies)	Pooled analysis	Pooled RR ≈ 1.51 (95% CI 1.17–1.95). Stronger signal for long half-life BZDs and use >3 years	Suggests dose/duration effect
Gerlach *et al*., (2021/22) [7]	Retrospective cohort	US Veterans (n ~528,000)	Small relative increases (HR ≈ 1.05–1.06) without clear dose-response gradient	Minimal association
Vom Hofe *et al*., (2024) [5]	Prospective (Rotterdam Study)	N = 5,443, mean FU 11.2 y + imaging	Overall use not associated with increased risk (HR 1.06 [0.90–1.25]). Current use linked to smaller hippocampal volumes and accelerated hippocampal loss	No overall risk, but suggests a potential neurobiological footprint
Teverovsky *et al*., (2024) [8]	Community-based	n ~1,959	BZDs associated with increased risk of MCI but not dementia at follow-up	May influence intermediate cognitive stages
Shi Y *et al*., (2022) [6]	Animal mechanistic (mice)	Diazepam chronic exposure	Chronic diazepam → increased synaptic engulfment by microglia via TSPO → spine loss, reversible cognitive deficits	Provides biological plausibility for lasting effects

4. DISCUSSION

The variability in study results can largely be explained by methodological factors. One important element is protopathic bias or reverse causation. Insomnia, anxiety, and agitation—symptoms often treated with benzodiazepines (BZDs)—may actually be prodromal manifestations of dementia. When the exposure period includes the years immediately preceding diagnosis, prescriptions may reflect the onset of the disease rather than its cause [2-4]. Studies that exclude the final year(s) before diagnosis generally report weaker associations. Another issue is confounding by indication, since anxiety, depression, and insomnia are themselves risk factors or early markers of dementia, making causal attribution complex. Some more recent studies have attempted to control for these variables more rigorously. Differences in exposure measurement also contribute to heterogeneity. While some studies define exposure as "ever use," others rely on cumulative defined daily dose (DDD), duration of use (≥3 years), or pharmacological half-life. Stronger signals are often observed for long half-life BZDs and for prolonged use beyond three years [3]. Furthermore, failure to control for co-medications such as anticholinergics, opioids, and other psychotropics—which themselves increase cognitive risk—can significantly alter risk estimates when adjustments are made [7].

In terms of dose, duration, and half-life, meta-analyses consistently report a higher risk with prolonged use (>3 years) and with long half-life compounds such as diazepam [3]. Nevertheless, some large-scale cohort studies have not observed a clear dose–response relationship. This weakens the strength of a causal argument, but does not eliminate the possibility of a

clinically meaningful effect in more vulnerable subgroups of patients.

The biological plausibility of these associations is supported by several lines of evidence. At the acute level, BZDs act on GABA_A receptors, leading to transient impairments in attention and memory, a phenomenon that is well established. In the long term, animal studies provide more concerning findings. For example, Shi et al. (2022) demonstrated that chronic diazepam exposure increases microglial synaptic engulfment through TSPO, resulting in dendritic spine loss and cognitive deficits, which are only partially reversible after withdrawal [6]. Human imaging data further reinforce this hypothesis. Vom Hofe et al. (Rotterdam cohort) reported that current BZD use is associated with reduced hippocampal and amygdala volumes, as well as accelerated hippocampal atrophy [5].

Altogether, this body of evidence supports a plausible causal relationship between prolonged BZD use and cognitive decline. The convergence of epidemiological data, meta-analyses, animal models, and imaging studies points toward an increased risk, although methodological heterogeneity prevents definitive conclusions. For this reason, clinical caution is warranted, particularly among elderly individuals and those with pre-existing dementia risk factors.

Finally, the specific Moroccan context needs to be emphasized. National consumption data from 2004 to 2017 reveal significant and regular use of alprazolam, bromazepam, lorazepam, and zolpidem. Local studies have also reported cases of intoxication and long-term use [9, 10]. Moreover, prescriptions are frequently issued by non-psychiatrists, and prolonged exposure is common. These characteristics make the Moroccan population particularly vulnerable to iatrogenic risks if best prescribing practices are not consistently applied [9].

5. Practical Clinical Recommendations

- ***General Principles***
  - Avoid initiating BZDs in patients ≥65 years except for acute, short-term indications. Follow international guidelines (e.g., AGS Beers Criteria 2023).
  - If a BZD is necessary: prefer short/intermediate half-life molecules, minimum effective dose, and shortest possible duration (a few days → maximum 2–4 weeks depending on indication).
  - Avoid chronic use (>3 months); reassess regularly and document treatment goals.
  - Treat underlying causes of insomnia/anxiety (CBT, sleep hygiene) before long-term pharmacological treatment.
  - Use caution with comorbidities: anticholinergic burden, renal/hepatic impairment, history of falls, polypharmacy.
- ***Deprescribing Protocol (Simplified Algorithm)***
  - Step 0: Assess indication, duration, molecule, dose, risk of falls/delirium, dependence.
  - Step 1: Provide information and obtain consent.
  - Step 2: If use <4 weeks and no dependence → taper over 1–2 weeks.
  - Step 3: If chronic use (>3 months) or dependence → reduce gradually (10–25% every 1–2 weeks). Consider substitution with diazepam in selected cases (not in frail elderly).
  - Step 4: Provide non-pharmacological support: CBT-I, relaxation, CBT for anxiety, SSRIs/SNRIs if indicated.
  - Step 5: Ensure close follow-up at 1, 3, and 6 months.

6. Limitations of the Evidence and Research Directions

- Methodological heterogeneity (exposure, time windows, confounders).
- Prospective studies with phenotyping of prodromal symptoms are needed.
- Randomized deprescribing trials and neuroimaging of ex-users should test reversibility.
- Local data (Morocco, North Africa): pharmaco-epidemiological surveillance and prescriber training are priorities.

7. CONCLUSION

Evidence does not definitively prove causality between BZDs and dementia. However, epidemiological, mechanistic, and imaging findings argue for caution, especially in the elderly. In Morocco, high consumption justifies awareness campaigns and safe prescribing practices.

Statements and Declarations
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