

Targeting Hyperexcitability and Oxidative Stress in Dementia: Comparative Cognition-Sparing Anti-Seizure Strategies in *Drosophila*

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KEY TAKE-AWAY In a *Drosophila* dementia-relevant model, levetiracetam (LEV) uniquely preserved memory and locomotor function across two generations, while carbamazepine (CBZ) and lamotrigine (LTG) produced severe, dose-dependent cognitive and survival impairment. LEV is the cognition-sparing choice among off-label anti-seizure medications in dementia.

INTRODUCTION

Subclinical seizures and neuronal hyperexcitability are increasingly recognised contributors to cognitive decline in Alzheimer's disease (AD) and related dementias [1, 2].

Anti-seizure medications (ASMs) are routinely prescribed off-label in this population, yet their long-term neurotoxic versus neuroprotective effects in a dementia context are poorly characterised [3].

Oxidative stress is a core pathophysiological mechanism in dementia [5]. Several ASMs are known to modulate this pathway, but in opposite directions, some exacerbate it and some mitigate it.

This work compares four commonly prescribed ASMs head-to-head on cognition, locomotion, fecundity, eclosion, and longevity in a conserved invertebrate dementia model, across two generations, to identify the cognition-sparing choice.

METHODS

Model. Wild-type *Drosophila melanogaster* (Canton-S strain). Validated for conserved neurodegenerative pathways [4].

ASMs tested. Carbamazepine (CBZ), lamotrigine (LTG), valproic acid (VPA), levetiracetam (LEV).

Exposure. Chronic feeding at **0.03, 0.3, or 3 mM**. Two generations: **F1 (parental)** and **F2 (offspring)**. n = 20 per condition.

Behavioural assays.

- Fecundity: egg count at 24 and 48 h.
- Development: adult eclosion (dark pupa to adult emergence).
- Larval motility: line crosses per minute.
- Adult locomotion: negative geotaxis, flies crossing the 8 cm mark over 7, 14, 21, 28 days.
- Longevity: number of flies alive over 28 days.
- Associative memory: T-maze Discrimination Index (%DI).

Statistics. Mean ± SEM, n = 20 per group. Two-way ANOVA (longitudinal assays) or one-way ANOVA (single-timepoint), Tukey post hoc. *p* < .05 considered significant.

RESULTS

Headline: LEV preserves memory across both generations; CBZ and LTG collapse it. CBZ at 3 mM is lethal by day 14; LEV survival matches control.

Figure 1 (A-D, F1; E-H, F2). Effect of LTG, CBZ, VPA, LEV on associative memory (T-maze, %DI). CBZ and LTG produce dose-dependent memory loss in both generations (***) *p* < .0001. LEV preserves DI across generations and shows enhancement at 3 mM in F2 (*p* < .05).

Figure 2 (A-D, F1; E-H, F2). Effect of LTG, CBZ, VPA, LEV on longevity (flies alive over 28 days). CBZ at 3 mM causes complete mortality by day 14 in F1; LTG shows dose-dependent reduction. VPA and LEV survival profiles match control across both generations.

Figure 3 (A-D, F1; E-H, F2). Adult negative geotaxis (climbing ability) over 28 days. CBZ severely impairs climbing across the dose range; LTG produces dose-dependent loss. LEV maintains climbing performance, consistent with the preserved survival profile.

Biochemistry (oxidative-stress markers)

MDA (lipid peroxidation). CBZ and LTG groups showed significantly elevated MDA relative to control, consistent with oxidative damage.

SOD (antioxidant defence). LEV at 3 mM significantly upregulated SOD activity (*p* < .05), supporting an antioxidant-mediated neuroprotective mechanism.

CONCLUSIONS

LEV is uniquely cognition-sparing. Memory (%DI), locomotion (negative geotaxis), and longevity are all preserved across F1 and F2, with memory enhancement at 3 mM in F2.

CBZ is unambiguously neurotoxic in this model. 100 % mortality at 3 mM by day 14, dose-dependent climbing collapse, and complete memory abolition (DI = 0).

LTG produces dose-dependent cognitive and motor impairment across both generations, though less catastrophic than CBZ.

VPA shows the smallest behavioural footprint, but at the cost of fecundity and development effects (see Figure 1, F1 egg count).

Cross-generational concordance. F1 and F2 trends are directionally aligned for all four ASMs, suggesting the effects are not stochastic and may carry forward to offspring.

Clinical implication. Among ASMs used off-label for hyperexcitability in dementia, **LEV is the cognition-sparing choice**. CBZ and LTG warrant caution in older adults with AD. Aligns with the LEV-AD clinical evidence [3] showing levetiracetam improves cognitive performance in AD patients with epileptiform activity.

Next steps. Direct biochemical assays of oxidative stress (MDA, SOD) in tissue homogenates, plus head-to-head comparison with brivaracetam (LEV's higher-affinity SV2A analogue).

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CLINICAL & TRANSLATIONAL IMPLICATIONS				
Off-label ASM prescribing in dementia Of the four most commonly prescribed ASMs for hyperexcitability in AD, only LEV preserves cognition. CBZ and LTG should be deprioritised in older adults with dementia-relevant pathology; clinical risk-benefit tilts decisively to LEV.		Cross-generational signal F1 and F2 trends are directionally aligned for all four drugs, suggesting effects are not stochastic and may carry forward to offspring. Relevant to chronic ASM regimens initiated in mid-life and to gametic-window safety modelling.		Oxidative-stress mechanism Elevated MDA in CBZ / LTG groups plus LEV-induced SOD upregulation at 3 mM (<i>p</i> < .05) point to an antioxidant-mediated divergence in the four ASMs' neurotoxicity profile, providing a tractable mechanistic handle for follow-up.
				Next steps (1) Tissue-homogenate MDA / SOD assays for direct biochemical confirmation. (2) Head-to-head LEV vs brivaracetam (higher-affinity SV2A analogue). (3) Pharmacogenetic interaction with APP / MAPT transgenic <i>Drosophila</i> lines.