Summary of Recent Literature

Valproic Acid in Dementia Care

Summary of Key Studies | BPSD in Long-Term Care & Terminal Agitation in Hospice/Palliative Care

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Part One: VPA for BPSD in Long-Term Care — The Evidence Against

The following six studies represent the strongest and most current evidence base addressing valproic acid for behavioral and psychological symptoms of dementia (BPSD). The findings are consistent: VPA has not demonstrated efficacy over placebo, and carries meaningful harms — including a signal of accelerated brain atrophy.

1. Carnahan & Saliba — "Anticonvulsant Use in Persons Living with Dementia: When Is It Justified?"

Journal of the American Geriatrics Society. 2023;71(1):13–15. | Editorial / Clinical Commentary

The most direct and concise clinical verdict on VPA for BPSD available in the geriatrics literature. The authors reviewed the accumulated RCT evidence summarized in the Cochrane review, highlighted brain atrophy and functional decline as likely harms, and concluded flatly that no good justification exists for using valproic acid to manage BPSD. Particularly relevant for LTC clinicians given the JAGS readership and the paired national nursing home prescribing data it accompanies. Concise enough to share with colleagues or administrators as a one-stop reference.

Link: Access via Wiley / JAGS

2. Candon et al. — "Antiepileptic Prescribing to Persons Living with Dementia in Nursing Homes: A Tale of Two Indications"

Journal of the American Geriatrics Society. 2023;71(1):89–97. | National Cohort Study

Analysis of 973,074 nursing home residents with ADRD using MDS and Medicare Part D data from 2015–2019. Antiepileptic prescribing rose from 29.5% to 31.3% over this period, driven by VPA and gabapentin, while antipsychotic prescribing fell from 32.1% to 27.9%. Residents with disruptive behavioral symptoms were 10.9 percentage points more likely to receive VPA. The authors characterize this pattern as a regulatory displacement effect — a "valproic acid-for-antipsychotic switch" — rather than evidence-driven prescribing. Provides the real-world context that explains why VPA use is rising despite uniformly negative trial data.

Link: Access via PMC (Free Full Text)

3. Benjamin et al. — "Anticonvulsants in the Treatment of Behavioral and Psychological Symptoms in Dementia: A Systematic Review"

American Journal of Geriatric Psychiatry. 2024;32(10):1177–1190. | Systematic Review

The most current and comprehensive systematic review of non-benzodiazepine anticonvulsants — including valproate preparations — for BPSD, searching five databases through January 2023. Identified 12 studies. The Cochrane review of five VPA RCTs was incorporated and concluded VPA is likely ineffective for BPSD. Additional trials of carbamazepine, oxcarbazepine, and topiramate were reviewed with similarly discouraging results. Concluded that anticonvulsants as a class are unlikely to be effective for BPSD and may carry higher adverse effect rates than comparators. Open access. Ideal as a comprehensive, citable systematic review from a high-profile geriatric psychiatry journal.

Link: Access via AJGP (Open Access)

4. Lonergan & Luxenberg — "Valproate Preparations for Agitation in Dementia" (Cochrane Review, 2018 Update)

Cochrane Database of Systematic Reviews. 2018;10:CD003945. | Systematic Review & Meta-Analysis

The foundational and most authoritative synthesis of the RCT evidence. Includes five randomized, placebo-controlled trials with 479 participants. Concluded there is no evidence of beneficial effect on agitation or closely related behavioral outcomes, and found a higher risk of adverse effects including serious adverse events compared to placebo. Specific adverse effects documented: falls, gait disturbance, sedation, tremor, weakness, depressed mood, GI disorders, urinary tract infections, and thrombocytopenia. Cited in virtually every subsequent VPA-in-dementia review and represents the evidentiary floor from which all modern clinical guidance on this topic derives. Free access via PubMed/Cochrane Library.

Link: Access via PubMed / Cochrane Library (Free)

5. Watt et al. — "Guideline Recommendations on Behavioral and Psychological Symptoms of Dementia: A Systematic Review"

Journal of the American Medical Directors Association (JAMDA). 2024;25(5):837–846. | Systematic Review of Clinical Practice Guidelines

Identified and synthesized 23 moderate-to-high quality clinical practice guidelines on BPSD published between 2011 and 2022, covering 264 recommendations. Provides the authoritative view of what international guidelines recommend for BPSD management broadly. VPA is notably absent from guideline-endorsed pharmacologic options across all included CPGs. Useful as a broader framing document establishing what is and is not recommended across the full pharmacologic landscape of BPSD — with VPA's absence from endorsed options speaking for itself. Open access.

Link: Access via JAMDA (Open Access)

6. Fleisher et al. — "Chronic Divalproex Sodium Use and Brain Atrophy in Alzheimer Disease" (ADCS Neuroimaging Substudy)

Neurology. 2011;77(13):1263–1271. | Randomized Controlled Trial Neuroimaging Substudy

The neuroimaging companion to the landmark ADCS Phase 3 trial (Tariot et al., Arch Gen Psychiatry, 2011). Documented significantly accelerated whole-brain and hippocampal volume loss on MRI in patients receiving chronic divalproex sodium compared to placebo over 24 months. This finding — structural brain injury from a drug given to protect brain function — represents the most serious long-term safety signal from the VPA-in-dementia

literature and remains the most compelling single argument against its use in a population with ongoing neurodegeneration. Free via PMC.

Link: Access via PMC (Free Full Text)

Part Two: VPA for Terminal Agitation — Possible but Unproven

The following studies address VPA in the hospice and palliative care context — specifically for refractory hyperactive delirium and terminal agitation. The evidence is of low quality (no RCTs), but the clinical rationale is different from the chronic BPSD setting and the risk-benefit calculation shifts meaningfully at end of life.

7. Fernandez Cuartas & Davis — "Valproic Acid in the Management of Delirium"

American Journal of Hospice and Palliative Medicine. 2022;39(5):562–569. | Systematic Review

The only systematic review specifically examining VPA for delirium in a palliative-relevant context. Searched literature from 1946 to January 2021; identified 10 studies involving 252 patients. No randomized controlled trial was found. Studies were predominantly retrospective ICU analyses; the mean patient age was 59.7 years — younger and less frail than the typical hospice dementia patient. A 74% response rate was observed across studies, though antipsychotics were commonly co-administered, making attribution to VPA alone uncertain. The authors note VPA's advantages over antipsychotics in this context: no QTc prolongation, no extrapyramidal effects, and multi-neurotransmitter mechanism. Concluded with a call for prospective RCTs. This is the most authoritative single source for the salvage role argument.

Link: Access via SAGE / AJHPM

8. Jacobs, Mehta & Davis — "Inpatient Use of Valproic Acid in Agitated Delirium by Palliative Medicine"

American Journal of Hospice and Palliative Medicine. Published online February 2025. | Retrospective Cohort Study

The most recent and most directly relevant study to the hospice dementia population. Twenty patients seen by palliative medicine for hyperactive delirium received VPA for at least 24 hours; median age 81.5 years; five had dementia, nine had cancer. Patients using VPA for seizures or bipolar disorder were excluded, isolating the off-label delirium indication. Notable finding: hyperammonemia was present in 6 of 20 patients (30%) — a clinically important rate that can paradoxically worsen delirium and warrants active monitoring. Authors concluded VPA may be effective for agitation in this setting but called for RCTs to validate the benefit. Small, retrospective, and not limited to dementia patients, but directly relevant to clinical decision-making in the actively dying elder.

Link: Access via SAGE / AJHPM

9. Hui et al. — "Effect of Lorazepam with Haloperidol vs Haloperidol Alone on Agitated Delirium in Patients with Advanced Cancer Receiving Palliative Care"

JAMA. 2017;318(11):1047–1056. | Randomized Clinical Trial

The most important RCT in the palliative agitation literature and the evidence base for first-line combination therapy. Enrolled 90 patients with advanced cancer and terminal delirium at an acute palliative care unit. Patients

were randomized to haloperidol plus lorazepam versus haloperidol plus placebo as rescue medication for breakthrough agitation. The addition of lorazepam significantly reduced agitation scores at 8 hours compared to haloperidol alone, with reduced need for rescue neuroleptics and improved perceived comfort ratings from both nurses and caregivers. This trial establishes haloperidol plus lorazepam as the best-evidenced combination for terminal agitated delirium — the benchmark against which any proposed salvage agent like VPA must be considered. Free via PMC.

Link: Access via PMC (Free Full Text)

Quick Reference — All Studies at a Glance

Study / Authors	Journal & Year	Type	Link
Carnahan & Saliba — VPA in dementia: When is it justified?	JAGS 2023	Editorial	agsjournals.onlinelibrary.wiley.com
Candon et al. — Antiepileptic prescribing in NH dementia residents	JAGS 2023	Cohort Study	pmc.ncbi.nlm.nih.gov/articles/PMC9870979
Benjamin et al. — Anticonvulsants for BPSD systematic review	AJGP 2024	Systematic Review	ajgponline.org — S1064-7481(24)00333-6
Lonergan & Luxenberg — Cochrane: Valproate for agitation in dementia	Cochrane 2018	Meta-Analysis	pubmed.ncbi.nlm.nih.gov/30293233
Watt et al. — BPSD guideline recommendations: systematic review	JAMDA 2024	Guideline Review	jamda.com — S1525-8610(24)00223-8
Fleisher et al. — Brain atrophy with divalproex in Alzheimer disease	Neurology 2011	RCT Substudy	pmc.ncbi.nlm.nih.gov/articles/PMC3179649
Fernandez Cuartas & Davis — VPA for delirium: systematic review	AJHPM 2022	Systematic Review	journals.sagepub.com — 10499091211038371
Jacobs, Mehta & Davis — VPA for agitated delirium in palliative medicine	AJHPM 2025	Retrospective Cohort	journals.sagepub.com — 10499091251321084
Hui et al. — Lorazepam + haloperidol for terminal agitated delirium (RCT)	JAMA 2017	RCT	pmc.ncbi.nlm.nih.gov/articles/PMC5710357

Color key: *Blue rows = BPSD / LTC evidence | Yellow rows = Palliative / hospice evidence*

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