Valproic Acid in Dementia Care

A Clinical Summary: BPSD Evidence and Terminal Agitation

Prepared for Long-Term Care and Palliative Medicine Practice

April 2026

Overview

Valproic acid (VPA) and its formulations — divalproex sodium (Depakote), sodium valproate — are FDA-approved for epilepsy, bipolar disorder, and migraine prophylaxis. Their use in dementia care is entirely off-label. This report addresses two related but clinically distinct questions: (1) whether VPA has a supported role in the management of behavioral and psychological symptoms of dementia (BPSD) in the long-term care setting, and (2) whether VPA has a defensible role in terminal agitation in the hospice and palliative care setting. The answers differ importantly.

> *Summary Finding: VPA is not supported by evidence for routine BPSD management in long-term care, and should not replace antipsychotics in this role. In hospice and palliative care, VPA may have a narrow salvage role in refractory terminal agitation when first- and second-line agents have failed — but this use is not guideline-endorsed and remains supported only by low-quality retrospective data.*

Part One: Valproic Acid for BPSD in Long-Term Care

The Clinical Problem

Behavioral and psychological symptoms of dementia (BPSD) — agitation, aggression, psychosis, disinhibition, and sleep disturbance — affect up to 90% of people with dementia at some point during their illness. No pharmacologic agent is FDA-approved for BPSD. In U.S. nursing homes, CMS regulatory initiatives have driven significant reductions in antipsychotic prescribing since 2012, creating pressure to identify alternatives. Valproic acid has increasingly

filled this vacancy — not because of new evidence supporting its efficacy, but as a medication not subject to the same regulatory scrutiny as antipsychotics.

The Evidence Base

The clinical trial evidence for VPA in BPSD is consistent across multiple systematic reviews spanning two decades and reaches a clear conclusion: VPA does not demonstrate meaningful efficacy for BPSD, and carries a burden of adverse effects that is not justified by any demonstrated benefit.

Cochrane Review (Lonergan & Luxenberg, updated 2018): Five randomized, placebo-controlled trials involving 479 participants. The review 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.

Liu et al. Meta-Analysis (Journal of Psychiatric Research, 2020): Seven RCTs involving 770 randomized patients. No significant differences were found in Mini-Mental State Examination scores, Cohen-Mansfield Agitation Inventory scores, or adverse event rates between VPA and placebo groups. The authors concluded that evidence is insufficient to support VPA for cognitive or psychiatric symptoms of dementia, and described the outlook for future trials as "not optimistic."

Benjamin et al. Systematic Review (American Journal of Geriatric Psychiatry, 2024): A comprehensive review of non-benzodiazepine anticonvulsants for BPSD through January 2023 concluded that this drug class — including valproate preparations — is unlikely to be effective in BPSD and may be associated with a higher prevalence of adverse effects than comparator treatments.

ADCS Phase 3 Trial (Tariot et al., Archives of General Psychiatry, 2011): The largest and most definitive trial of divalproex sodium in Alzheimer's disease found no attenuation of agitation or clinical progression, and — critically — a companion neuroimaging study (Fleisher et al., Neurology, 2011) documented significantly accelerated whole-brain and hippocampal volume loss in the divalproex group compared to placebo over 24 months.

> *Key Finding: Across five Cochrane-reviewed RCTs and seven meta-analyzed RCTs involving up to 770 patients, valproic acid has demonstrated no statistically or clinically significant benefit over placebo for agitation, aggression, or any other domain of BPSD. This is not a case of insufficient evidence — it is a case of consistently negative evidence.*

Safety Concerns in the LTC Population

The adverse effect profile of VPA in older adults with dementia is substantial and, in one domain, potentially irreversible:

- Sedation, somnolence, and gait disturbance — significantly more common than placebo in pooled trial data; increase fall risk in an already high-risk population
- Thrombocytopenia — clinically significant in patients on concurrent anticoagulation
- Gastrointestinal effects — nausea, vomiting, anorexia, weight loss; weight loss is particularly harmful in the frail dementia population
- Tremor — dose-dependent; easily misattributed to disease progression
- Urinary tract infections — increased frequency documented in controlled trials
- Accelerated brain atrophy — documented on MRI in the ADCS Phase 3 trial; the most serious long-term safety signal
- Valproate-induced reversible cognitive decline (VIRCD) — a recognized syndrome of gradual cognitive and processing speed decline that can occur years after VPA initiation at therapeutic levels, can be mistaken for disease progression, and is potentially reversible with discontinuation
- Drug interactions — clinically significant interactions with warfarin, aspirin, carbapenems, and CNS depressants are highly relevant in the polypharmacy-heavy LTC population

Prescribing Trends and Regulatory Context

Despite the negative evidence, VPA prescribing in nursing homes has increased. A national cohort study (Candon et al., JAGS, 2023) of 973,074 nursing home residents with ADRD from 2015–2019 found antiepileptic prescribing rose from 29.5% to 31.3%, driven specifically by VPA and gabapentin, while antipsychotic prescribing declined from 32.1% to 27.9%. Residents with disruptive behavioral symptoms were 10.9 percentage points more likely to receive VPA.

A 2025 national survey of nursing home clinicians (Winter et al., Alzheimer's & Dementia) confirmed that 97% of clinicians reported that off-label VPA use for psychiatric symptoms drove

these increases, with 85% citing regulatory pressure to reduce antipsychotics as the primary driver. This pattern has been characterized as a "valproic acid-for-antipsychotic switch" — one that experts describe as likely worse on average than the treatment it is replacing.

Part One Conclusion

> *Valproic acid should not be used for the routine management of BPSD in long-term care. The evidence base is consistently negative across multiple high-quality systematic reviews. The adverse effect profile — particularly the signal of accelerated brain atrophy and VIRCD — makes this a medication that may actively harm the patients it is intended to help. Its increasing use in nursing homes reflects regulatory displacement of antipsychotics, not therapeutic merit. When VPA is currently prescribed to a nursing home resident for behavioral indications, careful review for deprescribing, with behavioral monitoring during taper, is clinically warranted.*

Part Two: Valproic Acid in Terminal Agitation — Hospice and Palliative Care

How the Clinical Question Changes

The palliative and hospice context reframes both the clinical target and the risk-benefit analysis. The goal shifts from managing chronic behavioral symptoms in a patient with ongoing life to controlling refractory hyperactive delirium and terminal agitation in a patient whose prognosis is days to weeks, and whose sole treatment goal is comfort. This changes the calculus in two important ways: long-term harms (brain atrophy, cognitive decline, functional deterioration) become largely irrelevant, and adverse effects such as sedation may be acceptable or even desired.

The pharmacologic target also shifts from BPSD — a chronic neurobehavioral syndrome — to terminal agitation and hyperactive delirium, which are neurologically distinct entities with different underlying mechanisms and different treatment frameworks. An estimated 45% of hospice patients with end-stage dementia will experience agitation refractory to standard

treatment with lorazepam, morphine, and atypical antipsychotics — representing a substantial unmet clinical need.

First- and Second-Line Agents in Terminal Agitation

Before VPA is considered, a structured approach using established agents should be followed. The following framework reflects current consensus guidelines and the best available RCT evidence in palliative care populations:

Tier	Agent(s)	Indication / Context	Notes
First-Line	Haloperidol	Psychosis, behavioral agitation, hallucinations	0.5–2 mg SQ/IV q4–6h PRN; SC-compatible; antiemetic benefit; avoid in LBD/PD
First-Line	Midazolam	Anxiety, distress, cognitive agitation	5–10 mg/24h CSCI anxiolytic; up to 100 mg/24h for deeper sedation; SC-compatible
Second-Line	Haloperidol + Lorazepam or Midazolam	Persistent agitation despite monotherapy	Supported by Hui et al. JAMA 2017 RCT; combination superior to haloperidol alone at 8h
Third-Line	Levomepromazine / Chlorpromazine	Refractory agitation requiring deeper sedation	Levomepromazine preferred in UK/Canada; chlorpromazine is the U.S. equivalent; sedating antipsychotic
Third-Line	Phenobarbital	Antipsychotic contraindicated (LBD/PD); refractory to above	Specialist supervision recommended; respiratory depression risk at high doses
Salvage / Adjunct	Valproic Acid	Refractory hyperactive delirium; antipsychotics failed or contraindicated; comfort is sole goal	No RCT evidence; retrospective data only; monitor for hyperammonemia; rational mechanism but not guideline-endorsed

The most important RCT informing this framework is Hui et al. (JAMA, 2017), which found that adding lorazepam 3 mg to scheduled haloperidol significantly reduced agitation at 8 hours compared to haloperidol alone in patients with advanced cancer and terminal delirium — the only direct RCT evidence for combination therapy in this setting.

The Role of VPA in Terminal Agitation: What the Evidence Shows

The palliative literature on VPA for agitation/delirium is limited in quality but provides a rationale for consideration in specific refractory circumstances:

Cuartas & Davis Systematic Review (American Journal of Hospice and Palliative Medicine, 2022): Searched 1946 to January 2021; identified 10 studies involving 252 patients. No randomized controlled trial was found. Studies were predominantly retrospective ICU analyses. The mean age was 59.7 years — younger and differently ill than the typical hospice dementia population. A response rate of approximately 74% was observed across studies, though antipsychotics were commonly co-administered, making attribution to VPA alone uncertain.

Sher et al. Case Series (Journal of Neuropsychiatry and Clinical Neurosciences, 2015): Sixteen patients with management-refractory hyperactive delirium treated with adjunctive VPA; complete resolution was achieved in 13 cases. Uncontrolled, but represents the most-cited positive signal for VPA in refractory delirium.

Swayngim et al. Retrospective Cohort (Journal of Pharmacy Practice, 2024): 108 ICU patients; VPA group had 1.7 delirium- and coma-free days versus 1.9 in the control group (P = .70). No significant difference in any primary or secondary outcome. This is the best-controlled comparison available and did not favor VPA.

Jacobs, Mehta & Davis (American Journal of Hospice and Palliative Medicine, 2025/2026): 20 palliative medicine patients with hyperactive delirium treated with VPA; median age 81.5 years; five had dementia. The study is the most directly relevant to the hospice dementia population, but is small, retrospective, and unpublished in final form. Notably, hyperammonemia was present in 6 of 20 patients (30%) — a rate that warrants attention.

VPA's Comparative Advantages in the End-of-Life Context

Several pharmacologic properties make VPA more attractive at end of life than in the chronic LTC setting:

- No QTc prolongation — meaningful advantage over haloperidol and many atypical antipsychotics in patients on multiple cardiac or antifungal medications

- No extrapyramidal effects — critical for patients with Lewy body dementia, Parkinson's dementia, or known neuroleptic sensitivity
- Multi-neurotransmitter mechanism — GABA potentiation, dopaminergic modulation, serotonergic activity, and sodium channel blockade provide a mechanistic rationale distinct from antipsychotics and benzodiazepines
- Sedation as benefit — in this context, sedation is often the therapeutic goal rather than an adverse effect

Persistent Risks Even at End of Life

The changed risk-benefit context does not eliminate VPA's risks entirely. Clinicians considering VPA in terminal agitation should remain aware of:

- Hyperammonemia (30% rate in palliative cohort) — can worsen delirium and agitation, directly counteracting the therapeutic intent; ammonia level monitoring is recommended
- Drug interactions — warfarin, aspirin, carbapenems, and CNS depressants remain clinically significant; particularly important in patients on concurrent opioids or anticoagulants
- Thrombocytopenia — relevant if concurrent anticoagulation or bleeding risk exists
- Route limitations — VPA is available IV, but the IV formulation is less routinely stocked in community hospice settings than midazolam or haloperidol; oral formulations are impractical in the actively dying patient who cannot swallow

Part Two Conclusion

> *Valproic acid is not a first- or second-line agent for terminal agitation in hospice or palliative care. It is a mechanistically rational salvage consideration when established agents — haloperidol, midazolam, lorazepam, and combination therapy — have been tried and failed, or when antipsychotics are contraindicated due to extrapyramidal sensitivity (as in Lewy body or Parkinson's dementia). Its use in this context is not guideline-endorsed, not supported by RCT data, and not validated in a hospice dementia-specific population. If used, ammonia monitoring, drug interaction review, and close symptom reassessment are essential. The decision should be made within a goals-of-care framework aligned with the patient's and family's values.*

Synthesis: Two Questions, Two Answers

	BPSD in Long-Term Care	Terminal Agitation in Hospice/Palliative Care
Clinical Target	Chronic behavioral symptoms in a patient with ongoing life	Refractory hyperactive delirium; terminal restlessness in actively dying patient
Goals of Treatment	Behavioral control; functional preservation; safety	Comfort; distress relief; dignified death
VPA Efficacy Evidence	Consistently negative — 5–7 RCTs show no benefit over placebo	No RCT data; small retrospective studies show mixed/uncertain signal
Brain Atrophy Risk	Major concern — documented accelerated atrophy in 24-month trial	Largely irrelevant given prognosis of days to weeks
Sedation as Adverse Effect	Harm — reduces function, increases fall risk, masks symptoms	Often acceptable or desired — comfort is the goal
Recommended Role for VPA	None — not supported; active deprescribing should be considered	Salvage/adjunct only — after first- and second-line agents have failed or are contraindicated
Guideline Endorsement	Not endorsed (NICE, Cochrane, AJGP, JAGS)	Not endorsed; not included in any formal palliative care guideline

Key References

- 1. Lonergan E, Luxenberg J. Valproate preparations for agitation in dementia. Cochrane Database Syst Rev. 2018;10:CD003945. doi:10.1002/14651858.CD003945.pub4.
- 2. Liu X, Wang S, Tan L. Efficacy and safety of valproic acid in dementia: A systematic review with meta-analysis. J Psychiatr Res. 2020;128:107–113. doi:10.1016/j.jpsychires.2020.05.015.
- 3. Benjamin S, Ho JMW, et al. Anticonvulsants in the treatment of behavioral and psychological symptoms in dementia: A systematic review. Am J Geriatr Psychiatry. 2024;32(10):1177–1190.
- 4. Tariot PN, Schneider LS, Cummings J, et al. Chronic divalproex sodium to attenuate agitation and clinical progression of Alzheimer disease. Arch Gen Psychiatry. 2011;68(8):853–861.
- 5. Fleisher AS, Truran D, et al.; ADCS. Chronic divalproex sodium use and brain atrophy in Alzheimer disease. Neurology. 2011;77(13):1263–1271.
- 6. Candon M, Strominger J, Gerlach LB, Maust DT. Antiepileptic prescribing to persons living with dementia in nursing homes: A tale of two indications. J Am Geriatr Soc. 2023;71(1):89–97.
- 7. Carnahan RM, Saliba D. Anticonvulsant use in persons living with dementia: When is it justified? J Am Geriatr Soc. 2023;71(1):13–15.
- 8. Winter JD, Candon M, et al. A national survey of nursing home clinicians to explain increased valproate prescribing. Alzheimers Dement. 2025. doi:10.1002/alz.70421.

- 9. Patel S, et al. Valproate-induced reversible cognitive decline presenting as dementia: A literature review. Seizure. 2023;111:86–93.
- 10. Hui D, Frisbee-Hume S, Wilson A, et al. Effect of lorazepam with haloperidol vs haloperidol alone on agitated delirium in patients with advanced cancer receiving palliative care: A randomized clinical trial. JAMA. 2017;318(11):1047–1056.
- 11. Fernandez Cuartas C, Davis M. Valproic acid in the management of delirium. Am J Hosp Palliat Care. 2022;39(5):562–569.
- 12. Sher Y, Miller AC, Lolak S, et al. Adjunctive valproic acid in management-refractory hyperactive delirium: A case series and rationale. J Neuropsychiatry Clin Neurosci. 2015;27(4):365–370.
- 13. Swayngim R, Preslaski C, Dawson J. Use of valproic acid for the management of delirium and agitation in the intensive care unit. J Pharm Pract. 2024;37(1):118–122.
- 14. Jacobs S, Herbst L, Fernandez C, Mehta ZY, Young A, Davis MP. Inpatient use of valproic acid in agitated delirium by palliative medicine. Am J Hosp Palliat Care. 2025/2026. doi:10.1177/10499091251321084.
- 15. Agar MR, Lawlor PG, Quinn S, et al. Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care. JAMA Intern Med. 2017;177(1):34–42.
- 16. Biesbrouck T, De Roo ML, Smets T, Van Den Noortgate N. Pharmacological treatment for terminal agitation, delirium and anxiety in frail older patients. Geriatrics (Basel). 2024;9(2):51.