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# Epilepsy in the Aging Brain: Time to Rethink the Narrative

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**Abstract**

This article reflects key themes and discussions from the American Epilepsy Society Annual Meeting 2025, Epilepsy and Aging Special Interest Group (SIG) session entitled "Multimodal Biomarkers of Epilepsy in Older Adults." The perspectives presented here are intended to highlight emerging priorities for the field. Epilepsy in older adults is the fastest-growing segment of the epilepsy population worldwide. Despite rising incidence, prevalence, and substantial morbidity, care for late-onset epilepsy (LOE) remains anchored to a seizure-centric framework that inadequately addresses the broader consequences of seizures in later life. Older adults with LOE face markedly increased risks of dementia, mortality, and stroke, yet are frequently excluded from epilepsy and Alzheimer's disease (AD) clinical trials. Patient-centered outcomes, including cognition, sleep, function, and quality of life, remain underprioritized. In this article, we argue that LOE requires multimodal biomarkers and multidisciplinary care. We contend that LOE should be reframed as a biologically meaningful warning signal of network vulnerability and overlapping brain pathology, rather than a late-life complication to be managed pragmatically. Cognitive dysfunction is common, heterogeneous, and often precedes overt neurodegenerative diagnoses, positioning cognition as an early clinical signal. Neuroimaging and electrophysiological evidence further place LOE along a continuum intersecting cardiovascular risk factors, sleep disruption, and AD biology, challenging traditional silos between epilepsy and dementia care. We argue for greater inclusion of older adults in antiseizure medication trials and for the inclusion of individuals with epilepsy in AD clinical trials. We propose a brain-health-centered framework for LOE that integrates longitudinal electroencephalography, particularly sleep-inclusive strategies, routine cognitive screening with targeted neuropsychological assessment, neuroimaging, vascular and sleep risk evaluation, and selective use of neurodegenerative biomarkers when clinically actionable. Together, these shifts move care beyond seizure counting toward a comprehensive brain-health model aligned with the realities of aging epilepsy.

**Keywords**

epilepsy, cognition, aging, late-onset epilepsy, multimodal

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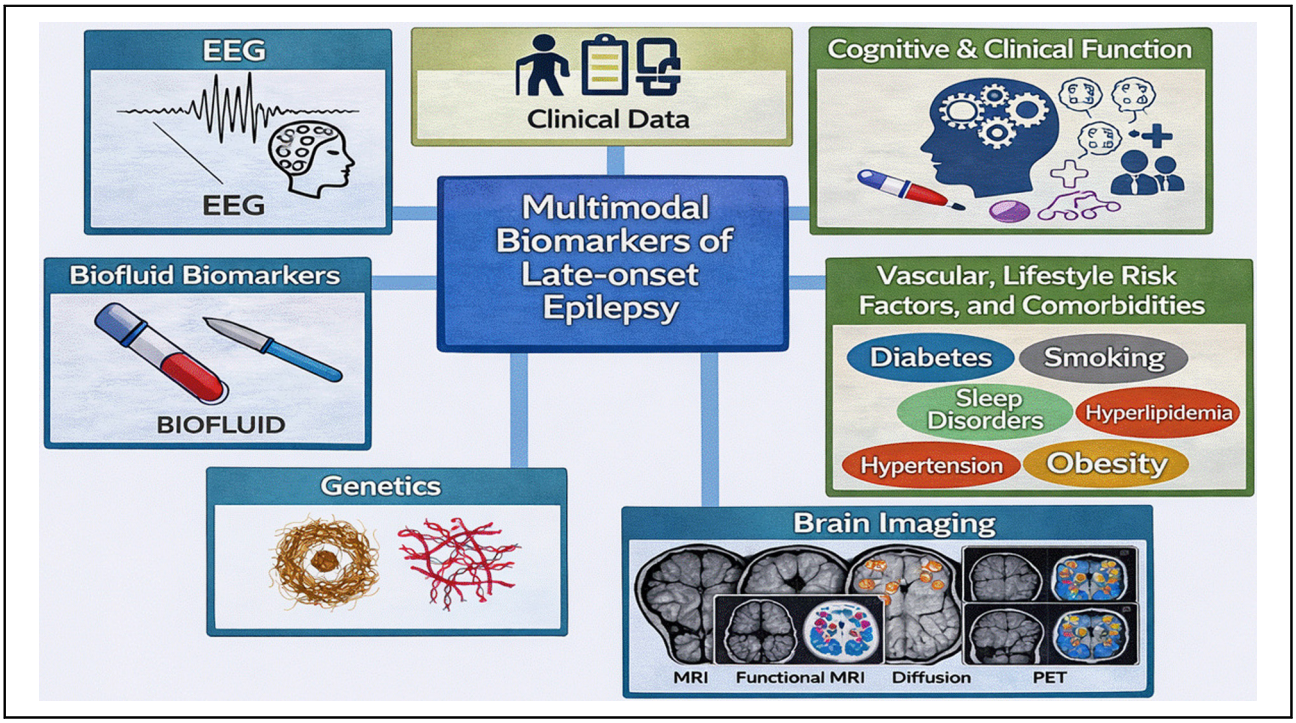


**Figure 1.** Proposed multimodal biomarker framework.

## A Provocation: Stop Treating Late-Life Epilepsy Like a Footnote

Epilepsy in older adults has become the fastest-growing epilepsy population worldwide, driven by an aging demographic, improved survival across the lifespan, and heightened recognition of late-onset epilepsy (LOE).[1] Incidence rates of epilepsy rise sharply after age 60,[1] yet the conceptual framework guiding care for these individuals remains stubbornly outdated.

Historically, seizures emerging in later life were often viewed as a clinical harbinger of inexorable decline, chronic disease, loss of independence, or institutionalization. **We now know that this view is incorrect and potentially harmful.** While LOE can confer an elevated risk for cognitive decline,[2] it also represents a *detectable inflection point*, one that offers an opportunity for recognition of network vulnerability, earlier intervention, and interdisciplinary care. The challenge for the field is to reinterpret later-onset seizures as biologically meaningful warning signals rather than endpoints.

The epidemiology alone demands urgency. Older adults with LOE face a 2- to 4-fold higher risk of subsequent dementia,[2] 1.5–3-fold higher all-cause mortality,[3–5] and an increased risk of future stroke.[6] Despite this, LOE remains strikingly understudied. Older adults are frequently excluded from status epilepticus and antiseizure medication (ASM) trials.[7,8] Patient-centered outcomes, such as sleep, function, and quality of life, are rarely prioritized in aging epilepsy research.[9] The International League Against Epilepsy task force has explicitly identified gaps in comparative evidence and emphasized the need for interdisciplinary, evidence-based diagnostic measures and care.[10] Yet clinical practice has been slow to respond.

The prevailing epilepsy care model continues to focus on seizure suppression as the dominant outcome, paying limited attention to broader neurological comorbidities. In older adults, this model fails outright, as in this population, seizures are often *not* the dominant determinant of disability.[9] Cognitive impairment, frailty, falls, sleep disruption, depression, polypharmacy, and loss of independence frequently generate more morbidity than the seizures themselves.[5,11] Yet epilepsy care continues to behave as if nonseizure outcomes are secondary considerations.

In clinical practice, LOE is rarely an isolated diagnosis. It is a *syndrome* unfolding at the intersection of network hyperexcitability, vascular injury, sleep disruption, medication vulnerability, and neurodegenerative biology.[12] Therefore, the fastest-growing epilepsy demographic demands a new framework.

In this perspective article, based on the *Epilepsy and Aging Special Interest Group* (SIG) *at the* 2025 AES Annual Meeting, we argue that LOE requires interdisciplinary care,[9] and multimodal biomarkers (Figure 1), and for clinical trials to stop excluding the very patients we most need to understand.

## Cognitive Dysfunction in LOE is not Noise; It's the Signal

If LOE is a warning signal, cognition is where it becomes clinically visible first.

One of the most persistent conceptual errors in epilepsy care is treating cognition as a uniform byproduct of seizure burden. In LOE, cognitive dysfunction is more common than not,

affecting nearly two-thirds of individuals and often resembling mild cognitive impairment (MCI).[13] Earlier work consistently demonstrated that older adults with epilepsy perform less well than age-matched controls on global cognition, episodic memory, and semantic fluency.[14] More recent studies have moved beyond treating LOE as a homogeneous entity by distinguishing LOE from early-onset epilepsy (EOE) and identifying distinct cognitive phenotypes within LOE itself.[15,16]

Cognitive impairment in LOE ranges from minimal to isolated single-domain deficits or multidomain impairment.[15] Among those with isolated deficits, executive function and processing speed impairment emerge as the most common phenotypes,[15] cognitive domains are typically associated with widespread vascular brain pathology.

A clinical dilemma is what cognitive impairment *means* in a given patient, and what to do about it? Cognitive dysfunction may reflect epileptic network instability, sleep disruption, vascular injury, emerging neurodegeneration, ASM effects, or combinations thereof.

This question naturally leads to others: should we routinely screen for cognitive deficits in LOE, and, if so, how? Recent multicenter validation of the Montreal Cognitive Assessment (MoCA) as a screening tool in older adults with epilepsy has shown the potential to reshape cognitive assessment, shifting cognitive screening from an ad hoc practice to an evidence-based gateway for targeted comprehensive neuropsychological referral.[17] Routine screening is a low-cost, high-yield intervention for LOE. We recommend MoCA (or equivalent) screening for all older adults with epilepsy, with referral for comprehensive neuropsychological evaluation when scores fall below the relevant threshold (24 out of 30 for MoCA) or when clinical concern persists despite "normal" screening. Similarly, electroencephalography (EEG) screening may be important for individuals with minimal cognitive impairment or early dementia, especially in those who may have fluctuating mental status.

## Seizures Leave Fingerprints: Neuroimaging Signatures of LOE

If cognitive heterogeneity in LOE is biologically meaningful, it should leave distinct structural fingerprints. Neuroimaging confirms that it may do exactly that. Alterations include widespread cortical thinning, predominantly involving the frontotemporal regions.[18] Kaestner et al[19] demonstrated that atrophy patterns in temporal-onset LOE closely resemble those seen in amnestic MCI, with bilateral cortical thinning in mesial temporal structures, particularly the hippocampus and amygdala. LOE had a thinner bilateral entorhinal cortex and fusiform cortex compared to amnestic MCI and a thinner bilateral fusiform cortex compared to EOE.[19] These differences underscore that LOE is a distinct biological entity.

Vascular injury is a critical mechanistic contributor. LOE is associated with a **higher burden of white matter hyperintensities**, reinforcing vascular pathology as both a risk factor and a disease modifier.[20] Epidemiologic data linking cerebrovascular disease to LOE incidence further support that vascular burden is foundational, not incidental.[21] Diffusion magnetic resonance imaging (MRI) adds another layer, demonstrating widespread white matter abnormalities with reduced fractional anisotropy and increased mean diffusivity across major tracts.[18] These findings implicate disrupted network connectivity rather than focal epileptogenic pathology.

Functional imaging suggests partial overlap with neurodegenerative syndromes. Fluorodeoxyglucose–positron emission tomography (PET) studies show hypometabolism in temporal and frontal regions similar to Alzheimer's disease (AD), while differing patterns in parieto-occipital regions hint at overlapping but nonidentical pathophysiology.[22] A subset of LOE demonstrates **amyloid and tau PET positivity**,[23] positioning LOE within a biological gray zone between epilepsy and neurodegeneration.

Taken together, neuroimaging reframes LOE as a ***multimodal brain aging syndrome***, marked by cortical thinning, white matter disruption, and vascular injury. Ignoring these signals diminishes epilepsy care, while recognizing them opens the door to earlier risk stratification, interdisciplinary intervention, and a brain-health-centered model of care.

## The Continuum Problem: Epilepsy and AD Share a Highway, not Crossroads

Epilepsy and dementia do not merely coexist; in many older adults, they appear to share many basic pathologic mechanisms. Late-onset unexplained epilepsy is associated with an increased risk of AD.[24] Midlife plasma Amyloid-deta42/40 ratios predict later development of LOE.[25] Yet, epilepsy has remained largely siloed from dementia research, despite mounting epidemiologic and mechanistic evidence demonstrating a bidirectional relationship.[26] For decades, epilepsy and dementia were treated as separate entities that occasionally collide. That framing is now collapsing under the weight of evidence.[2,25,27]

*Epileptic activity in AD is often silent and clinically consequential*. Up to 64% of individuals with AD experience seizures,[28] and up to 54% demonstrate subclinical epileptiform activity,[29] rates far exceeding those of cognitively normal peers. The landmark clinical description of seizures and epileptiform activity in early AD emphasized a critical point: this activity is often **underrecognized**, frequently nonconvulsive, and plausibly detrimental.[30]

Despite extended and sleep EEG recordings, epileptiform activity is detected in only a subset of patients using current non-invasive approaches, underscoring the need for more sensitive EEG biomarkers such as high-frequency oscillations (HFOs),[31] which may capture network hyperexcitability missed by standard scalp EEG.[32] Recent work in animal models suggests that HFOs may modulate interictal spiking in AD, highlighting their potential value for patient stratification.[33]

Also, subclinical epileptiform activity is not simply an epiphenomenon. Longitudinal EEG studies show faster cognitive decline in individuals with AD who exhibit epileptiform activity.[34,35] More importantly, emerging evidence suggests this

hyperexcitability may represent a modifiable contributor to disease progression.[35]

The field needs to consider carefully what this implies: in a nontrivial subset of older adults, LOE may be an early clinical signal of neurodegenerative vulnerability rather than a mere downstream consequence. Given that neurodegenerative processes begin decades before overt cognitive impairment, the concept of an epileptic variant of AD, epilepsy starting during preclinical AD, warrants mainstream attention.[36]

Once epilepsy and neurodegeneration are placed on the same continuum, the remaining question is no longer *whether* they interact, but *how*.

## Network Amplifier Hypothesis: Epilepsy Does not Just Coexist With Neurodegeneration; it may Precede or Accelerate it

The most provocative implication of this continuum is that epileptic activity does not merely reflect underlying AD pathology but actively participates in its clinical expression and may accelerate it.[37–40]

Preclinical studies support a causal role for hyperexcitability. In mouse models of amyloid pathology, clusters of hyperactive neurons emerge near amyloid plaques, reflecting a localized excitatory–inhibitory imbalance.[41] Suppression of abnormal spike activity with levetiracetam (LEV) improves network function and reverses cognitive deficits in these models.[42]

Seizures can induce neuronal stress, excitotoxicity, and tau hyperphosphorylation.[26] Repeated seizures can upregulate kinases involved in tau phosphorylation, thereby accelerating neurofibrillary tangle formation.[43] Evidence also suggests a bidirectional relationship: seizures promote tau release, tau promotes seizures, and tau reduction decreases seizure burden.[26,38,39,41,42]

Human data echo these findings. A large postmortem study demonstrated that ongoing seizures before death were associated with worse AD pathology in AD and increased AD copathology in non-AD dementias.[12] Similarly, Gourmaud et al[39] found worse AD pathology in AD individuals with seizures compared to those without seizures. These findings suggest that **reducing hyperactivity can improve memory in humans**. To further support that possibility, in a randomized controlled trial, LEV improved executive function and spatial memory in AD individuals with epileptiform activity.[44]

Interestingly, epilepsy accelerates brain aging even in the absence of AD.[45] The implication is disruptive: network hyperexcitability may be a therapeutic target for cognition, not merely for seizures.

So let us now connect the dots: if LOE shows cognitive vulnerability and if hyperexcitability interacts with AD pathology, then epilepsy clinics may contain one of neurology's most actionable windows for early dementia intervention and risk stratification.

Yet we continue to underuse the simplest of biomarkers.

## EEG Early and Often: The Simplest Biomarker That We Underuse

We treat blood pressure as a longitudinal biomarker, yet treat EEG like a one-time formality. Epileptiform discharges in LOE and AD are frequently sleep-potentiated. Routine wake EEG can, therefore, miss such activity.[29,30,46] This creates a self-fulfilling cycle of undertesting, underdetection, and undertreatment.

The solution is not exotic; **it's operational**, where feasible, sleep-inclusive EEG strategies should be normalized (ambulatory, overnight, or targeted prolonged/serial recordings) in LOE and older adults with cognitive fluctuation, unexplained confusion, or paroxysmal symptoms. There are emerging, portable EEG devices that could be potentially used for first-level screening by non-neurologists.[47] EEG acquisition should also be improved. Higher sampling rates and wider bandwidths[32] may reveal pathological activity outside the traditional Berger frequency range, as with HFOs, raising the possibility that disease-relevant hyperexcitability is systematically being missed, in part because suboptimal record windows are used. These changes would move EEG from a diagnostic stamp to a longitudinal, functional biomarker of network vulnerability.

## Sleep is not Just a Brain State but a Driver of Comorbidity

Sleep is not a bystander. Individuals with LOE live at the intersection of sleep disruption and hyperexcitability. Sleep fragmentation, obstructive sleep apnea, medication sedation, and circadian disruption can worsen seizures, degrade cognition, increase falls, and amplifies caregiver burden.[11,46] Sleep is tightly linked to amyloid, tau, vascular health, and cognition.[46,48] Sleep can influence both seizure risk and cognition. A LOE clinic, therefore, needs a sleep pathway that includes screening for sleep disorders, measuring sleep quality, and treating sleep disorders as disease modifiers.

## The Vascular Trap: You Can't Talk About Brain Aging Without Talking About Vessels

Vascular disease is not a confounder; it is a substrate. Hypertension, diabetes, smoking, stroke, and white matter hyperintensities are risk factors for LOE and impact outcomes.[20,21] Modifiable cardiovascular risks magnify dementia risk in epilepsy several-fold.[49] If cardiovascular risks amplify the risk of epilepsy and further amplify the risk of dementia in epilepsy, then the epilepsy clinic becomes a critical site for vascular prevention strategy and coordination. This is where interdisciplinary care must be deployed. Epileptologists should not, for example, manage hypertension by themselves, but epilepsy care should *integrate* vascular risk management as part of a better brain-health strategy.

## Polypharmacy: The Invisible Iatrogenic Epidemic in Aging Epilepsy

Older adults rarely arrive with epilepsy alone. They potentially arrive with multiple comorbidities, long medication lists, and a unique risk profile: polypharmacy, drug–drug interactions, renal dosing complexity, sedative burden, and heightened fall risk.[11] Cognitive and gait decline are partly medication-mediated, yet medication review in epilepsy clinics frequently stops at ASM selection. Anticholinergic burden matters, sedating agents accumulate harm over time, and seemingly "benign" adverse effects such as hyponatremia and impaired bone health carry outsized consequences in older adults. Even "stable" regimens may quietly erode cognition, balance, and gait, with cumulative effects that only become apparent once functional decline has started to manifest.

As such, epilepsy care in older adults should routinely assess gait and balance, fall history, bone health, visual and visuospatial function, and real-world functional safety. Medication reconciliation should extend beyond ASMs, ideally in partnership with gerontology and pharmacy teams.

## Multimodal Biomarkers: The Biology is Integrated, but Clinics are not

Aging epilepsy increasingly demands multimodal characterization. (1) EEG can provide critical insight into network hyperexcitability, and with particular benefit from sleep recording, to capture sleep-potentiated epileptiform discharges. (2) Neuropsychological assessment clarifies domain-specific vulnerability and real-world functional impact. (3) MRI may reveal hippocampal vulnerability, vascular burden, patterns of cortical atrophy, and white-matter disease that shape both seizure risk and cognitive trajectory. (4) Sleep assessment could identify modifiable drivers. (5) Vascular risk assessment targets prevention. (6) Finally, where clinically relevant and actionable, fluid biomarkers might further refine risk stratification, as amyloid-β, tau, and neurodegeneration constructs (AT[N]) increasingly define AD biologically.[50] Together, these modalities will move LOE care toward a brain-health framework that recognizes epilepsy as a multidimensional disorder unfolding across electrical, structural, cognitive, functional, and molecular domains.

Not every patient needs every test. But the care of each person with LOE should be designed to detect, stage, and respond to comorbidities and disease overlap, not simply suppress seizures.

## The Clinical Trial Paradox: Parallel Exclusions, Shared Consequences

Despite established links between epilepsy and AD, AD trials routinely exclude individuals with epilepsy. Excluding these people limits generalizability and prevents understanding how disease-modifying therapies for AD interact with seizure disorders. Also, medications that may be helpful for people with AD and epileptiform activity will not reach the market, as the Phase II trials will not demonstrate benefit. Therefore, AD trials should include people with seizures, incorporate EEG phenotyping (even in subsets), and treat seizures/hyperexcitability as stratification variables rather than automatic exclusions. Similarly, the epilepsy field should prioritize trials of novel ASMs in older persons with cognitive endpoints, functional metrics, safety, and mortality outcomes.

## Global Reality Check: Scalability, Equity, and Cultural Validity

The global burden of LOE is rising most quickly in settings where access to neuropsychology, prolonged EEG, advanced imaging, and biomarker testing is more limited. This is where the field must avoid hypocrisy: it cannot call these tests "essential" while proposing tools and workflows that only wealthier health systems can implement. A global-facing agenda should prioritize scalable and culturally validated approaches, contextualized tools and translations, practical EEG strategies such as portable EEG devices that can be applied by nonspecialized ancillary personnel, and interdisciplinary models that can be deployed with telehealth and task-sharing. A pragmatic biomarker framework for aging epilepsy must acknowledge and accommodate variability in access and capacity. The goal is **tiered realism:** matching biological insight to clinical context, resources, and actionability while always building capacity and improving care sustainably.

### *Tier 1: What Every Epilepsy Clinic Can Do*

- Structured cognitive screening with domain awareness (it may not just be memory).
- Depression and anxiety assessment.
- Sleep screening.
- Fall risk evaluation.
- Medication burden review.
- Cardiovascular risk factor assessment.

These measures alone can identify individuals at high risk for cognitive decline, injury, and loss of independence. Crucially, they shift epilepsy visits from seizure-centric to brain-centric and quality-of-life-centric.

### *Tier 2: Network Vulnerability Assessment*

Here, EEG becomes the workhorse. Targeted EEG, especially with sleep inclusion, can identify subclinical epileptiform activity in those with cognitive fluctuation, unexplained confusion, or late-onset seizures without a clear structural cause. Ambulatory and overnight EEGs are increasingly feasible outside tertiary centers and can be deployed selectively rather than universally. Brain imaging, ideally MRI with attention to vascular burden and medial temporal integrity, should be standard in LOE, not merely to exclude lesions.

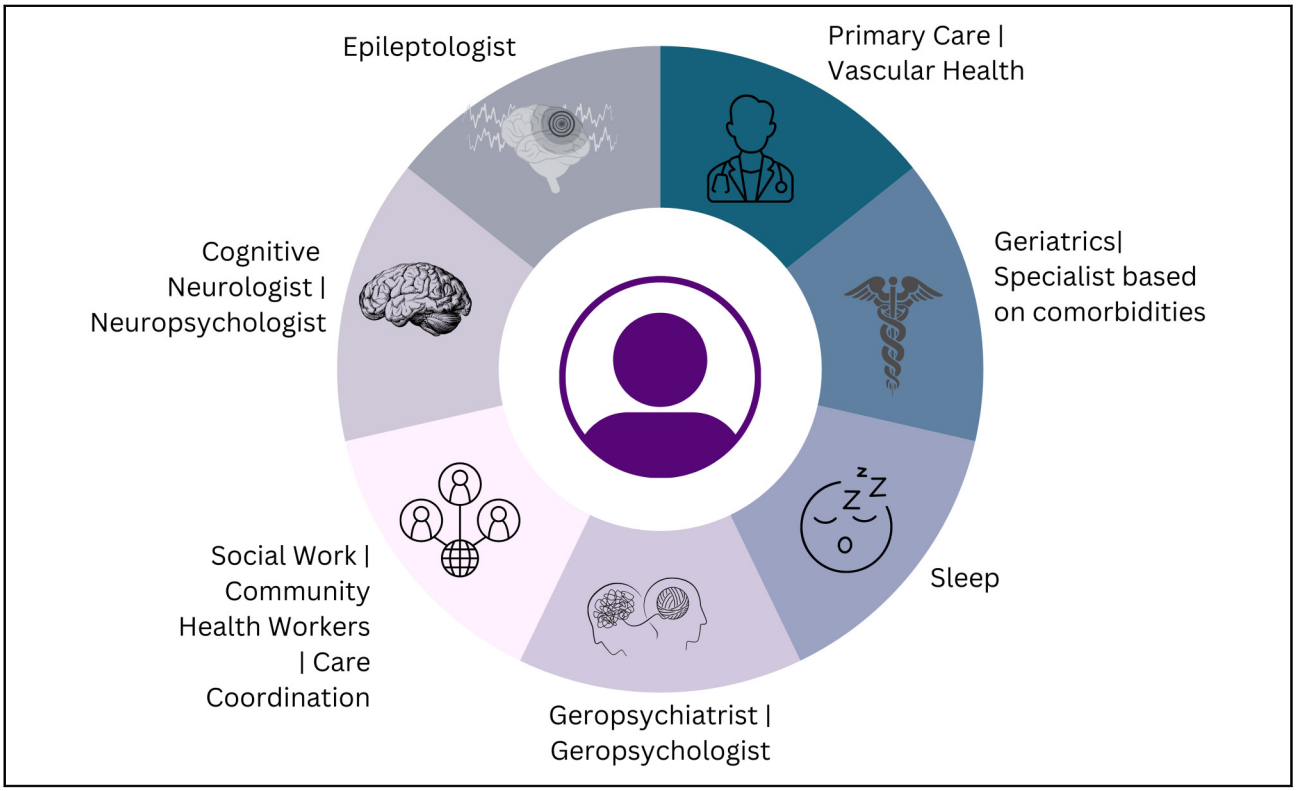


**Figure 2.** Proposed patient-centered interdisciplinary care for epilepsy in older adults.

If cognitive screening identifies deficits or if individuals develop cognitive difficulties over time, a referral for a comprehensive neuropsychological evaluation is appropriate. If a neurodegenerative disorder is suspected, work closely with a cognitive neurologist for appropriate work-up and treatment strategies.

### *Tier 3: Neurodegenerative Biomarkers*

Fluid biomarkers and PET imaging should be reserved for situations in which results change management, such as counseling about prognosis, eligibility for disease-modifying trials, anticipatory planning, or reframing the etiology.

Biomarker deployment must be realistic. Blood-based biomarkers hold particular promise for scaling neurodegenerative assessment beyond tertiary centers, but only if interpreted within a clinical and electrophysiological framework rather than as stand-alone diagnostics.

## Interdisciplinary Care is not Optional

It is high time that aging-epilepsy clinics integrate epileptology, cognitive neurology, neuropsychology, sleep medicine, geriatrics, psychiatry, and social care, with the patient at the center of this multidisciplinary approach (Figure 2). A staged care pathway is feasible and scalable.

## Where do we go From Here?

LOE is not simply a late-life complication that can be managed pragmatically with ASMs. Seizure control remains essential, but it is not the whole mission.

We argue for 5 shifts (Figure 3):

1. **From seizure counting to brain-health accounting.** (A) Cognition screening, comprehensive neuropsychological assessment, and phenotyping when feasible. (B) Screening, treating, and measuring sleep as a disease modifier. (C) Functional, quality of life, and safety assessment.
2. Using EEG and MRI with sleep-inclusive EEG strategies, wideband EEG, and high-resolution imaging.
3. From siloed clinics to interdisciplinary care (epileptology + cognitive neurology + sleep + geriatrics + neuropsychology + cardiovascular health).
4. **From treating vascular risk as brain-health care** embedded within epilepsy care, not outsourced as "someone else's problem," and
5. from exclusionary trials to real-world-based trials.

Without these shifts, we will keep failing the fastest-growing epilepsy population.

LOE is not a side plot. It is the main story. The only question is whether we are now willing to place it center stage

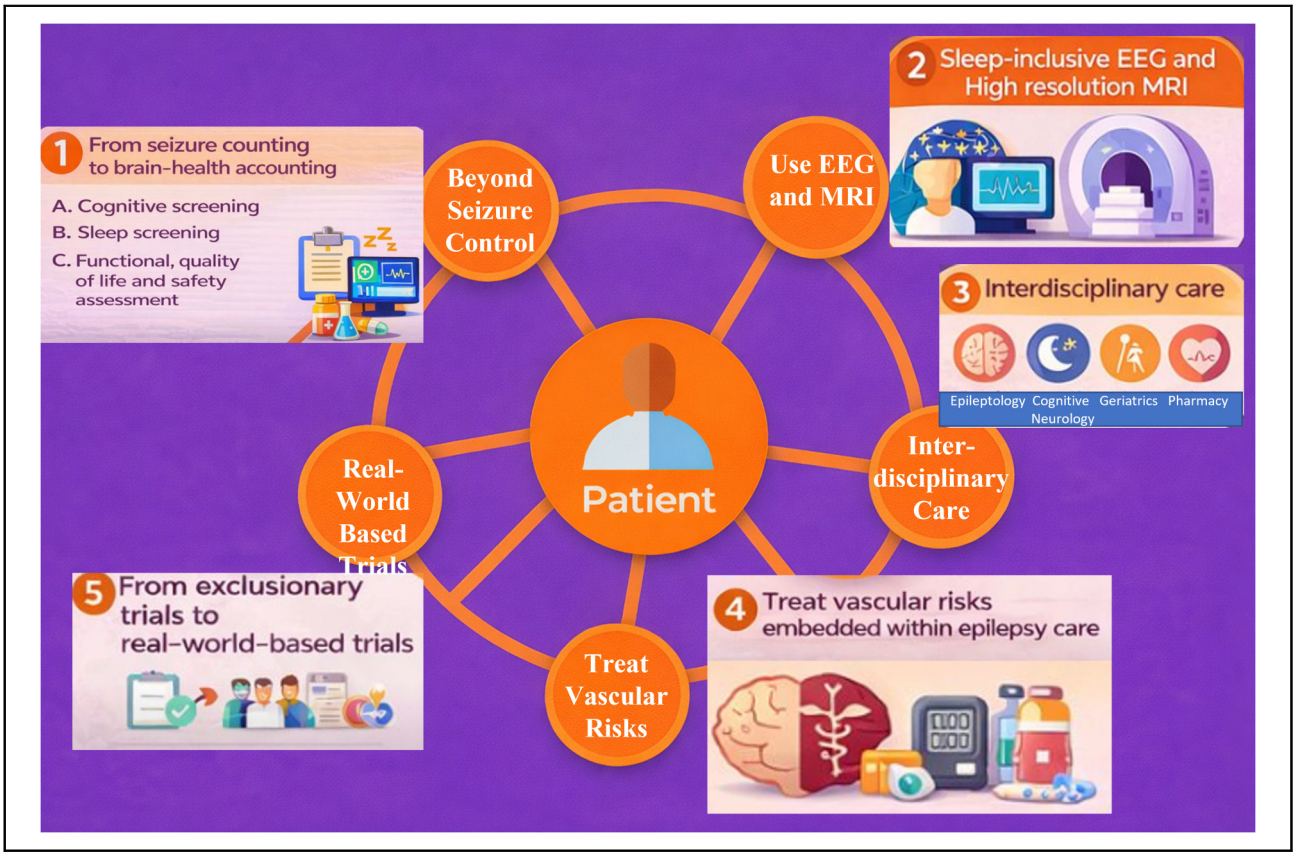


**Figure 3.** Proposed shifts in the care of older adults with epilepsy.

and make actionable changes to improve the care for those with late-life seizures.

## Declaration of Conflicting Interests

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## References

1. Sen A, Jette N, Husain M, Sander JW. Epilepsy in older people. *Lancet*. 2020;395(10225):735–748. doi:10.1016/S0140-6736(19)33064-8
2. Zawar I, Kapur J, Mattos MK, Aldridge CM, Manning C, Quigg M. Association of seizure control with cognition in people with normal cognition and mild cognitive impairment. *Neurology*. 2024;103(6):e209820-1–e209820-10. doi:10.1212/WNL.0000000000209820
3. Zawar I, Quigg M, Ghosal S, et al. Association of seizure control with mortality, cognition, and function in people with dementia. *Ann Neurol*. 2025;97(2):358–368. doi:10.1002/ANA.27125
4. Johnson EL, Krauss GL, Kucharska-Newton A, Lam AD, Sarkis R, Gottesman RF. Mortality in patients with late-onset epilepsy: results

from the Atherosclerosis Risk in Communities study. *Neurology*. 2021;97(11):E1132–E1140. doi:10.1212/WNL.0000000000012483
5. Hashmi SA, Gundlapalli R, Zawar I. Mortality in older adults with epilepsy: an understudied entity. *Epilepsia Open*. 2025;10(1):15–30. doi:10.1002/EPI4.13098
6. Wall J, Knight J, Emsley HCA. Late-onset epilepsy predicts stroke: systematic review and meta-analysis. *Epilepsy Behav*. 2021;(115):1–6. doi:10.1016/j.yebeh.2020.107634
7. Desmarais P, Miville C, Milán-Tomás Á, et al. Age representation in antiepileptic drug trials: a systematic review and meta-analysis. *Epilepsy Res*. 2018;142(2018):9–15. doi:10.1016/j.eplepsyres.2018.03.005
8. Woodward MR, Armahizer MJ, Wang TI, Badjatia N, Johnson EL, Gilmore EJ. Status epilepticus in older adults: a critical review. *Epilepsia*. 2025;66(9):3118–3137. doi:10.1111/EPI.18453
9. Eberhart T, Kämmer J, Ellßel C, Flemming D, Pelizäus H. Problems and needs in everyday life of people with late-onset epilepsy: a scoping review categorization using the international classification of functioning, disability and health (ICF). *Seizure: Eur J Epilepsy*. 2025;129(2025):88–107. doi:10.1016/J.SEIZURE.2025.04.009
10. Piccenna L, O'Dwyer R, Leppik I, et al. Management of epilepsy in older adults: A critical review by the ILAE Task Force on Epilepsy in the Elderly. *Epilepsia*. 2023;64(3):567–585. doi:10.1111/EPI.17426
11. Hashmi SA, Sachdeva S, Sindhu U, et al. The implications of frailty in older adults with epilepsy. *Epilepsia Open*. 2024;9(6):2128–2143. doi:10.1002/EPI4.13046
12. Zawar I, Luniewski A, Gundlapalli R, et al. The association of seizure control with neuropathology in dementia. *Brain*. 2025;148(7):2469–2480. doi:10.1093/BRAIN/AWAF017
13. Zawar I, Reyes A, Arrotta K, et al. Analysis of practical judgment in older adults with epilepsy: An exploratory, multicenter cohort study. *Epilepsia*. 2025;66(2):21–28. doi:10.1111/epi.18228
14. Martin RC, Griffith HR, Faught E, Gilliam F, Mackey M, Vogtle L. Cognitive functioning in community dwelling older adults with chronic partial epilepsy. *Epilepsia*. 2005;46(2):298–303. doi:10.1111/J.0013-9580.2005.02104.X
15. Reyes A, Schneider ALC, Kucharska-Newton AM, Gottesman RF, Johnson EL, McDonald CR. Cognitive phenotypes in late-onset epilepsy: Results from the Atherosclerosis Risk in Communities study. *Front Neurol*. 2023;14:1–15 ecollection. doi:10.3389/FNEUR.2023.1230368
16. Reyes A, Kaestner E, Edmonds EC, et al. Diagnosing cognitive disorders in older adults with epilepsy. *Epilepsia*. 2021;62(2):460–471. doi:10.1111/EPI.16780
17. Reyes A, Hermann BP, Prabhakaran D, et al. Validity of the MoCA as a cognitive screening tool in epilepsy: Are there implications for global care and research? *Epilepsia Open*. 2024;9(4):1526–1537. doi:10.1002/EPI4.12991
18. Gugger JJ, Walter AE, Diaz-Arrastia R, et al. Association between structural brain MRI abnormalities and epilepsy in older adults. *Ann Clin Transl Neurol*. 2024;11(2):342–354. doi:10.1002/ACN3.51955
19. Kaestner E, Reyes A, Chen A, et al. Atrophy and cognitive profiles in older adults with temporal lobe epilepsy are similar to mild cognitive impairment. *Brain*. 2021;144(1):236–250. doi:10.1093/BRAIN/AWAA397
20. Johnson EL, Krauss GL, Lee AK, et al. Association between white matter hyperintensities, cortical volumes, and late-onset epilepsy. *Neurology*. 2019;92(9):E988–E995. doi:10.1212/WNL.0000000000007010
21. Johnson EL, Krauss GL, Lee AK, et al. Association between midlife risk factors and late-onset epilepsy: results from the Atherosclerosis Risk in Communities study. *JAMA Neurol*. 2018;75(11):1375–1382. doi:10.1001/JAMANEUROL.2018.1935
22. Zhang X, Ahmed R, Thayer Z, et al. Late-onset epilepsy with cognitive symptoms: comparison of cognitive and imaging profiles with probable Alzheimer's disease. *Epilepsy Behav*. 2023;146:1–12. doi:10.1016/j.yebeh.2023.109371
23. Sarkis RA, Gale SA, Yang HS, et al. Utility of amyloid positron emission tomography imaging in older adults with epilepsy andcognitive decline. *Am J Alzheimers Dis Other Demen*. 2023;38:1–9. doi:10.1177/15333175231160005;REQUESTEDJOURNAL:JOURNAL:AJAE;WEBSITE:WEBSITE:SAGE;ISSUE:ISSUE:DOI
24. Lam AD, Johnson EL, Sarkis RA, et al. Late-onset unexplained epilepsy as a risk factor for cognitive impairment and dementia: protocol for a multi-center prospective longitudinal observational study (ELUCID). *Epilepsia Open*. Published online November 29, 2025:1–13. doi:10.1002/EPI4.70184
25. Johnson EL, Sullivan KJ, Schneider ALC, et al. Association of plasma Aβ42/Aβ40 ratio and late-onset epilepsy: results from the Atherosclerosis Risk in Communities study. *Neurology*. 2023;101(13):E1319–E1327. doi:10.1212/WNL.0000000000207635/SUPPL_FILE/SUPPLEMENTARY_TABLE1.PDF
26. Zawar I, Kapur J. Does Alzheimer's disease with mesial temporal lobe epilepsy represent a distinct disease subtype? *Alzheimers Dement*. 2023;19(6):2697–2706. doi:10.1002/ALZ.12943
27. Johnson EL, Krauss GL, Kucharska-Newton A, et al. Dementia in late-onset epilepsy: The atherosclerosis risk in communities study. *Neurology*. 2020;95(24):e3248–e3256. doi:10.1212/WNL.0000000000011080
28. Scarmeas N, Honig LS, Choi H, et al. Seizures in Alzheimer's disease: who, when, and how common? *Arch Neurol*. 2009;66(8):992–997. doi:10.1001/ARCHNEUROL.2009.130
29. Horváth A, Szucs A, Hidasi Z, Csukly G, Barcs G, Kamondi A. Prevalence, semiology, and risk factors of epilepsy in Alzheimer's disease: An ambulatory EEG study. *J Alzheimers Dis*. 2018;63(3):1045–1054. doi:10.3233/JAD-170925
30. Vossel KA, Beagle AJ, Rabinovici GD, et al. Seizures and epileptiform activity in the early stages of Alzheimer disease. *JAMA Neurol*. 2013;70(9):1158–1166. doi:10.1001/jamaneurol.2013.136
31. Lisgaras CP, Scharfman HE. High-frequency oscillations (250–500Hz) in animal models of Alzheimer's disease and two animal models of epilepsy. *Epilepsia*. 2023;64(1):231–246. doi:10.1111/EPI.17462
32. Lisgaras CP, Giménez S, Carmona-Iragui M, et al. High-frequency oscillations >250Hz in people with Down syndrome and associated Alzheimer's disease dementia. *Alzheimers Dement*. 2025;21(7):1–19. doi:10.1002/ALZ.70386
33. Lisgaras CP, Scharfman HE. Opposing interictal dynamics in Alzheimer's disease and epilepsy. *Prog Neurobiol*. 2026;256:1–12. doi:10.1016/j.pneurobio.2025.102844
34. Vossel KA, Ranasinghe KG, Beagle AJ, et al. Incidence and impact of subclinical epileptiform activity in Alzheimer's disease. *Ann Neurol*. 2016;80(6):858–870. doi:10.1002/ANA.24794
35. Horvath AA, Papp A, Zsuffa J, et al. Subclinical epileptiform activity accelerates the progression of Alzheimer's disease: a long-term EEG study. *Clin Neurophysiol*. 2021;132(8):1982–1989. doi:10.1016/J.CLINPH.2021.03.050

36. Zawar I, Kapur J. Seizing the link: Exploring the potential association between anti-seizure medications and Alzheimer's disease. *J Alzheimers Dis*. 2025;106(3):917–919. doi:10.1177/13872877251350291
37. Gourmaud S, Stewart DA, Irwin DJ, et al. The role of mTORC1 activation in seizure-induced exacerbation of Alzheimer's disease. *Brain*. 2022;145(1):324–339. doi:10.1093/BRAIN/AWAB268
38. Barbour AJ, Hoag K, Cornblath EJ, et al. Hyperactive neuronal networks enhance tau spread in an Alzheimer's disease mouse model. *bioRxiv*. 2024:2024.12.01.625514. doi:10.1101/2024.12.01.625514
39. Gourmaud S, Shou H, Irwin DJ, et al. Alzheimer-like amyloid and tau alterations associated with cognitive deficit in temporal lobe epilepsy. *Brain*. 2020;143(1):191–209. doi:10.1093/BRAIN/AWZ381
40. Barbour AJ, Gourmaud S, Lancaster E, et al. Seizures exacerbate excitatory: inhibitory imbalance in Alzheimer's disease and 5XFAD mice. *Brain*. 2024;147(6):2169–2184. doi:10.1093/BRAIN/AWAE126
41. Busche MA, Eichhoff G, Adelsberger H, et al. Clusters of hyperactive neurons near amyloid plaques in a mouse model of Alzheimer's disease. *Science*. 2008;321(5896):1686–1689. doi:10.1126/SCIENCE.1162844
42. Sanchez PE, Zhu L, Verret L, et al. Levetiracetam suppresses neuronal network dysfunction and reverses synaptic and cognitive deficits in an Alzheimer's disease model. *Proc Natl Acad Sci USA*. 2012;109(42):E2895–E2903. doi:10.1073/PNAS.1121081109
43. Alves M, Kenny A, de Leo G, Beamer EH, Engel T. Tau phosphorylation in a mouse model of temporal lobe epilepsy. *Front Aging Neurosci*. 2019;11(308):490080. doi:10.3389/FNAGI.2019.00308/BIBTEX
44. Vossel K, Ranasinghe KG, Beagle AJ, et al. Effect of levetiracetam on cognition in patients with Alzheimer disease with and without epileptiform activity: A randomized clinical trial. *JAMA Neurol*. 2021;78(11):1345–1354. doi:10.1001/jamaneurol.2021.3310
45. Hwang G, Hermann B, Nair VA, et al. Brain aging in temporal lobe epilepsy: Chronological, structural, and functional. *Neuroimage Clin*. 2020;2020(25):1–9. doi:10.1016/j.nicl.2020.102183
46. Moore JL, Carvalho DZ, St Louis EK, Bazil C. Sleep and epilepsy: A focused review of pathophysiology, clinical syndromes, co-morbidities, and therapy. *Neurotherapeutics*. 2021;18(1):170–180. doi:10.1007/S13311-021-01021-W
47. Biondi A, Santoro V, Viana PF, et al. Noninvasive mobile EEG as a tool for seizure monitoring and management: a systematic review. *Epilepsia*. 2022;63(5):1041–1063. doi:10.1111/EPI.17220
48. Rosenzweig I, Glasser M, Polsek D, Leschziner GD, Williams SCR, Morrell MJ. Sleep apnoea and the brain: a complex relationship. *Lancet Respir Med*. 2015;3(5):404–414. doi:10.1016/S2213-2600(15)00090-9
49. Tai XY, Torzillo E, Lyall DM, Manohar S, Husain M, Sen A. Association of dementia risk with focal epilepsy and modifiable cardiovascular risk factors. *JAMA Neurol*. 2023;80(5):445–454. doi:10.1001/JAMANEUROL.2023.0339
50. Jack CR, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535–562. doi:10.1016/J.JALZ.2018.02.018