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Alzheimer's disease as a multi-directional spectrum: Integrating neuroinflammation, synaptopathy, paranodal dysfunction, and metabolic trace deficits

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Abstract

Background: Alzheimer's disease (AD) remains an enduring challenge in neurodegeneration, with decades of emphasis on amyloid and tau yielding neither unifying explanations nor effective therapeutics [1-4,5].

Objective: We synthesise evidence across neuropathology, molecular and cellular neuroscience, imaging biomarkers, epidemiology, and interventional trials to propose a calibrated "Alzheimer's spectrum" model.

Methods: We conducted an integrative synthesis linking recurrent paradoxes in AD literature onto mechanistic explanatory nodes—amyloid/tau, neuroinflammation, synaptopathy, paranodal/myelin–axon interface dysfunction, and metabolic/trace-element (notably lithium) deficits—and derived operational criteria and a trial calibration checklist [6-8].

Results: The spectrum model explains (i) why amyloid lowering does not uniformly translate into cognitive benefit, (ii) why synaptic loss correlates more tightly with clinical status, (iii) the existence of biomarker-positive yet cognitively resilient individuals, and (iv) differential trial outcomes driven by phenotype heterogeneity and inadequate demonstration of central target engagement [9,10].

Conclusions: Reframing AD as a multi-mechanistic spectrum resolves key paradoxes, suggests phenotype-matched therapeutic strategies, and mandates trial designs that require central target engagement and mechanism-appropriate endpoints. Crucially, (i) Many neurodegenerative syndromes that resemble AD are part of a broader spectrum rather than classical AD (ii) a favorable prognosis does not imply functional recovery, since neuronal death is irreversible—instead, it should be understood as the absence of further exacerbation.

Introduction

Alzheimer's disease (AD) is the leading cause of dementia worldwide and remains a major unmet medical challenge [1,11]. For decades, the amyloid cascade hypothesis has framed both basic research and drug development [2-4]. However, numerous large, randomized trials that successfully reduce amyloid plaque burden have shown only modest, inconsistent, or no meaningful cognitive benefit, and in some cases have introduced substantial safety concerns such as amyloid-related imaging abnormalities (ARIA) [12-17]. Persistent gaps between biomarker changes and clinical benefit underscore limitations of a single-pathway model and motivate a broader, calibrated framework that can account for biological heterogeneity and reconcile paradoxical findings [5,10].

Materials and methods

We performed an integrative conceptual synthesis. Sources included randomized clinical trials (phase II/III), neuropathological series, *in vivo* imaging studies (amyloid/tau PET, SV2A PET, TSPO PET), single-cell transcriptomic analyses, mechanistic animal experiments, epidemiology (including trace-element studies), and meta-analyses [6-8]. Recurrent paradoxes reported in the literature were mapped to one or more mechanistic nodes within the proposed spectrum, and an operational taxonomy plus a trial calibration checklist were derived to guide future research.

Results

Anti-amylis reduction without commensurate clinical benefit

Multiple monoclonal antibodies (aducanumab, lecanemab, donanemab) clearly lower amyloid PET signal, yet clinical effects on cognition and function are variable and often modest; early γ-secretase inhibitors worsened outcomes, highlighting the complexity of pathway modulation [13-19].

Synaptopathy as the principal structural correlation of cognition

Neuropathological and *in vivo* SV2A PET data show that synaptic density loss correlates more strongly with cognitive decline than plaque load, suggesting that interventions that preserve or restore synaptic integrity are central to modifying clinical course [20-31].

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Table 1. Operational biomarker panel by phenotype

Phenotype	Dominant mechanism	Key biomarkers and endpoints	Potential therapeutic strategies
Classical AD	Amyloid-tau dominant	Amyloid PET, tau PET, plasma/CSF p-tau, NfL	Amyloid-lowering antibodies (e.g., lecanemab)
Inflammatory AD	Neuroinflammation dominant	TSPO PET, CSF cytokines, microglial markers (e.g., TREM2)	Immunomodulators, anti-inflammatory agents
Synaptopathic AD	Paranodal/myelin-axon dysfunction	SV2A PET, EEG connectivity, myelin imaging	Synaptic preservation, myelin-enhancing therapies
Metabolic/Trace-element AD	Lithium-deficient or similar	CSF/plasma lithium, metabolic panels	Lithium formulations, metabolic modulators
Mixed AD	Overlapping mechanisms	Comprehensive panel (all above)	Combination therapies matched to dominant nodes

Neuroinflammation: Microglia as Context-Dependent Mediators Single-cell transcriptomics and disease-associated microglia (DAM) literature reveal distinct microglial states with both protective and deleterious functions; genetic modifiers such as TREM2 shift microglial trajectories and influence phenotype expression [3-8,9-36,].

Paranodal and node of ranvier dysfunction can impair conduction without gross demyelination

Emerging proteomic and histologic studies describe paranodal protein alterations and nodal disruption that can reduce saltatory conduction and disturb network timing, producing symptoms disproportionate to neuronal loss [29-39].

Peripheral immune drivers and microbiome contributions

Epidemiologic and mechanistic evidence links periodontal pathogens (e.g., Porphyromonas gingivalis) and gut dysbiosis to enhanced systemic and central inflammation, providing plausible pathways for peripheral immune priming to exacerbate central synaptic dysfunction [40-44].

Trace-element/metabolic modulators: Lithium as an illustrative node

Epidemiologic studies associate trace lithium levels in drinking water with reduced dementia incidence and recent translational work demonstrating brain lithium depletion and lithium-mediated rescue in animal models suggest a metabolic vulnerability axis that modulates synaptic resilience [45]. These findings warrant cautious clinical translation and rigorous PK/target engagement strategy [46-50,49-68].

A calibrated taxonomy: The alzheimer's spectrum

We propose an operational taxonomy with five principal phenotypes: (i) Classical AD (amyloid–tau dominant), (ii) Inflammatory AD (neuroinflammation dominant), (iii) Synaptopathic AD (paranodal/myelin–axon interface dysfunction), (iv) Metabolic/Trace-element AD (e.g., lithium-deficit), and (v) Mixed AD. Each phenotype is defined by a priority set of biomarkers and mechanistic endpoints (Table 1) [10,69-71].

Trial and clinical implications

Adopting a spectrum view requires: (1) phenotype-stratified enrollment; (2) mandatory evidence of central target engagement for CNS-directed interventions (CSF drug levels, PET occupancy, or central biomarker modulation); (3) mechanism-appropriate primary endpoints (e.g., SV2A PET or EEG connectivity for synaptic targets; TSPO PET or CSF cytokines for immunomodulators); and (4) recognition that clinical stabilization or slowing of decline is a valid and meaningful outcome when neuronal loss is irreversible [9,20,26,51-54,72]. Many historical trial failures can be retrospectively rationalized by phenotype mixing, inadequate CNS exposure, or reliance on biomarker endpoints that were not proximal to the mechanistic node being targeted [13-19,58-61].

Practical trial calibration checklist

1. Baseline phenotype panel: amyloid PET, tau PET, TSPO PET (or CSF inflammatory panel), SV2A PET (if available), plasma/CSF NfL, APOE genotype, CSF/plasma lithium or surrogate, and cognitive reserve metrics.
2. Stratified randomization within phenotype strata.
3. Pharmacokinetic/target engagement confirmation: CSF drug level, PET occupancy, or central biomarker shift.
4. Primary endpoints aligned to mechanism + clinical co-endpoints with MCID and responder analyses.
5. Safety monitoring tailored to mechanism (e.g., ARIA monitoring for anti-amyloid antibodies; renal/thyroid for lithium formulations) [63,72].

Discussion

Reconceptualising AD as a spectrum reconciles multiple paradoxes and aligns therapeutic strategy with underlying pathobiology. For example, amyloid-lowering may be necessary but not sufficient in inflammatory or synaptopathic phenotypes. Conversely, immunomodulatory or metabolic strategies may deliver benefit only in phenotypes where central target engagement is demonstrable. Emphasis on synaptic endpoints, paranodal integrity, and central PK/target engagement will enhance the interpretability of trial outcomes and reduce false negatives driven by heterogeneity [73-80]. This framework also emphasizes early intervention: synaptic and conduction deficits precede overt neuronal loss, so interventions that restore conduction or synaptic function in prodromal stages are more likely to achieve clinical benefit than late-stage approaches [20,24,27,29,46,49].

Limitations

This manuscript is a conceptual and integrative synthesis rather than a novel primary data analysis. Some mechanistic links (notably trace-element depletion) are emergent and require confirmation in human randomized trials. Standardization of biomarker thresholds and broader access to advanced imaging (SV2A, TSPO) remain practical hurdles [52,81-85].

Conclusion

Alzheimer's disease is better described as a spectrum of overlapping mechanistic phenotypes. A calibrated approach that matches interventions to biologic phenotype, demonstrates central target engagement, and uses mechanism-appropriate endpoints promises to transform the interpretation of trials and accelerate discovery of clinically meaningful therapies. Adopting a spectrum-based approach has the potential to transform therapeutic discovery and deliver meaningful clinical benefit.

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Conflicts of interest

The author declares no conflict of interest.

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