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Review

Ferroptosis in Alzheimer's Disease: Molecular Mechanisms, Chemical Modulators, and Emerging Therapeutic Strategies

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Abstract

Ferroptosis, an iron-dependent form of regulated cell death driven by phospholipid peroxidation, has emerged as a potential contributor to neuronal dysfunction and degeneration in Alzheimer's disease (AD). This review critically examines the biochemical basis, AD-specific evidence, chemical modulators, and therapeutic prospects of ferroptosis, emphasizing the distinction between mechanistic compatibility and causal demonstration. Ferroptotic susceptibility is governed by the balance among polyunsaturated phospholipid substrates, redox-active iron, lipid-peroxyl radical propagation, and enzymatic or chemical termination systems, including glutathione peroxidase 4 (GPX4), FSP1, and radical-trapping antioxidants. Human and experimental AD studies show brain iron accumulation, enhanced lipid peroxidation, impaired glutathione/GPX4 defenses, and disrupted iron export, but none establishes neuronal ferroptosis as the predominant mode of cell death. Two randomized trials of brain-penetrant iron chelation lowered the bulk brain iron signal and worsened clinical outcomes, which refutes the proposition that depleting bulk brain iron is therapeutic; because neither trial measured the kinetically labile iron pool, the mechanism of that harm remains undetermined. Among emerging strategies, membrane-active radical-trapping antioxidants and substrate-directed approaches offer mechanistically rational alternatives, whereas many natural products and multitarget agents remain difficult to interpret pharmacologically. Future studies should integrate cell-type-resolved redox lipidomics, direct target engagement, and rigorous causal intervention to determine whether ferroptosis or chronic sublethal lipid peroxidation is therapeutically actionable in AD.

Keywords: ferroptosis; Alzheimer's disease; lipid peroxidation; radical-trapping antioxidants; iron chelation

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1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia and, on current demographic trajectories, will affect well over 100 million people by mid-century [1,2]. Two anti-amyloid monoclonal antibodies have now demonstrated statistically significant slowing of decline in early symptomatic disease, but the absolute effect sizes are small, the

safety burden is real, and neither agent addresses the downstream events that actually destroy neurons [3,4]. The wider development pipeline reflects the same shift of attention toward non-amyloid mechanisms [5]. The persistent gap between removing a pathological aggregate and preserving a cell has renewed interest in the terminal execution mechanisms of neuronal death, and ferroptosis has become the most heavily cited candidate.

Ferroptosis was named in 2012 to describe an iron-dependent, caspase-independent death that could be blocked by iron chelators and by a small aromatic amine, ferrostatin-1, but not by inhibitors of apoptosis, necroptosis, or autophagy [6]. Its defining biochemistry is the accumulation of phospholipid hydroperoxides in cellular membranes beyond the capacity of the cell to reduce them [7,8]. It is, at bottom, a chemistry problem: a free-radical chain reaction running in a two-dimensional lipid solvent, initiated by hydrogen-atom abstraction from a bis-allylic methylene, propagated by peroxyl radicals, and terminated enzymatically by reduction of the hydroperoxide, chemically by radical trapping, or by excision of the oxidized acyl chain [9]. How the resulting membrane damage is converted into loss of plasma—membrane integrity is a separate and still-active question, with osmotic and pore-forming models both supported, ESCRT-III-dependent repair opposing the process, and lipid peroxidation increasing membrane tension sufficiently to gate Piezo1 [10–12]. Every therapeutic strategy discussed below is an attempt to change one of the rate constants in that scheme.

The mapping of this chemistry onto AD looks, at first sight, unusually clean. The AD brain accumulates iron in the regions that degenerate, over and above the regional accumulation that accompanies normal aging [13–15]. Cerebrospinal fluid ferritin predicts subsequent cognitive decline and is modified by *APOE* genotype [16]. Both amyloid precursor protein (APP) and tau participate in neuronal iron export, so their loss of function traps iron intracellularly [17,18]. Glutathione falls early [19]. Lipid peroxidation end products, 4-hydroxynonenal and F_2-isoprostanes, are elevated in AD brain and biofluids [20,21]. Conditional deletion of *Gpx4* from forebrain neurons produces hippocampal degeneration and memory impairment that is rescued by a lipophilic radical-trapping antioxidant [22]. Each observation is compatible with ferroptosis.

Compatibility is not demonstration, and this is where the field has been insufficiently careful. Almost every one of those findings is equally compatible with generic oxidative stress, with iron acting as a bystander marker of tissue injury, or with a death mode that shares markers with ferroptosis without sharing its mechanism. More pointedly, the two randomized controlled trials that directly tested the causal claim, by lowering brain iron in patients with a brain-permeable chelator, both produced clinical worsening [23,24]. A review that treats those results as an implementation detail rather than as data is not a critical review.

Existing reviews of ferroptosis in AD are numerous and largely concordant [25–28], which is itself a warning sign; they tend to recount the pathway, list correlative findings from the AD literature, and enumerate compounds that were protective in a cell or mouse model. Our aim differs in three respects. First, we treat ferroptosis as chemistry rather than as a pathway diagram because the therapeutic decisions that matter, which node to attack and with what pharmacophore, follow from rate constants and partition coefficients rather than from arrow direction. Second, we grade the AD-specific evidence explicitly against the hallmark criteria the field has agreed on, and we report where the evidence is absent rather than smoothing over the gaps. Third, we take the failed chelation trials seriously as mechanistic information about which iron pool matters in the human brain, and we use them to derive design rules for the next generation of central nervous system (CNS) anti-ferroptotic chemistry.

2. Materials and Methods

This narrative review was based on searches of PubMed/MEDLINE, Scopus, and Web of Science conducted through May 2026, using combinations of the terms ferroptosis, lipid peroxidation, radical-trapping antioxidant, GPX4, FSP1, ACSL4, iron chelation, deferiprone, quantitative susceptibility mapping, and Alzheimer's disease, supplemented by Boolean operators and citation chaining from relevant primary mechanistic studies. We prioritized primary research over secondary reviews, favored physical—organic and kinetic studies where mechanism was at issue, and required clinical claims to rest on randomized controlled trials where these exist. Where a mechanistic claim is contested in the primary literature, for example, the role of DHODH, the attribution of protective effects to lipoxygenase inhibition, or the molecular target of RSL3, the disagreement is presented rather than a side selected. Studies were excluded if the sole evidence for ferroptosis was rescue by a single compound with no orthogonal confirmation, except where cited, specifically to illustrate that limitation. The evidence grading applied in Table 2 follows the hallmark criteria set out in the cell death nomenclature and ferroptosis reproducibility recommendations [29,30].

3. Ferroptosis as a Chemical Process

It is useful to decompose ferroptosis into three chemically distinct variables that can be manipulated independently: the substrate, the catalyst, and the kinetics of chain propagation versus termination (Figure 1). Confusion in the therapeutic literature can usually be traced to conflating them.

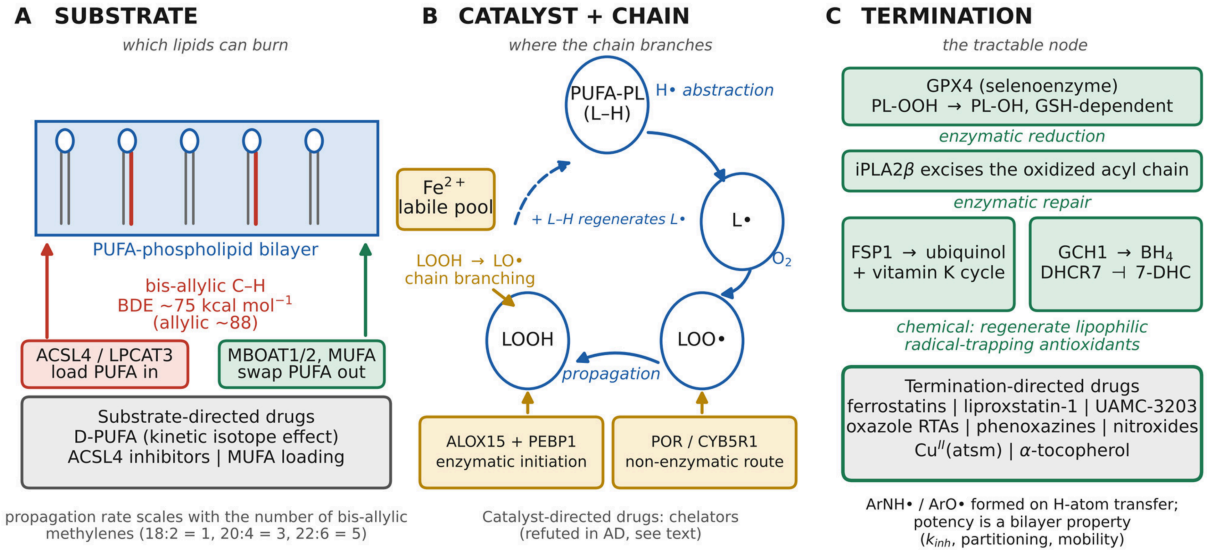


Figure 1. The chemistry of ferroptosis resolved into substrate, catalyst, and chain kinetics. (**A**) Initiation requires abstraction of a bis-allylic hydrogen from a polyunsaturated acyl chain esterified into a membrane phospholipid; ACSL4 and LPCAT3 set this substrate load, and MBOAT1/2 and monounsaturated fatty acids reduce it. (**B**) Propagation proceeds through peroxyl radicals; the labile iron pool converts the resulting hydroperoxide into an alkoxyl radical, branching the chain. Lipoxygenases (with PEBP1) and the flavin oxidoreductases POR and CYB5R1 can also generate the initial hydroperoxide. (**C**) Termination is enzymatic, through GPX4 reduction of the phospholipid hydroperoxide to the alcohol, or chemical, through radical-trapping antioxidants regenerated by FSP1 (ubiquinol, vitamin K), by GCH1 (tetrahydrobiopterin), or supplied by the distal cholesterol pathway (7-dehydrocholesterol). Drug classes are placed at the node they act on.

3.1. Substrate: Which Lipids Can Burn

Autoxidation requires a bis-allylic C–H bond. The bond dissociation enthalpy at that position, roughly 75 kcal mol^{-1}, is low enough for abstraction by a peroxyl radical, whereas the allylic C–H of a monounsaturated chain, at about 88 kcal mol^{-1}, is not [31,32]. The rate of chain propagation therefore scales with the number of bis-allylic methylenes: linoleate has one; arachidonate, three; and docosahexaenoate, five. Peroxyl radical clock measurements put numbers on this ordering. At 37 °C in organic solution, the propagation rate constant k_p rises from 62 M^{-1} s^{-1} for linoleic acid to 197 ± 13 M^{-1} s^{-1} for arachidonic acid and 334 ± 37 M^{-1} s^{-1} for docosahexaenoic acid, and the ranking is preserved for the corresponding phospholipids in phosphatidylcholine liposomes [31–33]. This single physical—organic fact determines much of ferroptosis biology. Cells become sensitive when polyunsaturated fatty acids (PUFAs) are esterified into membrane phospholipids and resistant when they are not.

The esterification step is enzymatically controlled. Acyl-CoA synthetase long-chain family member 4 (ACSL4) preferentially activates arachidonic and adrenic acid, and lysophosphatidylcholine acyltransferase 3 (LPCAT3) incorporates them into phosphatidylethanolamine; loss of either confers resistance [34,35]. Conversely, exogenous monounsaturated fatty acids displace PUFAs from phospholipids and produce a ferroptosis-resistant state in an ACSL3-dependent manner [36]. More recent work has refined the substrate picture considerably: phospholipids bearing two polyunsaturated acyl chains are disproportionately potent drivers of ferroptosis [37], and the essential sites of peroxidation have been narrowed to specific phospholipid species rather than to bulk membrane PUFA content [38]. MBOAT1 and MBOAT2 remodel membranes toward monounsaturated species and constitute a GPX4-independent surveillance arm that is under sex-hormone control [39].

The brain is an outlier on this axis. Gray matter phospholipids are among the most polyunsaturated in the body, with docosahexaenoate abundant in neuronal and synaptic membranes. If substrate loading alone determined risk, the brain would be the most ferroptosis-prone organ in the body, which it manifestly is not under physiological conditions. That discrepancy is informative: it implies that brain tissue is protected not by substrate scarcity but by surveillance capacity and by control of the catalyst. Reports that PUFA content, and docosahexaenoate in particular, is reduced in AD cortex [40,41] are therefore ambiguous. The loss is usually read as evidence of peroxidative consumption, and it may be; but a lower bis-allylic burden should, all else equal, lower ferroptosis susceptibility. Whether AD cortex is enriched or depleted in the specific oxidizable phospholipid species that matter remains unsettled by modern redox lipidomics, a tractable gap.

3.2. Catalyst: Which Iron Matters

Iron participates in ferroptosis in at least three chemically distinguishable ways, and the therapeutic implications differ sharply between them. First, ferrous iron reduces pre-existing lipid hydroperoxides to alkoxyl radicals, a branching step that multiplies chain-carrying radicals and is far more kinetically consequential than the classical Fenton reaction with hydrogen peroxide [42,43]. Second, iron is a structural cofactor of the lipoxygenases (ALOX15, ALOX15B, ALOX5), which can generate the initial hydroperoxides enzymatically and, via the scaffold protein PEBP1, be directed toward phosphatidylethanolamine substrates [35,44,45]. Third, iron is required for the flavin-dependent oxidoreductases cytochrome P450 oxidoreductase (POR) and CYB5R1, which contribute to phospholipid peroxidation independently of the lipoxygenases [46,47].

Only a small, kinetically labile fraction of cellular iron is available for any of this. The bulk is sequestered in ferritin, in iron—sulfur clusters, in heme, and in mineral phases; the

partition between these compartments is itself age-dependent, and senescent cells accumulate iron with impaired ferritin turnover [48]. Ferritinophagy, mediated by nuclear receptor coactivator 4 (NCOA4), which was identified as the ferritin cargo receptor by quantitative proteomics [49], converts storage iron into labile iron and is a genuine sensitizing mechanism [50,51]. Brain iron transport, storage, and regional distribution have been reviewed in detail elsewhere [52–54]. The distinction between the storage and labile pools is the single most important and most frequently elided point in the AD ferroptosis literature, and it is revisited in Section 7.2 in connection with the failure of chelation.

The mechanistic weight given to lipoxygenases deserves particular scrutiny. Physical—organic analysis by Pratt and co-workers established that ferrostatin-1 and liproxstatin-1 are potent radical-trapping antioxidants in phospholipid bilayers and are not effective inhibitors of 15-LOX-1 catalysis [55]. A follow-up study showed that many compounds used as lipoxygenase inhibitors in ferroptosis experiments, including baicalein, suppress lipid autoxidation directly, so their protective effects cannot be attributed to enzyme inhibition [56]. A substantial portion of the published evidence for a lipoxygenase requirement in ferroptosis, including in neuronal systems, therefore rests on pharmacology that has been reinterpreted. Lipoxygenases can initiate; the claim that they execute is not secure.

3.3. Propagation and Termination: Where the Kinetics Are Decided

Once a chain is running, its length is set by the ratio of the propagation rate constant to the rate at which chain-carrying peroxyl radicals are intercepted. This is the classical inhibited autoxidation problem, and it is quantitatively well understood [31,57]. A radical-trapping antioxidant (RTA) is characterized by its inhibition rate constant, k_{inh}, and by its stoichiometric factor, and, critically for membrane chemistry, by how it partitions and diffuses within the bilayer. α-Tocopherol reacts with peroxyl radicals at roughly 3×10^6 M^{-1} s^{-1} in homogeneous solution [57]; ferrostatin-1 and liproxstatin-1 are somewhat slower in solution yet markedly more effective in phospholipid bilayers, which Zilka and colleagues attributed to superior partitioning and mobility in the lipid phase rather than to intrinsic reactivity [55]. The practical lesson is that intrinsic antioxidant potency measured in an organic solvent is a poor predictor of anti-ferroptotic potency in a membrane.

Termination can also be achieved enzymatically. GPX4 is the only mammalian enzyme that reduces phospholipid hydroperoxides *in situ* within the membrane, converting the branching substrate into an inert alcohol before iron can act on it [58–60]. Its loss was shown, before ferroptosis was named, to translate oxidative stress into 12/15-lipoxygenase-dependent death [61], which is the historical origin of the lipoxygenase interpretation discussed above. The three known GPX4-independent systems all work by regenerating small-molecule RTAs: FSP1 reduces ubiquinone to ubiquinol [62,63], GCH1 supplies tetrahydrobiopterin [64], and the distal cholesterol biosynthesis intermediate 7-dehydrocholesterol acts as an endogenous RTA in its own right [65,66]. FSP1 additionally participates in a non-canonical vitamin K cycle that suppresses ferroptosis [67] and can regenerate α-tocopherol. A further, structurally distinct route exists: the calcium-independent phospholipase $iPLA_2\beta$ excises the oxidized acyl chain outright, removing the redox lipid death signal rather than reducing it [68]. Ferroptosis, viewed chemically, is what happens when the enzymatic, chemical, and repair capacity of a membrane are exceeded simultaneously.

One much-cited element of this scheme remains formally contested. Mitochondrial dihydroorotate dehydrogenase (DHODH) was proposed as an additional defense arm operating through mitochondrial CoQ [69], but a subsequent analysis attributed the observed effects of DHODH inhibitors to off-target FSP1 inhibition, and the original authors have replied in defense of their assignment; the exchange has not converged [70,71]. It is

therefore presented here as unresolved rather than as established, and any AD-directed strategy premised on DHODH would inherit that uncertainty.

4. Surveillance Systems Re-Weighted for the Brain

The termination and repair systems described above were characterized largely in transformed cell lines chosen for tractability, and their relative importance is not transferable to brain tissue without argument. Neurons are post-mitotic, highly oxidative, poorly glycolytic, and dependent on astrocytes for cysteine supply; oligodendrocytes carry the highest iron content in the CNS; microglia handle iron-rich debris; and astrocytes have their own ferroptotic route through NOX4-driven lipid peroxidation in AD [72]. Cell-type weighting is not a detail; it is the substance (Table 1). Two experiments make the point directly. Ferroptotic stress confined to microglia kills neurons non-cell-autonomously, so the cell that dies need not be the cell in which the chemistry ran [73]. Conversely, oligodendrocyte death in Pelizaeus-Merzbacher disease is rescued by iron chelation, showing that the same node can be protective in one CNS cell type, while, as discussed in Section 7, it is harmful when addressed indiscriminately across the whole brain [74].

Table 1. Core ferroptosis nodes, their chemical function, and the status of the evidence in AD. Direction indicates the reported change in AD brain or AD models relative to control. AD evidence tier: H, human tissue or biofluid; M, mammalian AD model; C, cell model only; N, not examined in AD. A dash indicates that no direction can be assigned because the node has not been measured in AD.

Node	Chemical Function	Direction in AD	Tier	Key Refs
ACSL4	Activates arachidonate/adrenate for phospholipid esterification; sets oxidizable substrate load	Increased	M	[34,35]
LPCAT3	Incorporates PUFA-CoA into phosphatidylethanolamine	Not established	C	[34,75]
MBOAT1/MBOAT2	Remodels membranes toward monounsaturated species; GPX4-independent surveillance	Not examined	N	[39]
ALOX15/PEBP1	Enzymatic generation of PUFA-PE hydroperoxides	Increased (contested role in execution)	H	[35,44,56]
POR/CYB5R1	Flavin oxidoreductases driving non-enzymatic phospholipid peroxidation	Not examined	N	[46,47]
Labile iron pool	Reduces lipid hydroperoxides to alkoxyl radicals; chain branching	Presumed increased; not directly measured	-	[6,7]
Ferritin/NCOA4	Iron storage and its autophagic mobilization	CSF ferritin increased; NCOA4 axis under-studied	H	[16,50,51]
Ferroportin (SLC40A1)	Sole cellular iron exporter	Decreased	H, M	[76]
APP	Stabilizes cell-surface ferroportin and thereby supports iron export; not itself a ferroxidase	Function impaired	H, M	[18,77–79]

Table 1. *Cont.*

Node	Chemical Function	Direction in AD	Tier	Key Refs
Tau (soluble)	Traffics APP to the surface, enabling iron export	Decreased soluble pool	H, M	[17,80,81]
System x_c^- (SLC7A11)	Cystine import for glutathione synthesis	Altered expression reported in AD brain	H	[82–84]
Glutathione	Cofactor for GPX4	Decreased (MRS, cortex)	H	[19]
GPX4	Selenoenzyme reducing phospholipid hydroperoxides *in situ*	Decreased	H, M	[22,85–87]
Selenium supply	Required for GPX4 selenocysteine; confers resistance to overoxidation	Not obviously deficient	H	[88,89]
FSP1 (AIFM2)	NAD(P)H-dependent regeneration of ubiquinol as a lipophilic RTA	Not examined in AD tissue	N	[62,63,67]
GCH1/BH_4	Supplies tetrahydrobiopterin as an RTA and lipid-remodeling signal	Not examined in AD tissue	N	[64]
DHCR7/7-DHC	7-DHC acts as an endogenous membrane radical-trapping antioxidant	Not examined in AD tissue	N	[65,66]
DHODH	Proposed mitochondrial CoQ-dependent defense; role formally contested	Not examined in AD	N	[69–71]
NRF2	Coordinates SLC7A11, GSH synthesis, ferritin and GPX4 expression	Decreased activity reported	H	[90,91]
APOE	Suppresses NCOA4-mediated ferritinophagy via PI3K/AKT, restraining storage-to-labile iron conversion; the common isoforms are equally protective *in vitro*	ε4 associated with lower apoE abundance, more oxidizable membrane lipid and greater peroxidation	H, C	[16,86,92]
iPLA$_2$β	Excises the oxidized acyl chain, removing the death signal	Not examined in AD tissue	N	[68]
Presenilin (PSEN1/2)	Familial AD mutations confer ferroptosis vulnerability	Vulnerability increased	C	[93]

4.1. GPX4, Selenium, and the Cysteine Supply Chain

GPX4 uses a selenocysteine residue in its active site. Ingold and colleagues showed that replacing it with cysteine yields an enzyme that retains catalytic activity but is irreversibly overoxidized under peroxide stress. The *in vivo* consequence is strikingly selective and is itself dependent on genetic background. Mice carrying the cysteine variant on a mixed C57BL/6J × 129S6SvEv background are born at the expected Mendelian ratio but selectively lose cortical parvalbumin-positive GABAergic interneurons, sparing calbindin- and calretinin-positive populations, and die of spontaneous seizures in the 3rd postnatal week;

on a congenic C57BL/6J background, the allele is lethal in mid-gestation [88]. The chemical rationale is that the selenolate is both more nucleophilic and, once oxidized, more readily reduced back to the active state, so selenocysteine confers resistance to inactivation rather than simply higher turnover. Deletion of *Gpx4* is, moreover, embryonic lethal [87]. This makes GPX4 an intrinsically selenium-limited enzyme and gives the brain's well-documented prioritization of selenium a direct mechanistic reading.

The upstream constraint is cysteine. System x_c^-, the SLC7A11/SLC3A2 cystine-glutamate antiporter, supplies the cysteine for glutathione synthesis, and its inhibition by erastin or by high extracellular glutamate produces the death originally described in neuronal cells as oxytosis, a decade before ferroptosis was named [82,83]. Oxytosis and ferroptosis are now generally regarded as the same process approached from two literatures [94], a point of some importance because the neuronal literature is older, was conducted in primary cells, and used different readouts. Brain glutathione is reduced in mild cognitive impairment and AD as measured by magnetic resonance spectroscopy [19], and GPX4 protein is reported to fall in AD cortex [85], but the two observations are rarely made in the same tissue.

4.2. FSP1-Ubiquinol and the GPX4-Independent Arms

FSP1 (AIFM2) is a myristoylated, membrane-associated NAD(P)H oxidoreductase that maintains a pool of ubiquinol acting as a lipophilic RTA at the plasma membrane [62,63]. Its activity is also regulated by condensate formation [95], and selective inhibitors are now available [96]. For AD, this arm has an obvious attraction because it can in principle be reinforced pharmacologically with ubiquinone or with vitamin K, both of which FSP1 can recycle [67], and because it is glutathione-independent and therefore insensitive to the cysteine bottleneck that limits GPX4 in an aged, astrocyte-compromised brain. It has also been almost entirely unexplored in AD tissue: no study appears to have quantified FSP1 protein, ubiquinol redox state, and lipid hydroperoxides together in human AD cortex with cell-type resolution. That is a striking omission given how prominent the FSP1 axis has become elsewhere.

The GCH1-tetrahydrobiopterin arm is similarly under-examined in AD, although it is of particular interest because tetrahydrobiopterin is also the cofactor for the aromatic amino acid hydroxylases and for nitric oxide synthase, so its depletion couples ferroptosis susceptibility to monoamine synthesis and to nitrergic signaling [64]. Any GCH1-directed intervention in the brain carries obvious pleiotropy.

4.3. The 7-Dehydrocholesterol Axis: An Unexploited CNS Node

The identification of 7-dehydrocholesterol (7-DHC) as an endogenous RTA is the most interesting recent development from a CNS perspective, and it has been almost ignored in the AD ferroptosis literature [65,66]. Two independent genome-wide screens converged on DHCR7, the terminal enzyme of the Kandutsch-Russell branch of cholesterol biosynthesis. Loss of DHCR7 causes 7-DHC to accumulate, and 7-DHC, whose conjugated diene in the B-ring makes it an unusually good hydrogen—atom donor, suppresses ferroptosis by trapping peroxyl radicals in the membrane. The apparent paradox is worth stating: peroxyl radical clock measurements had already established 7-DHC as one of the most oxidizable lipids known, with a propagation rate constant of $2260 \pm 40\ M^{-1}\ s^{-1}$ at 37 °C, some 200-fold that of cholesterol itself at $11 \pm 2\ M^{-1}\ s^{-1}$ [31,33], so it protects precisely because it is sacrificially consumed, diverting the chain away from the phospholipid pool.

Three features make this node CNS-relevant. Brain cholesterol is synthesized locally because lipoproteins do not cross the blood—brain barrier, so the distal pathway is constitutively active in the tissue of interest. Cholesterol metabolism is already implicated in AD

through *APOE* and through several genome-wide association loci. And DHCR7 is inhibited, as an off-target activity, by several widely used psychotropic drugs, which offers an unusual repurposing entry point. The caution is severe and must be stated with the proposal: profound 7-DHC accumulation is the biochemical lesion of Smith-Lemli-Opitz syndrome, and 7-DHC-derived oxysterols are themselves neurotoxic. The therapeutic window, if one exists, is a partial and probably transient elevation. This node is therefore flagged as a hypothesis worth testing, not as a recommendation.

4.4. APOE, Ferritinophagy, and a Genuine AD-Specific Link

One recent finding does connect the dominant genetic risk factor for late-onset AD to ferroptosis directly rather than by analogy. Apolipoprotein E was shown to inhibit ferroptosis potently in cultured neurons by activating PI3K/AKT signaling and thereby suppressing NCOA4-mediated ferritinophagy, which restrains the conversion of storage iron into the labile pool and so limits iron-driven lipid peroxidation [92]. The nature of the isoform dependence requires care because it is frequently misstated. In that study, the common apoE isoforms did not differ from one another in their capacity to protect against ferroptosis *in vitro*; the anti-ferroptotic activity is a property of the protein rather than of the variant. What differs between genotypes is the context in which that activity operates: apoE abundance, which is lower in ε4 carriers, and the lipid environment of the ε4 brain, which is comparatively enriched in polyunsaturated species. Consistent with a context-dependent rather than an activity-dependent effect, the same study found in a post-mortem series of 608 participants that the association between brain iron and clinically confirmed AD was stronger in ε4 carriers [92]. The mechanism therefore links *APOE* to ferroptotic susceptibility through apoE dose and membrane substrate loading, not through an isoform-intrinsic difference in protein efficacy. This dovetails with the earlier observation that cerebrospinal fluid ferritin is regulated by *APOE* and predicts cognitive outcomes [16], and with the finding that iron-associated lipid peroxidation in lipid rafts is most severe in ε4 carriers [86]. Confirmed with cell-type resolution in human tissue, the dose-and-substrate account would be the strongest AD-specific ferroptosis link available, tying an established genetic risk term to a defined step in the cascade rather than to a generic oxidative phenotype.

5. What Is Actually Established in AD

The field has converged on a hallmark set for claiming ferroptosis: iron dependence demonstrated by chelation, lipid peroxidation demonstrated directly rather than by a surrogate aldehyde, perturbation of the GPX4-glutathione or FSP1 axes, and rescue by a structurally distinct RTA that is not itself a chelator [29,30]. Applying that standard to the AD literature produces a much shorter list than a reading of recent reviews would suggest (Table 2).

Table 2. Evidence grading for the principal claims made about ferroptosis in AD. Tier A, demonstrated in human AD tissue or in a randomized clinical trial with orthogonal confirmation; Tier B, demonstrated in a mammalian AD model with genetic and pharmacological support; Tier C, demonstrated in cell models or by correlation only; Tier D, asserted in the review literature without primary support meeting the hallmark criteria.

Claim	Tier	What Supports It	What Is Missing
Iron accumulates in AD brain regions that degenerate	A	Histochemistry, synchrotron speciation, QSM cohorts, large post-mortem series [13,14,97–99]	Speciation of the labile, chelatable fraction as opposed to storage and mineral iron

Table 2. *Cont.*

Claim	Tier	What Supports It	What Is Missing
Lipid peroxidation end products are elevated in AD	A	4-HNE adducts, F_2-isoprostanes, lipid raft and whole-brain measurements [20,21,84,86]	Direct quantification of oxidized phospholipid species by redox lipidomics
GPX4 capacity is reduced in AD brain	B	Reduced GPX4 protein and activity in cortex and lipid rafts; reduced GSH by MRS [19,85,86]	Concurrent measurement of GPX4 activity, GSH and PLOOH in the same tissue
Neurons die by ferroptosis when GPX4 is removed	B	*Gpx4* conditional deletion causes hippocampal degeneration that liproxstatin-1 reduces and that a vitamin E-deficient diet accelerates [22,100]	Relevance to sporadic AD, where GPX4 is reduced but not deleted
Impaired neuronal iron export is a ferroptotic mechanism in AD	B	Ferroportin deletion; APP-dependent maintenance of surface ferroportin; tau-dependent APP trafficking [17,18,76,78]	Evidence that the graded changes of sporadic disease reach the threshold produced by gene deletion; the APP contribution to neuronal export is itself contested [101]
Ferroptosis is upstream of amyloid and tau pathology	C	Reciprocal *in vitro* and model data in both directions	Any staged interventional experiment establishing direction *in vivo*
APOE ε4 increases ferroptosis susceptibility	C	apoE suppresses ferritinophagy; CSF ferritin is *APOE*-regulated; the iron-AD association is stronger in ε4 carriers; raft peroxidation greatest in ε4 [16,86,92]	Evidence that the ε4 effect is carried by apoE abundance and membrane lipid composition rather than by isoform-intrinsic activity, and quantification of the risk fraction explained
Lipoxygenases execute ferroptosis in the brain	D	Protection by compounds annotated as LOX inhibitors	Those compounds are direct RTAs; enzyme-independent explanation not excluded [55,56]
Ferroptosis inhibitors improve cognition in AD models	C	Multiple reports of Fer-1 or Lip-1 benefit in rodent models; graded C rather than B because the supporting pharmacology lacks the controls that would make it interpretable [76]	RTA-inactive analogue controls; exposure-response; orthogonal RTA chemotype
Lowering brain iron is therapeutic in AD	A (refuted)	Deferiprone lowered the bulk brain iron signal and accelerated cognitive decline; the same agent worsened PD [23,24]	A measurement of the labile pool, and a compartment-selective chelator that separates labile from functional iron
Blocking chain propagation is therapeutic in AD	B	α-Tocopherol slowed functional decline in the randomized TEAM-AD trial, with a supporting earlier trial; no orthogonal mechanistic confirmation, so it does not reach Tier A [102,103]	A trial of a modern, potent, brain-penetrant RTA with a peroxidation biomarker
Natural products act on AD by inhibiting ferroptosis	D	Numerous rodent studies reporting marker normalization	Node-level attribution; most candidates are simultaneously RTA, chelator and NRF2 inducer [56]

5.1. Human Tissue and Imaging

Iron accumulation in AD brain is not in dispute. Histochemical and synchrotron studies place iron in and around plaques, in glia, and in the neuropil, and demonstrate mineralized phases, including magnetite, that are chemically distinct from ferritin-bound iron [97,98,104,105]. The wider case for biometals as therapeutic targets in AD has been argued at length [106,107]. *In vivo*, quantitative susceptibility mapping (QSM) shows regional iron elevation that tracks with amyloid burden and predicts subsequent cognitive decline [13,14,108], and a large post-mortem series relates regional iron to the rate of deterioration [99]. Cortical iron also tracks tau aggregation measured by PET [109], and cerebrospinal fluid ferritin predicts brain hypometabolism in amyloid-positive individuals [110]. Human tissue work has also reported iron dyshomeostasis, lipid peroxidation, and altered cystine/glutamate antiporter expression together in the same AD brains, which is closer to a hallmark set than most reports achieve [84]. These are strong, replicated data. What they do not establish is that the accumulated iron is in a redox-active, chelatable, chain-branching form. QSM reports bulk magnetic susceptibility, a quantity dominated by ferritin-bound and mineral iron, and no available human measurement resolves the small labile fraction that performs chain branching at the membrane (Figure 2).

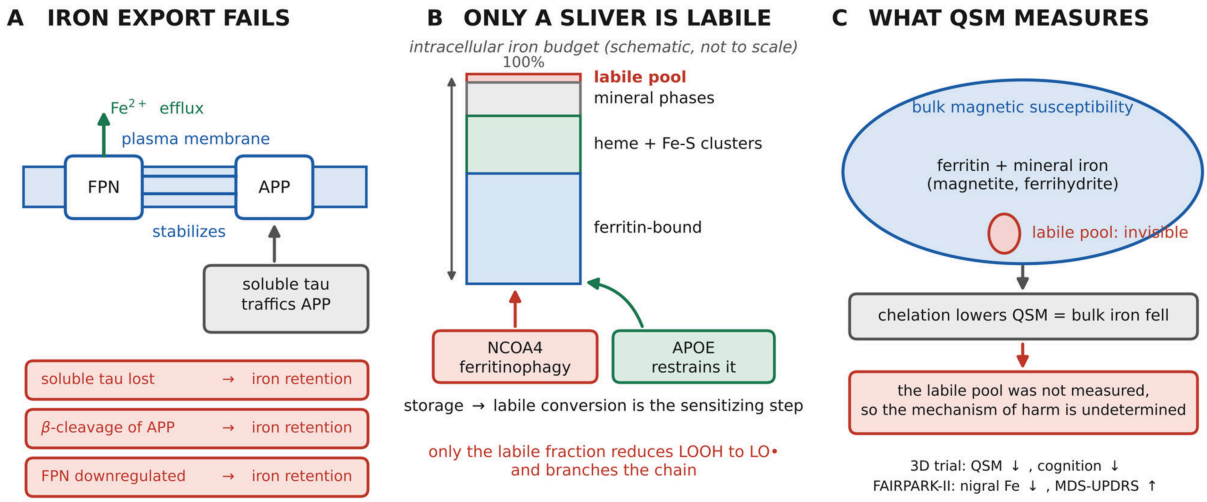


Figure 2. Iron handling in the Alzheimer brain and the pool that chelation actually reaches. Left: neuronal iron export requires soluble tau to traffic APP to the plasma membrane, where APP stabilizes ferroportin; loss of soluble tau, amyloidogenic APP processing, or ferroportin downregulation all cause iron retention. APP supports export by maintaining surface ferroportin and is not itself a ferroxidase [18,101]. Centre: the intracellular iron budget is dominated by ferritin, heme, and iron-sulfur clusters, with only a small labile pool competent for chain branching; NCOA4-mediated ferritinophagy converts storage iron into labile iron and apoE restrains it. Right: quantitative susceptibility mapping is dominated by ferritin-bound and mineralized iron, so a fall in the QSM signal after chelation establishes that bulk tissue iron was lowered. It is not a measurement of the labile pool, which was not assayed in either trial, and the mechanism by which chelation worsened outcomes therefore remains undetermined.

Direct evidence of lipid peroxidation in AD tissue is also solid at the level of end products: 4-hydroxynonenal adducts are increased [20], and F_2-isoprostanes are elevated in brain and cerebrospinal fluid [21], although peripheral F_2-isoprostanes are not [111], which is a useful caution for anyone proposing a plasma peroxidation biomarker. Changes in antioxidant enzyme activity accompany these end products in the same cortical tissue [85]. The most informative recent human study localized iron-associated lipid peroxidation to lipid rafts, with reduced GPX4 and glutathione synthetic capacity in the same fractions

and the most severe changes in *APOE* ε4 carriers [86]. Subcellular resolution of this kind is what the field needs more of because bulk homogenate measurements cannot distinguish a membrane in which a chain reaction ran from a tissue containing dying cells of any cause.

At the transcriptomic level, oxytosis/ferroptosis signatures are enriched in AD brain [112], and single-nucleus datasets show iron-handling and lipid-remodeling genes altered in specific glial populations [113,114]. Signature enrichment is a hypothesis-generating result. It cannot distinguish a cell that died by ferroptosis from a surviving cell mounting an anti-ferroptotic response, and in post-mortem tissue the cells that died are precisely the ones not sampled. This survivorship problem is intrinsic to human ferroptosis research in the brain and is rarely acknowledged.

5.2. Genetic and Model Evidence

The strongest causal evidence is genetic and comes from mice. Conditional deletion of *Gpx4* in forebrain neurons produces hippocampal neurodegeneration, elevated lipid peroxidation, neuroinflammation, and spatial memory deficits; withdrawing vitamin E from the diet markedly accelerates the phenotype, and the ferroptosis inhibitor liproxstatin-1 reduces the neurodegeneration [22]. The direction of the dietary experiment deserves emphasis because it is often reported the other way round: vitamin E was removed rather than supplemented, and the acceleration that followed is evidence that endogenous radical-trapping capacity restrains the lesion rather than evidence that supplementation reverses it. Broader neuronal deletion causes motor neuron degeneration and paralysis [100], and inducible whole-body deletion is lethal with neuronal loss [115]. These experiments prove that neurons require GPX4 and that they die by an RTA-suppressible mechanism when it is removed. They do not prove that this is what happens in AD; they establish sufficiency of the lesion, not its presence in the disease.

Deletion of ferroportin in principal neurons produces hippocampal atrophy, memory deficits, and ferroptotic markers, and ferroportin is downregulated in APPswe/PS1dE9 mice and in human AD brain [76]. Tau-deficient mice accumulate brain iron because tau is required to traffic APP to the cell surface, where APP supports iron export [17,78,80,81]. The nature of that support should be stated precisely because the original description has been revised. APP was first reported to possess an intrinsic, zinc-inhibitable ferroxidase activity that oxidized Fe(II) for loading onto transferrin [77]. On re-examination, the apparent oxidase activity was traced to phosphate in the assay buffer rather than to the protein and purified soluble APP did not oxidize Fe(II) under conditions controlled for pH and charge [18]. What survived re-examination is the cell—biological function: endogenous APP is required to maintain ferroportin at the neuronal surface, so APP promotes iron export without itself being a ferroxidase [18]. Even this role is not uncontested, since in primary hippocampal neurons, the ferroxidase activity required for ferroportin-supported efflux was attributed to hephaestin, with APP knockdown leaving surface ferroportin unchanged [101]. Amyloidogenic processing of APP itself induces cellular iron retention [78]. Human neurons carrying familial AD presenilin mutations show selective ferroptosis vulnerability [93], and unbiased CRISPR interference and activation screens in human neurons converge on ferroptosis as a principal death route, linking it to lysosomal failure [116]. This is a coherent set, and it is the best argument that the ferroptosis machinery is genuinely wired into AD-relevant biology rather than merely co-occurring with it.

Two caveats attach. First, most of these models create iron retention by removing a protein, which is a much larger perturbation than the graded changes seen in sporadic disease. Second, several of the AD models in which ferrostatin-1 or liproxstatin-1 improved outcomes did not report the control experiments that would exclude a generic antioxidant effect, in particular a comparison with an RTA-inactive structural analogue. Ferrostatin-1

rescue is often treated as diagnostic of ferroptosis, but ferrostatin-1 will also suppress non-ferroptotic lipid peroxidation, and circularity follows quickly if the same compound defines the phenotype and demonstrates the mechanism.

5.3. The Direction of Causality Remains Open

The literature commonly asserts that ferroptosis is upstream of amyloid and tau pathology. The evidence for direction is thin in both directions. Iron promotes amyloid aggregation *in vitro* and amyloid-β can generate reactive oxygen species in the presence of redox-active metals; equally, amyloidogenic APP processing reduces surface ferroportin and causes iron retention [78], and soluble tau loss impairs iron export [17]. The amyloid-ferroptosis link has been reviewed in detail and remains bidirectional on the available data [117]. The system is reciprocal, which means correlational human data cannot resolve it and only staged interventional experiments can. In practice, the honest statement is that ferroptosis in AD is at least partly a consequence of the proteinopathy and may additionally be a driver, and the relative weights are unknown.

There is one further consideration that the field tends to avoid. Ferroptosis is, in most systems, a rapid death: hours, not years. AD removes neurons over a decade or more. Either ferroptosis in AD is a rare, stochastic event in a small fraction of vulnerable cells, almost undetectable by bulk assays, with an open cumulative contribution, or the relevant process is chronic sublethal lipid peroxidation that damages synapses and mitochondria without executing the cell, a distinct process that should be named differently. Sublethal membrane oxidation may well be the more important process in AD, and it would still be treatable with the same chemistry, but conflating it with ferroptosis has caused the field to search for an execution event where it should be measuring a chronic flux.

6. Chemical Modulators: Structures, Mechanisms, and CNS Suitability

Modulators are grouped here by the chemical variable each manipulates rather than by their provenance because compounds from very different sources converge on the same node and are subject to the same constraints (Table 3, Figure 3). For a CNS indication, three properties dominate: whether the compound acts at the propagation step or elsewhere, whether it survives long enough in plasma and tissue to act, and whether it reaches the brain at a free concentration above its effective potency.

Table 3. Chemical modulators of ferroptosis relevant to AD, grouped by the chemical variable each manipulates. CNS exposure summarizes reported brain penetration after systemic dosing. Strongest evidence indicates the most advanced setting in which the compound has been tested for a neurological indication; RCT, randomized controlled trial. Limitations are the principal chemical or translational objection to each agent.

Agent/Class	Node	Mechanism	CNS Exposure	Highest Evidence	Principal Limitation	Refs
Ferrostatin-1	Termination	Arylamine RTA; H-atom donation to peroxyl radicals in bilayer	Poor	Rodent models	Ester is hydrolytically and metabolically labile; tool compound only	[6,55]
Liproxstatin-1	Termination	Spiro-quinoxalinamine RTA	Limited	Rodent models	Modest exposure; not optimized for CNS	[55,59]
UAMC-3203	Termination	Third-generation ferrostatin with stabilized scaffold	Moderate	Rodent models	No AD data	[118]

Table 3. *Cont.*

Agent/Class	Node	Mechanism	CNS Exposure	Highest Evidence	Principal Limitation	Refs
Oxazole RTAs	Termination	Reduced-polarity UAMC-3203 analogues; oral, high brain levels	High	Preclinical	New chemotype; no *in vivo* AD data	[119]
Phenoxazines	Termination	Tricyclic amine RTAs with very high k_{inh}	Variable	*In vitro*	Autoxidation and coloration; no CNS programs	[120]
Nitroxides (TEMPO type)	Termination	Catalytic peroxyl trapping via nitroxide/oxoammonium cycling	Moderate	Rodent models	Redox pleiotropy; reduced *in vivo* to hydroxylamine	[121]
Cu^{II}(atsm)	Termination	Intact bis(thiosemicarbazonato)Cu(II) complex acts as an RTA	High	Phase 1 in ALS (NCT02870634) and in PD	Not tested in AD; copper redistribution effects; clinical reports not yet verified here	[122,123]
α-Tocopherol	Termination	Chromanol RTA; k_{inh} approx. 3×10^6 M^{-1} s^{-1}	Moderate	RCT in AD (functional benefit)	Modest potency; tocopherol-mediated peroxidation at high load	[57,102,103]
Deuterated PUFA (RT001)	Substrate	Bis-allylic C–D bonds; primary kinetic isotope effect slows H-atom transfer	High (dietary lipid)	Phase 1/2 in several neurological diseases	Months to steady state; cost; controlled FRDA trial negative on all endpoints	[124–129]
ACSL4 inhibitors	Substrate	Reduce arachidonate incorporation into phospholipids	Variable	Rodent models	Available chemical matter is polypharmacological	[34]
LPCAT3 inhibitors	Substrate	Block PUFA incorporation into phosphatidylethanolamine	Not reported	Cell models	No *in vivo* or CNS data yet	[75]
Exogenous MUFA/SCD1	Substrate	Displace PUFA from phospholipids (ACSL3-dependent)	n/a	Cell models	Blunt remodeling of neuronal membranes	[36]
Deferoxamine	Catalyst	Hexadentate siderophore	Very poor	Small early AD trial	Parenteral; essentially excluded from brain	[130]
Deferiprone	Catalyst	Bidentate 3-hydroxypyridin-4-one; brain-penetrant	High	RCT in AD and PD (both negative or harmful)	Lowered the bulk brain iron signal and worsened outcomes in both diseases; labile pool not measured	[23,24]
Clioquinol/PBT2	Catalyst	8-Hydroxyquinoline metal-protein attenuating compounds	Moderate	Phase 2 in AD	No convincing clinical efficacy	[131,132]
M30/HLA20	Catalyst + defense	8-Hydroxyquinoline-propargylamine multitarget chelators	Moderate	Rodent models	Polypharmacology complicates attribution; preclinical	[133,134]

Table 3. *Cont.*

Agent/Class	Node	Mechanism	CNS Exposure	Highest Evidence	Principal Limitation	Refs
NRF2 activators	Defense	Induce SLC7A11, GSH synthesis, ferritin, GPX4	Variable	Approved in Friedreich ataxia (omavelox-olone)	Broad transcriptional effects; not AD-tested	[90,91,135]
Selenium/se-lenoproteins	Defense	Supports GPX4 selenocysteine and adaptive transcription	Moderate	RCT (PREADViSE, negative)	Narrow safety window; brain Se not clearly deficient	[88,136,137]
Ubiquinone/ vitamin K	Defense	Substrates for FSP1-mediated regeneration of lipophilic RTAs	Poor to moderate	Preclinical	Poor brain penetration of CoQ10; FSP1 status in AD unknown	[62,67]
CMS121	Substrate + defense	Fisetin-derived; inhibits fatty acid synthase, lowers lipid peroxidation	Moderate	Rodent AD models	Mechanism partly indirect; IND approved, early clinical stage	[138,139]
Polyphenols (baicalein, thonningianin A, α-lipoic acid)	Multiple	Simultaneously RTA, chelator, LOX modulator and NRF2 inducer	Variable, usually low	Rodent models; several outside AD	Mechanistic attribution unreliable; disease context often transferred from non-AD models	[56,140–142]

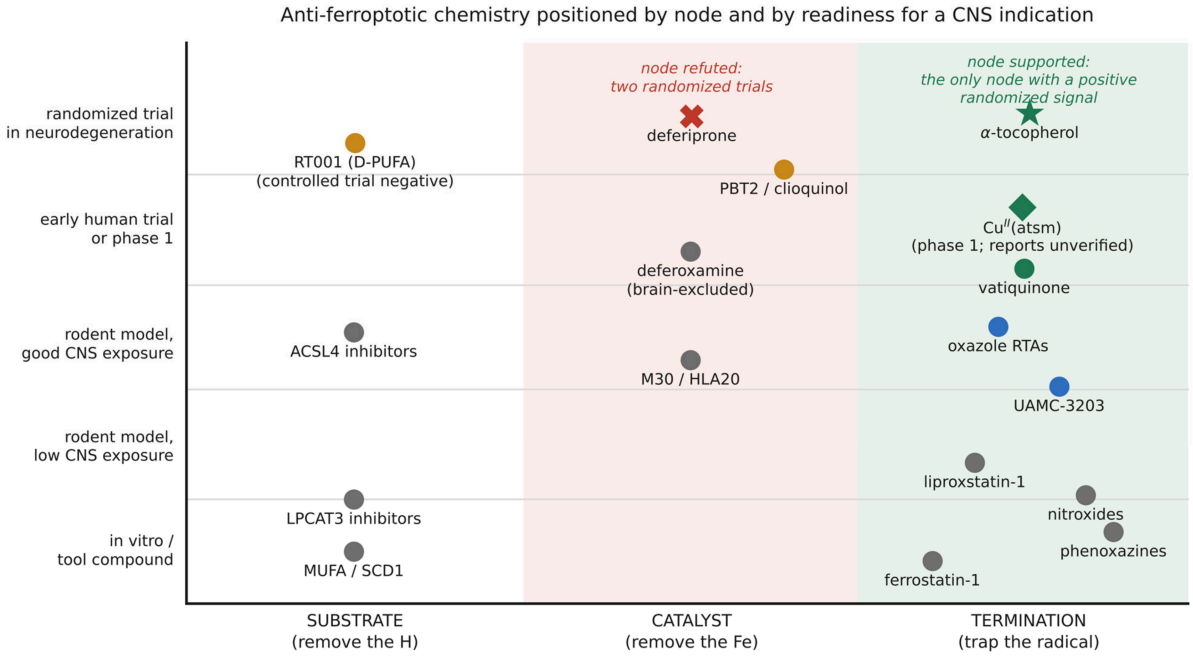


Figure 3. Chemical modulator landscape positioned by node of action against readiness for a central nervous system indication. The vertical axis combines demonstrated unbound brain exposure with clinical stage; the horizontal axis is the chemical variable each agent manipulates. Agents in the upper region have human exposure data; agents in the lower region remain tool compounds. The two agents with completed randomized trials in neurodegeneration that lowered the bulk brain iron signal are marked as refuted at that node, while the only randomized signal consistent with the hypothesis sits at the termination node.

6.1. Radical-Trapping Antioxidants: The Best-Understood Class

Ferrostatin-1 is an arylamine bearing an ester, and both features matter. The arylamine is the pharmacophore, donating a hydrogen atom to a chain-carrying peroxyl radical to give a relatively stable aminyl radical [55]. Its cytoprotective mechanism has been dissected in detail [143]. The ester is a liability: it is hydrolytically and metabolically labile, which is why ferrostatin-1 is an excellent tool compound and a poor drug despite protecting in a wide range of disease models [144]. Second- and third-generation ferrostatins addressed this, culminating in UAMC-3203, in which the ester is replaced, and the compound acquires sufficient stability and exposure for *in vivo* use [118]. Further optimization has produced oxazole-containing RTAs with oral bioavailability and high brain concentrations, explicitly designed for CNS indications [119]. Liproxstatin-1, a spiro-fused quinoxalinamine, follows the same logic with a different scaffold [55,59].

The structure-activity relationship for this class is unusually well grounded because it derives from inhibited autoxidation kinetics rather than from cell-based screening alone. Good RTAs share a heteroatom-substituted aromatic that stabilizes the radical formed after hydrogen—atom transfer, sufficient lipophilicity to partition into the bilayer, and no strongly electron-withdrawing substituent adjacent to the donating group. Phenoxazines and related tricyclic amines are exceptionally reactive on this basis [120], and 2,2,6,6-tetramethylpiperidine-1-oxyl-type nitroxides are catalytic rather than stoichiometric: they reduce peroxyl radicals by electron transfer and are regenerated through hydride transfer to the derived oxoammonium ion followed by hydrogen—atom transfer from the resulting hydroxylamine, a cycle that operates in liposomes and in cells [121]. A related cross-dismutation of hydroperoxyl and alkylperoxyl radicals accounts for their unusual efficiency at low radical flux, which is the regime a chronic neurodegenerative process actually presents, and the same catalytic behavior has since been demonstrated for the most potent ferroptosis inhibitors acting on phospholipid-derived peroxyl radicals [145,146]. Copper(II) and nickel(II) bis(thiosemicarbazone) complexes are a chemically distinct entry to the same node: Zilka and co-workers demonstrated that their anti-ferroptotic activity derives from radical-trapping antioxidant behavior of the intact complex rather than from metal delivery or chelation [123], which explains and reframes the earlier observation that Cu^{II}(atsm) inhibits ferroptosis [122]. Because Cu^{II}(atsm) has already entered phase 1 clinical study in amyotrophic lateral sclerosis (ClinicalTrials.gov NCT02870634) and in Parkinson's disease, it is, on the chemistry, the most clinically advanced anti-ferroptotic chemotype in neurology, and it has not been tested in AD. The trial registry is cited rather than a published report because no peer-reviewed clinical output was identified at the time of writing; the mechanistic claim rests on the two chemistry papers cited above and not on the trials.

That radical trapping is not merely pharmacological but physiological in neurons is shown by the requirement for vitamin A or an equivalent radical-trapping antioxidant during neuronal development [147]. α-Tocopherol belongs to this class and is the only member with a randomized clinical signal in AD, which is discussed in Section 7.3. Its limitations are chemical rather than conceptual: a modest k_{inh}, a stoichiometric factor of two, dependence on co-antioxidants for regeneration, and, at high concentration, the well-described tocopherol-mediated peroxidation whereby the α-tocopheroxyl radical can itself abstract a bis-allylic hydrogen. Newer RTAs were designed precisely to avoid these liabilities, and none has entered an AD trial.

6.2. Substrate-Directed Chemistry

If the substrate is the problem, remove the abstractable hydrogen. Site-specific deuteration at the bis-allylic position exploits a primary kinetic isotope effect to slow the rate-

limiting hydrogen-atom transfer; because the deuterated lipids act as chain-terminating defects rather than having to displace every oxidizable chain, partial replacement of the cellular PUFA pool suppresses autoxidation substantially [124,125]. This is a rare instance of a therapeutic strategy that follows directly from physical—organic chemistry. Deuterated linoleate (RT001) has been administered to patients across several neurodegenerative indications with acceptable tolerability, and an early trial in Friedreich ataxia reported signals of efficacy [126]. That result did not hold: a subsequent double-blind, placebo-controlled trial in the same indication, in 65 subjects over 11 months with maximum oxygen consumption as the primary endpoint, found no significant benefit at the doses tested in any primary, secondary, or exploratory measure [127]. In animals, the picture is more encouraging: deuterium-reinforced PUFAs improved cognition in an aldehyde dehydrogenase 2 null mouse model of sporadic AD, cutting cortical and hippocampal F_2-isoprostanes by roughly half [128]. The counter-result deserves equal weight: in APP/PS1 transgenic mice, the same dietary strategy lowered brain lipid peroxidation and hippocampal amyloid-β but produced no discernible behavioral benefit [129]. Read together, these two experiments say that suppressing peroxidation is achievable in the brain and that doing so does not automatically rescue cognition in an amyloid-driven model, which is precisely the distinction between target engagement and efficacy that the chelation trials also expose. Taken together, the deuteration strategy remains chemically compelling and clinically unproven: no positive controlled readout exists in any indication. The approach nonetheless has notable advantages for a chronic CNS indication: the agent is a dietary lipid, distributes to all membranes including brain, and does not need to be present at the moment of a stochastic ferroptotic event because the protection is built into the membrane. Its disadvantages are cost and the months required to reach steady-state membrane enrichment.

Enzymatic substrate control offers an alternative. ACSL4 inhibition reduces the incorporation of arachidonate into phospholipids and confers resistance [34], and thiazolidinediones have been used as ACSL4 inhibitors in AD models, though their polypharmacology makes attribution difficult. Selective LPCAT3 inhibitors have since been developed and shown to remodel the polyunsaturated phospholipid content of human cells and protect against ferroptosis, which makes the acyltransferase step the better validated substrate target of the two [75]. Stearoyl-CoA desaturase 1 activity and exogenous monounsaturated fatty acids shift membranes toward oxidation-resistant compositions [36]. For the brain, deliberate remodeling of neuronal membrane lipid composition is a blunt intervention with predictable consequences for synaptic function, and it is the least attractive of the substrate strategies despite its mechanistic clarity.

6.3. Iron-Directed Agents

Deferoxamine is a hexadentate siderophore, highly hydrophilic, essentially excluded from the brain after systemic administration, and requiring parenteral dosing. An early intramuscular trial in AD did report slowed functional decline, the rate of loss of daily living skills over 2 years being roughly half that of the untreated group, but it enrolled 48 patients, was single-blind with an untreated comparison arm rather than double-blind, and has not been replicated [130]. Deferiprone is a bidentate 3-hydroxypyridin-4-one, orally active, and genuinely brain-penetrant, which is why it became the test article for the causal hypothesis. Deferasirox is tridentate and less CNS-directed. The rationale for targeting chelatable iron in neurodegeneration, and the case for conservative rather than aggressive chelation, were set out before either trial reported [148]. The case for and against targeting iron pharmacologically in AD has been set out in detail elsewhere [149]. The 8-hydroxyquinolines, clioquinol and its successor PBT2, were developed as metal-protein attenuating compounds that redistribute rather than deplete metals; both reached clinical

trial in AD with modest or absent clinical effect [131,132]. Multitarget chelators built on the 8-hydroxyquinoline scaffold with propargylamine substituents, such as M30 and HLA20, combine metal binding with monoamine oxidase inhibition and NRF2 activation and remain preclinical [133,134].

The chemical objection to systemic chelation in a chronic neurological disease is straightforward and was clear before the trials read out. A chelator does not distinguish the small labile pool that catalyzes chain branching from the iron required for mitochondrial respiration, myelin synthesis, monoamine synthesis, and iron—sulfur cluster assembly. In an organ where iron is compartmentalized between neurons, oligodendrocytes and microglia, a freely distributing bidentate chelator lowers bulk iron in whichever compartment it reaches, and target engagement measured as a fall in bulk susceptibility is not evidence that the relevant pool has been touched.

6.4. Defense-Directed Agents

Reinforcing endogenous surveillance is attractive because it is self-limiting and spatially targeted by the cell's own machinery. NRF2 activation upregulates SLC7A11, glutathione synthesis, ferritin, and GPX4 in concert [90,91], and the NRF2—ferroptosis interface has been argued specifically for AD [150]. One NRF2-directed drug, omaveloxolone, was approved in 2023 for Friedreich ataxia on the strength of a randomized placebo-controlled trial, the first approved therapy for that disease [135], establishing that this pharmacology can be delivered clinically in a neurological disease. Selenium supplementation raises GPX4 activity and drove a protective transcriptional program in a stroke model [136], but the PREADViSE trial of vitamin E and selenium for dementia prevention was negative [137], brain selenium status in AD is not obviously deficient on meta-analysis [89], and a randomized pilot trial of supranutritional sodium selenate showed that selenium can be delivered to the central nervous system without establishing clinical benefit [151]. Ebselen and related organoselenium compounds mimic peroxidase activity but have substantial thiol reactivity and questionable selectivity. Vatiquinone and related quinone-based agents inhibit ferroptosis in neuronal systems and have reached clinical study in mitochondrial disease, illustrating that this node is clinically approachable [152]. Direct GPX4 activators, as opposed to inducers, do not yet exist as validated chemical matter, and claims that a natural product activates GPX4 usually rest on increased protein abundance rather than on catalytic activation.

6.5. Natural Products: What Survives Scrutiny

A large fraction of the AD ferroptosis literature consists of reports that a polyphenol, flavonoid, or traditional medicine extract reduced markers of ferroptosis and improved behavior in a rodent model. Thonningianin A and α-lipoic acid are cited this way, the latter having mitigated ferroptosis and tauopathy in P301S mice [141,142]. A second problem sits alongside the mechanistic one and is easy to miss: for several of these compounds, the anti-ferroptotic evidence does not come from AD at all. Baicalein, routinely listed among anti-ferroptotic agents for AD, was shown to suppress ferroptosis in a post-traumatic epilepsy model rather than an AD model [140], and the related baicalin data come from intracerebral haemorrhage. Transferring such findings into AD reviews without noting the change of disease context is common and should stop. The mechanistic claims attached to these reports should be treated cautiously for a specific chemical reason: polyphenols are, almost by construction, radical-trapping antioxidants and iron chelators simultaneously, and many also inhibit lipoxygenase catalysis and modulate NRF2. Attribution of their effect to any single node therefore requires evidence that is rarely provided. The demonstration that baicalein suppresses lipid autoxidation directly rather than through 15-LOX inhibition

is the clearest illustration of how these attributions go wrong [56]. This does not invalidate the therapeutic potential of these compounds; rather, it underscores the need to distinguish experimentally demonstrated effects from inferred mechanisms and to establish disease-specific relevance before extrapolating findings to AD. If a natural product is genuinely a potent membrane RTA, the appropriate development path is to treat it as a screening hit and optimize it against inhibited-autoxidation endpoints and brain exposure, the same path that produced the oxazole RTAs [119]. CMS121 illustrates the same discipline applied to a natural-product starting point: derived from the flavonoid fisetin but optimized as a drug candidate, it lowers lipid peroxidation and mitigates cognitive loss in a transgenic AD model, and its activity is assigned to inhibition of fatty acid synthase rather than to unspecified antioxidant capacity [138,139]. The mechanism is still partly indirect, but the development path is the one this literature generally fails to take.

7. The Translational Reckoning: Two Negative Trials and What They Mean

7.1. What the Trials Showed

In the 3D trial, 81 participants with amyloid-confirmed mild cognitive impairment or early AD were randomized 2:1 to deferiprone 15 mg kg^{-1} twice daily or placebo for 12 months. Deferiprone lowered hippocampal QSM, establishing that the drug reached the tissue and reduced the bulk iron signal, and accelerated cognitive decline on the primary neuropsychological composite, an effect driven by executive function, with greater frontal volume loss and a higher withdrawal rate in the treated arm [23]. In FAIRPARK-II, 372 participants with newly diagnosed Parkinson's disease who had not received levodopa were randomized to deferiprone 15 mg kg^{-1} twice daily or placebo for 36 weeks. Deferiprone lowered nigrostriatal iron on MRI and worsened the MDS-UPDRS total score, which rose by 15.6 points against 6.3 on placebo, a difference of 9.3 points (95 percent confidence interval 6.3 to 12.2); dopaminergic therapy was started in 22.0 percent of the deferiprone group versus 2.7 percent on placebo [24].

These are not underpowered null results that can be attributed to dose, duration, or population. In both cases, the drug produced the intended change in the imaging measure that was used to define engagement, and in both cases, the clinical direction was opposite to the hypothesis. Taken together, they constitute the most informative data the ferroptosis-in-neurodegeneration field possesses, and they falsify a specific version of the hypothesis: that bulk brain iron in these diseases is a pathogenic reservoir whose depletion is therapeutic.

7.2. Storage Iron, Labile Iron, and the Limits of Target Engagement

What these trials observed and what can be inferred from them should be kept apart, and the standard applied elsewhere in this review, that compatibility is not demonstration, applies here with equal force. The observations are these: deferiprone reached the brain, lowered the regional MRI iron signal in both trials, and was followed by worse clinical outcomes than placebo. What was not observed is the quantity that the ferroptosis hypothesis is actually about. QSM reports bulk magnetic susceptibility and R_2*-weighted measures likewise report bulk tissue iron; both are dominated by ferritin-bound and mineralized iron, and synchrotron speciation of AD plaque cores confirms that a substantial fraction of plaque-associated iron is present in mineral phases [98,105]. Neither modality resolves the small, kinetically labile pool that performs chain branching at the membrane, and neither trial measured that pool, in any compartment or cell type, before or after treatment.

It follows that the mechanism of the harm is not determined by the data, and the candidate explanations below are offered as hypotheses rather than as conclusions. The chelator may have drawn down functional iron required for mitochondrial respiration,

myelin maintenance, monoamine synthesis, and iron—sulfur cluster assembly, a plausible route to harm in a tissue with highly oxidative neurons and continuously iron-dependent oligodendrocytes. Alternatively, because ferritin sequestration is itself an anti-ferroptotic defense, converting stored iron into a chelator-bound and redistributable form might transiently raise rather than lower the labile pool in some compartments. A third possibility, that the labile pool fell as intended and that the harm arose by an unrelated route, cannot be excluded either. Adjudicating between these requires a measurement of the labile pool that neither trial made and that no validated human assay currently provides, so the frequently invoked mismatch between bulk susceptibility and the labile pool must be treated as an untested conjecture rather than as the explanation of the clinical result.

7.3. The Vitamin E Signal and What It Implies

Against two negative chelation trials sits one modestly positive antioxidant trial. In TEAM-AD, 613 patients with mild-to-moderate AD on background cholinesterase inhibition received 2000 IU per day of α-tocopherol, memantine, both, or placebo. Over a mean follow-up of 2.27 years, ADCS-ADL scores declined 3.15 units less in the α-tocopherol arm than in placebo, corresponding to a 19 percent per year slowing of functional decline; all-cause mortality did not differ between arms [102]. Caregiver time increased in every arm; it increased least in the α-tocopherol arm, by 1.8 h less than placebo, and that difference was nominally significant but did not survive adjustment for multiplicity, so it should not be counted as an independent benefit. An earlier trial in moderately severe AD had reported delayed progression on a composite functional endpoint [103], whereas α-tocopherol did not delay conversion in mild cognitive impairment [153], and combined vitamin E and selenium did not prevent dementia in older men [137].

TEAM-AD does not validate ferroptosis. The effect was on function rather than cognition; the trial was not designed around a lipid peroxidation biomarker, and vitamin E has activities unrelated to radical trapping. But the pattern across the six randomized trials of these two strategies, two of chelation and four of antioxidant supplementation, is internally consistent in a way that is worth stating plainly: the intervention that acts on chain propagation produced a signal in symptomatic disease, and the interventions that acted on the iron pool did not or did harm. If ferroptotic and sublethal peroxidative chemistry contributes to AD, this is the distribution of results one would expect, because propagation is the step at which a chronic, low-grade radical flux can be intercepted without disturbing an essential nutrient. The pattern is suggestive and not probative, since the trials differ in population, duration, and endpoint, and none carried a peroxidation biomarker.

7.4. Design Rules for CNS Anti-Ferroptotic Chemistry

Five requirements follow from the foregoing analysis, and they are stringent enough to disqualify most compounds currently described as anti-ferroptotic in the AD literature. First, act on propagation or on termination capacity, not on total iron. Second, demonstrate radical-trapping activity in a phospholipid bilayer assay, not only in homogeneous solution or in a cell viability screen, and report k_{inh} and the stoichiometric factor. Assays for exactly this purpose now exist, and there is no longer an excuse for inferring radical-trapping activity from a cell viability curve [154,155]. The intrinsic and extrinsic limits on how far such inhibitors can be optimized have also been mapped, which sets a realistic ceiling on what this class can deliver [156]. Third, achieve free brain concentrations above the effective potency at a tolerated dose, verified by unbound brain-to-plasma partitioning rather than by total brain levels, and avoid hydrolytically labile linkers of the ferrostatin-1 type. Fourth, carry a biomarker of the intended chemistry into the clinic; oxidized phospholipid species measurable by redox lipidomics in cerebrospinal fluid or plasma are the natural

candidates, and F_2-isoprostanes are an imperfect but available proxy whose responsiveness to intervention has been quantified across human conditions [157]. Fifth, define the target population by evidence of the mechanism rather than by diagnosis alone, since if only a subset of patients carries a substantial peroxidative burden, an unenriched trial will dilute any effect to invisibility.

8. Assay Artifacts and Reporting Standards

Much of the inconsistency in this literature is methodological, and the specific failure modes are chemical. Thiobarbituric acid reactive substances remain in use as a lipid peroxidation readout despite decades of evidence that the assay is non-specific, sensitive to sample handling, and prone to artifactual peroxidation during workup [158]. Immunodetection of 4-hydroxynonenal adducts reports a downstream aldehyde whose abundance depends on decomposition chemistry and on protein availability, not on the flux through the peroxidation chain. C11-BODIPY 581/591 is a good ratiometric membrane probe but is itself an oxidizable lipid that can be consumed, is photosensitive, and does not distinguish enzymatic from non-enzymatic oxidation [159]. The composition of the extracellular environment matters as much as the probe and is rarely controlled: melanoma cells travelling in lymph are protected from ferroptosis relative to those in blood because the surrounding fluid differs in oleic acid and glutathione content [160]. Culture media differ from one another in the same way, which confounds comparisons between laboratories. None of these measures a phospholipid hydroperoxide, which is what ferroptosis is defined by; that requires redox lipidomics by liquid chromatography with mass spectrometry, and it is still rare in AD studies.

The rescue-based definition is a second problem. Defining ferroptosis operationally as death blocked by ferrostatin-1 and by an iron chelator was reasonable in 2012 and is no longer sufficient because both classes of compound have activities beyond the pathway. A minimum control set for an AD study claiming ferroptosis should include: an RTA-inactive structural analogue of the protective compound; a second, structurally unrelated RTA; genetic rather than only pharmacological perturbation of at least one surveillance node, which for any claim resting on RSL3 or ML162 means direct genetic manipulation of *GPX4* rather than reliance on the inhibitor alone; direct measurement of at least one oxidized phospholipid species, since excessive phospholipid peroxidation is what distinguishes ferroptosis from other death modes [161]; and demonstration that the protective concentration in tissue is compatible with the *in vitro* potency. Consensus recommendations along these lines now exist [29,30], and adherence in the AD literature is poor. A further requirement is that any claim of ferroptosis in human AD tissue should state explicitly how the survivorship problem was addressed.

A third class of problem sits in the inducers rather than the readouts, and it is the one most likely to have corrupted the AD literature quietly. RSL3 and ML162, used almost universally as GPX4 inhibitors, do not inhibit purified recombinant GPX4 in enzymatic assays; both are instead potent inhibitors of the selenoprotein thioredoxin reductase 1 (TXNRD1), and the cell death produced by structurally unrelated TXNRD1 inhibitors is not suppressed by ferrostatin-1 [162]. The conclusion needs qualifying in both directions because the compound has not simply changed targets. In cells, exposure to RSL3 is still followed by loss of GPX4 activity, so the enzyme is inactivated indirectly even though it is not the direct binding target; and subsequent target deconvolution has shown that RSL3 engages the selenoproteome broadly rather than GPX4 selectively, with knockdown of *GPX4* failing to reproduce the compound's full potency in the cells in which it was tested [163]. The usable conclusion is narrower than either "RSL3 inhibits GPX4" or "RSL3 does not inhibit GPX4": sensitivity to RSL3, or rescue from it, cannot on its own be taken

as evidence that a phenotype is GPX4-specific, and any claim of that kind now requires genetic perturbation of *GPX4* alongside the compound. Sorafenib, widely described as a ferroptosis inducer, fails to trigger ferroptosis across a broad cell line panel [164]. Even phenol red in the culture medium can act as a confounder in pharmacological ferroptosis induction [165]. Any AD study whose mechanistic claim rests on one of these tools should be re-read with that in mind.

9. Research Gaps and Falsifiable Tests

The eight gaps below are stated as testable propositions rather than as aspirations, in descending order of estimated value.

G1. Redox lipidomics of AD brain with cell-type and subcellular resolution. Determine whether oxidized phosphatidylethanolamine species accumulate specifically, in which cell type, and at which Braak stage. This is the single measurement that would move the hypothesis from plausible to established or refute it.

G2. Quantify the labile iron pool, not bulk iron, in AD tissue and relate it to QSM. If the two dissociate, the candidate explanations for the chelation result set out in Section 7.2 become testable rather than conjectural, and QSM must in any case be abandoned as a surrogate endpoint for anti-ferroptotic efficacy.

G3. Test whether the surveillance arms other than GPX4 are altered in AD. FSP1 protein and ubiquinol redox state, GCH1 and tetrahydrobiopterin, and 7-DHC concentrations have not been systematically measured in human AD cortex.

G4. Distinguish chronic sublethal peroxidation from ferroptotic execution using an assay with temporal resolution, for example, a genetically encoded lipid peroxidation reporter in a slice or organoid model, and determine which is quantitatively relevant over a disease-length timescale.

G5. Determine how the *APOE*—ferritinophagy axis is modulated in ε4 carriers. Because the common apoE isoforms protect equally against ferroptosis *in vitro*, the testable proposition is not that ε4 protein is intrinsically less effective but that ε4 raises ferroptotic susceptibility through lower apoE abundance and a more oxidizable membrane lipid environment. Varying apoE concentration independently of isoform, combined with redox lipidomics in isogenic ε3/ε4 human neurons and astrocytes, would separate the two contributions and establish whether either accounts for a measurable part of the ε4 risk term.

G6. Take a CNS-optimized RTA with demonstrated bilayer kinetics and unbound brain exposure into an AD model with a pre-specified lipid peroxidation biomarker. The oxazole RTAs and $Cu^{II}(atsm)$ are the obvious candidates; the latter has entered phase 1 study in other neurodegenerative indications, although no peer-reviewed report of those results could be verified at the time of writing.

G7. Establish whether the deferiprone harm signal is on-mechanism. This requires measuring the labile pool rather than inferring it. If chelation worsens outcomes by depleting functional iron, a compartment-selective chelator should separate the two effects; if it worsens outcomes by mobilizing labile iron, it should not. Until a validated human assay for the labile pool exists, the competing explanations offered in Section 7.2 cannot be distinguished.

G8. Retrospectively test whether the α-tocopherol benefit in TEAM-AD is concentrated in patients with high baseline peroxidation. Stored samples exist. This is the cheapest available test of the central claim of this review.

10. Conclusions

Ferroptosis provides AD research with something it has lacked: a chemically specified, quantitatively tractable account of how neurons might actually be destroyed, with rate constants that can be measured and nodes that can be drugged. The mechanistic infrastructure now exists in detail, from the bond dissociation enthalpy of the bis-allylic C–H to a set of parallel surveillance and repair systems and a growing set of purpose-built radical-trapping antioxidants with brain exposure.

What the field does not yet have is proof that this chemistry runs in the human AD brain at a rate sufficient to matter. The human evidence is dominated by end-product measurements and transcriptomic signatures that cannot distinguish ferroptotic execution from generic oxidative injury, and it is subject to a survivorship problem that post-mortem tissue cannot escape. The strongest causal data come from mouse genetics, where they establish sufficiency rather than presence. Against this background, two well-conducted randomized trials lowered the bulk brain iron signal as intended and worsened patient outcomes, while the one randomized signal consistent with the hypothesis came from a mediocre radical-trapping antioxidant acting on chain propagation.

We draw three conclusions. Bulk iron depletion is, on present evidence, the wrong therapeutic strategy in AD, and bulk iron reduction should be retired as a surrogate endpoint; whether this reflects removal of functional iron, redistribution of storage iron, or some other mechanism cannot be settled until the labile pool is measured directly, and we resist the temptation to assert a mechanism the trials did not test. Propagation and termination are the defensible targets, and the chemistry to attack them, bilayer-active radical-trapping antioxidants with verified unbound brain exposure, site-specifically deuterated lipids, and reinforcement of the FSP1-ubiquinol and NRF2 arms, exists but has not been tested in AD. And the field's most urgent need is not another modulator but a measurement: direct, cell-type-resolved quantification of oxidized phospholipid species in human AD brain, with the labile iron pool measured alongside it. Until that experiment is done, ferroptosis in AD will remain an unusually well-specified hypothesis rather than an established mechanism, and the therapeutic literature will continue to expand faster than the evidence that justifies it.

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