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PERSPECTIVE

Reversing Alzheimer's disease dementia with clemastine, fingolimod, or rolipram, plus anti-amyloid therapy

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Abstract

A few anti-amyloid trials offer a slight possibility of preventing progression of cognitive loss, but none has reversed the process. A possible reason is that amyloid may be necessary but insufficient in the pathogenesis of AD, and other causal factors may need addressing in addition to amyloid. It is argued here that drugs addressing myelination and synaptogenesis are the optimum partners for anti-amyloid drugs, since there is much evidence that early in the process that leads to AD, both neural circuits and synaptic activity are dysfunctional. Evidence to support this argument is presented. Evidence is also presented that clemastine, fingolimod, and rolipram, benefit both myelination and synaptogenesis. It is suggested that a regimen that includes one of them plus an anti-amyloid drug, could reverse AD.

KEYWORDS
anti-amyloid compounds, clemastine, fingolimod, reversing Alzheimer's dementia, rolipram, supporting drugs

1 | INTRODUCTION

Experimental treatments for Alzheimer's disease (AD) that have undergone clinical trial, have largely been based on the mainstream view that amyloid or its precursor, oligomeric amyloid beta (Aβ), has a primary role in pathogenesis. Very few anti-amyloid trials offer a slight possibility of preventing progression of cognitive loss, but none has reversed the process. There are many possible reasons for the numerous failures, one of which is that amyloid may be necessary but insufficient in the pathogenesis of AD.[1] Related to this, other causal factors may need addressing in addition to amyloid. If that be the case, then one should choose as the optimal partner for anti-amyloid therapy a drug that benefits other factors that participate most importantly in the pathogenesis of AD. Here it will be argued that drugs addressing myelination and synaptogenesis are the optimum partners, because there is much evidence that early in the process that leads to AD, both neural circuits and synaptic activity are dysfunctional. This article will, first, describe the relevant details of oligodendrocytes, including the sequence of their formation, their myelinating properties, and the concurrence of myelination and synaptogenesis; next, it will present some facts about myelination and synaptogenesis in relation to their disturbance in AD; and finally, it will provide the evidence that clemastine, fingolimod, and rolipram might benefit myelination and, therefore, AD, although the mechanism for this is unknown.

1.1 | Myelinating oligodendrocytes and their precursors

To be able to produce myelin, oligodendroglial cells progress through a series of highly regulated steps for the differentiation from oligodendrocyte precursor cells (OPCs) to pre-myelinating, then myelinating, mature oligodendrocytes; the latter have an elaborate morphology with many branched processes that wrap around naked axons

to form the sheaths of myelin. A small fraction of OPCs is maintained in an immature and slowly proliferative or quiescent state in the adult central nervous system (CNS) where they are called "adult OPCs," which are present in all brain structures and account for up to 9% of the total cellular population of the CNS. Typical OPC markers are platelet-derived growth factor receptor-alpha (PDGF-Rα), neuroregulin 2 (NG2), and Olig1; when OPCs start to differentiate to pre-oligodendrocytes, they express different antigens such as O4, while NG2 and PDGF-Rα become downregulated; typical mature oligodendrocytes' markers include myelin-oligodendrocyte glycoprotein (MOG), myelin associated glycoprotein (MAG), galactocerebroside (GalC), and myelin basic protein (MBP). Adenosine (A) receptor subtypes (A_1, A_{2A}, A_{2B}, A_3) are expressed on both OPCs and mature oligodendrocytes.

Oligodendrocytes are particularly vulnerable to dysfunction for three reasons. First, the mechanism of myelination requires that oligodendrocytes have an extremely high metabolic rate. Second, myelination involves many enzymes that require iron as a co-factor, causing OPCs and oligodendrocytes to have the largest intracellular stores of iron in the brain, which may lead to formation of reactive oxygen species (ROS). Third, oligodendrocytes have only low concentrations of the anti-oxidative enzyme glutathione. For these three reasons, oligodendrocytes are particularly vulnerable to oxidative damage. Finally, oligodendrocytes express N-methyl-D-aspartate receptors (NMDARs), making them liable to excitotoxicity from glutamate.

Abnormal myelination of white matter tracts at a very early age was demonstrated by Desai et al. in mice transgenic (Tg) for mutations that occur in familial AD.[2] 3×Tg-AD mice harbor three mutations: human presenilin-1 M146V ($PS1^{M146V}$), human amyloid precursor protein Swedish mutation (APP^{Swe}), and the P301L mutation of human tau (tau^{P301L}). They display white matter disruption and alteration in myelin marker expression in subregions of the hippocampus and the entorhinal cortex brain regions as early as 2 months of age; in these mice, Desai et al. reported that mechanisms incited by $A\beta_{1\text{-}42}$ undermine the oligodendrocyte lineage. Oligomeric Aβ was significantly elevated by 2.2-fold at age 6 months but was already substantially increased by 1.3-fold (N.S.) at 2 months. At age 6 months, myelin deposition was also abnormal. Using an intrabody, which is an antibody functioning within a cell (see Paganetti et al.[3]), showed that blocking parenchymal $A\beta_{1\text{-}42}$ accumulation abrogated the abnormalities in both oligodendrocytes and myelin.

1.2 | Role of adenosine in oligodendrocyte precursor maturation

Adenosine is relevant because it has a key role in oligodendrocyte maturation. Thus, a selective A_{2A} receptor agonist, CGS21680, inhibited OPC differentiation and reduced levels of both $O4^+$ pre-oligodendrocytes and MAG^+ mature oligodendrocytes. Adenosine A_1 receptors have a pro-differentiating effect on oligodendrocytes whereas the A_{2A} receptor prevents myelin deposition; so, a high level of the A_{2A} receptor, as was seen in AD, would have a deleterious effect on myelination. Merighi et al. evaluated the expression of A2A receptors in frontal white matter, frontal gray matter, and hippocampus/entorhinal cortex, in the brains of six patients with AD and four age-matched controls. In the AD patients, the expression of A_{2A} receptors in frontal white matter, frontal gray matter, and hippocampus/entorhinal cortex was, respectively, increased 1.7-fold, 2-fold, and 3-fold ($P < .01$).[4]

1.3 | Diffusion tensor imaging and mean diffusivity

Microstructural changes in white matter are shown by diffusion tensor imaging (DTI), which measures the fractional anisotropy of proton diffusion and decreases with decreased myelination. By contrast, higher values of mean diffusivity tend to reflect a downturn in the health or integrity of the tissue in which it is measured. As will be seen below, fractional anisotropy and mean diffusivity often identify abnormal myelination but in different brain areas.

1.4 | Myelin and cognition in healthy persons and in AD

1.4.1 | Myelination in cognitively normal persons

Bendlin et al. studied 120 cognitively normal persons aged 18 to 83 years who, on the day of the brain scan, received comprehensive neuropsychological testing.[5] Fractional anisotropy showed a negative correlation with age in frontal, parietal, temporal, and occipital white matter; that is, increasing age correlated with decreased myelination in those locations. General processing speed measured by Trail Making Test Part A was negatively related to fractional anisotropy, that is, a worse result in Trail Making Test Part A correlated with decreased myelination. The Brief Visuospatial Memory Test (BVMT) total score (which assesses visuospatial learning and memory) was positively correlated with white matter in the bilateral anterior thalamus, right internal capsule, left anterior corona radiata, bilateral posterior corona radiata, right superior corona radiata, and right external capsule, that is, better visuospatial learning and memory were correlated with better myelination in those locations. Thus, even in health, myelination and cognition are associated.

1.4.2 | Myelination in cognitively normal persons at risk for AD, and also in aged monkeys

Ringman et al. studied persons who either had, or were at risk for having, known pathogenic PS1 or APP mutations.[6] Compared to the 8 non-carriers of mutations, the 12 carriers had reductions of fractional anisotrophy in the fornix of 24% ($P = .02$) and in frontal white matter of 12.5% ($P = .02$). It is worth mentioning that similar findings, vis-à-vis age, were reported by Makris et al., who compared DTI results from seven young and seven elderly rhesus monkeys.[7]

1.4.3 | Myelination in patients with mild cognitive impairment

Liu et al. performed DTI scans on 83 patients with amnestic mild cognitive impairment (aMCI) and 85 healthy controls.[8] The patients with aMCI showed decreased mean fractional anisotropy in the fornix, and higher mean diffusivity in the fornix and bilateral uncinate fasciculus, that is, had decreased myelination in those areas. These results were confirmed in two subtypes of aMCI: 32 with single-domain aMCI, and 23 with multiple-domain aMCI, compared to 23 healthy controls.[9] Neuropsychological measures and DTI data showed that both aMCI groups had significantly reduced fractional anisotropy in the right superior longitudinal fasciculus.

1.4.4 | Myelination in patients with AD

Many studies have reported abnormal results in AD. Two earlier and two later are cited here but there are several others. Rose et al. compared mean diffusivity and fractional anisotropy in the brains of 13 AD patients and 13 age-matched controls.[10] Increased diffusivity was seen in the posterior cingulate gyrus bilaterally; fractional anisotropy was significantly reduced in the thalamus, parietal white matter, and posterior limbs of the internal capsule. Naggara obtained measurements in 12 patients with early AD, having mean Mini-Mental State Examination (MMSE) score of 27.[11] Diffusivity was increased in the splenium of the corpus callosum and in white matter of the frontal and parietal lobes; fractional anisotropy was bilaterally decreased in the white matter of the temporal lobe, the frontal lobe, and the splenium. A more recent report was by Mayo et al. from studies in 49 individuals with AD and 48 matched healthy older adults.[12] Those with AD had significantly lower fractional anisotropy in the corpus callosum, left internal capsule, corona radiata, posterior thalamic radiations, inferior longitudinal fasciculi, inferior fronto-occipital fasciculi, external capsule, cingulate gyri, right hippocampal cingulum, right fornix, superior longitudinal fasciculi, and tapetum; and they had significantly higher mean diffusivity in the corpus callosum, internal capsule, corona radiata, left posterior thalamic radiation, left inferior longitudinal fasciculi, inferior fronto-occipital fasciculi, cingulate gyri, right hippocampal cingulum, fornix, superior longitudinal fasciculi, uncinate fasciculi, and tapetum. Despite the widespread changes in white matter, Mayo et al.[12] found no significant association between DTI metrics and memory scores. Chen et al. showed that MBP+ areas, that is, myelinated ones, were significantly decreased in AD patients in both the cortex and hippocampus, indicating widespread myelin loss in regions that are critical for memory and other cognitive functions.[13]

1.5 | Synaptogenesis is associated with myelination

Some studies have suggested that the effects of neuronal activity on myelination may be mediated by the release of neurotransmitters from synaptic vesicles, and it is known that stimulation of neuronal firing can promote myelination along manipulated axons. Almeida et al. used zebra fish to study the mechanism of this in vivo, by imaging synaptic vesicle fusion in individual neurons in living larvae of zebra fish.[14] Larvae were paralyzed by mivacurium and immobilized in agarose on their sides; images could then be photographed for analysis. They identified the vesicle by imaging synaptophysin, that is specifically localized to synaptic vesicles, and saw robust vesicular fusion along axons during their myelination. Blocking axonal vesicular fusion reduced the growth and stable formation of nascent myelin sheaths. Piorkowska et al. examined synaptogenesis and myelination of neuronal connections in growth-restricted guinea pig fetuses, using synaptophysin and synaptopodin as markers of synaptic development and maturation.[15] The fetuses had reduction of synaptogenesis, synaptic maturation, and myelination. Human pre-term infants are susceptible to white matter injury of their brain and many reports show that they also have widespread death of pre-oligodendrocytes under conditions that do not trigger significant degeneration of cortical neurons.[16] Interestingly, the high-risk period for white matter injury occurs at a time when the injured area is populated primarily by pre-oligodendrocytes that are a principal target for cell death. Wang et al. noted that in human neonates, non-myelinating OPCs are often plentiful in the area of white matter injury and that there is a persistent maturation arrest.[17] Wang et al. also observed that in the brains of hypoxic mice, myelination as demonstrated by expression of MBP was greatly reduced; and concurrently with that, the densities of immunostaining for the presynaptic marker synapsin1 and the postsynaptic marker Homer 1 were also decreased. Synaptic function was also severely attenuated as shown by decreased excitatory postsynaptic currents (mEPSC) recorded from pyramidal cortical neurons. The muscarinic receptor 1 (M1R) in OPCs is a negative regulator of oligodendroglial differentiation; Wang et al. used M1R knockout (ko) mice, and showed that deletion of M1R in OPCs resulted in the expected enhancement of the ability of oligodendrocytes to differentiate and myelinate axons. Importantly, the densities of synapsin1 and Homer1 positive puncta were rescued in the M1R ko hypoxic brains compared to the hypoxic wild-type littermates. Their results demonstrate that chronic hypoxia results in hypomyelination plus disruption of synaptogenesis, and that restoration of myelination concurrently restores synaptogenesis.

1.6 | Summary to this point

The presented data show widespread abnormalities in white matter in patients with preclinical AD, MCI, and AD, confirming the abnormality of myelin in AD and its precursor states. The data also show that there is a close association between the occurrence of myelination and synaptogenesis, although the mechanism is unknown. Addressing myelination and synaptogenesis offers a possibility of reversing the white matter abnormalities and thereby of reversing AD.

1.7 | Drugs to benefit oligodendrocytes and myelination

1.7.1 | General background justifying drugs to benefit oligodendrocytes and myelination

Major myelin proteins are MBP, MOG, MAG, and proteolipoprotein (PLP), which are mainly expressed at the peripheral processes of the oligodendrocytes that cover the myelin sheath.[18] Demyelination by specific antibodies against MOG caused disintegration of myelin sheaths.[19] Papuć et al. sought antibodies against MOG, MBP, MAG, and PLP in 26 AD patients and 26 age-matched controls (mean MMSE scores were, respectively, 16.9 and 28.7).[20] Immunoglobulin G antibodies against all of those proteins were significantly elevated in AD compared to controls: against MOG were 14.7-fold higher, against MBP were 14.7-fold higher, and against PLP were 18.8-fold higher. These results suggest that treatment with anti-B cell medication such as rituximab might reduce the formation of those antibodies, if they are present, and benefit myelination.

1.7.2 | Clemastine

Mei et al. cultured oligodendrocytes with micropillar arrays of compressed silica and demonstrated that the micropillars became ensheathed with an MBP-positive membrane.[21] They used that system in a high-throughput screen of 1000 bioactive molecules and identified a cluster of antimuscarinic compounds that significantly enhanced oligodendrocyte differentiation. Among those molecules, the most efficacious was clemastine, a widely available antihistamine that crosses the blood–brain barrier and has a favorable safety profile. They administered clemastine to adult mice at a concentration of 10 mg per kg body weight per day before inducing demyelination by injecting lysolecithin into the dorsal funiculus and ventrolateral white matter of adult mouse spinal cords. Clemastine promoted differentiation of oligodendrocytes, and it also enhanced remyelination in a gliotoxic model of demyelination.[21] Li et al. gave clemastine to mice with cuprizone-induced demyelination and in the demyelinated regions saw more mature oligodendrocytes and greatly enhanced myelin repair.[22] Further, clemastine enhanced myelination in the prefrontal cortex of socially isolated mice.[13,23]

Note that Mei et al.[21] used a dose in mice of 10 mg/kg, which is approximately 100 times the maximum recommended dose for humans. Nevertheless, in 50 patients with multiple sclerosis (MS), Green et al. performed a randomized, placebo controlled, cross-over, double-blind study of clemastine 5.36 mg twice daily (this dosage was approved by the Food and Drug Administration [FDA]) for 60 to 90 days;[24] 56% of their patients had a previous history of optic neuritis. The primary outcome was assessed by visual function, which is almost always impaired in people with MS. The investigators recorded the number of letters the patients reported correctly. The prespecified efficacy endpoint for the trial was met, with reduction of a latency delay of 1.7 ms/eye. Importantly with respect to the present topic, no serious adverse events occurred although, expectedly, a frequent adverse event was fatigue. The authors also reported that clemastine induced human induced pluripotent stem cell–derived oligodendroglia to produce MBP+ve material.

The disruption of both myelination and synaptogenesis by hypoxia in neonates is described in an earlier section. Adults may, rarely, also develop post-hypoxic leukoencephalopathy after a period of prolonged cerebral hypoxia. Cree et al. reported a 45-year-old man who had had a period of prolonged hypoxia and developed severe cognitive decline; results from a Montreal Cognitive Assessment (MoCA) were only 6/30.[25] This patient was administered clemastine fumarate 5.36 mg twice daily (see below for discussion of clemastine treatment); 5 months later, when still taking clemastine, his cognitive function had markedly improved and MoCA score was now 30/30.

In brief, clemastine as an adjunct to anti-amyloid therapy might justifiably be used, probably in the dose used by Green et al.,[24] in a trial of therapy aimed at remyelinating the brain in patients with AD.

1.7.3 | Rolipram

Cyclic AMP (cAMP) is central to many signaling pathways, including protein kinase A (PKA) and extracellular regulated kinases (ERKs), and via PKA, cAMP is the major positive regulator of the cAMP response element binding protein (CREB), because it controls the transcriptional, translational, and post-translational modifications of key molecules involved in long-term potentiation (LTP), synaptic plasticity, and memory consolidation and retrieval. As reviewed by Pugazhenthi et al., CREB is a constitutively expressed nuclear transcription factor that regulates the expression of genes involved in neuronal survival and function, and is essential for the formation and retention of memory in several species.[26] CREB-mediated gene expression is increased in the hippocampus during LTP. cAMP is hydrolyzed by phosphodiesterase 4 (PDE4), which is abundant in the brain, and rolipram is a high-affinity inhibitor of PDE4, which should be beneficial in AD because Aβ triggers hydrolysis of cAMP with deleterious consequences. Wang et al. infused rats with A$\beta_{1\text{-}42}$, which induced memory deficits that were reversed by rolipram in a dose-dependent manner.[27] In another study that used mini-syringes to deliver rolipram to the hippocampus, Monti et al. were able to show that this enhanced both CREB phosphorylation and the expression of the cAMP-dependent, memory-related Arc gene, causing a significant slowing down of the memory extinction rate.[28]

In the brains of six AD patients with Braak stages V-V1, Liang et al. found a selective reduction in the levels of regulatory and catalytic subunits of cAMP-dependent PKA as well as of its enzymatic activity.[29] They also observed that in mouse brain, PKA subunits were proteolyzed by calpain, and that the levels of those subunits correlated negatively with calpain activation in the AD brain—inferring that decreased levels of PKA components that they saw in AD brain were most likely caused by calpain overactivation. Further, PKA levels produced by extracts of brain were reduced in AD compared to age-matched controls. Their findings led them to propose that in the brain of AD, overactivation of calpain because of calcium dysregulation causes increased degradation and thus decreased activity of PKA, which contributes, in turn, to downregulation of CREB and impaired cognition and memory.

Sun et al. investigated the effects of rolipram on remyelination after demyelination by cuprizone or lysolecithin; rolipram treatment promoted OPC maturation and enhanced remyelination.[30]

A group of proteins, collectively known as myelin-associated inhibitory proteins (MAIs) and produced by oligodendrocytes, inhibit CNS regeneration: these proteins are Nogo-A, MAG, and oligodendrocyte-myelin glycoprotein (OMgp); they all bind a single receptor, the Nogo receptor (NgR1). Upon binding to NgR1, the MAIs impede axonal growth by promoting growth cone collapse via stimulation of Rho-A, which in turn activates Rho-Kinase (ROCK) and thus inhibits axonal cytoskeletal assembly. Beneficially, Rho activation is inhibited by cAMP-PKA,[31] which may explain why prevention of the hydrolysis of cAMP by rolipram could be helpful. Nikulina et al. showed that when rolipram was delivered 2 weeks after a spinal cord hemisection, with embryonic spinal cord tissue implanted at the injury site, there was a significant increase in axon growth and in recovery of function in the impaired forelimb.[32] Beaumont et al. produced a contusive cervical spinal cord injury and saw that rolipram caused an increase in oligodendrocytes and improved conductivity in the descending and ascending ventrolateral funiculus.[33] In other rodents with a spinal cord injury, Schaal et al. found that rolipram treatment produced a 167% increase of mature oligodendrocytes.[34] Sun et al. showed, in studies of rolipram mentioned above, that the increased numbers and function of oligodendrocytes was dose dependent.[30]

In brief, the approved drug rolipram benefits both the myelination and function of the brain.

Rolipram has not been used in AD but has been used for depression in several trials but in doses of 1.5 to 3.0 mg daily. In those doses, headache and nausea have affected 10% to 20% of subjects. It seems unlikely that .25 mg twice daily would cause major side effects.

1.7.4 | Fingolimod

Fingolimod treatment benefits mature, myelinating oligodendrocytes, neural tracts, synaptic function, and dendritic spine density. Zhang et al. induced experimental autoimmune encephalitis (EAE) in mice and scored neurological function based on diminished tail tone, ataxia, paresis of hind limbs or forelimbs, or tetra-paresis.[35] Fingolimod increased the OPCs, which led to an increased area of myelination, and improved neurological function. Miron et al. demyelinated cultured slices of hind brain and cerebellum by adding lysolecithin; they then added fingolimod to the cultures for 2 weeks, which led to production of mature oligodendrocytes and many myelin sheaths.[36] Miron et al. also administered fingolimod during the 4–6 weeks after initiation of EAE, which resulted in reduced demyelination, decreased paralysis, and normalized neurologic function. Gurevich et al. administered fingolimod to 30 patients with relapsing MS, and assessed axonal and myelin integrity in specific white matter tracts before and 1 year after starting treatment.[37] In patients with impaired pyramidal function at baseline, fingolimod induced a significant increase in fractional anisotropy ($P = .002$) and a decrease of radial diffusivity ($P = .03$) in the corticospinal tract. Gol et al. induced myelin damage in their hippocampus and cerebral cortex by treating mice with pentylenetetrazol; fingolimod protected against demyelination in the CA1 and CA3 hippocampal regions and significantly increased neuronal cell number.[38] Thus, this evidence shows that, via improved function of oligodendrocytes, fingolimod induced repair of damaged neural tracts.

Fingolimod also benefits synaptic function. Sphingolipids, particularly S1P, have a prominent and enabling role in the molecular biology that defines therapies which benefit synaptic function, which is why fingolimod, an analog of S1P and a modulator of its receptor, might be expected to improve synaptic function. Yin et al. reported an analysis showing that four of the six genes most highly enriched regarding the targets of fingolimod in AD, involved synaptic function.[39] They used databases to predict fingolimod targets that are both predicated on its chemical structure and experimentally confirmed, and then they identified the genes controlling those targets. Next, using microarray data in a database for 423 AD patients and 266 normal controls, they identified genes that are differentially expressed in AD. Finally, they compared the genes identified as targets for both fingolimod and AD, and found that among 188 AD-associated fingolimod target genes, 6 are enriched more than 5-fold. Four of those six fingolimod target genes involved synaptic functions that include signaling, chemical transmission, and transsynaptic transmission. In AD model mice, Joshi et al. found that fingolimod induced an increase of NMDARs on dendritic spines; and neurons treated with soluble Aβ plus fingolimod had 22% ($P \leq .001$) more post-synaptic densities, as measured by the presence of GluN2a, than had neurons treated with soluble Aβ alone.[40] Using cultures of healthy, mature primary hippocampal neurons, Patnaik et al. showed that fingolimod regulated the architecture of dendritic spines and induced an approximately 10% increase in their density.[41] In EAE, Rossi et al. saw that fingolimod markedly decreased the loss of dendritic spines as well as causing a reversal of both pre-synaptic hyperactive NMDARs and post-synaptic hypersensitive AMPARs.[42] This confirmed the earlier findings of Sim-Selley et al., that S1P receptors are prevalent throughout the cerebral cortex and amygdala in rats, and that their activation inhibited, beneficially, glutamatergic neurotransmission.[43] In 13 patients, Landi et al. applied transmagnetic stimulation (TMS) to the motor cortex at baseline before starting a daily dose of fingolimod.[44] Measurements at baseline and then 60 days later showed that fingolimod caused a significant reduction in the stimulatory effect of TMS, which is mainly mediated by glutamate.

In brief, the approved drug fingolimod benefits both myelination and synaptogenesis.

There are potentially serious side effects of fingolimod but should be minimized with use of the decreased dosage of .25 mg daily. The manufacturer's brochure should be consulted for full details. Contraindications include recent myocardial infarction, unstable angina, stroke, transient ischemic episode, congestive heart failure, heart block, and QTc interval ≥500 ms. Life threatening and fatal infections have occurred in association with fingelimod, which should be interrupted if a patient develops a serious infection, and should not be commenced in patients with active acute or chronic infections.

Before starting treatment, an ophthalmologist should rule out pre-existing macular edema. Moreover, an electrocardiogram must be obtained; fingolimod is contraindicated if it shows atrioventricular block, sick-sinus syndrome, or QTc > 470 ms (women) or > 450 ms (men). Other contraindications include treatment with β-blockers; class-I or -III antiarrhythmics or other medications causing bradycardia; chronic or active infections; severe liver insufficiency; and malignancies. Although side effects seem formidable, their frequency is low and with reduced dosage of 0.25 mg daily should be even lower.

The Freedoms 2 trial in MS allocated 358 to fingolimod 0.5 mg, and 355 to placebo.[45] The increases caused by fingolimod 0.5 mg versus placebo, were: lymphopenia in 8%, increased alanine aminotransferase in 6%, hypertension in 6%, first-dose bradycardia in ≈0.5%, first-degree atrioventricular block in 3%, herpes zoster in 2%, basal-cell carcinoma in 2%, macular edema in 1%, infections in 2%.

1.8 | Clinical trial

The benefit of the proposed drugs should be validated by clinical trials. Each drug should be used with adacanumab, an antiamyloid preparation approved by the FDA. The drug, its dosage, and use in which particular stage of AD is based upon the severity of its side effect profile: clemastine 5.36 mg twice daily for non-amnestic MCI; rolipram 0.5 mg daily for amnestic MCI; fingolimod 0.25 mg daily for established AD. Note that the dosages for rolipram and fingolimod are half the usual ones, to minimize the risks of side effects.

2 | DISCUSSION

There have been very limited clinical benefits from hundreds of clinical trials of anti-amyloid therapies despite the encouraging pre-clinical evaluations showing that those therapies reduce the cerebral burden of amyloid. One possible reason for this is that pyroglutamate Aβ is more toxic than unmodified Aβ;[46] yet even donanemab, which antagonizes pyroglutamate Aβ, gave only slight benefit.[47] Perhaps the many failures are not surprising, in light of the multiple pathways that participate in the pathogenesis of AD,[48] and it seems likely that those failures show the need to address more than one major pathogenetic influence. Clearly important as determinants of AD are the effects of myelination and synaptogenesis; and they are benefitted by available drugs clemastine, fingolimod, and rolipram. It is argued here that using one of those three in combination with anti-amyloid therapy offers a good chance of reversing AD. This article provides the evidence that supports that argument, which could be validated by clinical trials.

3 | CONCLUSIONS AND SUMMARY

- Because anti-amyloid drugs have been largely unsuccessful in either halting progression of AD or reversing it, addition to such treatment might be effective.
- Abnormal myelination and synaptic dysfunction occur in MCI and AD, and correlate with cognitive loss in them as well as in healthy individuals.
- Clemastine, fingolimod, and rolipram benefit myelination and, therefore, synaptogenesis.
- Using one of those three drugs in combination with anti-amyloid therapy might reverse the dementia of AD.

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