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Perspective

Prevention of Alzheimer's disease by treating mild cognitive impairment with combinations chosen from eight available drugs

Jeffrey Fessel*

Department of Medicine, University of California San Francisco, San Francisco, CA

Abstract Several hundred clinical trials of initially promising drugs have failed to produce meaningful clinical improvement of Alzheimer's disease (AD), which is probably because there are at least 25 biochemical pathways known to be aberrant that underpin the disease, and unless there is a single drug that addresses all or most of them, even promising drugs if given alone are unlikely to succeed. Because so many pathways are potentially at fault, it is quite possible that no treatment might succeed. However, because amnestic mild cognitive impairment (aMCI) often precedes AD and, assuming that those with aMCI who progress to AD commence with insufficient risk factors for AD but accrue them later, then it is likely that fewer pathways need addressing in aMCI than in AD to either prevent progression of aMCI to AD or effect its reversion. Published reports show that eight drugs, that is, dantrolene, erythropoietin, lithium, memantine, minocycline, piracetam, riluzole, and silymarin, address many of the pathways underlying MCI and AD. Among those eight drugs, combinations between either two or three of them have combined nonoverlapping actions that benefit enough of the approximately 25 pathways at fault so that their convergent efficacy has the potential to prevent aMCI from progressing to AD. The combinations should be subjected to a clinical trial in persons with aMCI to establish their safety and efficacy.

1. Introduction

It came as a great surprise to this author, so presumably might be the same for others, to recognize that the published literature suggests that combinations of two or three chosen from eight drugs, that is, dantrolene, erythropoietin, lithium, memantine, minocycline, piracetam, riluzole, and silymarin, have a potential efficacy for the treatment of amnestic mild cognitive impairment (aMCI). This presentation will summarize the mechanisms of and the evidence for the efficacy of the eight drugs. Multiple biochemical pathways are either actually or potentially impaired in the pathogenesis of mild cognitive impairment (MCI), and enough must be addressed for treatment to be successful. The combined and convergent actions of either two or three of the eight drugs cover as many as 21 of the approximately 25 biochemical pathways known to be relevant in the pathogenesis of AD. If used at the stage of aMCI, such combinations have the potential to halt its progression, whereas it is possible that by the time overt dementia has developed, far more pathways have become aberrant and thus reversal of the process is more difficult to achieve. The suggested combinations merit trials in aMCI to validate both their efficacy and safety.

2. Biochemical pathways underpinning AD and MCI

Although these biochemical pathways involve more than biochemical reactions, they are also biological, affecting the plasma membrane of both the cell itself and its nucleus. It is useful, however, to use the shorthand "biochemical pathways" in referring to them. Those pathways cluster, somewhat arbitrarily, into approximately 25 categories, involving synaptic function; neural plasticity; neuronal apoptosis; mitochondrial function; deposition of amyloid or its precursor $A\beta_{42}$; tau deposition; glutamatergic neuronal function; cholinergic neuronal function; adrenergic neuronal

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*Corresponding author: Tel.: 415 563 0818; Fax: 415 563 0818.
E-mail address: Jeffreyfessel@gmail.com

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function; GABAergic neuronal function; Ca^{2+} release from the endoplasmic reticulum affecting the NMDAR and causing excitotoxicity; locally excessive Ca^{2+} causes mitochondria to release free radicals, leading to peroxidation of unsaturated fatty acids in cell membranes and cell death of neurons, astrocytes, and endothelial cells; phosphoinositide kinase and phosphoCREB activation; JNK activation; the unfolded protein response; autophagy; insulin resistance; oxidative stress; release of β-catenin from the Wnt/β-catenin complex; microglial activation producing immune activation in the brain; systemic inflammation transmitted to and affecting the brain; genetic mutations; abnormal gene expressions; deficient cerebral microcirculation; and impaired astrocyte function. The 25th category underpinning AD is the influence of brain aging. Besides the above, depression, obesity, and cardiovascular disease have contributory roles.

3. Why combination therapy is necessary for successful therapy?

Targeting only one or a few of the aforementioned pathways must be inadequate but were a sufficient number addressed, then major clinical benefit might ensue. No single drug addresses all the potential aberrances in those pathways, whereas combinations of drugs may have convergent actions upon many of them; some possible combinations and the pathways they benefit are described below. Next, there are multiple interactions between the pathways, as illustrated in great detail in reference [1]. Those interactions produce an abundant redundancy, such that blockade of one pathway leaves several alternative routes still open. For example, if one wishes to prevent result 'b', and both a→b and c→b operate, then blocking the pathway from 'a' will not prevent formation of 'b' if the c→b pathway remains open. The problem is compounded if, besides from 'a' and 'c', there are d……n other possible routes to 'b'. Combination therapy is required, to block as many alternative routes as possible.

Two further points are important. First, a previously unsuccessful trial with a particular drug given singly is no bar to its use in a combination that provides a wider coverage. Second, it is also possible that the dosages of drugs used in a combination will be lower than when used as single agents.

4. The time to intervene so as to prevent progression is when aMCI is identified

Important data showing the time relations of events antedating AD derive from the Colombian kindred of around 5000 individuals, among whom approximately 39% have been genotyped and found to be affected by the *PSEN1* E280A mutation [2]. Dementia appears at an average age of 49 years but brain imaging of their brains shows amyloid 15 years before and tau deposition 6 years before the dementia [3]. Four years after amyloid deposition, there were subjective memory symptoms; and approximately when tau deposition was shown (6 years before dementia), aMCI appeared with memory complaints now affecting daily living activities. Clearly, intervention to prevent dementia should be made without needlessly overtreating too many people, which means starting when aMCI appears. In this large family although not necessarily in either other families or individuals, that means when tau deposition is seen. However, intervention in a population cannot be based on imaging because of both its expense and unavailability of facilities. Therefore, intervention should be usually based on the presence of aMCI because during that gap before AD develops, there are, surely, more pathogenetic events being added and contributing to subsequent dementia. Because there is no way to know if there is merely one or several additive factors, the advantage to using a triple or dual drug combination is that it modifies multiple, potential pathogenic factors.

5. List of drugs (in alphabetical order) with potential efficacy in treatment combinations for MCI

5.1. Dantrolene

The endoplasmic reticulum (ER) represents the major dynamic Ca^{2+} intracellular pool, where Ca^{2+} levels are highly concentrated (≈100–500 μM) compared with cytosolic levels (≈100 nM) [4]. Ca^{2+} is released from ER stores mostly via the receptors for ryanodine (RyR), and because mitochondria have close proximity to the ER, the Ca^{2+} released from ER stores may be excessively concentrated in mitochondria, causing them to release free radicals that lead to neuronal apoptosis [5]. Ryanodine receptors (RyRs) are increased in early AD (Braak stage I–II), as shown by increased [H^3]ryanodine binding, which was particularly prominent in the subiculum and CA1 and CA2 regions of the hippocampus [6]. Their increased number may heighten liability to excessive and potentially dangerous intraneuronal levels of Ca^{2+}. RyRs have three isoforms, RyR1, RyR2, and RyR3. RyR1 is expressed at low levels in cerebellum and Purkinje cells. RyR2 is predominantly expressed in Purkinje cells of cerebellum and cerebral cortex, and in the dentate gyrus of the hippocampus, and RyR3 is found in the hippocampal CA1 pyramidal cell layer [6]. In MCI, RyR2 mRNA levels were increased by 2-fold in midtemporal cortex ($P < .05$) and by 1.8-fold ($P < .08$) in the midfrontal cortex [7]. Thus, blocking RyRs with dantrolene would be beneficial by lowering release of calcium (see also Table 1).

Although results from TG animal models must be interpreted with caution [8], three reports using animal models substantiate the potential benefits to MCI from dantrolene. In the first study, the dantrolene was administered to 3xTg-AD mice for 8 months [9]. Dantrolene significantly reduced both memory deficits and amyloid load. In the second study, dantrolene normalized synaptic transmission and neural plasticity in mice transgenic for AD [10]. Those authors showed that dantrolene treatment not only normalized ER Ca^{2+} signaling but also diminished Aβ

Table 1
Benefits from eight drugs

Dantrolene	Ca^{2+} release↓; memory↑; synaptic transmission↑; neural regeneration↑; neuronal apoptosis↓; amyloid load↓; BCl2↑
Erythropoietin	Memory↑; synaptic plasticity↑; neural regeneration↑; AKT activated; BCl2↑; Bax↓; pTau↓; EPCs↑; astrocytes↑; insulin resistance↓.
Lithium	Neuronal excitability↓; synaptogenesis↑; plasticity↑; IMP-ase↓; unfolded protein response↑; autophagy↑; NF tangles↓; BCl2↑; VEGF↑; TGF-β↑; activated Wnt/β-catenin↑; oxidative stress↓; amyloid load↓; mitochondrial function↑; insulin resistance↓.
Memantine	Ca^{2+}-induced excitotoxicity↓; NO-induced excitotoxicity↓; mitochondrial function↑.
Minocycline	JNK↓; amyloid↓; insulin resistance↓; mitochondrial function↑; brain immunity↓; transmitted systemic immunity↓.
Piracetam	Mitochondrial fusion/function↑; neuronal excitability↓; synaptic markers↑; plasticity↑; neurite outgrowth↑; cognition↑; oxidative stress↓; cerebral microcirculation↑.
Riluzole	Hyper-pTau↓; cognitive decline↓; excessive glutamate release & excitotoxicity↓; EEAT↑; $Aβ_{40-42}$↓; synaptic transmission↑ (downregulated genes for neurotransmission become upregulated).
Silymarin/silybin	Memory↑; dendritic spines↑; learning↑; soluble and insoluble Aβ↓; JNK↓; ERK↓; antioxidative enzymes↑; insulin resistance↓; decreased dopamine in PFC↓; brain immunity↓; transmitted systemic immunity↓.

↑ implies improvement; ↓ implies decrease.

load and reduced neurohistological lesions. Others confirmed the reduction of Aβ load by dantrolene [11]. In several cell types, dantrolene use was associated with a marked increase in the antiapoptotic protein Bcl2 and reduced neuronal apoptosis [12].

5.2. Erythropoietin

Erythropoietin offers several benefits to AD, besides its correction of any current anemia. (1) It improved both synaptic plasticity and memory [13]. (2) Erythropoietin supported regeneration of both cholinergic and dopaminergic neurons, and neuronal proliferation in the dentate of AD [14]. (3) By activating AKT-enhancing, anti-apoptotic BCl-2 expression, and downregulating proapoptotic Bax expression, it was neuroprotective [15–17]. (4) Erythropoietin prevented the hyperphosphorylation of tau causing neurofibrillary tangles, which is induced by β-amyloid [18]. (5) Erythropoietin enhanced both the differentiation of astrocytes and generation of endothelial progenitor cells, and improved memory in both humans and animals, presumably because receptors for erythropoietin are present on neurons and astrocytes [19], and on endothelial cells [20] (i.e., on all of those cellular elements that are impaired in AD [1]). (6) Erythropoietin reverses insulin resistance [21].

5.3. Lithium

Lithium has many beneficial actions for MCI. (1) It was shown to increase synapse formation between hippocampal neurons in culture [22]. (2) Lithium reduces oxidative stress, as reflected by lower levels of ROS, 4-HNE, and protein carbonyls; increased levels of antioxidant enzymes including catalase and heme-oxygenase; and increased levels of glutathione (reviewed in ref [23]. (3) Lithium inhibits GSK-3β, which has several actions promoting the pathogenesis of MCI/AD: (a) its hyperphosphorylation of tau protein causes neurofibrillary tangles [24]; (b) it enhances production of Aβ, thus deposition of amyloid [25]; (c) it inhibits the actions of CREB, which are important for neuronal survival, proliferation, and memory [26]; (d) GSK-3β phosphorylates β-catenin which is then degraded by ubiquitination and the proteasome system [27]; and (e) lithium increased proliferation of adult hippocampal neuron precursor cells compared with controls, whereas upregulation of GSK-3β activity halved proliferation of those cells [28]. Thus, by inhibiting the phosphorylation of GSK-3β and thereby its activity, lithium also reduces formation of neurofibrillary tangles, Aβ, and amyloid neuropathology; benefits neuronal survival, proliferation, and memory; and maintains the presence and accumulation of β-catenin, that then translocates to the nucleus and activates genes that transcribe proteins participating in the formation of dendrites and synapses [29]. (4) Lithium also inhibits inositol monophosphatase, thus maintaining high levels of inositol triphosphate and enhancing both upregulation of the unfolded protein response, and autophagy of degraded and toxic cell proteins [30]. (5) Lithium upregulates Bcl2 [31,32], which is reduced in AD [32] and which is anti-apoptotic and neuroprotective, so its upregulation counteracts the neuronal loss seen in AD [31]. (6) Another advantage of lithium is reversal of insulin resistance [33], which is a feature of MCI [34]. (7) Lithium upregulates vascular endothelial growth factor produced by brain endothelial cells and astrocytes [35], thus benefiting the cerebral microcirculation. (8) Finally, telomere shortening, which promotes genome instability, is a consistent finding in AD [36] and, which should be advantageous, lithium was found to increase telomere length in the 3xAD-TG mouse model [37].

Benefiting so many pathways relevant to MCI/AD, it is not surprising that lithium has been used in patients with MCI/AD. Some but not all studies saw benefit from lithium. A short, 10-week study gave negative results [38] but a metaanalysis of 3 trials involving 232 participants found that lithium significantly decreased cognitive decline as compared to placebo [39], and in MCI, a two-year study saw cognitive and functional decline over two years in those receiving placebo, whereas the patients treated with lithium

remained stable [40]. Both duration of exposure and its dosage are important determinants of effects from lithium, as shown by a nationwide study in Denmark, which found 73,731 individual patients with an incident diagnosis of dementia, matched them with 733,653 persons without that diagnosis (overall median age was 80.3 years), and was able to match each person, based on municipality of residence, with the level of lithium in the local drinking water consumed over a 19-year period [41]. The incidence rate of dementia was significantly less in those exposed to >15 mcg/L ($P < .001$) as compared with those exposed to 2.0–5.0 mcg/L, although that exposure provided only low doses of lithium for a prolonged period. Concordant findings were made in a group of 61 patients with aMCI who had beneficial results from deliberately low dosages of lithium, that were prescribed to yield subtherapeutic concentrations (0.25–0.5 mEq/L) [42]. After 24 months of treatment, lithium treatment gave better performance on memory and attention tests, whereas those given placebo had cognitive and functional decline. The gain from low dosage lithium was further established in McGill-R-Thy1-APP transgenic rats which were administered a microdose lithium formulation delivering lithium at blood concentrations below the detection limit of 0.06 mM/L [43].

5.4. Memantine

Memantine enters the NMDAR ion channel only when it is already open and decreases the permeability of that channel; by doing so, it prevents an influx of Ca^{2+} and thus also prevents excitotoxicity. The influx of Ca^{2+} induces mitochondrial production of free radicals and release of apoptosis-inducing factors, leading to neuronal apoptosis. Memantine has low affinity for the channel pore and quickly dissociates from it and does not cause either an excessive or lengthy block, and for unknown reasons, memantine more effectively blocks the extrasynaptic NMDARs' activity that contributes the most to excitotoxicity, than it blocks synaptic NMDARs that contribute the least [44]. Furthermore, memantine via an indirect mechanism prevents formation of toxic levels of nitric oxide (NO): that is because Aβ1-42 activates astrocytic α7-nicotinic-acetylcholine receptors (α7-nAchR) that have high Ca^{2+} permeability which induces astrocytes to release glutamate; the latter stimulates excessive production of neuronal NO synthase, after which toxic levels occur of NO [45]. Memantine, besides blocking the ion channel of NMDARs, also blocks those of α7-nAchRs and indirectly prevents NO toxicity [46]. In patients with severe AD, memantine improved certain behavioral measures, particularly those reflecting aggression, and prolonged the duration of time spent before needing to enter a long-term care facility; it did not, however, benefit mild AD [47]. Although most studies have shown no benefit from using memantine as a single agent in MCI, it is worth repeating that failure of an agent when applied as a sing drug is no bar to its use as a part of a multidrug regimen. Memantine administered with galantamine gave a suggestive benefit to MCI [48]. Using memantine as a single agent in MCI gave 40% marked or great improvement and another 35% with moderate improvement [49].

5.5. Minocycline

Minocycline prevents activation of JNK [50], prevents the deposition of amyloid [51], and stabilizes mitochondria [52]. JNK is particularly emphasized because, although it has almost 100 substrates and therefore extremely diverse effects (for a review, see ref [53]), in adults the brain has the highest expression of JNK [53]. Of its three isoforms, active JNK2 and JNK3 were seen in association with neurofibrillary tangles and plaques [54], and in cultured cortical neurons, cell death induced by excitotoxicity was prevented by inhibition of JNK [55]. Inhibition of JNK also interfered with cleavage of the amyloid precursor protein (APP) and reduced the levels of its soluble oligomers [56]. Another deleterious effect of JNK relevant to AD is its mediation of insulin resistance [57]. Thus, aside from its other benefits, the action of minocycline in preventing activation of JNK makes it an important member of the proposed triple therapy. Acting as an antibiotic, minocycline also reduces the systemic, humoral inflammatory reaction that is due to infection and may cross the blood-brain barrier. Minocycline produces the anti-inflammatory response, including release of TGF-β1, TNF-α, IL-6, and IL-8, both systemically and, in the brain, via glial cells; gene expression analysis showed that this is caused by the downregulation of NFκB [58].

5.6. Piracetam

Piracetam shifted the balance of mitochondrial fission or fusion toward fusion, which is more favorable for ATP production [59]. That study showed that with piracetam, neurite outgrowth in cultured cells was increased and mitochondrial permeability was decreased. A review indicated favorable effects on neurotransmission, neuroplasticity, and microcirculation [60]. Another report showed that the increased neurite length after piracetam treatment was accompanied by increased expression of the synaptic marker, GAP43, thus improving neural plasticity [61]. After oxidative stress induced by sodium nitroprusside and serum deprivation, piracetam induced a nearly complete recovery of mitochondrial membrane potential and ATP levels; and piracetam protected individual complexes of the mitochondrial respiratory chain after treatment with different respiratory chain complex inhibitors [62]. Levetiracetam, a derivative of piracetam, reversed synaptic and cognitive deficits in a mouse model of AD [63]. Meta-analysis of 19 double-blind, placebo-controlled studies, in which a total of 737 elderly persons with cognitive deficits were given active treatment with piracetam, showed that improvement was gained in the clinician-rated Global Impression of Change by 60.9% of those given piracetam versus 32.8% in those given placebo [64]. In hippocampal slices, piracetam reduced neuronal excitability [65].

5.7. Riluzole

Riluzole, a glutamate modulator, inhibits excessive presynaptic glutamate release that can cause excitotoxicity and neuronal death [66]. In rats, it caused a clustering of dendritic spines, enhancing neuroplasticity, and preventing age-related cognitive decline [67]. Also in rats, multiple genes that are downregulated in AD were upregulated by riluzole: the most upregulated genes were those controlling regulation of synaptic transmission, learning and memory, transmission of nerve impulses, regulation of synapse vesicles, and regulation of synaptic plasticity [68]. Furthermore, riluzole increased the gene expression of the excitatory amino acid transporter, which helps maintain the correct amount of glutamate in the synaptic cleft, and is decreased in both aging and AD. In mice, riluzole decreased the level of hyperphosphorylated tau, which would be expected to decrease deposition of tau protein [69]. In mice transgenic for 5 familial AD mutations, riluzole ameliorated cognitive decline and reduced levels of Aβ40-42 by ~50% [70]. In that study, riluzole rescued hippocampal expression of both synaptic and extrasynaptic NMDARs. Finally, for certain animals including the Mongolian gerbil, transient forebrain ischemia produced degeneration of pyramidal cells in the hippocampal C1 area but when riluzole was administered after the ischemia, that degeneration was prevented by 50+% [71].

5.8. Silymarin/silybin

Silymarin, whose main component is silybin, is an extract of *Silybum marianum* (milk thistle) and has multiple effects. One major role is to decrease levels of pERK and pJNK [72]. Furthermore, APP-transgenic mice fed silymarin/silibinin, 16 mg/kg/d for 6 months, had decreased deposition of amyloid plaques and of soluble Aβ oligomer levels [73]. Dosage for a 70 kg human is 1120 mg/day, almost double (600 mg/day) that used in a study of diabetics that produced a decrease in insulin resistance [74]. Further benefits of silymarin/silibinin include increased superoxide dismutase, glutathione peroxidase, and catalase [75], and inhibited activation of JNK [76,77]. In addition, silymarin/silibinin decreased acetylcholinesterase, increased the density of dendritic spines by > 2-fold, and improved spatial learning [78], and ameliorated the impaired recognition memory and reduced the decreased level of dopamine in the prefrontal cortex caused by methamphetamine [79]. That is relevant because dopamine plays a role in higher cognitive functions such as memory, learning, attention, and decision making. Of the five dopamine receptors, D1 and D2 dominate in the brain. D1 is largely excitatory and potentiates LTP; D2 is largely inhibitory and potentiates LTD. A major loss of D1 receptor expression was seen in the frontal cortex of AD brains, whereas the D2 receptor expression was only moderately reduced [80]. Others saw a 34% reduction of D2 receptor binding in the hippocampus of AD patients [81]. Thus, it should be beneficial that silymarin/silibinin might prevent reduction of dopamine in the brain. A final advantage of silymarin/silibinin is that it has potent anti-inflammatory effects, that, as with minocycline (see above), is via inhibition of NFκB activation so that gene transcription by NFκB does not occur [82]. That would apply to systemic inflammation, and probably also to brain inflammation because silymarin/silibinin inhibits activation of microglia [83] and microglia also use the NFκB pathway [84].

6. Choosing a combination of drugs from the aforementioned list

Formulating an appropriate combination of drugs must be guided by using the fewest of them covering the most biochemical pathways, has an acceptable toxicity profile, and involves no serious drug-drug interactions. Table 1 summarizes the main effects, both positive and negative, resulting from each of the 8 drugs described previously in detail. A number of different combinations have potential for success, including both dual and triple combinations. Lithium and silymarin/silibinin contribute more coverage than any of the others and some of the gaps are filled by suggested companion drugs. As regard to the pill burden of combination therapy, it should be pointed out that sometimes as many as five drugs may be required in other serious medical situations; examples include infection by multidrug resistant tuberculosis or human immunodeficiency virus, diabetes, and rheumatoid arthritis. The following are some possible combinations available for treating MCI; other combinations are certainly possible. For obvious reasons, the triple combinations provide wider coverage than the dual combinations but not greatly so. The latter, however, have the advantage of a lower pill burden plus the possibility that the affected, relevant biochemical pathways in MCI may be fewer than in AD.

6.1. Lithium, memantine, and minocycline

Lithium addresses 16 of the 25 or more molecular pathways potentially participating in the pathogenesis of MCI; adding memantine covers 2 and minocycline covers 4, unaddressed by either lithium or memantine. Thus, that triple combination addresses 22 pathways. Even lithium with its broad coverage has not caused meaningful clinical improvement in AD when used alone; it is possible that the additional, supportive, coverage from memantine and minocycline might be shown in a clinical trial as sufficient to prevent progression of MCI to AD. Minocycline has some crucial effects: its ability to decrease activation of JNK is one of them; its reduction of brain inflammation and transmitted systemic inflammation are others; decrease of both amyloid deposition and of insulin resistance are two more; and improvement of mitochondrial function affects a central problem in AD. Its ability to decrease excitotoxicity is additionally valuable. That several effects of the compounds in a combination are overlapping might

be advantageous, especially for critical pathways such as mitochondrial function and insulin resistance.

6.2. Dantrolene, lithium, and silymarin/silibinin

This is another triple combination, and it covers 22 nonoverlapping biochemical pathways. Lithium, as noted, covers 16; silymarin covers 5 not covered by lithium and includes the important prevention of JNK activation plus both systemic and brain inflammation. It is an OTC drug but carries a very high pill burden. Dantrolene's contribution is to impede the release of Ca^{2+} and to further reduce the deposition of amyloid.

6.3. Riluzole, minocycline, and piracetam

Riluzole covers 5 pathways and, importantly, upregulates several of the genes that become downregulated in AD. Minocycline adds 6 pathways to those covered by riluzole. Piracetam also covers 4 pathways not covered by either riluzole or minocycline; it has valuable benefit for mitochondrial function; and its improvement of the cerebral microcirculation benefits both neurons and astrocytes. This triple combination covers 15 pathways.

6.4. Lithium and erythropoietin

This is a potent dual combination that provides coverage to as many as 22 pathways because erythropoietin adds coverage to 6 not covered by lithium; but it does not prevent activation of JNK, which may or may not be a serious disadvantage. The low pill burden is an advantage because lithium requires only one tablet twice daily (and use of only one tablet, for a lower dosage is worth considering); and erythropoietin requires only one injection weekly.

6.5. Lithium and silymarin

This dual combination covers 21 pathways because silymarin/silibinin adds coverage of 5 to 16 covered by lithium. Unlike the combination of lithium and erythropoietin, JNK activation is inhibited by silymarin/silibinin as are both brain and systemic inflammations. A disadvantage is the high pill burden imposed by silymarin.

6.6. Erythropoietin and silymarin

This dual combination covers 17 pathways.

6.7. Erythropoietin and minocycline

This dual combination covers 15 pathways.

6.8. Erythropoietin and piracetam

This dual combination also covers 15 pathways.

7. Structure of possible clinical trials

Clinical trials will be necessary to establish both the safety and efficacy of the suggested drugs. The following is a preliminary skeleton of such clinical trials. Two sequential pilot studies should be the initial step to establish safety as well as preliminary efficacy.

Persons with the clinical diagnosis of aMCI would be invited to enroll. Their predicted rate of progression may be calculated from data in a review detailing results of 15 studies reporting a total of 1320 patients with aMCI involving either single or multiple cognitive domains [85]; 537 (40.7%) of them progressed to AD over a period of 2.4 years/study, that is, 17%/year. A statistician would calculate the number of enrollees required to establish efficacy, based on a yearly decrease by 25% of conversion to established dementia, that is, a conversion rate of 12.75%/year, in those assigned the experimental treatment as compared with those assigned to standard of care.

All patients would have neuropsychological testing at baseline to confirm the diagnosis, then every 6 months. The trial duration would be 48 months but would be extended to 72 months if analysis at 48 months showed a decrease of $<12.75>5$%/year because confirming even a small percentage decrement would encourage testing different combinations. Patients would be randomized 1:1 to experimental treatments or standard of care. At screening, patients would have a routine, complete physical examination, and laboratory tests (CBC, chemistries, serologies for syphilis, hepatitis B, hepatitis C). Exclusion criteria would include uncontrolled hypertension (BP $>$ 150/90 if age >80, $>140/85$ if age 70-79, $>130/85$ if age 60–69), active hepatitis B (positive HBsAg), untreated hepatitis C (detectable HCRNA), active syphilis, cancer except for squamous cell skin cancer, and history of cerebrovascular disease. Laboratory testing, drug levels, and targeted physical examination would be repeated every 12 weeks. Targeted physical examination will be performed every 6 months. A nested study would examine pharmacokinetics of the tested drugs. A Data Safety Monitoring Board would review results of adverse events, drug levels, routine laboratory tests, and neuropsychological examinations, every 6 months. The first pilot study would use a triple combination composed of lithium, minocycline, and memantine, as the experimental treatment. After complete accrual of the first study, the second study would start enrolling a second cohort of patients and would use a triple combination of lithium, dantrolene, and silymarin, as the experimental treatment. Later, the triple combination of piracetam, riluzole, and minocycline, and the dual combination of erythropoietin plus lithium, could be subjected to trial. The study sites would be five or more major centers having large numbers of potential subjects and investigators willing to act as principal investigators.

8. Conclusions

The epidemic of AD may be staunched by impeding progression of aMCI. That aim might be achieved by addressing simultaneously, as many biochemical pathways as possible that contribute to the pathogenesis of MCI. Eight drugs that are all currently available and that cover many of those biochemical pathways are described. Combinations chosen from these drugs, some using three and some using two of them, potentially benefit as many as 22 of the 25 relevant biochemical pathways. The choice between these combinations should be based on safety, pill burden, drug-drug interactions, and total number of nonoverlapping pathways covered. The safety and efficacy of any chosen combination must be established by a clinical trial.

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RESEARCH IN CONTEXT

1. Systematic review: Using Google Scholar, PubMed, and citations provided in existing publications, the author identified drugs addressing the pathogenesis of mild cognitive impairment (MCI) and Alzheimer's disease (AD).
2. Interpretation: This review disclosed the following. The pathogenesis of MCI and AD may involve 25 or more different biochemical pathways. Although the precise, operative number differs from case to case, evidence suggests that >>2 pathways are usually involved. Because amnestic MCI (aMCI) is often the forerunner of AD, it is likely to have fewer impaired pathways in its pathogenesis than has AD, so therapeutic intervention should optimally occur when the diagnosis is made of aMCI. The fact that many clinical trials of single drugs have produced no clinical benefit supports the concept that treatment should cover as many potentially aberrant biochemical pathways as possible. Each of the eight currently available drugs addresses one or more elements of aMCI's pathogenesis. Combinations chosen from those eight drugs cover many of the 25 pathways. Triple and dual combinations are described that together address between 15 and 22 of the pathways and therefore might potentially be effective in preventing the progression of aMCI to AD.
3. Future directions: Clinical trials should test both the efficacy and safety of the suggested combinations of drugs.

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