Review

Formulating Treatment to Cure Alzheimer's Dementia

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Formulating Treatment to Cure Alzheimer's Dementia

Short title: Curing Alzheimer's dementia

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Abstract: There are two generic approaches to curing any medical condition. The first treats every patient for all of the known possible causes that contribute to pathogenesis; the second individualizes potentially curative therapy by identifying in each separate patient only those components of pathogenesis that are actually operative, and treating those. This article adopts the second approach for formulating a cure of Alzheimer's dementia (AD). Components of AD's pathogenesis are, in alphabetical order: circadian rhythm disturbances, depression, diabetes and insulin resistance, dyslipidemia, hypertension, inflammation, metabolic syndrome, mitochondrial dysfunction, nutritional deficiencies, TGF-β deficiency, underweight, vascular abnormalities, and Wnt/β-catenin deficiency. For each component, data are described that show the degree by which its prevalence is more in the patients with mild cognitive impairment (MCI) who did not revert to having normal cognition than in those who did, because the former group is the pool of patients from among which future AD may develop. Addressing only those components that are present in a particular individual, is potentially a curative strategy. Published data indicate that curative therapy requires that the number of such components to address should be ≥3. Although structural brain changes cannot be directly addressed, the impaired neural tracts result from many of the reversible causal elements, so correcting them will benefit those tracts.

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Introduction

Despite thousands of articles that detail its causal factors, there is still no cure for Alzheimer's dementia (AD). A likely reason for this failure, is that almost all clinical trials of potential treatments, have applied single drugs. There are, however, two generic principles applicable to curing any medical condition. Applied to Alzheimer's dementia (AD), the first of those principles would treat all of the known possible causes that contribute to its pathogenesis. AD has 15+ causes, the number of causes depending upon how they are counted; but that number is large, so potentially curative treatment would require an unmanageably large number of drugs. Also, in this first approach a cure would apply to every patient; thus, since causes of AD may differ from patient to patient, such a 'one size fits all' approach may be inappropriate. The second generic principle identifies for each separate patient only those components of pathogenesis that are actually operative, and treats those. Identifying those components can be difficult. However, for curing AD, identifying those components may be based upon the fact that many subjects (>30% in one large study[1]) with mild cognitive impairment (MCI) revert to having normal cognition (NC) while most do not. Addressing those causal elements whose prevalence is more in the patients who did not revert to NC than in those who did, is potentially a curative strategy because it is from among the non-reverters that future AD may develop. Note that AD itself has never been reported to have spontaneous remission; were it to have occurred, the causal elements less prevalent in non-remitters than remitters would also

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point to potentially curative treatment of persistent AD. This article describes the second approach to curing AD and considers how to formulate curative therapy that is correct for individual patients, i.e., is personalized and individualized medicine. The generic approach is illustrated in Table 1, showing that a condition would be treated if data show that it has been significantly associated with dementia, whether or not that condition was present at the time of MCI.

Table 1. Generic approach to determine conditions to treat if present in an individual patient after transition from MCI to dementia.

Condition.	Present at MCI	Present at dementia.	Treat at dementia?
Depression	+	+	+
Diabetes	+	+	+
Hypertension	−	+	+*
Lipids ↑	−	−	−
CRP ↑	+	+	+
Weight ↓	+	−	−
Wnt ↓	−	+	+*
Metabolic synd.	−	+	+*
Circadian rhythm ↑	**+**	**+**	**+**

Footnote: *although absent at MCI, it is treated at dementia since data show its association with dementia.

There are two preliminary issues. First, any treatment for AD can affect only those causal elements that are reversible; irreversible elements such as gender, prior education, and structural brain changes, must be ignored. It will be objected, that structural brain changes with impaired anatomy and physiology of neural tracts may produce dementia so must be the focus of curative treatment. It should be noted, however, that the impaired neural tracts result from many of the reversible causal elements, so correcting those will benefit the tracts. The second issue concerns the minimal number of conditions that need correcting in order to achieve cure. That number must be established by clinical trial but published data that will be shown below, suggest it is ≥3.

In brief, the approach proposed here is based on the biological changes that occurred in an individual patient, which means that curing AD may require different treatments for different patients. The following sections show all of the reversible, important causal elements that may require correction, and is largely based upon data showing the causal elements whose prevalence is greater in MCI patients who did not revert to NC than in those who did. Addressing a sufficient number of those elements in patients who have Alzheimer's dementia, should cure their dementia.

Depression and AD

Although studies show differences in the prevalence of depression in patients who progressed from having MCI to having AD, the general finding is that they had significantly increased occurrence of baseline depression when contrasted with those having MCI that reverted to normal cognition. Among participants with mild cognitive impairment, 52.0% in mid-life (<65 years) and 26.6% in later life (≥65 years) reverted to normal cognition after 4 years; and those whose age was <65, had more reversion to normal cognition after 4 years if at baseline they had had less depression [1]. Conversely, those with more depression at baseline, subsequently over a 2 year period, had more progression of MCI to dementia, with a hazard ratio (HR) 4.8[2]. A small study followed 105 persons with MCI and used the Montgomery-Asberg Depression Rating Scale (MADRS)[3]. At baseline, the 105 subjects had MADRS score 9.8; the 23 cases who had developed dementia, after 3 years' follow-up had baseline MADRS score 11.5 ($p < .01$). A similar observational study had 68 patients who progressed to dementia among the 279 patients with MCI; the odds ratio (OR) for baseline depression and subsequent dementia was 1.62[4]. Mourao et al., in a meta-analysis of 18 studies that had 10,861 MCI subjects, found that in the group of MCI subjects progressing to dementia, those with depressive symptoms at baseline as compared to those without them, had a pooled risk ratio (RR) of

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1.28 (p = 0.003)[5]. In 9 cohort studies of participants with MCI and depression, 8 had an increased risk of progression to dementia, for which the pooled RR was 1.35 patients[6].

There were discrepant findings in a 6 year follow-up of 441 community-dwelling persons with MCI, in which depression as measured by the Hamilton depression scale was no more common in those who progressed to dementia than in those with MCI who did not so-progress[7]. That discrepant finding may relate to the population that was studied, because a review of 14 published studies showed a 44.3% prevalence of depression in 1899 hospitalized patients with MCI but only 15.7% in 775 community dwelling patients.

In brief, the data show that treating depression, if present, should contribute to reversal of dementia.

Diabetes, insulin resistance, and AD

A study that followed 500 subjects with normal cognition at baseline, showed that the OR for subsequent MCI in 160 of them was 5.28 times in diabetics as compared with the 340 whose cognition remained normal[8], and another one that compared patients with MCI at baseline who progressed to dementia, with non-progressors, found that progression in those with diabetes was 3-fold higher than in those without diabetes[9]. The pooled RR was 1.92 in two reviews that analyzed 11 reports of patients with diabetes and MCI that progressed to dementia[6,10]. In another review of published studies in diabetic patients with MCI, their reduced rate of cognitive decline was clearly shown as due to treatment of the diabetes, since the RR in 4 studies was 0.53 when individuals taking medications were compared with those not taking them[11]. It is notable that prediabetes, defined as HbA_{1c} 5.7-6.4%, did not predict subsequent dementia for the 11,656 participants of the Atherosclerosis Risk in Communities (ARIC) study[12]. In that study, an earlier age of onset of diabetes had the strongest association with dementia: for onset before 60 years, HR 2.92; for onset at 60-69 years, HR 1.73; and for onset at 70-79 years, HR 1.23. Perhaps these differences stem from a longer duration of diabetes when its onset is earlier.

Regarding the mechanism for the association between diabetes and AD, a small but relevant study showed that those with MCI who progressed to dementia, had a reduced cerebral metabolic rate of glucose metabolism[13]; that is because cerebral insulin resistance is heightened in diabetics[14]. Additionally, diabetes affects microglial function: a review that examined 267 articles, found that diabetes modulates microglia by affecting their secretion of a wide variety of cytokines and chemokines (NF-κB, NLRP3 inflammasome, fractalkine/CX3CR1, MAPKs, and Akt/mTOR), their metabolic reprogramming, and their increased promotion of reactive oxygen species (ROS)[15]. Brabazon et al. showed that insulin reduced the pro-inflammatory M1 microglial phenotype[16]. They exposed cultured microglia to the pro-inflammatory stimulus of lipopolysaccharide, and then, after administering insulin they saw significantly reduced production of NO, ROS, and TNF, which showed that insulin diminished the pro-inflammatory M1 phenotype of microglia. Haas et al. added insulin to microglia in culture, and showed an increase of phosphorylated Akt Ser473, which is an M2 microglial protein and reflects a switch from the pro-inflammatory M1 microglial isoform to the anti-inflammatory M2 isoform [17].

Insulin resistance is another mechanism for the association, and its role in the pathogenesis of AD cannot be underestimated. It involves the endoplasmic reticulum (ER), the unfolded protein response (UPR), autophagy, and mitochondrial function. The complex molecular biology involved in insulin resistance has a key role in the pathogenesis of AD, and therefore in the quest for its cure. This is not the place for an exhaustive description of the details of the complex mechanisms; the following is a synopsis of the actions of the various components.

The endoplasmic reticulum (ER) is a major player because it regulates proteostasis, lipid metabolism, gluconeogenesis, and calcium signaling (see ref [18]); and it is the site where the early steps of insulin biosynthesis occur[19]. Disturbances in ER homeostasis are referred to as "ER stress"[20]. Hyperglycemia, hypoxia, and ROS, lead to ER stress and the UPR may follow[18]. Three proteins, protein kinase-like ER kinase (PERK), inositol requiring 1 (IRE1), and activating transcription factor 6 (ATF6), function as sensors controlling the UPR during ER stress[21]. Upon

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their activation, these three sensor molecules trigger a signaling cascade leading to the UPR, from which downstream effectors promote an adaptive response, feedback control, and regulation of cell fate. The adaptation initially involves activation of molecular chaperones and folding enzymes in order to enhance protein-folding. This leads to reduced ER workload through mRNA degradation and attenuation of translation, as well as elevated ER-associated protein degradation and clearance of unwanted proteins through autophagy. If the UPR becomes hyperactivated, e.g., from hyperglycemia or ROS, the UPR regulators switch-off so as to resolve the unwanted effects.

As occurs with so many intercellular and intracellular functions, there are multiple interconnectivities between the ER, the UPR, autophagy, mitochondrial function, and insulin resistance. Another protein, the mitogen-activated protein kinase (MAPK), orchestrates diverse events related to AD, such as tau phosphorylation, ROS, neurotoxicity, neuroinflammation and synaptic dysfunction[22], and there is cross-talk between the MAPK signaling pathways and the UPR[23]; and mitochondria, which control so many aspects off cellular metabolism, are physically connected with the ER through specialized proteins in a region that is called the mitochondria-associated ER membrane (MAM); one of these proteins is mitofusin 2, and links the ER and mitochondria with insulin signaling[24].

In brief, the UPR is important in the pathogenesis of AD in two ways: 1, because it affects both survival of critical cells i.e., neurons, astrocytes, microglia, and cell death i.e., neurocytotoxicity; and 2, because amyloid derives from unfolded proteins.

Regarding the actions of insulin in the brain, IRE 1 has a crucial function in insulin biosynthesis[25], is activated in response to ER stress, and helps maintain protein folding; IRS is central to insulin signaling and glucose regulation.

Regarding lithium, one of its benefits is reversal of insulin resistance that is a fundamental feature of AD[26]. Lithium restored insulin sensitivity in diabetic rats[27], and lithium increased, by approximately 2.5-fold, the transport of glucose induced by insulin[28]. Inhibitors of GSK3β, such as lithium, also produced improvements in whole-body insulin sensitivity in insulin-resistant animals[29]. Nevertheless, in this respect lithium is a two edged sword because it inhibits IRE1, that is required for insulin's biosynthesis[25].

In summary, aggressively treating diabetes if present, should contribute to reversal of dementia; and even if there is no diabetes, insulin resistance can be overcome by the use of intranasal insulin.

Vascular pathology and AD

Many studies have shown vasculopathy as associated with progression of MCI, and diabetes is merely one among a long list of risk factors for vascular disease. Among 298 patients with MCI who were followed for five years, percentages were significantly higher at baseline in those with progression to AD than in those without progression: for diabetes +9.7%, for hypercholesterolemia +5.9%, for, cardiovascular disease +9.9%, for hypertension 10.5%[15]. A literature review that included five reports of patients with both MCI and cerebrovascular disease, showed RR of 1.61 for that association[6]. The same review included three reports of patients with both atrial fibrillation and MCI that progressed to dementia; for that association the RR was 2.60. Vascular risk factors (VRF) were considered treated if they received specific medication at baseline. Compared with the subjects with untreated VRF, subjects with some or all VRF that were treated had lower risks of incident AD; and subjects with all VRF treated had less AD than subjects with only some VRF treated. Among 406 patients with MCI were 106 who developed AD over a one year period[30]. In that study, conversion to dementia was significantly associated with atherosclerotic plaque severity and intimal thickness. OR for progression from MCI to dementia were higher by 4.64 times in subjects with coronary artery disease, and 4.31 times in persons with a history of cerebrovascular disease[8]. Similar data were reported by others[6,31]. Associations of neuropathology with both atherosclerosis and arteriolosclerosis, were reported for 1143 subjects[32]. The OR was 1·33 between atherosclerosis, i.e., macrovascular disease, and AD; and atherosclerosis was associated with significantly worse scores in cognitive domains for episodic memory, semantic memory, perceptual speed, and visuospatial

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abilities. Arteriolosclerosis, i.e., microvascular disease, was also associated with worse scores for global cognition, episodic memory, semantic memory, working memory, and perceptual speed.

In brief, the data show that treating vascular pathology, if present, should contribute to reversal of dementia.

Dyslipidemia and AD

Although the brain has ~25% of the total amount of the body's cholesterol[33], little diet-derived cholesterol enters the brain, and all cholesterol accumulated in the brain during the period of rapid myelination can be explained by its local synthesis by astrocytes[34]. Nevertheless, patients with increased blood cholesterol and MCI that progressed to dementia, had RR of 1.61 for that association[6]. An epidemiological study found that hypercholesterolemia in MCI patients was associated with transition from MCI to AD; treatment that lowered cholesterol levels reduced the risk of MCI transitioning to AD[35].

Animal studies are confirmatory. Mice fed a high fat diet had worse performance on a spatial working memory task, and in their hippocampus they had a significant reduction of neurons[36]; they had an induced expression of BACE1; and they had a 3-fold increase in $A\beta_{40}$ accumulation[37]. Further, in their hippocampus, rats fed that high fat diet had increased ROS and TNF-α (i.e., inflammation)[38]; and the animals also had increased levels of phosphorylated tau[36].

In brief, the data show that treating dyslipidemia, if present, should contribute to reversal of dementia.

Hypertension in MCI patients who did not revert to having normal cognition

There is mixed evidence whether patients with MCI and hypertension have more conversion to dementia than normotensives. Thus, one review showed HR 1.39 for the association with hypertension in 1516 cases of dementia[39], and another that reviewed six reports, gave a pooled HR of 1.21[6]; but Cooper et al., in a systematic review of 76 reports, found consistent evidence in studies of people with any-type MCI that hypertension did not predict all-cause dementia[10]. However, Cooper et al., did note that the only large, higher-quality epidemiological study to investigate conversion from amnestic MCI to Alzheimer's dementia found that hypertension was a significantly predictor of subsequent dementia. Ravaglia et al., reporting on 165 patients followed for three years, found that each 10 mm decrement in either systolic or diastolic pressure was significantly predictive of a decreased risk of MCI conversion to dementia[40], suggesting that treatment of hypertension in patients with MCI might decrease incidence of dementia.

However, the essential query is not whether hypertension in patients with MCI predicts the conversion to dementia, which it does, or whether dementia cases have more hypertension, but is whether antihypertensives ameliorate established AD. Several reports show benefit to dementia from treatment of hypertension but several do not. The explanation for the conflicting evidence is probably because of the varied effects of different classes of antihypertensive drugs. In AD model mice, angiotensin receptor blockers (ARB) such as losartan, valsartan, and telmisartan, prevented cognitive decline [41]; but AD model mice, are imperfect analogs of human AD. Data from humans are more persuasive. The electronic health records of 14,269 patients with MCI, included 1,247 (8.7%) who progressed to AD and 2,501 (17.5%) who had any form of dementia[42]. β-blocking drugs either alone or in combination with diuretics, caused significant decrease dementia but benefit to dementia from other antihypertensive drugs classes was not significant. Shah et al., reviewed 12 studies, most involving patients with AD or vascular dementia; only ACE inhibitors and diuretics significantly reduced the risk for progression of dementia in the majority of those studies[43].

Antihypertensive drugs give benefits other than from decreased dementia, e.g., on amyloid deposition. That was examined by high throughput screening of 55 commercially available antihypertensive drugs, and identified four compounds that significantly reduced $A\beta_{1-42}$ oligomerization in a dose dependent manner[44]. Although these four compounds, furosemide

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(diuretic), nitrendipine (calcium channel blocker), candesartan cilextil (ARB), and diazoxide (vasodilator) showed no detectable Aβ lowering activities in primary neuron cultures. Nevertheless, furosemide, nitrendipine valsartan, and candesartan cilextil prevented oligomerization of both $A\beta_{1-40}$ and $A\beta_{1-42}$ in vitro; and furosemide also dissociated pre-aggregated $A\beta_{1-42}$ oligomers. Afflek et al., examined human brain tissue from cases medicated for hypertension: 46 AD and 33 controls matched for cerebrovascular disease[45]. Multivariate analyses showed that antihypertensive medication use was associated with a less extensive spread of AD proteins throughout the brain.

Interestingly, there is also increased dementia in subjects with prehypertension (≥120/80 - <140/90): it was less in black persons (HR 1.17) than in white persons (HR 1.35)(Gottesman)[39].

In brief, the data show that treating hypertension, if present, should contribute to reversal of dementia.

Inflammation and AD

The level of C-reactive protein (CRP), that may reflect either cerebral or systemic inflammation, or both, was examined in a cohort of 12,336 participants with baseline age of 56.8 years: for each standard deviation (SD) increase in CRP, there was a decline over 20 years of −0.035 SD on the cognitive composite score; participants with a midlife CRP in the top quartile had a 7.8% steeper cognitive decline, compared to participants in the lowest quartile; and elevated CRP in midlife was consistently associated with declines in memory[46]. Immune activation has a role in both the pathogenesis of AD and its progression[47]; it may be a primary event in the brain for the development of AD but may also be mediated by systemic inflammation[48]. Genome-wide association studies (GWAS) showed that genes encoding immune receptors link with AD[48]. One of the ways whereby cerebral inflammation contributes to causing AD, is because inflammatory mediators upregulate beta secretase that promotes APP processing and release of Aβ[49].

The gut microbiome is now recognized as playing a critical role in neurodegeneration and AD progression, doing so by affecting Aβ oligomers and plaques, tau aggregates, and neuroinflammation; manipulation of the gut microbiome with antibiotic, has resulted in both reduced progression of AD and a reduction of Aβ deposition [50]. The complex mechanisms that might modulate the connection between the gut microbiome and AD were summarized by Kohler et al., in whose model there is increased translocation due to a leaky gut (either caused by aging or environmental factors) of gram negative bacteria, lipopolysaccharide fragments that lead to the production of ROS, toxic catabolites from bacteria, increased levels of quinolinic acid, changes in energy metabolism, insulin resistance, and there are reduced levels of short chain fatty acids so the astrocyte-neuron glutamate-glutamine shuttle is impaired[51]. These mechanisms, all related to the gut microbiome and intestinal inflammation, would act together to reduce clearance of Aβ from the CNS, and to increase microglial activation that promotes neurotoxicity.

In brief, the data show that treating systemic inflammation, if present as shown by increased CRP, should contribute to reversal of dementia.

Underweight in MCI patients who did not revert to having normal cognition

A number of reports show that body weight differs between those patients who progress to AD in contrast to those who do not progress. For patients with cognitive impairment, being underweight was associated with progression to AD[52]. A literature review that involved patients in whom MCI had progressed to dementia and who had had body mass index (BMI) assessed, showed RR of 0.85 for that association[6]. That was confirmed by a report of almost two million people showing that being underweight in both middle age and old age carried an increased risk of dementia over two decades[53]; and by another study showing that over a one year's period, a lower baseline BMI was associated with significant declines in cognitive performance[54]. Further, in 521 patients with mild to moderate AD, rapid cognitive decline was associated with malnutrition[55]. That was also seen in a study of 414 patients with probable AD, for whom weight loss was defined as a loss of 4% or more during the first year of follow-up, and rapid cognitive decline was the loss of 3 points or more in MMSE over 6 months[56]. 87 (21.0%) of the 414 lost 4% or more of their initial weight during the first

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year; rapid decline of weight affected 57.6% of the patients after a median follow-up of 15.1 months, and after controlling for potential confounders was a significant predictor factor of rapid weight loss with HR = 1.50.

Related to the association of possible malnutrition and progression of MCI to dementia, was vitamin D deficiency (OR 3.13), present in 14% of 250 patients with MCI in Thailand; it is also noteworthy that in AD model mice, a diet enriched with vitamin D was associated with decreased levels of amyloid plaques in their brains[57]. Folate deficiency[10,40,58,59] may also be associated with malnutrition; OR was 0.38 for a lower folate present at baseline and 0.44 for a lower folate present at the five year follow-up[59].

The effects of a Mediterranean diet were examined in two systematic reviews; both found that the diet decreased the conversion from MCI to AD[60] [10]. Benefit from dietary modification might be mediated by saponins, which provide neuroprotective mechanisms, including free radical scavenging, modulation of neuroprotective signaling pathways, activation of neurotrophic factors, modulation of neurotransmitters, inhibition of BACE1 enzyme and tau hyper-phosphorylation[61].

Wu et al found that short-chain fatty acids (SCFA), which have fewer than six carbons and are largely derived from metabolism of dietary fiber by gut microbes, had strong predictive ability for the conversion from amnestic MCI to AD[62]. SCFAs include acetic acid, propionic acid, butyric acid, and valeric acid; they cross the BBB, and they promote inflammation in the brain by enhancing the function of microglia; they also provide energy to cells because they enter the citric acid cycle in the mitochondria to generate ATP. Both butyrate and propionate are active in neurons[63]. Sodium butyrate is an inhibitor of histone deacetylase, so enhances histone acetylation that promotes gene transcription by means of which it significantly facilitated associative memory function when administered to AD model mice[63,64]. More recently, a study reported that the modified Mediterranean-ketogenic diet modulated the intestinal microbiome, and the resulting increase in SCFAs in MCI patients was associated with the improved AD biomarkers in CSF[65]. Thus, a decreased formation of SCFAs in the intestine might be crucial mediators between the intestinal microbiome and AD[62].

In brief, the data show that treating reduced weight and correcting deficiencies of folate and vitamin D, if those are present, and following a Mediterranean diet, should contribute to reversal of dementia.

Mitochondrial abnormalities and AD

Impaired mitochondrial function affects virtually every aspect of brain function, and it has been known for several decades that there is mitochondrial dysfunction in AD[66]; that includes loss of mitochondrial structural and functional integrity, impaired mitochondrial biogenesis and dynamics, altered mitochondria interaction with the endoplasmic reticulum, altered mitochondrial proteostasis, and increased mitophagy[67]. Parenthetically, it is worth noting that all of those mitochondrial dysfunctions are attenuated by lithium. In AD, mitochondrial had reduced numbers[68], were morphologically abnormal[69,70], had fewer genes encoding subunits of the electron transport chain[71], and had decreased activities of the TCA cycle[72]; and the PPARɤ coactivator 1-α that regulates mitochondrial biogenesis, also had reduced levels[69].

Reactive oxygen species (ROS) and nitrogen species are formed in mitochondria; therefore, mitochondrial action may mediate neurotoxicity and thus can be a central element of the pathogenesis of AD.

Detection of acquired mitochondrial abnormalities may be problematic short of a tissue biopsy with observation by electron microscopy of the organelle; but clues might come from plasma enzyme deficiencies, including those of cytochrome oxidase, pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and ATP synthase (shown by reduced level of ATP).

In brief, if mitochondrial abnormalities can be established, then improving mitochondrial function with lithium, should contribute to reversal of dementia.

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Transforming Growth Factor β (TGF-β)

Although there is an increase of TGF-β1 with advancing old age, there is a concomitant decrease of its receptor, TGFR2, in the brain, resulting in reduced neurotrophic efficacy of TGF-β. In light of that, it is perhaps paradoxical that the level of TGF-β is not reduced in MCI[73] but in AD the level of FAMC, a key molecule in the formation of TGF-β, is reduced by ~30-50%[73,74]. Therefore, if in a particular patient with AD the plasma level of TGF-β is reduced, then its levels should be raised[75], which may be accomplished by administration of fluoxetine, which approximately doubled the levels[76]. Parenthetically, blood levels of TGF-β can be obtained in commercial laboratories.

In brief, if TGF-β levels are decreased in patients with AD, then raising them by the administration of fluoxetine, should contribute to reversal of dementia.

Wnt/β-catenin and AD

Studies by Inestrosa et al. showed that Wnt/β-catenin is involved in regulating synaptic plasticity and maintaining BBB integrity; Inestrosa et al. also found that activated WNT/β-catenin signaling prevented neural toxicity caused by Aβ; that WNT/β-catenin participates in a normal degree of tau phosphorylation and in learning and memory; and that WNT/β-catenin dysfunction results in Aβ production and aggregation[77]. Tay et al. followed 14 subjects with MCI and 74 with mild to moderate AD and measured the scores for the Clinical-Dementia-sum of boxes (CDR-SB) at baseline and after one year and assessed the correlations between changes in the CDR-SB and serum levels of Dickkopf-1 (Dkk-1), which is an antagonist of Wnt[78]. Decreased levels of Wnt, as shown by the increase in Dkk-1, which is an antagonist of Wnt/β-catenin, were significantly associated with progressively higher CDR-SB scores (indicating more impairment) among patients with AD but not among patients with MCI. Also important, reduction of canonical Wnt signaling promoted tau hyperphosphorylation, that may be causal of AD[79].

Three reports showed that doxycycline, a commonly used antibiotic, raised levels of Wnt/β-catenin. Noting that Wnt signaling is established as an essential bone-promoting mechanism associated with bone healing, Song et al. showed that both Wnt7b and doxycycline increased the density of callus at the site of a fracture[80]. Zhang et al. also found that doxycycline increased bone formation, and this was accompanied by up-regulation of β-catenin and TGF-β[81]. Gomes et al. reported that doxycycline decreased the immunostaining of Dikkopf-1 (Dkk-1), reflecting an increase of Wnt, by as much as 63% and increased the immunostaining of Wnt-10b by as much as 150%[82]. Parenthetically, blood levels of canonical Wnt can be obtained in commercial laboratories.

In brief, the data show that raising levels of Wnt/β-catenin, if low, should contribute to reversal of dementia.

EMT

EMT refers to the transformation of cells from the epithelial to the mesenchymal condition. In AD, there is a down-regulation of neurons with the M phenotype. This was shown by Liu et al., who immuno-stained FAM3C, a key molecule in causing the E-to-M transition, and found it 45% lower in AD brains than in controls[83]. Those findings were confirmed in studies by Watanabe et al., who also saw an overall 46% reduction of FAM3C; it was 27% reduced in Braak stages 3–4 as compared with non-demented controls having Braak stages 1–2 but was 51% reduced in Braak stages 5–6[84]. Hasegawa et al. demonstrated that TGF-β induced the neuronal expression of FAM3C[85].

In brief, the treatment with fluoxetine, described above, that increases the levels of TGF-β, may lead to an increase in FAM3C, then of M-neurons, and finally to neurogenesis that should benefit the attempt to reverse AD.

Metabolic syndrome and AD

The metabolic syndrome is characterized by the concurrence of three or more of the following conditions: diabetes, dyslipidemia with either low HDL cholesterol or high triglycerides, hypertension, and increased waist circumference. Unsurprisingly, since diabetes, hypertension, and

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dyslipidemia, have all been shown as related to the progression of MCI to dementia, several reports have indicated that metabolic syndrome is a risk factor for progression of MCI to dementia. For example. in the Italian Longitudinal Study on Aging, the HR was 4.4 comparing those subjects with MCI who progressed to having dementia versus with those without that progression[86]. In another example, after excluding individuals with known AD, Vanhanen et al., randomly chose 998 elderly subjects, age 69-78; 418 of them had metabolic syndrome, and 45 (4.7%) were the found to have either probable or possible, AD[87]. For those 45 individuals, multivariate logistic regression analysis including apolipoprotein E4 phenotype, education, age, and total cholesterol, metabolic syndrome was significantly associated with AD (OR 2.46); and, even after excluding diabetic subjects, metabolic syndrome was still significantly associated with AD (OR 3.26).

Treatment should be directed. In particular, to hypertriglyceridemia, increased waist circumference, and hypertension, which were the components that gave the highest rate of progression to dementia[86].

In brief, the data show that treating the components of the metabolic syndrome, if present, should contribute to reversal of dementia.

Disturbed circadian rhythm in AD: causal factor or epiphenomenon? If a causal factor, then treatment may benefit patients with AD

Abnormal circadian rhythm producing an impaired sleep/wake cycle contributes importantly to causing AD. Weldemichael and Grossberg noted that in AD, nocturnal sleep disturbance is associated with the degree of dementia[88]. Homolak et al pointed to the fact that some of the key processes involved in the pathogenesis of AD, show involvement of circadian rhythm [89]. However, including it as a causal factor that should be addressed in individual patients with AD, raises the question of whether this abnormal circadian rhythm is a cause or an epiphenomenon of AD. That question has no definitive answer; but abnormal circadian rhythm is included here as a possible causal factor, because several studies show that it is predictive of future MCI and, in one report, of dementia.

Sleep-wake cycles, i.e., circadian rhythms, may be assessed by an actigraph, an instrument worn on the wrist, to monitor movement over an extended period of time. That was used to collect data from 1282 healthy women, mean age 83 years; each of whom completed a neuropsychological test battery, and 4.9 years later had her clinical cognitive status adjudicated by an expert panel; it found that 195 (15%) women had developed dementia and 302 (24%) had developed MCI[90,91]. All analyses of the data were adjusted for demographics, BMI, functional status, depression, medications, alcohol, caffeine, smoking, health status, and co-morbidities, and showed that when peak levels of subjects' movements occurred later in the day than average, i.e., had a delayed circadian activity, there was an increased risk of MCI or dementia (OR 1.83); and when there was a decreased amplitude of circadian rhythm (the difference between the peak and trough levels of activity), there also was an increased odds for dementia or MCI (OR 1.57). A later analysis of the same data confirmed the higher risk of dementia but not of MCI)[92]. Analysis of data for 763 participants who wore an actigraph in the Women's Health Initiative, also determined the relation between rest-activity measures and centrally adjudicated MCI or dementia[93]. Reduced overall rhythmicity, lower amplitude and activity level, and activity later in the day, were all associated with higher risk for MCI and probable dementia; and women with lower amplitude of the circadian rhythm also exhibited faster cognitive decline over follow-up.

In cognitively normal participants, mean age 62.9 years, with a parental history of sporadic AD, and thus at risk for future AD, worse subjective sleep quality and daytime somnolence, were associated in CSF with lower $A\beta_{42}$, $A\beta_{40}$, and higher total tau:$A\beta_{42}$ and p-tau:$A\beta_{42}$[94]. Others found that progression of AD was mirrord by sleep/wake variables[95]. The mechanism linking decreased sleeping time and AD is reduced removal of potential toxins, particularly Aβ, in the awake brain in which there is reduced volume of the interstitial space and, therefore, a higher concentration of toxins. The cortical interstitial space was 66% higher in sleeping mice than in awake mice[96]. Another study showed hippocampal Aβ levels during sleep deprivation rising by 33.7% and, with sleep, immediately falling[97]. That diurnal fluctuation of Aβ in the brain's interstitial fluid was also seen

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in humans: one night of unrestricted sleep led to a 6% decrease in $A\beta_{42}$ levels, whereas sleep deprivation counteracted that[98]; but in sleep-deprived, cognitively normal subjects, the mean levels of overnight CSF $A\beta_{38}$, $A\beta_{40}$, and $A\beta_{42}$ increased above baseline levels by 30%[99]. Similarly with tau protein: in healthy men, plasma total tau increased by 17.5% in response to sleep loss, as compared with only 1.8% during normal sleep[100].

In view of the above explanation, it is surprising that therapy with light is also beneficial. Photobiomodulation (PBM) is the mechanism by which nonionizing optical radiation in the visible and near-infrared spectral range is absorbed by endogenous chromophores to elicit photophysical and photochemical events; and PBM therapy (PBMT) is a photon therapy that uses nonionizing forms of light, to cause physiological changes and therapeutic benefits[101]. Among 18 randomized controlled trials in persons with dementia, light therapy reduced night-time awakenings, and enhanced sleep quality[40]. Infra-red laser (780-1100 nm) triggered increased cerebral blood flow; mitochondrial activation that enhanced neuroprotection; activated N-methyl-D-aspartate receptor (NMDAR) that decreased intracellular overload of Ca^{2+} and prevented excitatory neurotoxicity; and it reduced excitatory neurotransmission in the hippocampus[102]. In response to light at 808 nM, microglia exposed to Aβ switched from glycolysis to enhanced anti-inflammatory activity, and when microglia were co-cultured with neurons and exposed first to Aβ and then to light, ROS production was decreased with less neurotoxicity[103]. Light induces beneficial pathways including extracellular signal-regulated kinase (ERK), mitogen-activated protein kinase (MAPK), and protein kinase B (Akt), and activates neurotrophic factors and secretases[104,105]. Exposing the frontal skull of rats, to a light-emitting diode, led to improvements in spatial memory, behavioral and motor skills after inoculation of the hippocampus with Aβ that had decreased them.

Thus, although there is benefit from apparently opposing therapeutic approaches, it is because each approach induces different mechanisms.

Discussion

This article has considered the biological changes that 1) accompany the transition from MCI to AD; 2) are present in AD but not in controls; and 3) are not present in MCI patients who revert to having normal cognition yet remain in those whose MCI persists, which is a group that forms the pool of patients from among which are those who will later develop dementia. The clinical significance is that if those biological changes are present in an individual who has Alzheimer's dementia, then correcting a sufficient number of those factors may contribute to curing the dementia. The causal factors considered in this article are only those that are modifiable by a therapeutic intervention, and are cerebrovascular impairment, circadian rhythm abnormalities, depression, diabetes mellitus, hyperlipidemia, hypertension, being underweight, malnutrition including deficiencies of folate and vitamin D, metabolic syndrome, mitochondrial abnormalities, TGF-β deficiency, WNT/β-catenin deficiency. Their presence should be sought using standard methods and their correction may be achieved by standard treatments.

It might be considered that if it has already been shown that treating a particular causal factor did not benefit AD, then that treatment has no role in curing the dementia. However, this article holds otherwise; because the essential question remains, i.e., how many reversible causes in any particular patient with dementia need to be treated in order to achieve a cure? Is that number of causes one, two, three, or more than three? Data suggest that it is more than one, which is why a previously negative report about any one patient applied singly, does not deny it a role in combination treatment: single treatments with neither lecanemab nor aducanumab cured the dementia despite there being much promising preclinical data for their potential efficacy, and many other compounds with equally promising preclinical data were also shown in clinical trials to be ineffective. Thus, background data indicate that curative therapy for AD requires administration of more than one drug. For a clue as to how many drugs are required, one must look at conditions other than AD. A study in diabetes provided useful data[106]. That randomized, controlled trial examined the risk of future cardiovascular disease (CVD) in diabetic participants who had no history of CVD, and contained three groups: those with low risk because of having only 0-1 risk factors, those with

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intermediate risk because of having 2-3 risk factors, and those with high risk because of having 4 risk factors. Intervention was for four years, during which each group had significantly fewer major cardiac events and deaths than expected; as the number of risk factors being addressed increased, the CVD prognosis progressively improved.

Adherence to treatment is obviously relevant, and was studied, in patients enrolled in a Medicare Advantage Prescription Drug plan, how outcomes were affected by ≤80% adherence to medications prescribed for treatment of diabetes, hypertension, and hyperlipidemia in a study population of 99,774 individuals with a mean age of 71.0 years[107]. Compared with patients who missed zero adherence measures, those who missed one measure had 23%–33% increased odds of cognitive decline (for any decline OR = 1.23; for dementia OR = 1.33; for Alzheimer's disease OR = 1.27; all *P* values <0.01); patients who missed 2–3 measures had 37%–96% increased odds of cognitive decline; and patients who missed ≥4 adherence measures had the greatest odds of cognitive decline (for any decline OR = 1.64; for dementia OR = 2.05; for Alzheimer's disease OR = 2.48; all *P* values <0.01). The potential likelihood of curing AD using the approach advocated in this article, requires adherence to the administered medications, which must be accounted for in a clinical trial that is intended to evaluate the validity of the approach.

In brief, the response to the question, 'how many reversible causes that are found in any particular patient with dementia, need to be treated in order to achieve a cure?', seems to be that the data suggest that correction of ≥3 off the factors listed in this present article might provide a strong likelihood of curing the dementia.

Conclusions and Summary

The cure of Alzheimer's dementia may be accomplished by treating ≥3 of the reversible factors that are present in individual patients. Those factors are identified as present in a greater number of MCI subjects who did not revert to having normal cognition than in in those who did revert. As such, this represents personalized medicine.

The reversible factors include circadian rhythm abnormalities, depression, diabetes, hyperlipidemias, hypertension, inflammation, cerebral vasculopathy, being underweight, low levels of vitamin D, folate, and niacin, reduced TGF-β, reduced Wnt/β-catenin, and metabolic syndrome. Addressing these issues with standard therapies, in patients with AD for whom ≥3 of these factors are identified, should achieve a high likelihood of curing the dementia.s,.

A clinical trial is necessary to validate both the accuracy and safety of the suggested approach.

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