OPINION ARTICLE

Midlife interventions are critical in prevention, delay, or improvement of Alzheimer's disease and vascular cognitive impairment and dementia [version 1; referees: 2 approved]

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Abstract

The basic strategy for focusing exclusively on genetically identified targets for intervening in late life dementias was formulated 30 years ago. Three decades and billions of dollars later, all efforts at disease-modifying interventions have failed. Over that same period, evidence has accrued pointing to dementias as late-life clinical phenotypes that begin as midlife pathologies. Effective prevention therefore may need to begin in midlife, in order to succeed. No current interventions are sufficiently safe to justify their use in midlife dementia prevention trials. Observational studies could be informative in testing the proposal that amyloid imaging and *APOEε4* genotype can predict those who are highly likely to develop Alzheimer's disease and in whom higher risk interventions might be justifiable. A naturally occurring, diet-responsive cognitive decline syndrome occurs in canines that closely resembles human Alzheimer's. Canine cognitive dysfunction could be useful in estimating how early intervention must begin in order to succeed. This model may also help identify and assess novel targets and strategies. New approaches to dementia prevention are urgently required, since none of the world's economies can sustain the costs of caring for this epidemic of brain failure that is devastating half of the over 85-year-olds globally.

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We are not winning the fight against Alzheimer's disease

The first generation of the "amyloidocentric" approach to Alzheimer's has recently drawn to a close, and we are left with the same approved symptomatic treatments that we have had for the past 30 years (i.e., cholinesterase inhibitors). The Alzheimer's disease-modifying drug discovery field remains at a perfect 100% failure rate when it comes to new approvable disease-modifying interventions. The two most promising amyloid-reducing interventions of 2016, solanezumab[1] and verubacestat[2], recently failed to modify decline in mild Alzheimer's disease (AD) and were abandoned.

This is a very serious situation for society, as the disease burden of Alzheimer's continues to skyrocket globally, yet the private profit-based pharmaceutical companies cannot, and will not, continue working on disease modifying drugs for Alzheimer's unless convincing new scientific avenues are opened. What this means is that new drug targets must be identified, but for this to happen, we must be open-minded about the trap laid by the early success of identifying genes and molecular mechanisms of the familial Alzheimer's patients. These early targets presented challenges in druggability, but for many years, these targets seemed scientifically rock solid. Now, this certainty and billions of dollars in trial funding are gone, and many large, prestigious pharmaceutical companies have closed their Alzheimer's drug discovery programs.

It is time to admit that we are experiencing a rare phenomenon in drug development where the molecular mechanisms uncovered in familial cases of the disease have not helped us manage the sporadic form of the disease. In order to explain our repeated failures, we first blamed the quality of the drug candidates. More recently, we put forward a "kinetic argument", causing trials to begin earlier and earlier in the course of the disease whilst making little or no effort to identify alternative or additional pathophysiologies beyond amyloidosis and tauopathy. The "kinetic argument" permitted us to remain focused on genetically-predicted drug targets as the most important drug targets, bringing to a halt virtually all other research. As those genetically derived targets continue to fail, experts are commonly overheard to say, "Of course that drug failed: the trial started too late in the progression of the disease; no one expected that to work." This is revisionist history; it was only five years ago when scientists at several major pharma houses were convinced that the odds of success were high enough to invest $50–100 million for phase 1 and 2 clinical trials, or up to $1 billion each for phase 3 trials, even though each will take 4 years and at least 3 separate successful iterations are required. What was truly surprising to the pharmaceutical industry was that immunotherapies and enzyme inhibitors converging on the same target through entirely independent mechanisms yielded failure after failure, with no new insights. The situation was so surprising that most experts hid their disappointment. As recently as last year, clinicians were telling patients and families how these "anti-amyloid" antibodies and BACE inhibitors were "the most promising drugs ever to enter the pipeline". To now turn around and say, "no one ever expected these drugs to work" is both disingenuous and hurtful to patients, who respond saying, "If no one expected that drug to work, then why did you recommend the trial to me?"

Each successively earlier trial failure condemns doctors and patients to another 5 to 7 years of purgatory while the next trial iteration moves five clicks earlier in enrollment age. Yet these trial designs move forward without sufficient ability to define the molecular pathology with precision at the level of the individual patient. This argues not only for diversifying the disease-modifying portfolio but also for redoubling efforts on symptomatic interventions that are also easier to get through the regulatory process.

Can we pinpoint how early is "early enough"?

Perhaps we should seek specific, empirical data about how early is "early enough" in humans. Patients with epilepsy and *APOEε4* alleles do not develop Alzheimer's yet they deposit plaques in their early 40s[3]. This rare but surprisingly early phenomenon argues strongly that we should initiate intervention to prevent amyloidosis or tauopathy not just a little earlier, as we are doing now, but far earlier; in other words, we should intervene in midlife, not later in life. This dovetails well with evidence that midlife risk factors lead to a late-life phenotypes. Midlife-onset hypertension is a risk factor for AD in late life; late life-onset hypertension appears to be *protective* of cognition[4]. What sorts of interventions might these be? Dietary interventions with small effect size but employed over decades might have important cumulative effects. Vaccines may provide lifelong or very long interventions when the proper antigens and adjuvants are identified and employed.

What might we do to refine our guess at what might be truly "early enough" for us to intervene? One might design an observational study of *APOEε4* carriers in their 40s[3,5]. Annual amyloid and tau imaging of *APOEε4* carriers could be used to identify those with evidence, or at highest risk, of progression[5]. Once an *APOEε4* carrier becomes amyloid-imaging positive, one could imagine entering them either into an observational study or into an authentic trial employing reducers of amyloid, tau, or both. An advantage of this design is the possibility that for serially imaged subjects observed to change from negative to positive proteinopathy imaging, it will be possible to know that the proteinopathy has been present for 12 months or less. If we jump back in age as far as the mid 40s, and show that we can engage the proteinopathy targets at that early point, but yet *still* fail clinically, that will be a strong indication that "anti-proteinopathy-only" will never succeed.

Mixed pathology may be the most common underpinning for dementia

It is worth keeping in mind that even if we have impact on Alzheimer's pathology, the frequent concurrent presence of multiple pathologies will continue to confound. These days, there is more research on the relationship between vascular cognitive impairment and dementia (VCID) and Alzheimer's dementia, but not yet enough, even though defining this is probably profoundly important. Among African Americans with clinical Alzheimer's, 70% have mixed pathology at autopsy[6]. Despite much attention being given to insulin signaling and brain proteinopathy, virtually all the accumulated data indicate that dementia of type-2 diabetes is not Alzheimer's but is primarily vascular in origin[7]. Synucleinopathy, which is present in about 1/3 of Alzheimer's patients, induces a plethora of epigenetic changes in the brain transcriptome[8]. This means that, currently, perfect antemortem diagnosis is sometimes impossible. Certainly, the more mixed

dementia subjects there are in a trial intended to assess the efficacy of a drug that only treats Alzheimer's, the lower the sensitivity to see a signal will be. There is a good chance that each of the various underlying pathogenetic mechanisms will have their own optimum time window for intervention, and that this will have to be factored in as well. On the other hand, improved midlife cardiovascular health could benefit cognition and may delay *all* causes of dementia.

Immunology of cognitive decline in Alzheimer's disease

While genetics and, more recently, multi-scale network-level genomics[9] have taught us, and continue to teach us, much about the molecular pathology of Alzheimer's, imaging and pathology have taught us just as much about the disappointingly poor clinicopathological and clinicoradiological correlation in this illness. Cognitive decline is poorly predicted by amyloid imaging in isolation, as was foretold by the Religious Orders study some 20 years ago[10].

Are there truly new drug targets? What might we be missing in our formulation of the pathogenesis of sporadic Alzheimer's? Of the two dozen genes linked by genome-wide association studies (GWAS), two thirds are lipid- or immune-related[11], raising the possibility of a neuroinflammatory/neurodegenerative dementia-causing pathway that might be worthy of further research. DeStrooper has recently proposed an alternative formulation of AD as a clinical umbrella under which "feed-forward" pathogenesis scenarios lie (e.g., inflammation causes or exacerbates tauopathy; then, in turn, tauopathy aggravates inflammation)[12]. This model fits the existing data at least as well as the classical linear amyloid hypothesis and explains some of the holes in the current predictive models. DeStrooper's formulation[12] includes scenarios where anti-proteinopathy drugs alone would probably be inadequate. Along the same lines, the *CR1* risk polymorphism is associated with increased risk for clinical Alzheimer's but in the setting of progression-related reduction in amyloidosis[13,14].

One other model might be worth investigating: Canine cognitive dysfunction (CCD)[15] is the only naturally occurring mammalian dementia to mimic Alzheimer's disease. In CCD, diet and lifestyle have measurable impact on disease progression[15]. The CCD model could contribute to our understanding of how early intervention must begin in order to be effective. And with CCD, one could test drugs as prophylaxis *in vivo*. In the meantime, the importance and potential benefit of safe and easy diet and lifestyle changes for humans should be a topic of much stronger advocacy. In fact, strong evidence that better cardiovascular health reduces prevalence of both Alzheimer's and VCID is already beginning to emerge and must be a clear part of patient education by clinicians[16–23]. To its credit, the April 2017 issue of *Scientific American* heralds "Success in the Fight Against Alzheimer's", a review of dementia risk reduction benefit that can be realized through modification of diet and lifestyle beginning in midlife[24].

There may be more "unknown unknowns" yet to be revealed

Finally, it is important to emphasize that researchers tackling Alzheimer's and other dementias must remain clear-eyed, challenged, and worried that there are still many gaps in our understanding. A simple backward jump to earlier intervention may require 5 more iterations at the current pace, if indeed we should be intervening when subjects are in their 40s. If the disease can be primarily driven by lipid pathology or inflammatory pathology even with little or no protein aggregate pathology as could be inferred from the nature of the GWAS hits[11], and from the variability in amyloid-first phenotypic sequences vs. neurodegeneration -first phenotypic sequences[25], then efforts focused solely on purging clumped proteins from brains in which they may have lingered silently for decades may always come up short.

Acknowledgements

Dedicated to the memory of Kerstin Iverfeldt, PhD (1957–2017) who made important contributions to our understanding of the biology of APP and the amyloid β peptide.

Author contributions

All authors contributed to drafting and editing.

SG prepared the first draft and the final submitted version.

Competing interests

No competing interests were disclosed. The opinions expressed here are exclusively those of the authors.

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Current Referee Status: ✔ ✔

Version 1

Referee Report 19 April 2017

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✔ **Domenico Pratico**
Department of Pharmacology, Center for Translational Medicine, Lewis Katz School of Medicine, Temple University, Philadelphia, PA, USA

This is a very interesting and stimulating opinion article in which the authors try to make sense of the current state of the Alzheimer's disease (AD) pharmacotherapy.
They present in a very objective fashion the disappointing scenario we are facing in this area, and at the same time they provide very insightful food for thought on how the research should move forward.
I would like the authors to spend some additional words on the followings:
1. The multifactorial nature of sporadic AD, and because of that a multi-target and may be personalized approach versus a one-size-fits-all solution is more likely to work.
2. While the large GWAS studies have provided evidence for good genetic leads, there is strong evidence indicating that environmental factors (i.e., lifestyle, diet) can ultimately influence the clinical phenotype.

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 18 April 2017

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✔ **W.Sue T Griffin**, **Orwa Aboud**
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Dr. Gandy and his colleagues have come to the heart of the matter – current anti-amyloid strategies have failed to change the course of Alzheimer's disease (AD). This important article is written as an "Aha, we can now address the question of what other strategies might hold promise toward preventing or delaying onset of Alzheimer's disease (AD)." They raise a number of very important questions, including how early should we treat; what is the role of multiple pathologies in Alzheimer pathogenesis; are the pathways that give rise to the neuronal dysfunction and loss noted in AD the same ones that obtain in the pathogenesis of other neurodegenerative diseases; are such pathways known and, if so, have the drivers of these pathways been identified? Most of these questions have been addressed in animal models and some have included evidence of the existence of such pathways in brain tissue from patients vs controls. A

great deal of effort has been given to one of the areas of interest noted by the authors “Immunology of cognitive decline in AD.” The authors’ discussion of a recent review of the potential relationship between lifestyle changes such as diet and exercise and how this may have a beneficial effect as a middle-age combatant of cognitive decline is laudable. However, implementation of such lifestyle changing practices would require individuals to be either coerced or otherwise convinced to adhere to such practices. At present, even though there is convincing evidence of tangible benefits of exercise and diet[1], the data is not with us regarding adherence to such regimens. Therefore, we would like to suggest inflammation, both in the brain and in the periphery, as a prime target for early intervention in Alzheimer pathogenesis through the use of currently available drugs or drugs developed so as to have fewer or more tolerable side effects. Data from the Framingham study of 691 cognitively intact individuals provide evidence of spontaneous increases in production by blood monocytes of two pluripotent proinflammatory cytokines, interleukin-1 (IL-1) and TNFα[2]; these increases were suggested to serve as markers that “strengthen” a link between inflammation and development of AD. In addition, an accumulation of epidemiological data has consistently sided with use of anti-inflammatory compounds as increasing the odds against being in the “Alzheimer group” and in favor of being in the non-demented, non-neuropathologically confirmed group. Data from the Rotterdam study of non-NSAID users vs NSAID users reported an adjusted relative risk ratio of 0.54 among NSAID users as support for the potential of NSAIDs to protect against development of AD[3]. In a larger study of the VA database (~50,000 clinically and neuropathologically confirmed AD patients vs ~200,000 non-AD patients), 5 or more years of ibuprofen use reduced the adjusted odds ratio to 0.56[4]. Further in the extended results of the ADAPT study, asymptomatic subjects who received naproxen had a reduced incidence of AD compared to those who received either celecoxib or placebo[5].

In view of the evidence implicating inflammation as increasing risk for later development of AD, it seems prudent to first explore what we know at present regarding early events in Alzheimer pathogenesis as such events may presage development, or help us pinpoint “when is the best time to intervene” to forestall formation of the aggregate defining neuropathological hallmarks of AD. In the McGeers’ early studies of neuroinflammation in AD, immune markers were identified on plaque-associated microglia in AD brain[6]. The following three discoveries: one showing that activated glia in AD brain overexpress IL-1, a second showing that microglial activation with overexpression of interleukin-1 (IL-1) as well as astrocyte activation and overexpression of the neurite-growth stimulating cytokine S100B are prominent in fetuses, newborns, children, and adults[7], and a third showing that IL-1 induces synthesis of APP in human cell cultures[8] opened a new field of investigation, viz., the potential of IL-1-directed pathways to promote neuropathogenesis. These two cytokines, IL-1 and S100B upregulate each other and both induce synthesis of βAPP in vitro and in vivo. This βAPP may then be cleaved for β-amyloid (Aβ) plaque formation or for sAPPα for further microglial activation and overexpression and release of IL-1β[9-10]. Moreover, IL-1β, via its ability to induce synthesis as well as activation of MAPK-p38, increases production of hyperphosphorylated tau, for formation of the paired helical filaments in neurofibrillary tangles, as well as α-synuclein for formation of Lewy bodies[11]. If such neuroinflammation, which has now been associated with immune challenges in the periphery is associated with risk for development of AD, it would seem prudent to develop an inflammatory index in order to decide when treatment should begin. In view of the appearance of neuroinflammation, noted as increased activation of glia and overexpression of IL-1 decades before frank pathology in Down’s syndrome, perhaps erring on the side of caution, beginning treatment sooner rather than later may be preferable.

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Is the topic of the opinion article discussed accurately in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Yes

Are arguments sufficiently supported by evidence from the published literature?
Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?
Partly

Competing Interests: No competing interests were disclosed.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.