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Stopping Cognitive Decline in Patients With Late-Life Depression: A New Front in the Fight Against Dementia

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DEMENTIA LOOMS AS A PUBLIC HEALTH CRISIS

The challenge is to bend the curve before the aging “tsunami” hits. According to the Alzheimer’s Association, we face 8.2 million cases of dementia in the United States in 2030. Prevention may be elusive in the near future, but just slowing down the decline could have a huge benefit. If discovered and disseminated by 2025, such an intervention could reduce these cases 30%, to 5.8 million.¹ The projected cost savings of such an intervention are \$83 billion in 2030—rising to \$367 billion in annual savings by 2050. This public health impact in the United States is huge, yet dwarfed by the worldwide impact of dementia prevention, with most of the projected 132 million cases worldwide (in 2050) in low- and middle-income countries.

These high stakes are translating into more federal research funding for Alzheimer disease (AD) prevention, yet such research is challenging because dementia is a multistage, multimechanism set of aging brain pathologies that unfolds over many years. Prevention trials must recruit a large cohort of individuals at high risk for dementia, target that risk with a potent intervention, and then follow the high-risk cohort on protocolized treatment for many years to detect the intervention’s effects on biomarker or clinical outcome trajectories.

In this editorial, we make the case for a new front in dementia prevention: focusing on individuals with depression as a high-risk cohort.

LATE-LIFE DEPRESSION IS A MODIFIABLE RISK STATE FOR AD AND OTHER FORMS OF DEMENTIA

A recent late-life major depressive episode increases the risk of dementia fourfold to sixfold, and this risk is especially high in those who have persistent depressive symptoms.^{2–6}

In this issue of *American Journal of Geriatric Psychiatry*, Gallagher et al.⁷ illuminate this link by examining the naturalistic course of cognitive decline in late-life depression (LLD). Analyzing the National Alzheimer’s Coordinating Center database, they show that 42% of

individuals with both mild cognitive impairment (MCI) and active or recent depression progressed to AD during a median follow-up of 27 months.⁷ This is a short time frame, and a feasible time frame in which prevention can be tested. These data agree with other studies of depression, MCI, and dementia risk.^{4–6,8,9}

WHAT IS THE PATHOPHYSIOLOGY OF THIS ELEVATED DEMENTIA RISK IN LLD?

We describe pathophysiologic studies along the continuum of AD pathology using the new National Institute on Aging and Alzheimer's Association research framework, also known as the A/T/N framework (for amyloid deposition, tau pathology, and neurodegeneration).¹⁰

Dementia associated with depression is typically AD. Studies in LLD show increased amyloid pathology, especially in patients with treatment resistant depression.^{11–15} These and other studies support the amyloid hypothesis of LLD, in which amyloid deposition may lead to persistent depression and then to AD.^{16–18} Other studies of LLD have shown hippocampal volume decline, temporal gray matter atrophy, and tau deposition in the entorhinal and inferior temporal cortices.^{19–30} Finally, postmortem studies of LLD show high rates of AD.^{31–33}

However, dementia is not *solely* AD. Cognitive impairment in LLD is a mixed, multidomain picture that prominently includes executive function impairment.^{17,34} Agreeing with this mixed picture, some studies have shown decreased amyloid deposition in LLD compared to nondepressed individuals with similar atrophy or cognitive decline.^{35–38} For example, in an early report from Pittsburgh,³⁹ 50% of patients with LLD and MCI were “amyloid positive,” with amyloid beta in the AD range; the rest had variable and lower amyloid beta burden (Fig. 1).

Subcortical white matter ischemic disease is another driver of accelerated cognitive decline.^{40–42} White matter disease is more than an independent co-traveler with AD; it is a part of the illness itself. Greater white matter hyperintensity (WMH) burden increases the risk and pathogenesis of AD,⁴³ and those with AD pathology and WMH have more precipitous cognitive decline.⁴⁴ This may be a key mechanism of increased risk for AD in our patients^{45,46} because LLD is associated with higher WMH burden^{41,47,48} and is highest in treatment-resistant cases.^{42,49–52}

Alongside this vascular risk there are shared physiologic pathways between LLD and dementia, including proinflammatory burden, lower neurotrophic support, and proteostasis dysfunction,^{9,53–56} possible mechanisms by which the stress or allostatic load of depression accelerates brain aging.⁵⁷

The elevated risk for dementia likely applies to other late-life psychiatric syndromes as well. The concept of mild behavioral impairment posits that affective and emotional dysregulation is a prodementia risk marker, or prodrome. This dysregulation could present as depression but, equally, it could also present as apathy, anxiety, irritability, and other “behavioral”

syndromes.⁵⁸ Late-onset mood and behavioral changes may be harbingers of dementia, indicating a critical time to intervene with preventive efforts.⁵⁹

THESE FINDINGS ARE A CALL TO ARMS FOR GERIATRIC MENTAL HEALTH: OUR PATIENTS ARE AT ELEVATED RISK AND SHOULD BE IN AD PREVENTION STUDIES

The AD field has moved to large prevention studies of at-risk cohorts: APOE ε4 carriers,⁶⁰ autosomal dominant AD carriers,⁶¹ and amyloid positive individuals.⁶² We should do likewise. We should recruit large cohorts of patients and test preventive interventions for AD. Doing so could elucidate the mechanistic pathways to dementia in late-life mental illness and generate treatments that both ameliorate psychiatric problems and prevent dementia. Conversely, *not* doing so is an unconscionable continuation of the status quo, namely the exclusion of mental illness such as LLD from many AD naturalistic and prevention studies.

OPTIMUM: AN EXAMPLE OF A HIGH-RISK COHORT

We recently started the Optimizing Outcomes in Older Adults with Treatment-Resistant Depression (OPTIMUM) study. OPTIMUM is a five-site study (Washington University, Columbia University, University of Pittsburgh, University of Toronto, and University of California, Los Angeles) funded by the Patient-Centered Outcomes Research Institute. OPTIMUM is recruiting 1,500 community-living men and women aged 60 and older with treatment-resistant depression, defined as major depression that persists despite two or more prior antidepressant trials of adequate dose and duration. Individuals with normal cognition as well as MCI are included.

OPTIMUM is the largest ever study of treatment-resistant LLD. Its goal is to compare the effectiveness of first-line augmentation and switch strategies for depression that are popular with providers treating LLD.⁶³ OPTIMUM is a comparative effectiveness trial; it tests medication strategies head to head in acute medication trials (such as augmentation with aripiprazole versus switch to bupropion). Participants are followed longitudinally, tracking traditional depressive symptom outcomes as well as critical geriatric outcomes, such as falls, based on perspectives from older adults with depression.⁶⁴

Recently, we received funding from the National Institute of Mental Health to carry out longitudinal neuroimaging, neurocognitive assessment, and peripheral biomarker testing in the OPTIMUM sample. This ancillary study, OPTIMUM-Neuro, will characterize the pathways of AD risk in treatment-resistant LLD. The large sample and intensive characterization of cognitive status and brain imaging in OPTIMUM and OPTIMUM-Neuro make this an ideal sample for testing dementia prevention strategies. We propose that our colleagues in geriatric mental health consider whether their large participant cohorts might be similarly ideal.

WHAT TREATMENTS SHOULD BE TESTED?

As we describe above, the progression from LLD to AD is a multimechanism process. Likewise, treatments to prevent AD in the context of LLD (and other mental disorders) should be multitargeted. One potential treatment strategy involves psychotropics; many of the medications we already use for symptoms also have putative neuroprotective properties. A prime example is lithium, which targets multiple neuroprotective mechanisms and may slow neurodegeneration and prevent dementia on multiple fronts.⁶⁵ Lithium reduces amyloid production, inhibits tau phosphorylation, induces autophagy to clear amyloid and tau from the brain, and increases neuronal survival in the face of exposure to toxic amyloid and tau proteins. Clinical and epidemiologic studies support its neuro-protective properties,⁶⁶ and a small clinical trial in MCI found preliminary positive evidence of its benefits for cognitive and AD biomarker outcomes.⁶⁷ There is concern about the risk of long-term lithium exposure, but a recent study showed that 4 years of lithium did not impair renal function in older adults with MCI.⁶⁸

Because OPTIMUM studies the antidepressant benefits of lithium augmentation, we are proposing to evaluate its AD prevention benefits by continuing to follow participants randomized to this medication. As happens often in psychiatry, we are repurposing an existing drug. Doing so has many advantages: its U.S. Food and Drug Administration-approved status, widespread availability, and low cost.⁶⁹ Cost is not a trivial point in any AD prevention intervention, as millions of older adults would need to receive the treatment chronically to “bend the curve” on cognitive decline in the United States and worldwide. Other promising treatments that are relatively low cost and scalable include cognitive training, neurostimulation treatments such as transcranial magnetic stimulation or transcranial direct current stimulation, and behavioral treatments targeting physical inactivity, stress, and insomnia. Combinations of these interventions will likely be needed, as well as precision medicine approaches that match these treatments to the patients most likely to benefit from them. Our field of geriatric mental health has studied all of these interventions but usually not with study designs that could detect dementia prevention.

WHAT SHOULD STUDIES OF DEMENTIA PREVENTION IN LATE-LIFE MENTAL ILLNESS LOOK LIKE?

First, *large*—likely several hundred to one thousand plus randomized individuals.⁷⁰ Second, *long*—they need to follow participants on treatment for several years. The current Gallagher study notwithstanding, we expect that 2 years is insufficient and 3–5 years (or more) is necessary. In fact, recent studies of prevention of cognitive decline in our field may have been “false negatives” because of short follow-up periods and inadequate sample sizes.⁷¹ Larger and longer clinical trials are feasible because the field of geriatric mental health research includes many excellent clinical trialists who can successfully randomize and retain participants, manage them for long periods of time, and deprescribe medications such as anticholinergics and benzodiazepines that obscure or undermine dementia prevention efforts.⁷²

Third, such studies need to be a collaboration between clinical trialists and neuroscientists who can use state-of-the-art measurement of AD outcomes. These ought to include a cognitive outcome battery akin to the Preclinical Alzheimer Cognitive Composite, which combines sensitive measures from multiple highly relevant domains.^{73,74} The advantage of using a composite is excellent validity and reliability within a single primary outcome, which reflects a range of pertinent aspects of age-related cognitive function. Additionally, an AD prevention study should include categorical outcome adjudication. This classifies patients as normal cognition, MCI, or dementia using a rigorous assessment of all data by a team of neuropsychologists, neurologists, and geriatric psychiatrists.⁷⁵

Finally, these prevention studies should assay the progression of the underlying neurodegenerative disease. We can do this using state-of-the-art positron emission tomography measures of amyloid and tau deposition, MRI to assess cortical thickness, WMH, and hippocampal volume, and functional MRI to examine physiologic health and functioning of key brain networks. Doing so links our illnesses to the known biomarker progression in AD - namely amyloid deposition, tau formation, and neurodegeneration - and in cerebrovascular disease - namely WMH. It also links our innovative findings about the network underpinnings of mental illness with brain health measures; at the level of functional MRI, we and the AD field X are speaking the same language.⁷⁶ Additional mechanistic assessments can include peripheral biomarker assessments (such as immune-inflammatory and cell health markers) to elucidate pathways to dementia and the interventions' mechanisms of action.

THE IMPACT OF COGNITIVE DECLINE IN LATE-LIFE MENTAL ILLNESS IS OUR MANDATE

If one or more studies finds that an intervention reduces cognitive decline, progression to dementia, and/or biomarker progression (amyloid, tau, neurodegeneration), then it transforms our field. We can shift from late-stage, symptomatic-only treatments, to first-line treatment strategies that ameliorate both mental disorders and reduce dementia risk. Moreover, such interventions could be used to prevent cognitive decline worldwide, regardless of behavioral status. Even negative findings would be of great benefit to the field, as they would give us a better understanding of the longitudinal relationship among late-life mental disorders and the pathophysiology of dementia. The time is now, and we are up to the task.

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FIGURE 1.

Pittsburgh compound B positron emission tomography images show varying amyloid deposition in three individuals with late-life depression.