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Alzheimer's Disease: Our Evolving View, Our New Interventions

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A Current and Future Public Health Crisis

Alzheimer's Disease (AD) looms over our aging population like no other health problem. Its soaring prevalence, high cost of care, and lack of a curative treatment threaten our entire health care system, which struggles to address the needs of an estimated 5.4 million affected Americans and their caregivers. This year alone, nearly half a million Americans age 65 or older will develop AD. By mid-century, someone in the U.S. will develop the disease every 33 seconds. Delaware, as a favored retirement destination, is home to some 26,000 people with AD or a related disorder, and this number will increase substantially in coming years.[1]

Barring the development of medical breakthroughs to prevent, slow, or stop the disease by 2050, the number of people age 65 and older with AD may nearly triple by then.

As the number of affected people skyrockets, the direct and indirect costs of care are also expected to explode. AD is already America's most costly disease in terms of health care and long term care expenses. The annual national cost of health care, long term care, and hospice is substantial for those with AD and other dementias. In 2016, the total payments for direct care of people with AD, including long term care and hospice, are estimated at $236 billion, of which $160 billion will be borne by Medicare and Medicaid.[2] In 2015, nearly 16 million unpaid caregivers, family members and others, provided 18.1 billion hours of additional care to people with AD and other dementias at an estimated value of $221.3 billion.[2] By 2050, total annual payments for care of people with AD and other dementias are projected to increase to more than $1 trillion (in 2016 dollars).[2] The Alzheimer's crisis demands urgent action.

A Disease Model In Evolution

Psychiatry's Diagnostic and Statistical Manual 5 (DSM 5), published in 2013, revised both the name of dementia, now termed Major Neurocognitive Disorder, and the criteria by which it is diagnosed.[3]

In contrast to DSMIV, which specified that there be not only a memory impairment sufficient to impair social or occupational functioning but also significant impairment in one of several specific neurocognitive domains, the DSM 5 instead permits diagnosis of a Major Neurocognitive Disorder when impairment of any one or more of six neurocognitive domains (memory, complex attention, executive function, visuospatial function, language, or social cognition) is impaired sufficiently to compromise independence. Among other benefits of these diagnostic criteria, this new definition permits diagnosis of AD even when memory disturbance is less prominent than another cognitive impairment. That important change facilitates the recognition of AD variants such as Posterior Cortical Atrophy, in which visual complaints may dominate the clinical presentation; or Primary Progressive Aphasia, a disturbance of language which can be caused by Alzheimer's or other neurodegenerative pathology.

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In addition to revising the diagnosis of dementia, DSM 5's new Neurocognitive Disorders category contains a syndrome new to the main body of the DSM: Mild Neurocognitive Disorder.[3] This new diagnostic entity is similar to Mild Cognitive Impairment, an earlier syndrome that has been informally recognized by clinicians and explored by researchers already for decades. Mild Neurocognitive Disorder is diagnosed when an individual is impaired in one of the six DSM neurocognitive domains enough to evoke compensatory behaviors, yet not so severely impaired as to endanger general independence. The inclusion of this new diagnosis is a recognition that neurocognitive impairment represents a spectrum of changes from very mild to very severe. Although mild neurocognitive disorder can reflect one or more of many possible causes, the link between amnestic mild cognitive changes and the later development of AD appears to be an important one.

Research now supports the idea that AD pathology is present even earlier than the stage of Mild Neurocognitive Disorder. Although DSM 5 has not yet incorporated this further evolution in diagnostic classification, the notion of a presymptomatic phase of AD encourages clinicians and researchers to explore the value of very early detection and intervention. The accumulation of amyloid plaques during a presymptomatic phase of AD is now recognized as evidence of the disease's extended preclinical development.[4] Data from sophisticated neuropsychological assessment tools and advanced neuroimaging tools such as voxel-based morphometry, diffusion tensor imaging, FDG-PET, and PET amyloid scans suggest possible approaches to early detection and measurement of preventive interventions' effects.

The Anguishing Problem of Noncognitive Behaviors

Although DSM 5 broadens the diagnostic criteria for AD very significantly, it remains as silent as earlier DSMs regarding the importance of the non-cognitive behaviors that complicate dementia diagnosis, treatment of affected patients, and support of caregivers' wellbeing. Auguste D, whom we know as Alzheimer's first patient with the disorder that later took his name, required institutionalization because of her delusions and agitation.[5] These symptoms, along with aggression, hallucinations, apathy, anxiety, depression, wandering, sexualized inappropriate behavior, and disturbances of eating and sleep, affect the vast majority of people with AD, complicating their lives and those of their caregivers. No approved treatment or universally effective treatment approach is available to guide management of these disruptive behaviors. The FDA-indicated medications for AD have limited effectiveness in treating AD's behavioral symptoms. The antipsychotics, still commonly in use for treatment of AD-associated agitation despite amassed evidence of their potential harm and limited benefits, are gradually being replaced by other medications with less potential for harm even though they are not always able to provide benefits. Citalopram, which carries a dose limit suggestion and boxed warning for use in the elderly related to QTC prolongation, and other serotonergic antidepressants reduce agitation in some individuals with AD.[6,7] Serotonergic antidepressants used for this purpose are off label, as are the other medications or approaches for which preliminary data suggest some utility: dronabinol,[7] quinidine/dextromethorphan,[7] prazosin[8] analgesics,[7] and electroconvulsive therapy.[9] Hormonal treatments have been employed in treating agitation and sexually inappropriate behavior, though their use must be carefully considered in light of adverse effects and limited efficacy.[10,11] These somatic approaches may sometimes be avoided, and always should be joined with nonpharmacologic behavioral approaches that shape behavior by understanding the behavior's origin and meaning, designing an effective environmental response, and monitoring that response's effectiveness. Descriptions of the behavioral method named

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DICE, for Describe/Investigate/Evaluate/Create, have offered useful detail on each of these nonpharmacologic approach components.[12]

Treatments On The Horizon

The FDA has approved 4 cholinesterase inhibitors and one NMDA modulator for treatment of AD. These medications statistically exceed placebo in effectiveness, yet the side effects of the cholinesterase inhibitors can be distressing or even dangerous, and many clinicians long for medications that will bring more clinically significant benefits to a greater number of patients. More than 1900 clinical trials in AD are currently listed at www.clinicaltrials.gov and many of them are actively recruiting subjects in order to test new treatment approaches.[13]

The "amyloid hypothesis," still regarded by many researchers as the key to understanding AD pathology, underlies many of these trials.

According to the amyloid hypothesis, the brain cell membrane amyloid precursor protein (APP) undergoes an abnormal clipping by β and γ secretase enzymes, producing toxic amyloid peptide fragments termed-amyloid oligomers (abbreviated as Aβ). These oligomers circulate in blood and cerebrospinal fluid, where they interfere with synaptic function. They also aggregate and deposit in the brain, stimulating an inflammatory reaction and brain cell death as they produce the amyloid plaques of AD. Aβ is implicated also as a factor in the hyperphosphorylation of tau protein, which destroys the internal structure of neurons, resulting in AD's other hallmark finding, neurofibrillary tangles. The amyloid hypothesis has led to testing of medications which target toxic amyloid's production, aggregation, and persistence in the brain. So far, this approach has produced results positive enough to encourage further exploration. Current focus is largely on a second generation of immunotherapy agents that induce "passive immunity" through injection of pre-made antibodies possessing a limited duration of action before their destruction or elimination. Several of these experimental agents have been shown to reduce CNS amyloid load. A more limited body of evidence has linked treatment with a delay in cognitive decline, but only in early-stage individuals. A new generation of studies is testing these passive immunotherapy agents on prodromal AD subjects. The newer members of this class of medications appear less frequently to cause the microhemorrhages noted with the earlier agents.

While the amyloid hypothesis continues to dominate, other AD research is addressing the effects of experimental agents on non-amyloid aspects of the disease. The destructive role of tau hyperphosphorylation is being challenged with medications which inhibit tau aggregation or target modified tau protein. The recognized glycemic dysregulation of AD is being addressed by medications which improve glycemic control or medical foods designed to provide the brain with a non-glucose energy source. Anti-inflammatory agents are being tested in order to understand the role of inflammation in AD's pathology. Other new experimental agents address potential issues with serotonergic or other neurotransmitter function.

Behavioral treatments currently being studied include yoga, physical activity, and hearing aids to reduce the sensory isolation experienced by some AD patients. More invasive non-medication approaches in current testing include electroacupuncture, repetitive transcranial magnetic stimulation, direct cranial stimulation, and deep brain stimulation. For a more detailed discussion of current approaches to AD treatment research, the interested reader is referred to www.clinicaltrials.gov[13] or the excellent recent review by Godyń and colleagues.[14]

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Alzheimer's Disease is a Public Health Priority Nationally and Locally

The impact of AD is felt across all sectors of society and has become a pivotal public health issue. In 2012, the first ever National Alzheimer's Plan to Address AD was enacted with the goal of preventing and effectively treating Alzheimer's by 2025. As the scientific community races towards this goal, it is vitally important that the clinical needs of individuals and families already impacted by AD be addressed as well. The same year that the National Alzheimer's Plan was enacted, Delaware began the development of its own plan to address the state's current and future needs with respect to AD. The Delaware State Plan to Address Alzheimer's Disease and Related Disorders, a blueprint to enhancing the state's dementia-capability, was published in 2014.[1]

The Plan includes five overarching goals:

1. Promote public awareness of Alzheimer's disease;
2. Improve the delivery of services to persons with Alzheimer's disease;
3. Strengthen the support of caregivers of persons with Alzheimer's disease;
4. Achieve an Alzheimer's competent workforce in the State of Delaware; and
5. Improve and expand Delaware's Alzheimer's and dementia-related infrastructure (data, quality assurance, research) by supporting the creation of a Delaware Center for Alzheimer's and Related Dementias [DECARD].

This plan is currently in an implementation stage, overseen by a Steering Committee and being carried out by interdisciplinary stakeholder committees charged with working towards the State Plan's goals and recommendations.

Know and Use Delaware's Resources

A diagnosis of AD is life changing, and can leave an affected person and the members of his or her care system feeling isolated and unsure of where to turn for information and support. It is important for individuals and caregivers to know that they are not alone; that there are supportive resources available in the community to help families navigate the journey required in order to cope with AD.

The State of Delaware has already committed considerable resources to assisting individuals with AD and their caregivers. The Delaware Aging and Disability Resource Center (ADRC) provides information about such services in Delaware as adult day care programs, respite care, care management, and elder law providers.[15]

The Alzheimer's Association, the leading voluntary health organization in Alzheimer's care, support and research, is very active in Delaware through its Delaware Valley Chapter. The Alzheimer's Association offers a variety of programs and services to support those living with the disease as well as their families and caregivers throughout every stage of the disease's progression. The Association's mission is to eliminate AD through the advancement of research; to provide and enhance care and support for all affected; and to reduce the risk of dementia through the promotion of brain health. The regional office in Newport and a branch office in Georgetown offer programs and services addressing the unique needs of caregivers and people living with dementia. Clinicians and caregivers are likely to find useful information in the

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Alzheimers Disease Pocket Card App.[16] The chapter's 24/7 free Helpline, at 800-272-3900, is its primary and most popular service. Translation is available for as many as 200 languages. Online, information is available the national organization's website (www.alz.org) and at the Delaware Valley website (alz.org/delval). The association's annual Delaware Dementia Education Conference, to be presented this year on 11/16/2016 at the Dover Downs Conference Center, provides health care providers and caregivers with an opportunity to network and to learn from national and regional dementia experts. Early registration is encouraged, at act.alz.org/2016DEconference or by calling 800.272.3900.

The Swank Memory Care Center, the first and only outpatient program in Delaware dedicated to evaluating and consulting on patients with neurocognitive disorders, has recently moved to new quarters in the Gateway Building of the Wilmington Hospital. Appointments can be scheduled by calling 302-320-2620. Most referrals are from primary care or specialty health care providers, and patients can be seen by one or more members of an interdisciplinary team comprising a geriatrician, neurologist, geriatric psychiatrist, nurse practitioner, and social worker. Collaborative input is available from neuropsychology, physical therapy, occupational therapy, speech therapy, and rehabilitative medicine. The Swank Center hosts a monthly caregiver support group and will soon be recruiting appropriate subjects for clinical trials. The Swank Center also is an active provider of symposia and other educational opportunities for peers and public.

A Brighter Horizon

As a public health burden unlike any other, AD justifiably inspires our fear and concern. Recent progress in understanding AD's early stages and prolonged presymptomatic development raise hope for the future. Successful advances in early detection, the development of new interventions to delay or prevent disease progression, and the investigation of new treatments may in time lighten the burden that this illness imposes on patients, caregivers, and our society as a whole.

Continued progress will demand an investment of our resources, our support of treatment and research efforts, and a commitment to defeating a public health burden unlike any other.

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