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CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

Should Slowing Senescence Be Regarded as a Legitimate Enterprise of Health Care?

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Abstract

Dementia is one of the most common developments in our increasing human lifespan. Preventing and postponing it have been important projects of health care that rely on the approval and use of interventions, sometimes in the absence of clinical or ethical consensus about what constitutes meaningful clinical improvement, outcomes, or risk factor modification. This commentary on a case considers these variables and proposes how to improve the general health and well-being of older persons.

Case

Multiple news stories have been touting so-called "anti-aging effects" of newly approved drugs that affect fundamental physiological processes of aging. DD, a healthy 78-year-old patient, asks Dr C, "I want to live long enough to see my grandchildren grow up, but I am frightened by the possibility of developing dementia. I've seen advertisements about new drugs. Would you prescribe these for me, Dr C?" Dr C wonders what is known about these new drugs' safety and efficacy and considers how to respond.

Commentary

Cognitive decline, including development of dementia, is associated with aging and is a prominent component of senescence. The quest to avoid dementia and especially Alzheimer's disease (AD) appeals to people as they age, drives demand for any help and hope practitioners can offer their patients, and enjoys widespread support for research. The attraction of and search for a pill to avoid age-associated decline seems everlasting.[1]

The author was one of a then-small cadre of dementia practitioners and clinical researchers in the late 1970s when the field of dementia research began to emerge from the backwaters of clinical care and research.[2] We looked for any kind of medication that might offer hope to patients receiving a dementia

diagnosis, as patients and their families wanted to "do something." Popular medications used then included drugs like isoxsuprine and ergoloid, now abandoned because they lacked evidence of effectiveness.[3,4] Their presumed effect of widening blood vessels, and thereby improving circulation, provided a rationale for their off-label use for dementia and allowed physicians to offer tangible help and hope to some. Unlike drugs used for dementia today, these drugs' costs and side effects were minimal and didn't attract much attention.[5]

Over the past 50 years, we have learned a lot more about AD.[6,7] Evidence supporting the efficacy of new drugs, ranging from those that inhibit acetylcholinesterase (as acetylcholine is the neurotransmitter thought to be most involved in AD) to drugs designed to remove brain amyloid, has been accumulating from long-term trials.[6,7] Over several decades, intense research efforts have been based on the notion that buildup of amyloid plaque in the brain is one culprit of neurodegeneration in the brains of persons who develop AD and dementia; slowing the rate of plaque buildup is key to preventing or reducing AD burden. However, there is no consensus on what constitutes clinically meaningful change. This commentary examines this issue and proposes how to improve general health and well-being in older persons.

Statistical, Detectable Differences

The US Food and Drug Administration (FDA) has recommended that researchers use sensitive measures of cognition in clinical trials to evaluate an experimental drug and to test the validity of hypotheses (eg, about the roles of amyloid and acetylcholine in AD).[8] To demonstrate an effect of an intervention—usually on persons in earlier stages of the disease, with mild AD, or with minimal or so-called mild cognitive impairment—cognitive outcomes of treatment and placebo groups are compared over time using standardized psychometric tests. The FDA recommended that such measures be used in multi-year clinical trials[8]; a difference between the treatment and placebo groups' cognitive decline, if statistically significant, is unlikely to be due to chance and is believed to indicate that the intervention is effective, at least in minimizing unwanted cognitive decline.[9] While there is indeed controversy over the effectiveness of AD treatments,[9] it is generally agreed that the benefits shown in clinical trials are, at best, modest, limited to statistically significant but small, mostly imperceptible, differences in rates of decline or in rates of disappointing side effects. Neither of the 2 major classes of drugs (anti-amyloid and anticholinergic drugs) is believed to "cure" the disease.[6] Nevertheless, after decades of work, the field can finally "do something" rather than standing by helplessly as AD progresses.

However, one important question is this: What constitute clinically important differences in trials of drugs designed to slow a progressive disease like AD?[9] Unlike diseases like cancer or life-threatening cardiac diseases that present clear-cut dichotomous outcomes—such as mortality, recurrence of the disease, or of a measurable event—a progressive dementia, like AD, leaves investigators, regulators, clinicians, and patients and their families with a different question: How much difference is worth the cost, effort, and, especially, side effects of

treatment? Should any difference in outcomes that is unlikely to be a chance difference be regarded as clinically significant?

Determining Clinical Significance

An important issue for AD, in common with many other progressive conditions, is whether a statistically significant difference favoring treatment in one or more outcomes can be taken as a threshold for a minimal clinically important difference, or minimal detectable difference. There is no gold-standard method to define or calculate minimal clinically important differences.[9] Regulatory bodies, including the FDA, generally rely on statistically significant changes.[9,10] Clinicians, certainly[9]—and patients and their proxies—likely recognize that a difference, albeit statistically significant, favoring treatment on any trial endpoint might not represent a meaningful clinical benefit. That an FDA expert committee convened to review a highly publicized anti-amyloid monoclonal drug recommended non-approval due to lack of compelling evidence of a treatment effect[11,12]—a recommendation the FDA did not accept—reflects the lack of consensus on a threshold for a clinically meaningful benefit.[9] In 2019, Weinfurt proposed a way to "clarify the meaning of clinically meaningful benefit in clinical research: noticeable change vs valuable change."[13] More recently, Liu et al have proposed a helpful 3-step approach to evaluate clinical benefit of Alzheimer's disease therapies. First, is a change noticeable—that is, "clear, perceptible, and … easily communicated"? Second, is it valuable, or "judged to be important"? And third, is it worthwhile, in the sense that "the value of the change outweighs specific considerations such as side-effects, costs, inconvenience, or required duration"?[9]

In the absence of consensus on what constitutes a clinically important difference, the field uses not only psychometric outcomes but surrogate endpoints like brain amyloid. Together, these outcomes measures are likely to increase the number of treatments in development and approval pipelines. However, except for donepezil, which is now relatively cheap and easy to administer, the newer anti-amyloid antibodies have more serious side effects (eg, infusion reactions, dizziness, falls or stroke, and even death[7,9]). Moreover, in the absence of consensus on what constitutes a clinically meaningful benefit, we are also left with serious resource implications, ranging from costs ($26 500 per year for lecanemab) to infrastructure and resource issues.[14] Indeed, the market for new drugs and the costs of their widespread delivery and monitoring is staggering. Improvements in longevity in higher-income countries and now in lower-income countries have created a new epidemic, what was once called the silent epidemic.[7,15,16] The global estimate of the number of persons living with dementia was 57 million in 2019, and that number is expected to grow to 153 million by 2050.[17] At the time of the approval of the first anti-amyloid antibody drug, aducanumab, in 2021, the US Centers for Medicare and Medicaid Services and the Health Care Financing Administration programmed a 14.5% increase in Medicare Part B premiums[18] to cover the newly approved drug's expected costs, given its widespread market and projected price. The drug company promoting aducanumab has since discontinued this drug as a treatment for AD.[19]

The United States already has much higher health care costs than any other advanced economy.[20] Treatments adopted on the basis of minimal detectable differences will undoubtedly contribute to health care cost inflation. Added to that is the fact that amyloid, the target of these drugs, is not the only culprit implicated in AD and associated neurodegenerative disorders. Most people with AD, especially older persons, have co-occurrences of other neurodegenerative changes: tangles of Tau proteins, microinfarcts, macroinfarcts, Lewy bodies, and other neuropathological changes.[21,22,23] These pathologic changes would not likely be affected by the newer drugs. If anything, the minimal effectiveness of these newer drugs might be because they ignore other, commonly co-occurring pathologic changes seen in AD and related dementias.

Reframing Prevention

Large investments required to market, provide, and monitor drugs of relatively minimal effectiveness—including for dementia—could be used for better purposes. An example is investments to address "moral determinants of health" as outlined by Berwick,[24] which refer to the solidarity required to problematize structural determinants that undermine health and exacerbate inequity. For chronic diseases, including dementia, prevention has become more promising and evidence based. For example, observational studies conducted in high-income countries suggest that age-specific dementia incidence rates have decreased, supporting the notion that prevention is possible, to an extent, and might have already occurred due to improved socioeconomic conditions and education levels, better control of cardiovascular risk factors, and better well-being overall.[25] The third report of the *Lancet*'s Standing Commission on Dementia, published in 2024, identified 14 potentially modifiable risk factors for dementia and concluded: "The potential for prevention is high and, overall, nearly half of dementias could theoretically be prevented by eliminating these 14 risk factors."[7]

An ethical issue posed by relying on minimal detectable differences is that the use of these as evidence of effectiveness in clinical trials and to justify FDA approval decisions has led to the dawn of an era in which expensive treatments of minimal effectiveness will forestall better uses of collective resources. It is relatively easy to prey on people's fear of dementia with appeals like that of the president and chief executive officer of the Alzheimer's Association, who credited a new anti-amyloid drug with giving patients "more months of recognizing their spouse, children and grandchildren"[26] without any good supportive evidence for this claim.[9]

I would argue that for reducing the burden of dementia on individuals and society, prevention or delay of onset of dementia is now on the verge of being deployed in the ways that, many decades ago, led to the decline of heart disease and stroke. An evidence-based strategy to reduce risk factors throughout the life course is likely to be better at preventing or delaying dementia than relying on medications that are judged to be effective based on minimal detectable differences. Evidence-based prevention across the life course addresses a

universal desire to delay senescence without producing socially irresponsible trade-offs that accompany treatments whose minimal benefits are mostly unnoticeable to individuals taking them. Better to do "something" that aging persons can experience and that offers better overall health.

Patient Advice

Based on the above analysis, Dr C should inform patient DD that the new expensive drugs that might offer hope on the basis of minimal detectable differences will not likely prevent the disease or even have much present benefit that DD can perceive. They do come with high individual costs, including side effects and taking time away from other things important to older people. An alternative would be to focus on elements that promote both general health and well-being and, especially, those that reduce risk of dementia and decline. And, of course, DD should enjoy his current relatively good health and grandchildren as they grow into adults.

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Editor's Note

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