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Perspective

Accelerating Alzheimer's disease drug innovations from the research pipeline to patients

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Abstract In June 2017, a diverse group of experts in Alzheimer's disease convened to discuss how to accelerate getting new drugs to patients to both prevent and treat the disease. Participants concluded that we need a more robust, diversified drug development pipeline. Strategic policy measures can help keep new Alzheimer's disease therapies (whether to treat symptoms, prevent onset, or cure) affordable for patients while supporting innovation and facilitating greater information sharing among payers, providers, researchers, and the public, including a postmarket surveillance study system, disease registries, innovative payment approaches, harmonizing federal agency review requirements, allowing conditional coverage for promising therapeutics and technology while additional data are collected, and opening up channels for drug companies to communicate with payers (and each other) about data and outcomes. To combat reimbursement issues, policy makers should address the latency time between potential treatment—which may be costly and fall on private payers—and societal benefits that accrue elsewhere.

Keywords: Alzheimer's disease; dementia; innovation; pricing; drug pipeline; drug development

There have been some disappointing results from Alzheimer's disease (AD) trials recently. In February 2018, Merck announced that it would cease trials of verubecestat, the first in a new generation of beta-secretase drugs, due to negative results, and in September, Axovant reported that intepirdine did not improve cognition or functional status relative to placebo in patients with mild-to-moderate AD. Experimental therapies from Eli Lilly & Co, Pfizer, and Johnson & Johnson have been similarly disappointing [1,2]. Yet the burden of disease is so severe that many of these companies remain committed to future research, and several important clinical trials will read out in the next few years. Without any intervention, dementia prevalence could triple over the next several decades. However, interventions could dramatically alter this trajectory [3]; a 1-year delay in onset, for example, could generate billions in savings in medical and caregiving costs [4]. These potential benefits explain why experts going back to the 1990s have proposed incremental goals to reduce both the incidence and rate of decline for AD and AD-related disorders [5].

The history of AD and AD-related disorders trials suggest that any progress in forestalling or mitigating symptoms will be incremental. In an era of rising health care costs, how can we ensure that we can afford these medications and that patients will have access to them? In June 2017, patient advocates, academic researchers, payers, pharmaceutical innovators, and policy makers met in New York City to begin an early discussion about how to accelerate getting new

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drugs to patients to both prevent and treat. The meeting's goal was to identify policies that might more efficiently and effectively move incremental AD and AD-related disorders drug innovations from the research pipeline to patients in the United States' health care system, which is already struggling with high and rising costs.

1. We need a robust pipeline

The most significant hurdle we face in combating AD right now is widespread drug failure, due in part to a lack of diversity in novel targets and a lack of validated preclinical models. Unfortunately, there has not been a novel drug approved to treat AD since 2003 when Namenda came to market. There are 105 agents moving through the development pipeline, targeted in three main areas: primary prevention before changes in the brain occur; secondary prevention when changes in the brain have already occurred, but before symptoms appear; and treatment when symptoms have appeared [6].

As new drugs come to market in the United States, private insurers will rely on evidence that is generated through short-term clinical trial results to make coverage decisions for specific populations and subpopulations of beneficiaries. (For Medicare, oral agents are eligible for reimbursement if they are Food and Drug Administration–approved and included in a compendium. If, however, drugs are not self-administered and therefore require a physician service, they are reimbursed under Medicare Part B and would therefore need to demonstrate evidence of improved outcomes in the Medicare population.) Either way, most of the near-term coverage decisions likely will involve modest improvements in symptoms or delays in disease progression. Nonetheless, payers are wise to begin thinking now about how to finance both a breakthrough treatment, which is more likely to be a long-term therapy than a one-dose cure, and a preventive drug that would have to be administered to tens of millions of patients, some of whom may never manifest the disease.

2. There is a high price to drug development failure

Pharmaceutical manufacturers often cite high research and development costs as the main reason for high drug prices. However, the high cost of developing drugs is driven largely by the number of failures; the drug approval process is not particularly expensive. The overall success rate of advancing the AD compounds studied from 2002 to 2012 to regulatory submission was just one in 244, or a failure rate of 99.6% [7]. Without Namenda, the failure rate would have been 100%. To reverse the trend, innovators need to adopt practices that are more likely to lead to drug approvals, primarily by building on successful phase 2 trials to get robust results on both cognitive function and activities of daily living.

Pharmaceutical innovators also need to facilitate enrollment of patients with dementia in clinical trials. There are significant hurdles to AD clinical trial enrollment; potential volunteers are often concerned about risks, invasive procedures, and the time required for participation, while providers cite a lack of their own time, lack of available diagnostic tools, lack of proximity to a research center, and patient comorbidities as factors that prevent them from referring patients. In addition, many prerequisites for AD trials can be prohibitive for possible participants, including a study partner or conflicting medication [8].

To address some of these barriers, at least one pharmaceutical company has established an account with Lyft to transport study participants directly to their sites so that patients do not need to pay for a taxi upfront and wait for reimbursement. Development of more precise biomarkers can also help make sure appropriate patients are enrolled in trials and help avoid the costs of overtreatment [9]; however, the demands for testing these biomarkers can also make studies much more complex and expensive. Social media can help increase awareness of trials, especially for difficult-to-reach populations, but its efficacy in boosting enrollment is unclear [10].

Pharmaceutical innovators must conduct more phase 4 clinical trials for AD drugs to demonstrate long-term outcomes for both patients and caregivers and avoidance of downstream medical costs such as hospitalizations. To that end, participants agreed there are tremendous opportunities for innovators and payers to partner in phase 4 trials by linking trial data to claims and electronic health record data and examining outcomes over 5 or 10 years (or more) to determine clinical effectiveness and cost offsets over time.

3. We need creative financing mechanisms

With dozens of new AD drugs in the pipeline involving many different mechanisms of action, it is likely that, in the near term, treatment innovations will be incremental—possibly similar to a stepwise approach for illnesses such as type-2 diabetes or hypertension. Longer term, many are hopeful that researchers will find a cure for AD or a way to prevent the disease. And while AD is a worldwide problem, payer systems are heterogeneous and national. In some respects, the United States through its market-based system finances pharmaceutical R&D for the rest of the world. Complicating the financing picture, AD innovations would likely involve early treatment with downstream benefits decades later, but our health care system is operated on annual contracts.

Public and private payers also face different risks—in the near term, most cost exposure for AD is in the Medicare population, where potential utilization and cost savings would accrue to Medicare for inpatient care and Medicaid for nursing home care. But a breakthrough innovation aimed at people aged 50 to 60 years that prevented the disease would be financed by private insurers, who would incur much of the cost and get little, if any, savings. This is a fundamental problem that policy makers and the Alzheimer's community must address.

Payers also lack long-term follow-up studies that can guide coverage decisions. Increasingly, payers are turning