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EDITORIAL ARTICLE

Are the Newest Anti-Alzheimer's Medicines Being Evaluated Under Outdated Pricing Paradigms?

Charles S. Wilcox, Ph.D., M.P.A., M.B.A.

Praxis Research Consulting, 1400 Quail Street, Suite #285, Newport Beach, California 92660 (USA); Alzheimer's Association (Orange County); Alzheimer's Impact Movement

Charles@praxisresearchconsulting.com

ABSTRACT

The 2021 approval of aducanumab in the United States, was not followed by approvals in Europe, Canada, Australia or elsewhere; nonetheless, the initial pricing of $56,00.00/year created a firestorm of controversy. The 2023 Food and Drug Administration approval of lecanemab has been followed by approvals in Japan and China. The current (2024) costs are $26,500 in USA, $20,438 (National Health Insurance) in Japan and $28,180 (private market) in China. In Europe, a health technology assessment will drive coverage decisions and set single-payer prices for each health system for lecanemab and subsequently approved new treatments. For comparison, 2024 average pricing for the top five selling drugs for cancer [$198,273], arthritis [$83,666], hepatitis C [$75,118] and multiple sclerosis [$86,765] far exceed lecanemab's annual cost. Could there be an anti-brain-health bias?

The International Consortium for Health Outcomes Measurement notes that patient-centered outcome measures represent the ultimate measure of quality and they are always multi-dimensional. Quality-adjusted life-years (QALY) seem to be absent from the computation of pricing for anti-dementia treatments. Although global consensus on QALY calculations remains elusive, currently extant data are compelling. The QALY calculation is the change in utility value induced by the treatment, which is then multiplied by the duration of treatment effect to provide the number of QALYs gained. QALY ranges differ quite significantly, even amongst the most industrialized nations. Value-based pricing from double-blind, placebo-controlled trial results, demonstrating statistically significant beneficial effects on cognition and/or global function, would reward manufacturers for innovation whilst also enabling payer systems to remain solvent.

Now that the first truly disease-modifying treatment for Alzheimer's (lecanemab) has been approved, a second disease-modifying treatment (donanemab) appears to be heading for regulatory approval as well. The full value of these newest anti-dementia treatments may be understated when quantified under older pricing models and, hence, could unwittingly be a disincentive to further innovation. We now have disease-modifying and symptomatic relief treatments for Alzheimer's disease to be included within the treating clinicians' armamentarium and, when priced appropriately, access should be widely available whilst also encouraging further innovative anti-Alzheimer's clinical research.

Keywords: Alzheimer's Disease; AD, dementia; Quality-Adjusted Life-Years; QALYs; Disease-Modifying Treatment; DMT; aducanumab; lecanemab; donanemab; value-based pricing; Pharmacy Benefits Managers; PBMs; pricing paradigms; cost-benefit analysis; risk-benefit analysis; health technology assessment; HTA; patient-centered outcome measures.

Introduction

Public Opinion surveys during the height of the pandemic reflected a robust boost with respect to the pharmaceutical industry's public image. Short-lived indeed, before the conclusion of 2023, that improved public sentiment went crashing to an end. A Gallup poll reflected that Pharma was once again in last place – 25th out of the largest 25 industries and enterprises, as it was in 2019 as well.[1] Unquestionably and inextricably, there is a significant linkage between the costs of prescription medicines and the persistent public perception and firm belief that many drugs are "tremendously over-priced," as "Big Pharma" is maximizing shareholder value. There have been several publications delving into nearly all of the factors which contribute to this perception, including the fact prescription costs are often the last and most visible percentage of the health care dollar.

Between the current high costs for Research and Development (R & D) and the costs for treating rare diseases, we see Lenmeldy™ priced at $4.25 million as a one-time gene therapy for metachromatic leukodystrophy,[2] Hemgenix® priced at $3.5 million for a one-time dose to treat hemophilia B, Elevidys® priced at $3.2 million for a one-time dose to treat children (ages four and five) with muscular dystrophy and Skysona® priced at $3.0 million for a one-time dose to treat boys with early, active cerebral adrenoleukodystrophy (CALD), also a rare genetic disease.

Leading-edge, innovative and carefully-conducted clinical research is incredibly expensive. Clinical research for neurodegenerative diseases such as Alzheimer's is no exception. Over the past four decades billions *and billions* of dollars have been invested with, up until recently, painfully little success. For example, it was reported in *Alzheimer's Research & Therapy* that between 2002 and 2012, 244 different compounds were tested in 413 different clinical trials. The results? Only one (1!) new drug was approved: Namenda®.[3] This equates to a 0.4 percent success rate, a.k.a. a 99.6 percent lack of a successful outcome.

Far removed from the popular lay-press, we read that a company like Eli Lilly has invested 29 years and $USD 8 billion, embracing failures, faith and conviction, to have their monoclonal antibody (donanemab) for the treatment of Alzheimer's disease (AD) on the presumed apparent brink of regulatory approval and presumably imminent commercial availability.[4] As of the date this article is going to press, there is no preliminary projected pricing information for donanemab; nonetheless, with the current pricing for lecanemab at $USD 26,500/year, it seems likely that Lilly's new chemical entity will be priced similarly. AD kills more people than breast cancer and prostate cancer combined! In harmony with the typical prolonged multi-year course of AD and other dementias, according to the Alzheimer's Association, costs in the US (for 2024) will be $360 billion.[5] These, of course, are only the tangible costs.

We believe that, when evaluated within the contexts of Cost-Benefit, Risk-Benefit and perhaps most importantly, Quality-Adjusted Life Years (e.g., QALY's), these new disease-modifying treatments (DMTs) for AD are expensive, yet appropriately priced when their benefits are objectively quantified and especially when compared with treatments for

other indications. To wit, is there possibly an anti-brain-health bias when valuing these novel and new DMTs for the treatment of Alzheimer's disease? Moreover, would an updated comparison of the costs of treatments for other indications and/or a more comprehensive evaluation of the value(s) associated with sustained cognition and global function potentially create a more equitable pricing paradigm?

Aim and scope

Although officially identified, described and categorized by Dr. Alois Alzheimer 118 years ago, the pursuit of safe and effective treatments for Alzheimer's disease has been persistently elusive and extraordinarily expensive. Prior to the approvals of aducanumab (USA only) and lecanemab, no disease modifying treatment for Alzheimer's disease had ever received regulatory approval. The multiple reasons for the lackluster sales and eventual withdrawal from the marketplace for aducanumab began with its tumultuous clinical development and exceedingly controversial Food and Drug Administration (FDA) approval.[6]

One of the FDA expert consultants who resigned, Dr. Aaron Kesselheim, a Professor at the Harvard Medical School, sent a scathing letter of resignation which included "Accelerated Approval is not supposed to be the back-up that you use when your clinical trial data are not good enough for regular approval... [this is] probably the worst drug approval decision in recent US history... It is clear to me that FDA is not presently capable of adequately integrating the [Advisory] Committee's scientific recommendations into its approval decisions.[6]

Even the mainstream lay-press reported that the U.S. Congressional 18-month investigation into the approval process (for aducanumab... Aduhelm®) found it to be "rife with irregularities" including "atypical collaboration" between the company (Biogen) and FDA.[7] Factoring-in the initial pricing of $56,000.00/year which, of course, excluded the costs for infusions, possibly a positron emission tomography (e.g., PET) scan, and periodic magnetic resonance imaging (MRIs), there was substantial push-back from Medicare, while patient advocacy groups, including The Alzheimer's Association and Global Alzheimer's Platform (GAP), were largely boisterous in their support.

In contrast, from a regulatory, lay-press and scientific-press perspective, the approval and commercial availability of lecanemab (Leqembi®), with initial annual pricing at $26,500 (USA), $20,438.00 (National Health Insurance) in Japan, and $28,180.00 (private market) in China, has (comparatively speaking) enjoyed smooth-sailing! One can certainly argue this is largely because the published results demonstrate statistically significant benefits for both cognition and global function, versus placebo, with lecanemab. Importantly, and currently being the only commercially available DMT for Alzheimer's disease, we believe that between the subjective nature of pricing in general and the probability of an anti-CNS-bias in particular, the pricing of these new DMTs should not be compared with the limited number of older medicines which provide time-limited meaningful but modest symptomatic relief for AD patients.

These novel and new DMTs are creating a class of their own! Similarly, we believe that the respected and often-cited team at Institute

for Clinical and Economic Review (ICER) may have used an outdated (for this indication) and/or an overly restrictive conceptual lens for its valuation determination that an appropriate price range for Leqembi® would be in the $8,900 to $21,500 price range.[8] For example, and in significant contrast, one of the pricing models used within Eisai (and Biogen) also took into account the long-term cost savings which they were able to specify and quantify as having a societal value in excess of $37,000.[9, 10]

Assessment: Controversy and Context

As mentioned above, the lay-press has, in our opinion, ambitiously addressed and publicized, if not outright promoted, the controversial nature of pharmaceutical company pricing of drugs. We agree that there is significant potential merit to the controversy, particularly as it relates to fact that the three largest pharmacy benefits managers (PBMs) control approximately 80% of the total (US) market.[11] Indeed, in the US this is a very politically charged message that resonates with politicians and voters alike. However, beneath the veneer of politically charged public distrust and at times disdain for "Big Pharma," there are tremendously potent economic factors that often go unacknowledged and therefore unspoken. These economic factors drive countless decisions and, most importantly, have an impact on millions of lives all around the world. This is not hyperbole; it is bottom line economic reality! Furthermore, it is especially relevant to the millions of individuals suffering from CNS diseases in general and Alzheimer's disease in particular. Return-on-investment (ROI) is not a concept that is limited to hedge funds, venture capitalists, private equity people and shareholders, it is a harsh reality for research and development leaders faced with tough resource, plus "ROI," decisions. They must evaluate and render long-term multi-billion-dollar decisions taking into account the opportunity costs, and net present value calculations, of pursuing new treatments in one therapeutic area versus another, including their "odds of success."

Some relatively recent Big Pharma CNS/Neuroscience-related history seems warranted. In fact, as recently as ten-to-fifteen years ago, the paring down and, in many cases, complete exodus from neuroscience by numerous large companies was completely unprecedented. For examples, in April 2009 Sanofi overhauled its pipeline and cut hundreds of jobs, citing its reduced CNS research; January 2010 GlaxoSmithKline ended its neuroscience R & D in England, including depression and pain; July 2010 Merck & Co. closed their United Kingdom (UK) neuroscience lab and downsized their U.S. operations; December 2011 Novartis announced the closure of its neuroscience R & D site in Basel, Switzerland; February 2012 AstraZeneca announced the layoffs of 2,200 scientists, most of whom worked in neuroscience.[12] In November 2013 Bristol-Myers Squibb exited CNS, noting a heightened focus on HIV, hepatitis B, oncology, etc.[13] Following this trend, in February 2018, Pfizer announced its exit from neuroscience, noting that eight neuroscience products (in Phase I and II) were being discontinued, whilst also citing the "estimated 99.6% failure rate" in the area of Alzheimer's drug development.[14] Admittedly, in retrospect rather than real time, the devastating depth and breadth of witnessing seven (7) multinational multi-billion-dollar pharmaceutical companies redirecting their R & D dollars away from CNS/neuroscience and into other indications may

seem unremarkable. At the time, it was a *truly remarkable* phenomenon for all of us working within the neuroscience arena, not to mention the patients and families all around the world desperately in need of new, safe and efficacious medicines for CNS indications. Our point? *When the necessary ROI on an R & D investment is perceived, modeled and quantified to be highly improbable, a decisive redirection of goals, objectives and resources is inevitable!*

Update on Pricing Models and Paradigms

While no drug pricing model is perfect, there are six models that have garnered the most attention and acceptance around the world over the years: financial risk-based contracts, health outcomes contracts, mortgage models, subscription or Netflix models, indication-specific pricing and volume-based purchasing.[15] This last one, volume-based purchasing/pricing is especially useful in the case of preventive therapies, such as flu shots. Indication-specific pricing is widely used by large pharmacy benefits managers (PBMs), especially for oncology and autoimmune products. It is also used for products that are approved to treat more than one type of disease. In these cases, pricing agreements reflect a higher price for a drug when it is highly effective in treating one disease and a lower price for an indication where the drug is less effective. Pioneered in Australia, the subscription or "all you can treat" model allows purchasers to pay a pre-set/fixed amount for unlimited access for a set period of time. All three of the pricing paradigms have advantages; we do not foresee their utilization for anti-Alzheimer's DMTs.

The mortgage model offers the benefit of allowing purchasers to spread the cost of an expensive therapy over an extended period of time, as opposed to requiring the total payment-in-full upfront. This is especially useful and applicable with orphan drugs targeting rare diseases, as well as new immunotherapy products for oncology. Here too, we do not (now) foresee this model as being applicable to anti-Alzheimer's treatments.

This leaves us with two (of the six) pricing models that warrant further discussion. First, there are the financial risk-based contracts. Here we have value-based contracts that are designed to link prices with the efficacy of a treatment in the real world, as opposed to having prices based solely on the data collected during the well-controlled clinical trial process. In the rapidly evolving world of wearables and remote monitoring devices, gathering health data has accelerated the use of value-based contracting and, in some instances, has also helped to improve patient access to therapy. However, even in 2024, the challenges of data collection and sharing, as well as operational hurdles remain as substantial. It's noteworthy that, in Europe, single-payer healthcare systems have pushed pharma companies to collaborate on risk-based or outcomes-based agreements. This has garnered the most attention in the case of innovative specialty drugs and (again) orphan products. Additionally, it is also believed that when there are similar competing therapies, such as in therapeutic areas like oncology, cardiology and rheumatoid arthritis, contracts can focus on providing financial savings to help mitigate purchaser risk associated with high-cost therapies.

While this model clearly has merit, given the paucity of proven anti-Alzheimer's DMTs and complicated assessment measures for AD (as

well as multiple pertinent clinical domains) for demonstrating efficacy, we do not believe it will be appropriate and applicable in the foreseeable future. To underscore our strong contentions about complexity of AD, one of the key instruments for diagnosis, staging and treatment efficacy is the widely-utilized well-validated Clinical Dementia Rating scale (CDR).[16] This instrument is almost always one of the two primary outcome measures in an AD clinical trial. We use this instrument when working with patients and their significant other(s), or at least a study partner, who consistently spends a significant amount of time with the patient (on a weekly basis). We not only use this to evaluate the patient's Memory, there are five additional domains including Orientation, Judgment and Problem-Solving, Community Affairs/Participation, Housework and Hobbies, plus Personal Care.

Alas, this illuminates, particularly for European governments' health systems and the provision of anti-Alzheimer's treatments, the potential, admittedly "loose" applicability and appropriateness of some refined version(s) of health outcomes-based contracts for this indication. In an ideal situation health outcome-based contracts offer full or partial reimbursement to purchasers, if patients do not respond to therapy or do not achieve the targeted health outcome. While we can look at a diabetic patient's HbA1c to assess the degree to which one's blood glucose is under control, or a reduction in the number of asthma attacks for an asthma patient, unfortunately, in patients with AD there is not a singular easily quantified meaningful outcome measure. In fact, even the removal of amyloid has not translated into a reliable efficacy measure. Moreover, given the heterogeneity of the causative factors coupled with the heterogeneity of the manifestation of symptoms of AD, and how to measure them, an agreed upon outcomes-based measure for contracting purposes is not yet within reach.

We would be remiss to not briefly mention and acknowledge the burgeoning promise and active clinical development of several biomarkers, including some that have recently become commercially available as a diagnostic, staging and/or efficacy measure for AD; nonetheless, we do not (yet) believe that any one of these should now be considered a gold standard for a health outcomes-based contract for an AD DMT or even an AD symptomatic relief treatment. In 2023, the Alzheimer's Association issued an official policy statement advocating continued utilization of these biomarkers only within the context of clinical research (rather than clinical practice); nonetheless, several of them are in fact commercially available to the general public at this time.

It is well-known that European single-market payers have been able to negotiate prices for drugs that can be less than those being paid in a free market system, such as the US. Independent of whether this is an indication of price-gouging in the US, one can argue that patients living in the free market systems for prescription drugs are in fact subsidizing governments and patients in the single-payer systems. A 2021 RAND report on 2018 drug costs in the U.S. versus 32 other countries in the Organisation for Economic Co-operation and Development (OECD), reported that on average, U.S. prices were 256% of those in the 32 other countries; moreover, for brand-name drugs, prices in the U.S. were 344% of those

in comparison countries.[17] Returning to the core issue of reasonable and equitable drug pricing that will incentivize innovation by rewarding the risks taken for R & D in AD, with sufficient ROI without bankrupting health care payers, over the past twelve to eighteen months several increasingly challenging and very pertinent developments have unfolded in Europe.

For example, Bayer recently and openly redirected their attention away from Europe in favor of the US and China. Over the past decade, France has so successfully negotiated rebates for prescription medicines that their net prescription drug(s) budget *declined* by 4.5% per year from 2011 to 2023; and most recently, that's during a time of significantly increased inflation rate(s). In Spain, a more formal cost-effectiveness criterion was implemented as part of their national price approval and this, in turn, will have an impact on the number of drugs that will be deemed viable for launch. In the United Kingdom, the National Health Service wants to recoup 24.4% of their drug expenses as a rebate. This is also in tandem with a decline in their willingness to pay consumer price index adjustments on prescription medicines.

Perhaps most importantly, as of 2023, the European Commission was also evaluating legislation that would reduce prescription medicine patent lives from ten to eight years and/or make it mandatory for manufacturers to commercially launch newly approved drugs in all of the European Union (EU) member states, irrespective of the locally determined price. The economically important implication here is that a mandatory launch at the lower price range of European prices could then spread throughout the EU.[18] The recent and relatively widespread downward pressures on drug prices in Europe are too recent to determine the long-term implications and overall (net) effects. While some pharma companies may have pivoted away from the EU, e.g., Bayer, for companies with strong evidence of patient benefit(s) associated with their new treatment(s), one can still see a compelling case for early commercialization.

For the new DMTs for AD, these trends and challenges raise at least two central questions: 1. Since the clinical evidence of safety and efficacy was sufficiently strong for regulatory-related approval, is it also convincingly strong to warrant and receive the targeted pricing? 2. If so, in what manner or format can the benefit(s) be presented, quantified and verified? The initially disclosed Press Release (November 30, 2022) from Eisai, reported that lecanemab produced highly statistically significant results ($p = 0.00005$), on the global cognitive and functional scale, that represented a 27% slowing of decline, over 18 months, as compared with placebo.[19] The subsequent publication in the New England Journal of Medicine (January 5, 2023) reported that the primary outcome measure results corresponded with a 25% less decline in cognitive function with the lecanemab treatment group, as compared with the placebo treatment group. There was also a positive change in the amyloid burden on PET scan results.[20]

Similarly, and although regulatory review is still ongoing at FDA, the published results for Eli Lilly's AD DMT, donanemab, stated that there was a 38.6% risk reduction of disease progression as measured by the CDR-Global score, over the 18-month study.[21]

Notwithstanding the positive results set forth within the New England Journal of Medicine (NEJM) publication, after FDA's reportedly thorough initial review of the data, a number of regulatory-related questions remained and/or arose. These reportedly pertained to the safety results, the statistical analyses, the use of an atypical primary outcome measure, the notion that treatment would be time-limited (roughly 18 months) and one or two other concerns as well. Accordingly, on March 8, 2024, the Food and Drug Administration notified Lilly that there would be a delay in the agency's approval (or disapproval) decision. The current, publicly disclosed, plan is for the agency to convene an Expert Advisory Panel to review the data and more thoroughly address the aforementioned concerns.[22] Indeed, some of these same regulatory-related concerns underscore the complexity of the disease as well as the difficulties associated with evaluating benefits which, in turn, leads us back to the challenge of proper pricing.

To that end, we believe that the objectively quantified global measure(s) reflecting a 27% lessened decline with lecanemab, as well as a 38.6% lessened decline with donanemab, are a very important and useful measure of clinical benefit, which in large part, can serve as the basis for value-based pricing of a DMT for AD. Furthermore, given the duration of double-blind treatment in both Phase III programs, we believe that QALYs will be an appropriate metric. Perhaps most noteworthy and directly applicable, for dementia the International Consortium for Health Outcomes Measurement (ICHOM) has reported that patient-centered outcome measures represent the ultimate measure of quality and they are always multidimensional. Although global consensus on QALY calculations is evasive, currently extant data are compelling. Briefly, QALY calculation is the change in the utility value (with a range of 0 to 1) induced by the treatment, which is then multiplied by the duration of the treatment effect to provide the number of QALYs gained. Inflation adjusted (for 2024) QALY ranges (in U.S. $) vary widely from one country to another, such as those in Australia ($33,955 to $57,687), Germany ($27,070 to $86,922), Japan ($58,751 to $69,943), Sweden ($53,760 to $62,030) and the United Kingdom ($51,616 to $102,084).[23-25]

These new, seemingly reasonably safe and efficacious DMTs for AD, have demonstrated vitally important benefits in terms of cognition and global function for patients and their caregivers. When diagnosed with AD at age 75, the lifetime costs for caregiving out-of-pocket payments were estimated to often exceed $500,000 (in the U.S.) and that was in 2017. Factoring-in government-endorsed cost-of-living increases over the subsequent years increases those costs to approximately $629,217. What happens when we quantify caregiving costs as a key component of a cost-benefit analysis?

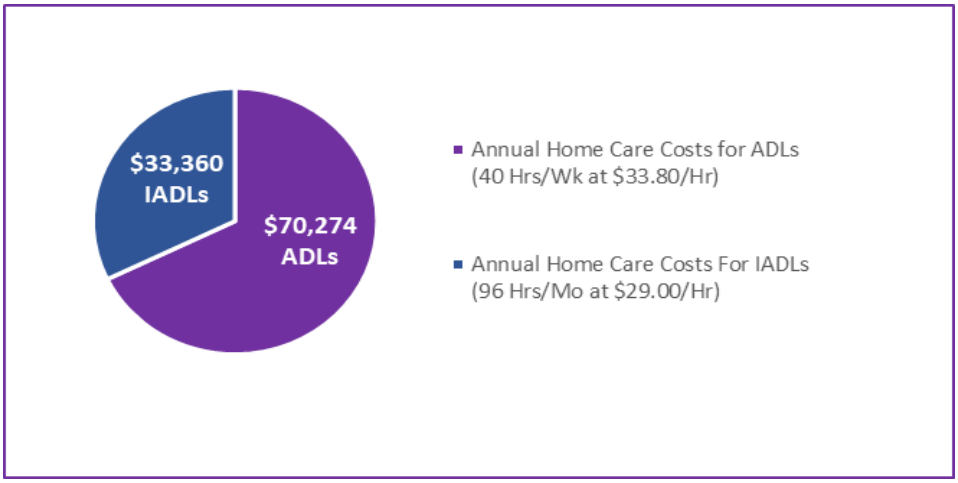
Figure: 1

Activities of Daily Living (ADLs)	Instrumental Activities of Daily Living (IADLs)
Eating	Managing Money
Walking	Remembering Appointments
Toileting	Planning and Preparing Meals
Grooming	Housework and Chores
Bathing/Showering	Shopping, Groceries, Necessities
Dressing/Undressing	Managing Transportation Needs

Published and verified metrics allow us to quantify the value (range) associated with preserving cognition and global function for 12- or 24-months, (inflation adjusted, for 2024) ranging from $33,360/year to $103,634/year.[26]

Moreover, these cost estimates do not include the direct and/or indirect physical and emotional costs incurred by spouses and adult children whom step-up to help their loved ones. (Figures 1 and 2) These include and are not limited to (their own) greater risk of anxiety, depression, personal medical challenges and a poorer quality-of-life than caregivers of people with many other medical conditions. [27-30].

Figure: 2



The prolonged paucity of safe and efficacious medicines, coupled with the current availability of only one commercially accessible disease modifying treatment for Alzheimer's disease, consistently highlights the fact that AD is an incredibly complex disease. In harmony with the complexity of the disease is a sustained track record of infrequent successful financial return-on-investments in CNS disorders in general and AD drugs in particular.

1. We believe the true economic value of a safe and effective DMT for AD needs to be reconceptualized.
2. Value-based pricing of a new DMT for AD, which fully takes into account the beneficial effects on both cognition and global function for patients, is essential.
3. Quantifying the patient- and caregiver-related benefits, of an efficacious

treatment which transcends multiple domains, can be appropriately priced in terms of QALYs.

4. Equitably priced DMTs for AD will encourage much-needed additional research investment whilst also allowing for wide access for patients, along with providing cost-benefit ROI for health payer systems.

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