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THERAPEUTIC DIGEST

NEUROLOGY

IN COLLABORATION WITH thinkgen

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EDUCATION HAS AN IMPACT

Digital Clinician Education: A Vital Component in Multiple Sclerosis Management

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Multiple sclerosis (MS) is a chronic neurologic disease that affects nearly 1 million adults in the United States.[1] Although MS may be familiar to many, diagnosis of the disease can be challenging; delays in diagnosis and the onset of effective treatment can lead to irreversible disability.[2]

Treatment selection largely depends on the type of MS (there are 4) and the absence or presence of inflammatory activity and disease progression. In addition to some mainstay therapies, new treatments have been developed to manage MS; however, clinicians may not be sufficiently aware of them or confident in their use.

Education that is unbiased, scientifically rigorous, and easily accessible can reduce the gaps in clinician knowledge and confidence. Digital continuing medical education (CME) is a particularly effective and powerful method because it is flexible and accessible, allowing clinicians to learn at their convenience and incorporate education into their busy practice schedules. Digital CME also enables "just in time" education[3]—reaching clinicians at the moment they need the information. Physicians spend more than half of their time online expanding their medical knowledge, searching for materials to support their clinical practice, or answering questions that arise during visits with patients.[4] Therefore, the accessibility and availability of digital CME provides a timely solution for those who aim to learn.

Over the past 5 years, Medscape Education has developed nearly 100 digital educational interventions focused on MS. These programs have reached clinicians as well as patients to provide the education they need, and they have had an impact. For example, the Medscape activity *Understanding the Science of MS: Immunologic Basics of Pathophysiology of MS* had a significant educational impact for neurologists and primary care physicians (PCPs).[5] An analysis of same-learner responses to pretest and post-test questions showed that the activity improved or reinforced knowledge for neurologists and PCPs. Self-reported confidence in understanding the neuroimmunology of MS improved in both specialties.

In 2021, Medscape Education was named the Multiple Sclerosis Association of America's (MSAA) Corporate Honoree at their Improving Lives Benefit. Since 2013, Medscape and MSAA have worked together to educate and engage Medscape's clinician membership on topics highly relevant to the care of patients with MS. Currently, Medscape and MSAA are collaborating on a program devoted to the impact of race and ethnicity on MS care.

As MS management continues to evolve, Medscape Education is devoted to remaining on the cutting-edge and a leader in developing digital education for clinicians who treat patients with MS.

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NEUROLOGY

Introduction

Amid the continued effects of the global Covid-19 pandemic, 2021 has been a year of remarkable activity in **neurology therapeutics**, encompassing treatments for the brain, spinal cord and nerves. New medicines for Alzheimer's disease, migraine, and a host of rare conditions have been prominent in the medical literature and popular news and have been a major focus of industry educational and promotional activity.

Additionally, as there remain significant and in some cases profound unmet needs across the treatment categories under the neurology umbrella – almost none of the major conditions is amenable to disease modification or is curable - the pharmaceutical pipeline continues to abound with new drug candidates and new and more advanced mechanisms of action.

As this report will show, investigational treatments for rare, pediatric neurological diseases may be the most promising territory of drug development in this space and may hold wider promise in other neurological ailments.

The Approval of Aduhelm for Alzheimer's Is Driving Both Hope and Controversy

The most prominent new development in neurology this year is undoubtedly the approval and launch of Biogen's Aduhelm (aducanumab-avwa) monoclonal antibody therapy for Alzheimer's disease (AD), whose surprise approval was greeted by a mix of both high hopes and major controversy.

In June of this year, the US Food and Drug Administration (FDA) announced its Accelerated Approval of Aduhelm based upon a surrogate endpoint of clearance of beta-amyloid, a protein that gathers between neurons and disrupts their functioning. As the first new AD medication approved since 2003, FDA broadcasted Aduhelm's targeting the underlying pathophysiology of the disease – as well as the staggering scope, impact and societal cost that the condition inflicts. Over 6 million patients in the US and their families are impacted by this debilitating and devastating progressive

illness for which there is a relative paucity of effective options. The cost of treating AD dementia in 2020 is estimated at over $300 billion and is expected to continue growing markedly as the US population ages.

inThought

Almost immediately after the FDA's announcement, the controversy began. **"It was a complete shock to many of us in the US healthcare system that Aduhelm was approved,"** commented Dr. Leon Henderson-MacLennan, a practicing physician and Medical Advisor' at *in*Thought Research, a competitive intelligence consulting firm. During 2019, there had been previous questions as to whether Aduhelm could achieve its primary endpoint, and then in November of 2020 an overwhelming majority of the Peripheral and Central Nervous System Drugs Advisory Committee voted against approving it. The fact that the FDA's eventual decision countermanded its independent external committee led two, and then ultimately three members of that committee to resign in protest.

While the Accelerated Approval pathway stipulates that Biogen conduct post-marketing evaluation of Aduhelm, with confirmatory trial results within 9 years, the fact that the approval was based upon surrogate endpoints and not improvement in cognition or memory was exceptionally divisive. Indeed, in a similar situation in 2016, the FDA sparked internal division when it approved Sarepta Therapeutics' Duchenne muscular dystrophy treatment Exondys 51 (eteplirsen). There too, the FDA had to weigh the potential therapeutic benefit of eteplirsen based upon a surrogate endpoint (dystrophin increase in skeletal muscle) in a rare disease category where there exists staggering therapeutic unmet need.

Another major factor that has fueled the controversy with Aduhelm is its list price, $4,312 per infusion for a patient of average weight, or approximately $56,000 per year. Indeed, the price point quickly drew the attention and condemnation of the Alzheimer's Association as well as top government officials. Soon after its approval, Senators Elizabeth Warren, D-Massachusetts and Bill Cassidy, R-Louisiana called for a hearing into Biogen's business practices and into how the approval of Aduhelm would impact the Medicare budget. At the list price of $56,000 per year, the Senators pointed out, treating even a third of the 6 million AD patients in the US could drive a significant increase in Medicare spending. Further, Aduhelm has been cited as among the factors that is now leading the US government to develop legislation as part of the Infrastructure package to permit the Department of Health and Human Services to negotiate drug prices for Federal health care programs.

Biogen has been quick to counter the criticism. They have defended the price by spotlighting the overall direct and indirect costs of treating AD – approximately $600 billion in the US. During the Company's second quarter earnings call in July, CEO Michel Vounatsos and his executive team spent much of the conference striving to dispel concerns and mounting criticism about Aduhelm. Dr. Vounatsos and his colleagues pointed out that not only was it approved based upon the largest AD dataset ever generated, EMBARK, but there are multiple post-marketing trials underway to further support its approval. He spoke about Biogen's efforts to ensure access, particularly for vulnerable patients, as well as risk management programs to address the management of ARIA, a class side effect. During the call, Executive Vice President-Research & Development Dr. Al Sandrock also sought to dispel a misperception that all anti-amyloid antibodies clear amyloid from the brain, hence striving to distinguish Aduhelm from first-generation anti-amyloid antibodies, such as bapineuzumab, solanezumab, and crenezumab, none of which were FDA approved. **"There is no evidence,"** he stated, **"that the first-generation antibodies against amyloid actually removed amyloid plaque. There is no basis for using the failure of these antibodies as a reason not to approve aducanumab."**

At the present time, Aduhelm is experiencing **"modest deployment,"** in the words of *in*Thought's Dr. Henderson, having garnered just over 100 commercial patients since it became available. This slow commercial ramp was, in fact, largely expected and is attributable to several factors. Most importantly is its controversial approval basis and thus physicians' questions about Aduhelm's efficacy and safety. Second is that Aduhelm is still being evaluated by payers. The Centers for Medicare and Medicaid Services (CMS) has not yet decided whether it will be covered. This decision is not likely to occur until the Spring of 2022. Third, based upon its labeling, patients need to have beta amyloid pathology confirmed through positron emission tomography (PET) scanning to qualify for Aduhelm – the process of determining patients' candidacy will take a period of time. And fourth, many potential treatment centers are still in the process of evaluating Aduhelm and preparing to administer it. Per its label, Aduhelm is administered as an IV infusion every 4 weeks, and at least 21 days apart.

Reports indicate that many providers have been slow to start using Aduhelm, which stems in large part due to their ongoing uncertainty and skepticism about its efficacy in terms of an association between reducing beta amyloid and impacting AD disease progression. **"The approval of Aduhelm,"** notes Dr. Henderson, **"is a large series of snowballing unknowns. As a physician, we look for a strong base of evidence; and with Aduhelm, the boxes for evidence behind the approval were not all checked. The approval is based upon a set of subclinical markers that have never foreshadowed an improvement in clinical status."**

Indeed, there have been several high-profile institutions who have announced their intent not to offer Aduhelm, including Massachusetts General Hospital, Cleveland Clinic, and Mount Sinai. One large Washington, DC based practice, The Neurology Center, made a point of excluding all Biogen sales representatives from detailing its members, according to a Twitter post by Mizuho health care analyst Salim Syed.

The approval of Aduhelm also has raised questions about the role of the FDA, especially in treatment areas of high unmet therapeutic need. **"Is the role of the FDA to be a regulatory body, whose seal of approval indicates that a product is effective, or do they change the bar to spur innovation?"** asks Joe Young, CEO of Vault Bioventures. **"One wonders whether the aim is to send the signal to manufacturers about the unmet need."** Indeed, as a result of the Aduhelm approval, several other large players have raised the visibility of their AD clinical development programs, especially Lilly, Roche and Biogen's development partner for Aduhelm, Eisai. Based upon the potential precedent set by FDA's approval of Aduhelm, they see their anti-amyloid beta candidates as having a greater potential for approval.

Despite all of the controversy and questions, one clear benefit of Aduhelm's approval has been an increased focus and discussion of AD, which remains among the biggest unmet needs given the rising incidence and few effective treatment options. In the words of Dr. Dan Zaksas, a neurology expert with Fishawack Health, **"Biogen has done a very good job raising disease awareness and encouraging patients to get screened for early Alzheimer's; more critically, they've reignited an important conversation in society and in healthcare about tradeoffs between risks, benefits, and costs."** Indeed, Biogen launched a campaign in July called "It's Time We Know" which encourages early screening; and the Company is partnering with CVS Health in an effort to educate patients about brain health and cognitive impairment, according to **FiercePharma**.

Another dividend of Aduhelm's approval is that other commercial heavyweights developing new AD medications are starting to queue at the FDA's doorstep. Eli Lilly, which had previously attempted to get approval for solanezumab for AD, is now working on another antibody for AD, donanemab. In

June, FDA granted Breakthrough Therapy designation for donanemab. And during the recent Cantor Global Healthcare 2021 Conference, Patrik Jonsson, a top Lilly executive, expressed optimism about the profile of their candidate. **"We are extremely confident in the differentiated profile of donanemab. We know it has a rapid and deep clearance and also with a fixed duration therapy that's very different with aducanumab. We saw in the studies 40% of patients were amyloid negative after six months, 60% after one year and 70% after 18 months."** He went on to explain that the results of their pivotal trial, TRAILBLAZER, and especially its safety profile, is contributing to their confidence in putting a winning dossier in front of the FDA. **"[This] will be the first time ever we are submitting a file that has actually demonstrated a statistically significant difference versus placebo on a disease-modifying endpoint,"** added Jonsson.

More recently, Roche's gantenerumab also received a Breakthrough Therapy designation by the FDA for AD based upon evidence showing that it too achieved significant reduction in amyloid plaque in the brain. The Phase III clinical trials are expected to read out in the second half of 2022. Fishawack Health's Dr. Zaksas is bullish on gantenerumab due to its subcutaneous mode of administration. **"For patients living with Alzheimer's to go in for infusions once a month with aducanumab or donanemab, or once every two weeks as in the case of Eisai's lecanemab, that's a lot to ask. Once you identify patients whom the therapy is likely to benefit, having a subcutaneous option is going to be a huge boon."** Similar to Biogen and its partner Eisai, Roche and Genentech have prioritized the development of new and novel entities to treat AD.

Migraine Treatment Is Experiencing a Surge of Innovation

When you talk to Neurologists and especially those who are Headache Specialists these days, the therapeutic area that is typically mentioned first when it comes to important new therapeutic innovations which are translating to meaningful patient benefits is in migraine headache. Over the past few years, there has been a flurry of new drug introductions, mainly representing a new class of medications – most of which focus on Calcitonin gene-related peptide (CGRP) inhibition – that are demonstrating clear advantages. At the same time companies are re-thinking approaches to existing migraine medications by combining them to achieve synergistic advantage.

The main challenges, however, in the treatment of migraine are that despite the new medications, treatment approaches and treatment responses are not consistent. Treatment remains somewhat hit or miss, necessitating health care providers to deploy an array of therapeutic strategies depending upon the patient's migraine experience, co-morbidities, and – perhaps most frustrating – their insurance

coverage. Fishawack Health's Dr. Zaksas explains, **"The understanding of migraine, underlying mechanisms, and drug targets has improved, but there hasn't been a consistency with which neurologists or other practitioners have either understood migraine or have approached evaluation and diagnosis. As a result, the therapeutic regimens they recommend are not particularly consistent. There's also a limiting factor in the uptake of preventative treatments due to payer constraints; physicians and patients have to jump through a number of hoops to gain access."**

Migraine headache is an extremely common condition, with an estimated 40 million people in the US suffering from this condition. According to the **Migraine Research Foundation**, migraine is among the three most prevalent illnesses in the world, impacting nearly 1 in 4 US households. It disproportionally affects women and younger people between the ages of 18 to 44. There are two general types of migraine, chronic and episodic. Per the International Headache Society (IHS) guidelines, chronic migraine is defined as the sufferer experiencing 15 or more headache days per month for more than 3 months. Episodic migraine is where the sufferer experiences fewer than 15 headache days per month.

The big recent focus of media attention and momentum in migraine is Biohaven's Nurtec Orally Dissolving Tablet (ODT), which has taken the category by storm. Nurtec ODT represents a new class of medications under the CGRP MOA umbrella called the "gepants," nicknamed for the suffix of the generic name. The other gepants are Allergan's (AbbVie's) Ubrelvy (ubrogepant) and Abbvie's Qulipta (atogepant), the latter of which was approved at the end of September for the prevention of episodic migraine.

While the company marketing Nurtec, Biohaven, is a rookie to the pharmaceutical industry, having been founded in 2013, it has rapidly carved out a reputation for itself as a CNS category disruptor. While Nurtec is its only commercial product at present, its pipeline includes several investigational candidates for both more common as well as rare neurological and neuropsychiatric diseases. And with the latest Nurtec label expansion that encompasses both treatment and prevention, Nurtec ODT has blockbuster potential by mid-decade – despite going head-to-head against some of the industry's largest companies.

Nurtec ODT was approved by the FDA and launched early in 2020 for the immediate, acute treatment of migraine. Its launch was recognized as an example of how to achieve commercial success despite the massive disruption of the pandemic, which upset

every aspect of the medical system and care, as well as traditional modalities of pharmaceutical promotion. While other major brands struggled to connect with customers in the first months after March 2020's widespread shut down, Biohaven built a message that resonated with health care providers and consumers and rapidly stood up an array of digital initiatives. Timing of the roll out of these initiatives also made a difference.

Quoted in FiercePharma, Biohaven CEO Vlad Coric stated in April 2020 that: **"Companies often have sales forces in the field for a few months before starting direct-to-consumer messaging, but we did accelerate because we had to get the message out to patients throughout this time of social distancing. We're part of the drug supply chain and we have to get treatments to people with migraines. This can be the worst time to have a migraine."**

As larger companies struggled to adapt to the promotional constraints of the pandemic, Biohaven quickly stood up digital resources that allowed its reps to connect with physicians virtually, and for patients to access Nurtec via tele-health platforms, which at the time were dramatically increasing in use. Coric noted at the time that Biohaven's being a relative newcomer was an advantage in the sense that the Company could adapt to the rapidly changing market reality in an agile manner.

The branded campaign, "Onederful," was credited as being very authentic in reflecting the real-life experience of the migraineur community. Their celebrity spokesperson, Khloe Kardashian, brought a great deal of public attention to the brand as well.

Despite its initial success, Nurtec ODT is competing in an increasingly crowded marketplace that includes an array of other compelling newcomers as well as a bevy of generic options that insurers typically require patients to try and fail before using branded options. While the triptans and NSAIDs and an array of non-indicated agents (e.g., anti-hypertensives and anti-epileptics), most of which are generic, have been used to treat migraine, the advent of multiple new agents has constricted their usage. Other recent new approvals in episodic migraine include Ubrelvy and Qulipta, as well as Eli Lilly's 5-HT1F receptor antagonist Reyvow (Lasmiditan), which received a thumbs up in October 2019.

While the "gepants" are increasingly being used primarily in episodic migraine, the migraine prevention category also has recently experienced an expansion of innovative new product offerings. That includes the subcutaneously administered preventive anti-CGRP monoclonal antibodies: Amgen's Aimovig (erenumab), Teva's Ajovy (fremanezumab), Lilly's Emgality (galcanezumab); and Lundbeck's Vyepti (eptinezumab).

Looking to the migraine pipeline, Axsome Therapeutics' AXS-07 stands out as having strong potential. Despite a potential PFUDA setback with another asset for major depressive disorder over the summer, Axsome regained its momentum with the September FDA acceptance of its NDA for AXS-07 for the treatment of acute migraine. The PFUDA date was set for next Spring.

Referred to by CEO Herriot Tabuteau during the Q2 2021 earnings call as "multi-mechanistic," AXS-07 combines rizatriptan with an enhanced version of meloxicam. In its public disclosures, Axsome touts its proprietary MoSEIC™ (Molecular Solubility Enhanced Inclusion Complex) delivery system as "substantially increase[ing] the solubility and speed of absorption of meloxicam after oral administration, while maintaining its extended plasma half-life." In a statement released in September, the Company announced AXS-07 demonstrated superior pain relief compared to rizatriptan.

Neurological Rare Diseases Holds the Most Promise for the Future

Looking forward to the future, the analysts we interviewed for this report pointed to gene and cell therapy for rare diseases, especially pediatric rare diseases, as the source of future promise of advancing neurology medicine. The reason they gave is that these investigational treatments are expected to be more targeted, and thus more effective than today's options. Further, the experience gained from developing and commercializing these new treatments will eventually contribute to better ways to treat more common neurological ailments affecting adults, including Alzheimer's and Parkinson's disease.

Fishawack Health's neurology expert Dan Zaksas pointed to AADC deficiency as an example of a rare childhood developmental condition where gene therapy holds significant promise. **"This disease stems from dysfunction of neurotransmitter synthesis, and results in developmental delays and myriad behavioral and autonomic symptoms. Over the past few years, gene therapies have been developed to directly address AADC activity and generate**

neurotransmission in the dopaminergic system. Gene therapy for AADC deficiency can have incredible results: children who would never have a shot at reaching developmental milestones suddenly have the potential of a much-improved life trajectory." He added that these discoveries also have implications for dopamine production, which could help advance new therapies for Parkinson's disease.

Duchenne muscular dystrophy and spinal muscular atrophy are two other pediatric neurological conditions where there have been dramatic therapeutic advancements over the past 5-6 years, and there is a continued focus on advancing new medications. Zaksas notes that the advantage of focusing on pediatric rare conditions is that there is often enormous social and community support for new treatments for children that facilitates the regulatory and market access process. In comparing Sarepta's Exondys 51 to Biogen's Aduhelm, Zaksas opined that: "**There's a very different level of social outcry for progress in childhood diseases compared to those mostly affecting the elderly. The subjective perception of impact on patients' and families' lives tends to differ, and there's certainly emphasis on fighting for causes that impact the future of children, even in ultra-rare diseases. Despite the size of the Alzheimer's market and the scale of its devastation on families and global healthcare, it will take a truly revolutionary therapy to generate similar levels of demand and tolerance for risks and associated costs."**

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THERAPEUTIC DIGESTS

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