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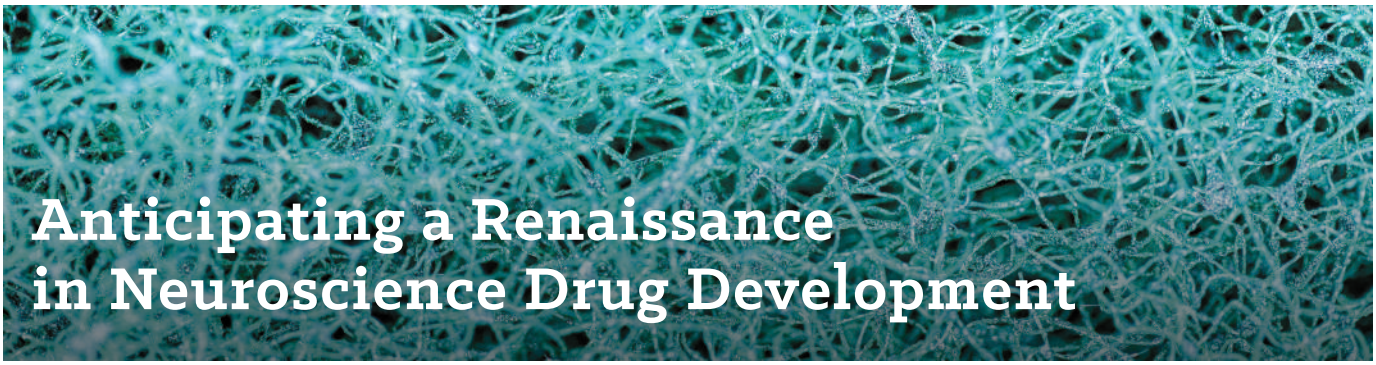


# Anticipating a Renaissance in Neuroscience Drug Development

Ten years ago, our team published a commentary on what at the time appeared to be the "Death of CNS Drug Development: Overstatement or Omen" after several large pharmaceutical companies abandoned or severely restricted neuropsychiatric drug development efforts citing costly and long development periods with relatively lower chances of successful drug applications.[1] Development of central nervous system (CNS) drugs is fraught with obstacles not typically encountered in other therapeutic areas, in part due to a general bias regarding psychiatric illness and treatment – mental health issues are largely viewed as being less significant than "real" diseases or more "physical" ailments – with an accompanying perceived less favorable risk to benefit ratio. CNS trials also have intrinsic complexities generally not shared in other therapeutic areas including:

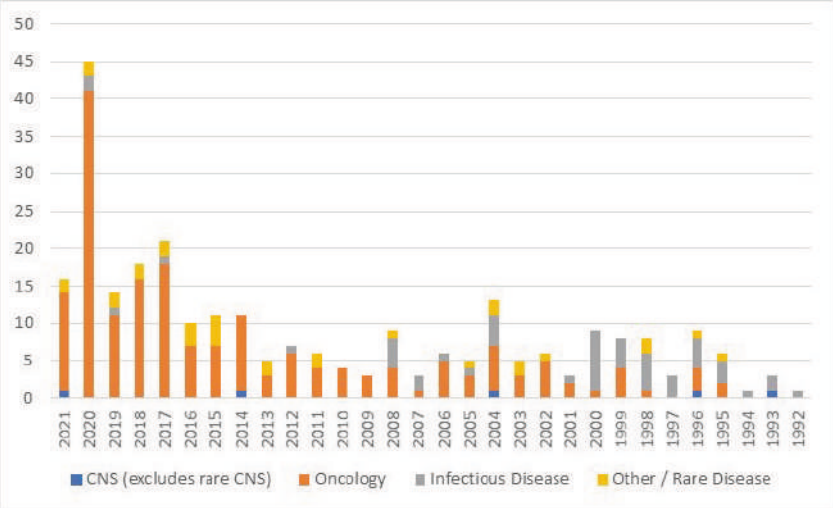
- a relative lack of understanding of basic biology and underlying pathophysiology
- poor predictive validity of preclinical models and uncertain correlation of potential surrogate biomarkers with clinical benefit
- more frequent use of subjective "soft" endpoints (ultimately resulting in heightened placebo response)
- more frequent failure to differentiate active treatment from placebo suggesting a lack of assay sensitivity
- variability in both disease course and response over time, and
- relatively novel mechanisms of action for many CNS drugs that are by definition associated with a higher risk of failure.

For these reasons, the discovery and development of drugs for a variety of CNS indications has yielded one of the lowest success rates of any therapeutic area. Not only are the number of novel compounds available for clinical development in CNS lower compared with other areas, but regulatory approval times are also consistently longer.[2,3] Investment in novel neuroscience drug development is therefore often regarded as "too risky" by drug developers.

The outlook for availability of new treatments for patients with neurological and psychiatric diseases has not been promising for the past decade, and when new treatments are approved they are often not accessible to patients.[2] The gaping unmet medical need remains high in neurodegenerative diseases, neurological rare diseases, and psychiatry. Mental and addictive disorders afflicted more than one billion people globally in 2016, causing 7% of all global burden of disease,[4] which has only been exacerbated by the COVID-19 pandemic.[5] Neurological disorders are one of the leading causes of disability-adjusted life-years and the second leading cause of death globally.[6]

Notwithstanding these known challenges, there appears to be a renaissance of CNS drug development in which both big pharma and smaller biotech have renewed their focus on CNS drug development and financing in recent months (Acadia, Biogen, Denali, Nuemora, Novartis, Sage, and Voyager Therapeutics to name a few). This resurgence is in part due to a changing funding model. Traditionally, drug companies have relied heavily on profits from their commercialized products to fund not only extensions of their approved products, but also their own bench work on novel molecular entities. Now funding through government agencies and public-private partnerships is becoming more common to facilitate drug development. For example, the National Institutes of Health has increased funding for research by 78% in the last 5 years for Alzheimer's disease; importantly NIH funding was directly or indirectly associated with every one of the 210 new drugs approved across therapeutic areas by the FDA from 2010 to 2016.[7,8] Public-private partnerships have also emerged for a number of specific CNS indications, including for example the National Cooperative Drug Discovery/Development Group for psychiatric disorders, the Parkinson's Progression Markers Initiative, European Autism Interventions, the NIH HEAL Initiative, and the Alzheimer's Disease Neuroimaging Initiative.[9] For Alzheimer's disease specifically, public-private partnerships have increased 214% in recent years, which allows leveraging of resources, spreading costs, and managing risk of drug development across several sponsors.[6] A large increase in venture activity in neuroscience has followed and is now second only to oncology. One example of this is ARCH Ventures which has significantly invested broadly in both psychiatry and neurodegenerative disease with the creation of the biotech company Neumora, who aims to match distinct patient populations to targeted therapeutics.[10] Neumora includes BlackThorn Therapeutics, the start-up Abelian, Syllable Life Sciences, and a deal with Amgen to license two of their abandoned neuroscience products.

Not only have government-backed funding and public-private partnerships increased significantly, but regulatory agencies have taken deliberate albeit sometimes provocative steps to encourage innovative neuropsychiatric drug development. Four regulatory approaches to making CNS drugs available as rapidly as possible are available within the US Food and Drug Administration's Accelerated Approval program: Fast Track status, Accelerated Approval, Priority Review, and more recently Breakthrough Therapy designation introduced in 2012 as part of the Safety and Innovation Act.[11] Similarly, the European Medicines Agency (EMA) developed programs beginning in 2005 that include accelerated assessment, conditional marketing authorization, and a priority medicines scheme (PRIME) added in 2016. Utilization of these programs has remained fairly stable over the past decade until 2020 when they increased sharply. An estimated 34% of approvals were expediated in 2000 compared to 60% of new drugs approved through at least one expedited program in 2019.[12] Historically, the majority of applications taking advantage of these programs have been in oncology,[13] with the exception of limited rare CNS diseases (e.g., Duchenne muscular dystrophy). The only CNS exceptions are the recent approval of aducanumab in 2021,




*FDA Accelerated Approvals since Program Inception*[15]

droxidopa for orthostatic hypotension in 2014, and natalizumab and Betaseron for multiple sclerosis. The FDA has also awarded more than $15 million to academia and industry to enhance the development of products for patients with rare diseases across therapeutic areas through the Orphan Products Clinical Trials Grants Program.[14]

Regulators have also attempted to make robust and distinct efforts to facilitate the pathways to treatment solutions. In fact, the FDA published five separate guidance documents for industry in 2018 and 2019 alone for neurological conditions including Duchenne Muscular Dystrophy, migraine, early Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and partial onset seizures.[16] Similarly, EMA has issued or revised guidance for autism, pain, ALS, Duchenne and Becker Muscular Dystrophy, multiple sclerosis, and Alzheimer's disease since 2015.

In addition to increased funding, accelerated approval pathways, and regulatory collaboration with sponsoring companies, other reasons for the renewed interest in neuroscience drug development have also been postulated:

- Rapidly growing scientific knowledge about the nervous system and how CNS diseases are diagnosed and characterized, which for many years has been poorly understood.[14] Some authors note we may be simply observing a new wave of medical breakthroughs, not just in CNS indications such as Huntington's disease and ALS, but across therapeutic areas.[17,18]
- Biomarkers and genetic targets are increasingly being considered as surrogate endpoints, which allows for less reliance on predictive preclinical models and enables targeting patients who are more likely to produce a positive response.[15,19] Given the FDA and EMA's accelerated approval pathways, those surrogate endpoints may be used to speed commercialization and patient access. Although the program is not without criticism and is intended to strike a balance in bringing products to market more quickly while allowing for "reasonably likely" surrogate endpoints, these programs encourage innovation and development. Biomarkers and genetic targets are also increasingly used not just as surrogate endpoints, but in determining the optimal patients to enroll in a trial which is useful for heterogeneous disease populations like Alzheimer's disease.
- Emergence of novel therapeutic modalities such as RNA interference (RNAi) and regenerative medicine with gene therapy based on adeno-associated virus (AAV) vectors, particularly for neurodegenerative diseases, has fueled many recent licensing deals and investments.[20]

Given this increased scientific knowledge across CNS diseases and the advancement of biomarkers intended to predict clinical improvement, companies can in turn be more vigilant with licensing compounds, evaluating risk, and identifying potential failures earlier in development.[15]

Following are some recent examples of drug development successes in neurology, rare disease, and psychiatry that have borne out the fruit of these advances.

**Neurology (specifically Alzheimer's Disease)**

Earlier this year, Biogen's aducanumab became the first newly approved treatment for Alzheimer's disease since 2003, and importantly is the first that targets the underlying pathophysiology of the disease with reduction of amyloid beta plaque, a hallmark of the disease. Biogen accomplished this partially by seamlessly blending components of early and late phase trials which accelerated the pathway to approval and took advantage of more recent regulatory opportunities. Aducanumab was conditionally approved by the FDA using an accelerated pathway (fast track designation) where a drug's effect is based on a surrogate endpoint that is "reasonably likely" to predict clinical benefit to patients. The FDA considered the reduction of amyloid load, as measured with amyloid positron emission tomography (PET), to be a valid surrogate endpoint of clinical benefit in AD; essentially the approval was based on an endpoint that "is thought to predict clinical benefit but is not itself a measure of clinical benefit."[21] This position was unprecedented in CNS and raised numerous questions regarding whether amyloid plaque reduction is a reliable surrogate endpoint (others like Roche's crenezumab and Eli Lilly's solanezumab targeted amyloid plaques with no evidence of clinical benefit and development was subsequently discontinued).[22] Many are hopeful this approval will invigorate the formerly stagnant field, increase investments in new treatments, and encourage greater innovation.[23] Eli Lilly is now pursuing donanemab's effect on beta amyloid plaques much like Biogen, also hoping to demonstrate a clinical effect on the slowing of cognitive decline. Roche has resurrected the previously shelved gantenerumab. Both have been newly granted breakthrough therapy designation by the FDA. Eiasi and Biogen have also recently submitted a rolling submission to the FDA for lecanemab, a follow on to aducanumab under the accelerated approval also granted breakthrough therapy designation. The rolling submission allows completed portions of the application to be submitted to the FDA for review on an ongoing basis.[24]

**Rare Diseases**

The use of the accelerated approval pathway is especially pertinent

to patients with rare diseases. Recruiting patients for participation in traditional confirmatory rare disease clinical trials is often very difficult, which delays potentially beneficial products in entering the market. Reliance on surrogate endpoints can allow for trials with smaller sample sizes with less cost and potentially earlier access.x One example of the renewed investment in the rare disease space is Novartis's 2018 acquisition of the gene therapy company, AveXis, reportedly for $8.7 billion. The acquisition was in part meant to accelerate Novartis's strategy to pursue high-efficacy, first-in-class therapies, and broaden their leadership in neuroscience.[26]

The following year the FDA approved Zolgensma (onasemnogene abeparovec-xioi), the first gene therapy approved to treat children under age two with spinal muscular atrophy. Later in 2020, the FDA granted accelerated approval to Viltepso (viltolarsen) injection for the treatment for Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. Further approvals followed with Amondys 45 (casimersen) injection for patients with DMD who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping.[27] Additionally, the FDA approved Epidyolex (a cannabidiol oral solution also approved for Lennox-Gastaut and Dravet syndromes) from Greenwich Biosciences for the treatment of seizures associated with tuberous sclerosis complex based on Priority Review, along with Fintepla (fenfluramine; Zogenix) for seizures associated with Dravet syndrome. The FDA cited 2020 as a strong year for innovation and advances in neurological rare disease despite challenges from COVID-19 pandemic.[28]

The FDA very recently accepted the submission of Amylyx's amyotrophic lateral sclerosis (ALS) drug based on phase 2 evidence only without requiring a phase 3 trial, purportedly because they recognize the urgency and unmet need for patients.[29] The ALS Association and patient advocacy efforts pushed for the expedited approval – an example of a public awareness campaign that led to increased funding and regulatory flexibility.

As with neurology, associated critiques of the accelerated pathway have also been raised in the rare disease space. For example, accelerated approval of eteplirsen for DMD in 2016 was questioned on the reasonable likelihood of clinical benefit. Payers balked at making it accessible to patients, and Sarepta didn't launch required post-marketing studies until 2019. Complete data on the drug's safety and efficacy are still not publicly available, but despite this the FDA granted approvals to their second and third DMD drugs in 2019 and 2021.[30]

**Psychedelics**

The recent resurgence in psychiatry is exemplified by the incredible growing interest and revitalization in psychedelics. Hallucinogenic drugs have been lauded as potential treatments for anxiety and depressive disorders as well as addiction, each of which have exhibited a recent rise in prevalence and high rates of relapse. Decades old treatments for these and other conditions are associated with side effects and only modest improvement in symptoms. Regulatory agencies have demonstrated their willingness to consider the approval of psychedelic treatments as noted by FDA's recent breakthrough designation for 3,4-methylenedioxymethamphetamine (MDMA), two psilocybin-based compounds, and the recent approval of esketamine for treatment-resistant depression – perhaps one of the biggest breakthroughs in depression treatment since SSRIs and now one of the world's most commonly used antidepressants.[31] The psychedelic market is expected to grow from an estimated $2 billion in 2019 up to $10 billion by 2027,[32] with over 30 organizations with psychedelic drug development programs underway. Several companies already have promising initial safety and efficacy data in small proof-ofconcept studies that lend encouragement to initiate larger studies, some of which have launched. While there are still regulatory hurdles that differ from country to country as well as licensing obstacles for psychedelics, there appears to be a ground swell of acceptance of not only this class of drugs but also of the disorders they are treating. Ironically the stigma associated with many psychiatric disorders has recently lifted partially due to the resurgence and newfound acceptance of one of the most highly stigmatized class of drugs of the past.

**Summary**

The advances in our knowledge of pathophysiology of neuro-psychiatric diseases including development of potentially more predictive biomarkers and new treatment modalities, permissive regulatory guidance and rulings, increased sources of funding and a general de-stigmatization of CNS disorders have created the perfect storm to help drive the recent renewed interest in CNS drug development that will likely be sustained well into the future. While continued refinement of the pathways to accelerated approval and the resolution of payer/pricing issues to help ensure patient accessibility are needed, some have opined that the next five years will be known as another "golden era" of neuroscience drug development much like 25 years ago when Prozac, Zoloft, and Paxil were all introduced to the market followed by a new wave of antipsychotic medications. This anticipated renaissance of CNS drug development is encouraging for greatly improving both the quality and extent of life for those afflicted with various CNS disorders.[33]

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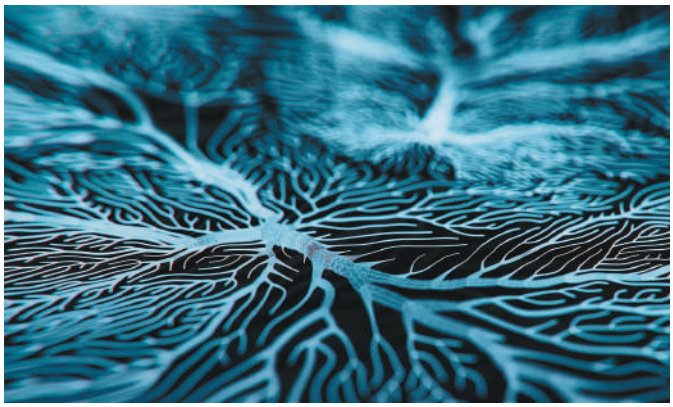

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