Comprehensive Analysis of Drug Development and Transactional Deal Landscape for Neurodegenerative Disorders

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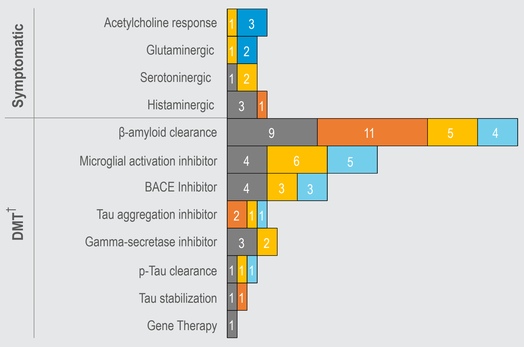
ABSTRACT

Neurodegenerative disorders (NDDs) impact a significant number of the US and the global population and are the leading cause of disability and morbidity in US. As the number of individuals 65 years or older in the US will double between 2012 and 2050, the increase in NDD prevalence will present new medical, social and economic challenges. About 7.5 million Americans are currently living with Alzheimer's (AD), Parkinson's (PD), Huntington's (HD) and Amyotrophic Lateral Sclerosis (ALS). In 2050 this number is likely to increase to 18 million. The current total cost burden for NDDs at $250 billion is likely to increase to upwards of $1100 billion, which is higher than current overall US healthcare spend. There is a long history of failed attempts to develop effective therapies and currently there are no treatments that can prevent, slow down or cure NDD. Here we present an in-depth analyses of the current development pipeline for AD, PD, HD and ALS by phase and mechanism of action with the focus on symptomatic versus disease modifying approaches. Furthermore, we provide insights on the challenges in the drug development for NDD and how they can be addressed. An analyses of the transactional deals in the space reveal that despite the challenges and multiple failures, the number of transactions have increased in the past 5 years driven primarily by early clinical (Phase I/II) deals.

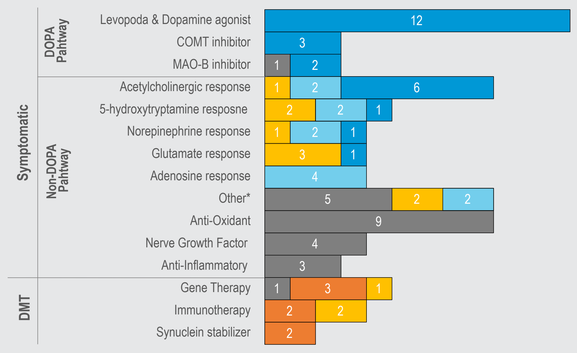
DEVELOPMENT PIPELINE ANALYSIS

Alzheimer's Disease (AD)



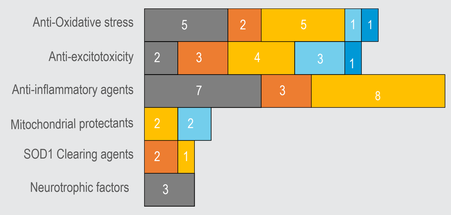
- Currently there are over 50 assets in clinical development
- The only approved drugs, Donepezil and Memantine, address limited set of symptoms and are not curative of AD
- A number of disease modifying therapies are under investigation. Amyloid clearance is the most explored MOA with the most advanced investigational therapies; Biogen's Aducanumab, Roche's Crenezumab and Gantenerumab have demonstrated encouraging early stage data in prodromal/mild
- Aβ clearance has also seen the most failed clinical drugs, primarily due to minimal efficacy in moderate and severe patients
- Strong association between microglia hyper activation in amyloid plaques formation and AD progression have accelerated several NSAIDs and inflammation inhibitors into phase 3--Pfizer's Azeliragon, AZTherapy's ALZT-OP1

Parkinson's Disease (PD)



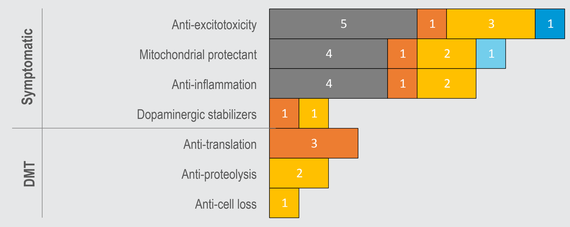
- Currently there are over 30 assets in clinical development
- Approved drugs are addressing disease symptomology and impaired motor skills. Of the 26 approved, 17 act by increasing dopamine concentration in the brain cells. Non-dopaminergic agents address motor fluctuations and dyskinesia associated with PD
- Misfolded α-synuclein or ongoing neuronal cell death may trigger inflammatory response and anti-inflammation agents, anti-oxidants are being developed as targets to protect microglia and astroglia surrounding the motor neurons
- Disease modifying approaches including active and passive immunization against α-synuclein, and modulators of α-synuclein accumulation are being explored
- Gene therapies to deliver L-amino acid decarboxylase (AADC), glutamic acid decarboxylase (GAD) and neurotrophic factor transgenes are in early stages of clinical testing utilizing AAV- and Lenti-approaches and face significant challenges in demonstrating clinical benefit

Amyotrophic Lateral Sclerosis (ALS)



- Currently there are over 30 assets in clinical development
- Currently approved drugs, Riluzole- glutamate modulator, only extends life for ~3 months. Recently approved Edaravone, an anti-oxidative and radical scavenger, reportedly slows down disease progression based on a 6 month clinical trial, however data is yet to mature on the benefit to life extension
- Anti-inflammatory agents are currently in Phase 2 and agents addressing glutamate excitotoxcity follow in interest, however number of these agents have recently reported negative late stage clinical results (Ceftriaxone, Talampanel)
- Mitochondrial protectants aim to reduce the probability of neuron apoptosis, thereby reduce motor neuron loss and improve motor function. However, Olesoxime and Dexpramipexole failed to demonstrate disease efficacy in phase 3

Huntington Disease (HD)



- Currently there are over 30 assets in clinical development
- Number of symptomatic treatments are in trial including agents attempting to reduce excitotoxicity, improve voluntary motor function (dopamine stabilizers) and prevent cell death (anti-inflammation and mitochondrial protectants); this class of agents have seen a number of drug failures
- Fewer disease modifying therapies are in development; RNA interference is being pursued for destruction of mutant huntingtin mRNA from two biotechs - Wave Life Sciences and Ionis

†DMT: Disease Modifying Therapy
*Other-Opioid, Calcium channel blocker, Iron Chelator, GLP-1 agonist, Nicotine, Hematopoietic growth factors
**Excluded from all analyses are nutritional and herbal supplements, devices, cell-based-and behavioral therapy, agents for agitation and aggression, active pipeline 2013- 2017

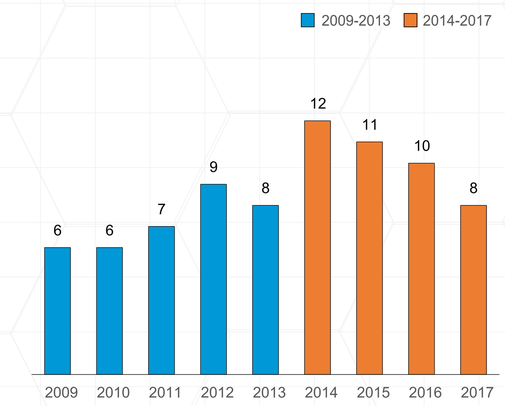
DEAL ANALYSIS

After analyzing publicly available information about completed deals (license and M&A) in neurodegenerative diseases, we have observed several trends, including significant increases in deal volume, size and stage of development since 2014.

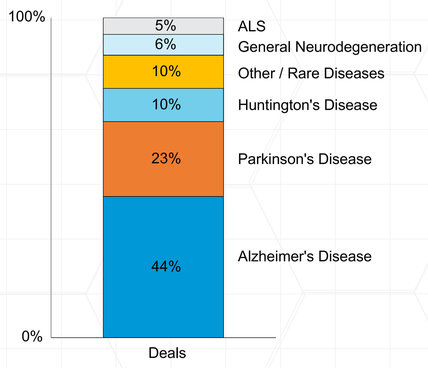
- Increasing deal volume: There has been a ~50% increase in annual deal volume since 2014 compared with the 5 years prior, with 2017 on a similar pace
- Increasing deal size: Total deal sizes have increased, with the distribution of deal size since 2014 weighted toward larger deals
- Driven by key indications: The increase in activity is led by deals in Alzheimer's Disease and (to a lesser extent) Parkinson's Disease, which together comprise a large majority of deals in NDD
- Later stage deals: Whereas preclinical deals were a major driver in the earlier period, early clinical deals (phase 1 / 2) have been a major driver since 2014

Conclusion: An advancing pipeline and invigorated deal space bode well for the future of business and drug development in neurodegenerative diseases

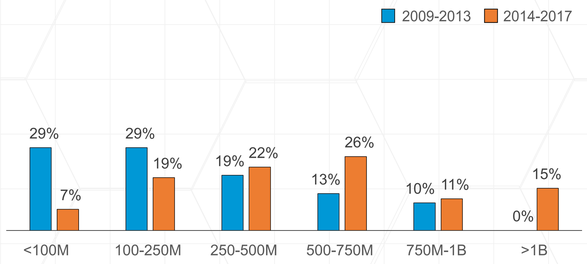
Distribution of Deals by Year (no. of deals)



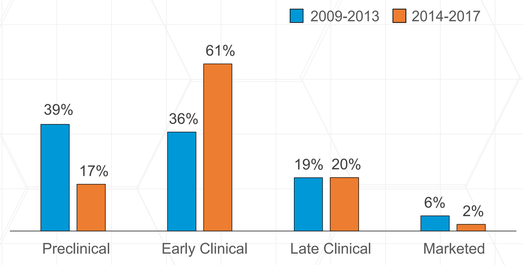
Deals By Indication (2009-2017)



Trends in Deal Size by Period (% of deals)



Deals Distribution by Stages of Lead (% of deals)



DEAL CASE STUDY

Teva acquisition of Auspex:
High-value deal driven by a late-stage therapy for a neurodegenerative disease

- 2015 acquisition of Auspex Pharmaceuticals by Teva is illustrative of the recent increase in deal activity in NDD
- A significant deal value with $3.5B equity value has not been seen in the earlier analyzed period (2009-2013)
- Primary value driver for the deal was a late stage (phase 3) compound SD-809 (deutetrabenazine) for the potential treatment of chorea associated with Huntington's disease
- The drug has since been approved (2016, marketed as Austedo) and is forecasted to generate peak sales of >$1.3B and is expected to enhance Teva's revenue and earnings growth profile and strengthen its core CNS franchise

NDD DRUG DEVELOPMENT CHALLENGES

Neurodegenerative diseases (NDD) have the highest failure rates in the drug development- clinical studies in Alzheimer's have demonstrated failure rates at 99.6% and Huntington's disease at 97.5%. There are a number of factors that contribute to the highly challenging drug development environment

- Complex disease etiology: Significant gaps exist in our understanding disease etiology of complex NDDs. In ALS, only 5–10% of ALS cases are familial with at least 13 genes and loci known to contribute to pathology. Of these, toxic gain-of-function mutations in the SOD1 gene have been most extensively investigated. In Alzheimer's disease, Aβ dyshomeostasis has emerged as the most extensively validated and compelling hypothesis with additional genetic (ApoEe4) and environmental factors have been suggested to contribute to the disease onset and severity

  Lack of clarity of disease etiology presents a challenge during drug discovery and development in identifying the right target or combination of targets for proof of biology and in segmenting the right population for clinical trials

- Early disease detection: Disease diagnosis is almost always based the clinical presentation; however, clinical research in AD and PD suggests that the disease-related plaques and depositions occur early in the disease course before appearance of any clinical symptoms. In sporadic ALS, diagnosis is difficult and disease progression is rapid

  Early disease detection presents a challenge in identifying pre-symptomatic and mild-symptomatic patients for clinical trials for NDDs. A majority of AD's clinical trials are aiming to identify and enroll prodromal and mild patients to show early response to the clinical drugs on disease progression

- Challenging clinical endpoints and surrogate biomarkers: Endpoints assessing cognitive and behavioral performance have proven subjective, highly variable, often with not enough resolution particularly in the context of variability of symptoms

  Currently no surrogate biomarkers are acceptable by the FDA and additional supporting research is needed to identify and validate new biomarkers, including neuroimaging and blood- and tissue-based biomarkers

- Design of adequate, well controlled trials: Leveraging biomarker discoveries, imaging, wearable technology for assessment of patients' performance and integration of artificial intelligence (AI) for evaluation of complex enrollment criteria can enable in designing and recruitment of innovative clinical trials

- Overall, stronger proof-of-concept in earlier stages of clinical development, clearly defined patient population, and validated endpoints can potentially improve the success rates of NDD drug development. These attributes will provide an opportunity to change the precedents, improve the trial designs and deliver value to patients

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