EXECUTIVE INSIGHTS

Trends In Neuroscience Drug Discovery And Development

Key Takeaways

- Advances in understanding disease heterogeneity have enabled the development of novel targets and biomarker science, including the discovery of new blood-based biomarkers and the development of imaging and digital metrics to enable precision medicine strategies in neuroscience.
- Novel mechanisms of action, advanced modalities and delivery technologies that cross the blood-brain barrier are creating opportunities in previously intractable diseases.
- Developers are incorporating surrogate endpoints and accelerated timelines in response to evolving regulatory precedents; cases in Alzheimer's and ALS illustrate how these strategies are shaping trial execution, interpretation and approval dynamics.
- Large- and mid-cap pharmas are using major M&A and business development and licensing to accelerate reentry or expansion into neuroscience, and competition for attractive pipeline assets is intense.

The Landscape of Neuroscience Drug Development

Neurological and psychiatric diseases are among the greatest healthcare challenges of our time. In 2019, neurological diseases led to 108 million disability-adjusted life years (DALYs), and psychiatric conditions contributed another 138 million DALYs. Combined, these illnesses impose a global economic burden of approximately $5 trillion annually.

Despite growing unmet need, drug development in neuroscience has been deprioritized by many major pharmaceutical companies due to disease heterogeneity among patients and high clinical failure rates. Between 2010 and 2019, pharma leaders such as AstraZeneca, GSK, Pfizer and Amgen exited or downsized their neuroscience programs.

Today, this picture is shifting. Advances in clinical technology, greater understanding of disease mechanisms and renewed biotech investment are driving resurgence. This momentum is translating into high-value deals and increased commitment to neuroscience innovation. For example, BMS, AbbVie and Sanofi have reentered or intensified their presence in neuroscience with recent acquisitions, while Roche has increased early R&D activity through strategic biotech and academic partnerships.

Challenges in Neuroscience Drug Development

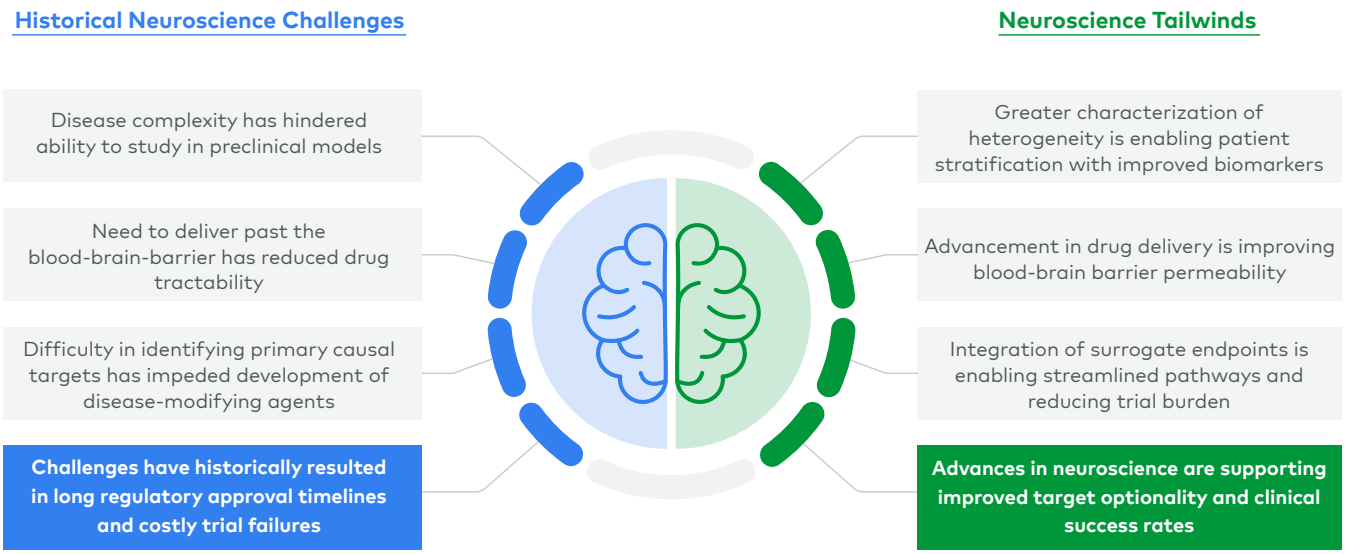
Many neuroscience indications have complex, multifactorial etiologies that are poorly understood and difficult to segment and model (see Figure 1). The heterogeneous nature of these diseases has hindered target identification (i.e., finding one target that significantly modulates disease pathology) and clinical development planning (e.g., patient identification, trial design and length). Even in indications with good biological understanding, the blood brain barrier has historically presented target accessibility challenges.

Identification of biomarkers in neuroscience has additionally been challenging due to the difficulty of sampling tissue at the site of pathology, poorly defined diagnostic criteria and the lack of animal models for validation. While examples like neurofilament light chain show promise across multiple neurological conditions, most biomarkers, including those regularly used in clinical trials (e.g., amyloid beta and tau in Alzheimer's disease), do not fully capture the complexity of disease progression or response to therapy. This has contributed to the challenge of patient identification and stratification.

These factors together have contributed to delayed approvals, trial inefficiencies, and a higher rate of clinical failure in neuroscience programs. Greater success has typically been seen in diseases that are more genetically defined or pathologically simpler (e.g. spinal muscular atrophy, certain lysosomal storage disorders).

Figure 1

Neuroscience headwinds and tailwinds



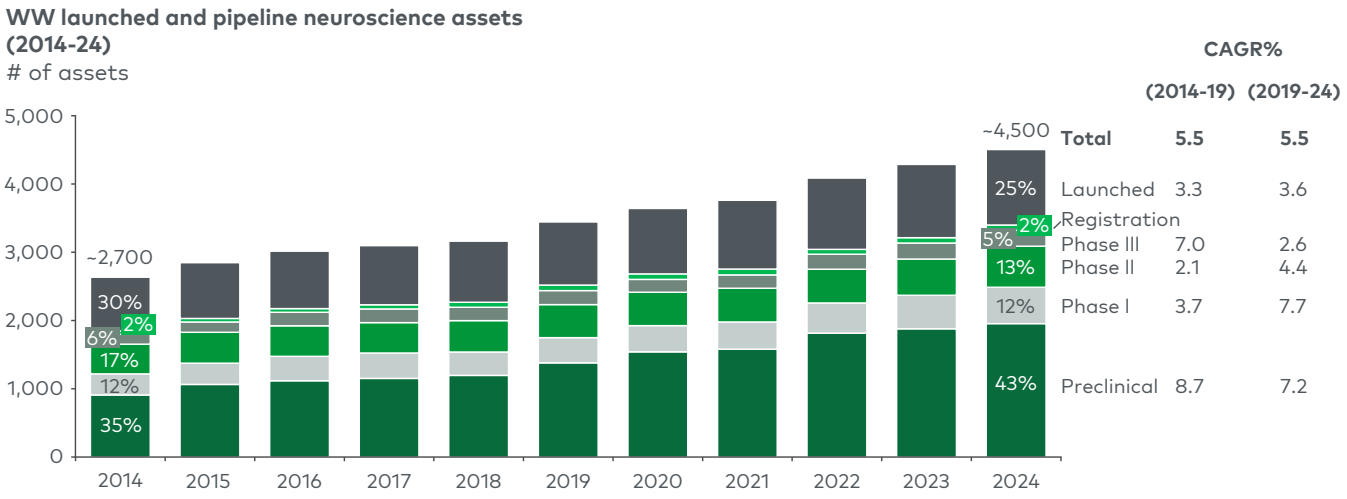
Source: L.E.K. research and analysis

Clinical development tailwinds

Despite persistent difficulties in neuroscience drug development, activity in the space has seen early-stage growth in recent years, driven by progress in understanding disease etiology and patient heterogeneity, the emergence of better validated biomarkers (e.g., blood-based and digital biomarkers in Alzheimer's, imaging and electroencephalogram-based biomarkers in neuropsychological indications), and exploration of novel mechanisms of action (MOAs) to appropriately target historically intractable conditions. The neuroscience pipeline has expanded, growing approximately 6% annually over the past five years, with early-stage assets (preclinical and Phase I) growing even faster, at rates of around 7% and 8% annually, respectively (see Figure 2a). This trend is due to repurposing of less-risky MOAs with proven success in other therapeutic areas (e.g., immunology) as well as novel target development.

Figure 2a

The number of neuroscience pipeline assets has been increasing steadily



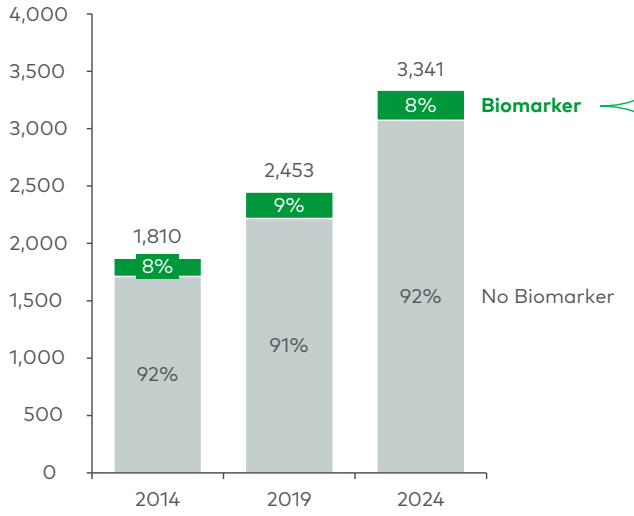
Source: Pharmaprojects

As disease knowledge grows, precision medicine strategies are increasingly viable, enhancing patient stratification and trial selection to boost clinical success in genetically defined or biomarker-defined subgroups. There have also been major gains in technology supporting high-throughput sequencing and proteomic profiling, with these molecular tools now becoming more widely available for clinical use to help support drug discovery and clinical evaluation. These advancements have supported the increasing number of clinical programs over the past decade (see Figure 2b). And while many of these new strategies and technologies have enabled the use of emerging modalities such as gene therapies, antisense oligonucleotides (ASOs) and siRNA/RNAi, small molecules still represent the majority of the neuroscience development pipeline (roughly 60%), highlighting their continued value in new treatment development.

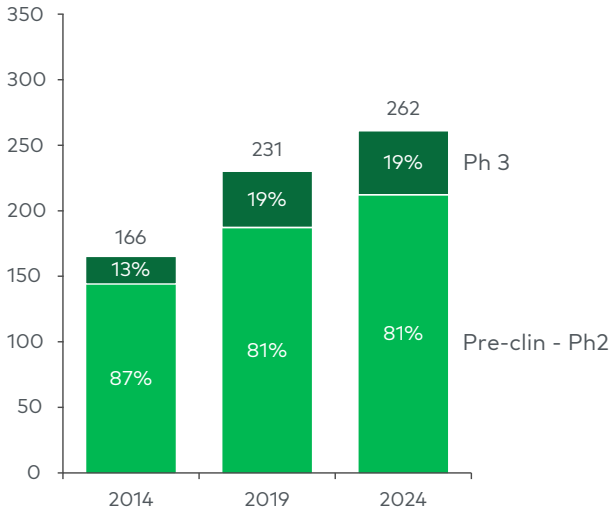
Figure 2b

Biomarker utilization in neuroscience has continued and is linked to more late-stage activity now vs. years prior

Worldwide pipeline of neuroscience assets (2014-24)
Number of assets, with vs. without biomarker usage



Worldwide pipeline of neuroscience assets with preclinical or clinical research involving biomarkers* (2014-24)
Number of assets by phase



Note: *Includes Pharmaprojects records with descriptions of preclinical and Ph. I-III stages containing the word "biomarker"
Source: Pharmaprojects

Novel targets are being identified to address major unmet needs in prominent disease areas. Innovation is concentrated within the broader categories of indications (see Figure 3), including, for example:

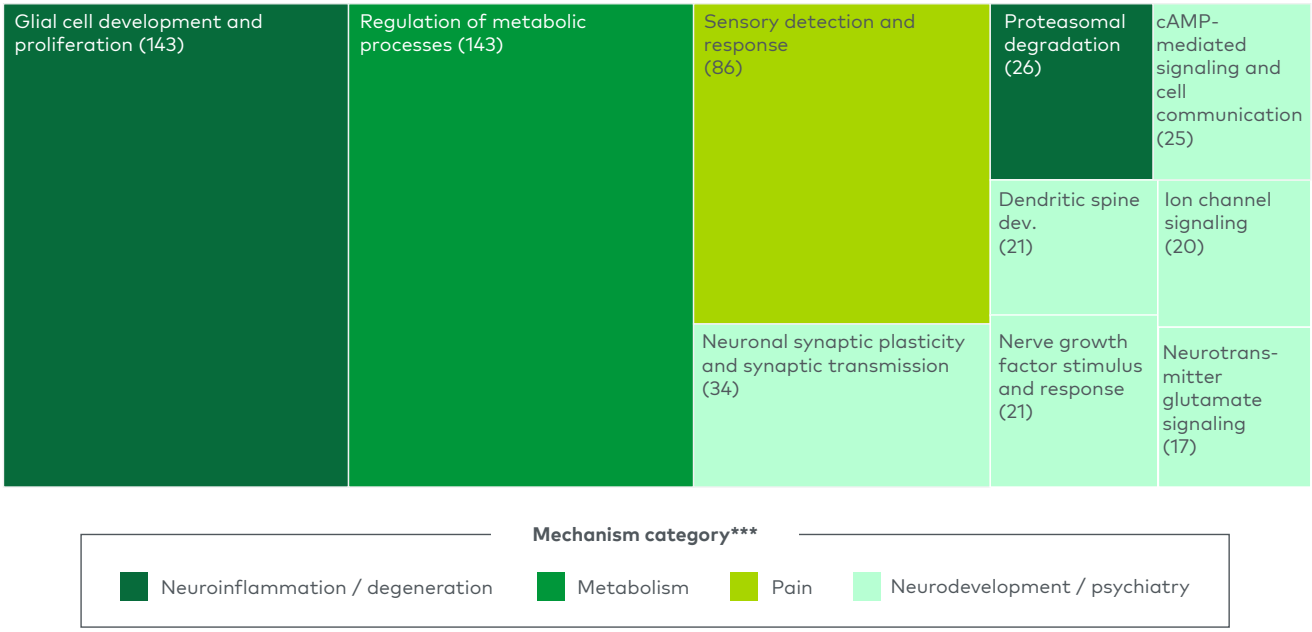
- Neuroinflammation/degeneration — multiple sclerosis, Parkinson's disease, traumatic brain injury
- Metabolism — Batten disease, Krabbe disease, Niemann-Pick disease
- Pain — erythromelalgia, nociceptive/neuropathic pain, spinal cord injury
- Neurodevelopment/psychiatry — bipolar disorder, major depressive disorder, Rett syndrome

The highest concentration of activity is focused specifically on glial cell development and on the proliferation and regulation of metabolic processes. Beyond these, novel target activity is significantly enriched for pain/itch-related mechanisms that look to modulate sensation/physical reception, which can be off-balance in moderate-to-severe pain indications, and neuronal plasticity mechanisms that better manage the patient's ability to retain function, which can be limited in neurodevelopmental/neuropsychiatry disorders.

Figure 3

Recent novel target R&D is heavily concentrated in neuroinflammation/degeneration and metabolism mechanisms

Top MOA concentration among novel neuroscience targets* (2019-24)
MOA concentration by target fold enrichment value**



Note: * A novel target is defined as a publicly disclosed target that is first identified in the preclinical / clinical pipeline during the recorded year. Neuroscience targets are identified based on any drug target activity associated with a Neurological indication. Neuroscience targets may also have activity in other therapeutic areas; ** Top MOAs and associated target fold enrichment (% of novel targets associated with process over Panther database reference genome) identified through an adapted biological processes GO analysis. Top 10 biological processes, or MOAs, are visualized here; *** Broader MOA overlap may exist between categories
Source: Pharmaprojects; Ashburner et al. Nat Genetics. 2000; The Gene Ontology Consortium. Genetics. 2023

Innovations supporting novel target development include the emergence of improved drug delivery strategies as well as advanced modalities that safely deliver effective pharmacological treatment across the blood-brain barrier. One example is Zolgensma, the U.S. Food and Drug Administration-approved gene therapy for SMA, which uses an AAV9 vector capable of successfully crossing the blood-brain barrier to transduce motor neurons and drive improved survival and motor function. Gene therapy momentum continues to rise, especially in neurodegenerative diseases with clear genetic components (e.g., Parkinson's disease, Huntington's disease). For example, uniQure's AMT-130 Phase I/II recently showed meaningful slowing of Huntington's disease progression vs. baseline.

Newer platforms are now building on the progress of AAV-based delivery. For example, transferrin receptor-mediated transport platforms are being developed to help deliver a range of modalities across the blood-brain barrier, including nucleotide therapies, larger small

molecules and antibodies. These technologies expand the number of druggable targets in the central nervous system (CNS), supporting more opportunities to pursue mechanisms previously considered inaccessible. As more advanced therapies near launch, neuro-associated care sites will need to build the appropriate capacity (e.g., supporting IV infusion needs) and policies (e.g., coverage of high volume diseases) to drive fast adoption and broad patient access.

Clinical trial strategies in neuroscience have also been changing in response to both unmet needs and advances in biomarker science. Surrogate endpoints such as amyloid plaque reduction or fluid biomarkers are being integrated into trial designs to enable earlier readouts and efficient development timelines. The approval trajectory of anti-amyloid therapies in Alzheimer's disease exemplifies this shift: Aduhelm received accelerated approval based on amyloid positron emission tomography (PET) imaging, bringing renewed attention to surrogate endpoints in place of conclusive clinical outcomes. Leqembi followed a similar path, receiving accelerated approval based on amyloid PET and full approval following a confirmatory Phase III trial.

In amyotrophic lateral sclerosis (ALS), Qalsody was granted approval based on reductions in neurofilament light chain, signaling growing incorporation of mechanistic biomarkers into trial endpoints. While still evolving, these approaches reflect a broader trend toward adaptive trial designs and pathways that expedite approvals, reduce development burden, and align early efficacy signals with long-term clinical outcomes.

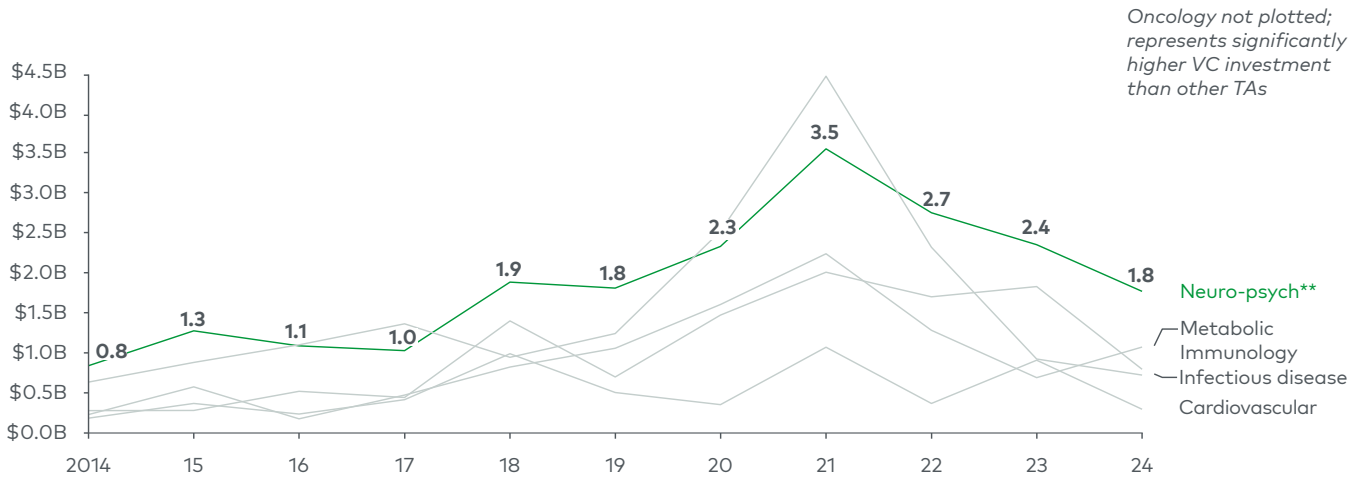
Funding and Dealmaking Trends

Alongside the pursuit of novel targets, development of greater delivery tools, and presence of more favorable regulatory support, investor sentiment toward neuroscience has improved considerably (see Figure 4). While total biotech venture funding has declined since its 2021 peak, neuroscience has increased its share of available capital, ranking as the second most funded therapeutic area after oncology from 2022 to 2024 and widening its lead over other non-oncology fields since 2021.

Figure 4

Neuroscience-focused biotechs have seen an increase in venture capital funding and were the second most funded therapeutic area behind oncology in 2024

Venture capital funding for emerging therapeutic companies* by disease area, globally (2014-24)
Billions USD

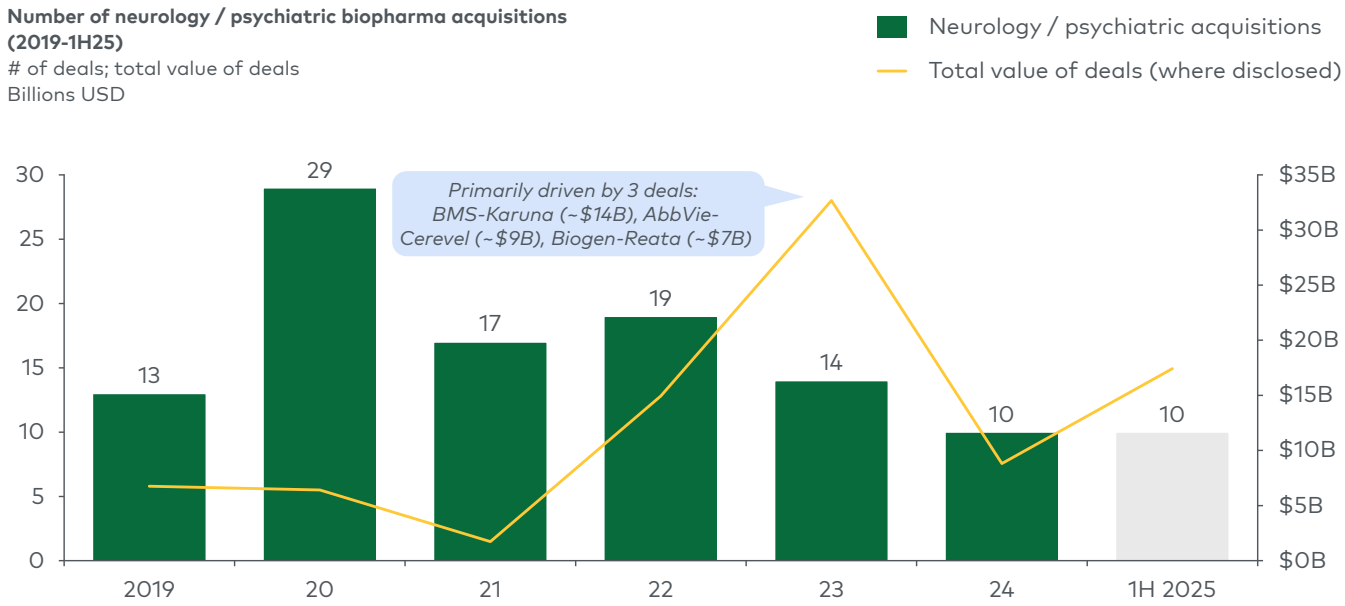


Note: * Emerging therapeutic companies include companies either with a lead drug in R&D or with a drug on the market with less than $1B in sales at the time of funding; ** Includes Neurology and Psychiatry
Source: Biotechnology Innovation Organization

Additionally, M&A activity in neuroscience over the past five-plus years has remained strong (see Figure 5). 2023 was a breakout year, surpassing $30 billion in deal value, driven by three large acquisitions: BMS-Karuna ($14 billion), AbbVie-Cerevel ($9 billion) and Biogen-Reata ($7 billion). This trend continued into early 2025 with Johnson & Johnson's announcement of its acquisition of Intra-Cellular Therapies ($15 billion). The growing interest from large pharmaceutical companies is evident in these high-profile acquisitions. Neuroscience is becoming a priority investment area, with valuations rising as companies seek to reenter or expand their presence in the field.

Figure 5

Neuroscience M&A has continued to remain active over the last several years, with the first half of 2025 already matching 2024 in total deal count



Source: Cortellis; Biomedtracker

While funding and dealmaking trends underscore a growing resurgence, committed neuroscience players are still mindful of the therapeutic area's inherent risk and volatility. Some are complementing their neuroscience pipelines with assets in other disease areas to balance risk. For example, Acadia Pharmaceuticals has expanded into rare disease with their Rett syndrome therapy Daybue and are building on this momentum with pipeline therapies in Prader-Willi and Fragile X syndromes. Similarly, Biogen continues to invest in Alzheimer's and ALS while advancing late-stage systemic lupus erythematosus assets as part of a growing immunology presence. These strategies highlight that even among a scientific renaissance in neuroscience, long-term success may depend on pairing innovation in this area with a diversified portfolio.

Areas for Continued Investment

Despite recent progress, significant unmet needs persist across various areas within neuroscience, particularly in neuropsychiatric, pain, neurodevelopmental, neuromuscular, and neurodegenerative conditions – fueling total pipeline activity (see Figure 6). Looking ahead, promising avenues for innovation and investment are emerging, including:

- Developing new approaches to validated pathways, including through the adaptation of learnings in other therapeutic areas (such as leveraging immunology targets within neuroscience indications)
- Exploring complementary disease mechanisms within attractive pathways, including the use of polypharmacy or combination regimens that engage multiple MOAs, whether within the same pathway or across converging biological axes
- Investigating new modality/delivery approaches to expand on the types of targeted therapies that can be utilized within the CNS
- Leveraging enabling technologies to enhance drug development, support patient identification, and improve clinical outcome measurements

In neuropsychiatric disorders, including treatment-resistant depression, addiction, and schizophrenia, emerging treatments such as NMDA modulators and psychedelic-based therapies build on established areas of excitement but require further clinical validation. Additionally, approvals and clinical activity against first-in-class M1 and M4 muscarinic targets (e.g., Cobenfy, Emraclidine) expand beyond established approaches to target dopamine-specific pathways for antipsychotic treatments. Meanwhile, advances in functional imaging and digital phenotyping (e.g., Alto Neuroscience's Precision Psychiatry Platform) are supporting more targeted and biomarker-guided approaches to clinical development.

Similarly in pain indications, the focus has been on developing novel, non-opioid targeting treatment to move beyond historic strategies for chronic or severe pain management. Attractive mechanisms being pursued today include identifying how targeting different sensory pathways , such as itch, can help alleviate conditions of pain. Recent advancements into new targeted therapies include Vertex's Journavx, a first-in-class non-opioid treatment (targeting NaV1.8) for patients with moderate-to-severe acute pain. Additionally, Kriya Therapeutics recently raised over $300M to advance its pipeline of gene therapies, including a program targeting trigeminal neuralgia, further illustrating how diverse modalities are now being applied to historically underserved pain conditions.

Neurodevelopmental and neuromuscular disorders, especially rare genetic conditions such as Duchenne muscular dystrophy (DMD), present both technical challenges and opportunities for modality innovation. For example, in DMD, the development of gene therapies has been complicated by the size and complexity of the DMD dystrophin gene and safety concerns regarding gene therapy use. Sarepta's Elevidys has faced a series of clinical and commercial setbacks, but newer micro-dystrophin constructs utilizing different AAV vectors are in development and have the potential to offset both efficacy limitations and the safety concerns seen with Elevidys.

Alternative marketed strategies exist to target the DMD gene mutations (e.g., exon-skipping ASO therapies) but have yet to achieve sufficient efficacy, partly due to limitations in tissue targeting. However, companies are currently working to develop more targeted therapies that can improve on current safety and efficacy standards. For example, Avidity is developing a next-generation exon skipper designed to better target muscle cells by utilizing an antibody-oligonucleotide conjugate to increase tissue specificity.

In neurodegenerative diseases, inflammation-targeted therapies are gaining attention as potential disease-modifying treatments. In ALS, therapeutic progress has been difficult due to disease heterogeneity and rapid progression, as underscored by the recent withdrawal of Amylyx's Relyvrio. However, pipeline candidates are exploring upstream mechanisms like TDP-43, mitophagy and axonal transport, and are directly targeting inflammatory signaling as in RAPA-501, an autologous T-cell therapy that enhances regulatory immune function. These programs represent a multimodal strategy tailored to a disease landscape where heterogeneity limits the likelihood of a single, uniform solution.

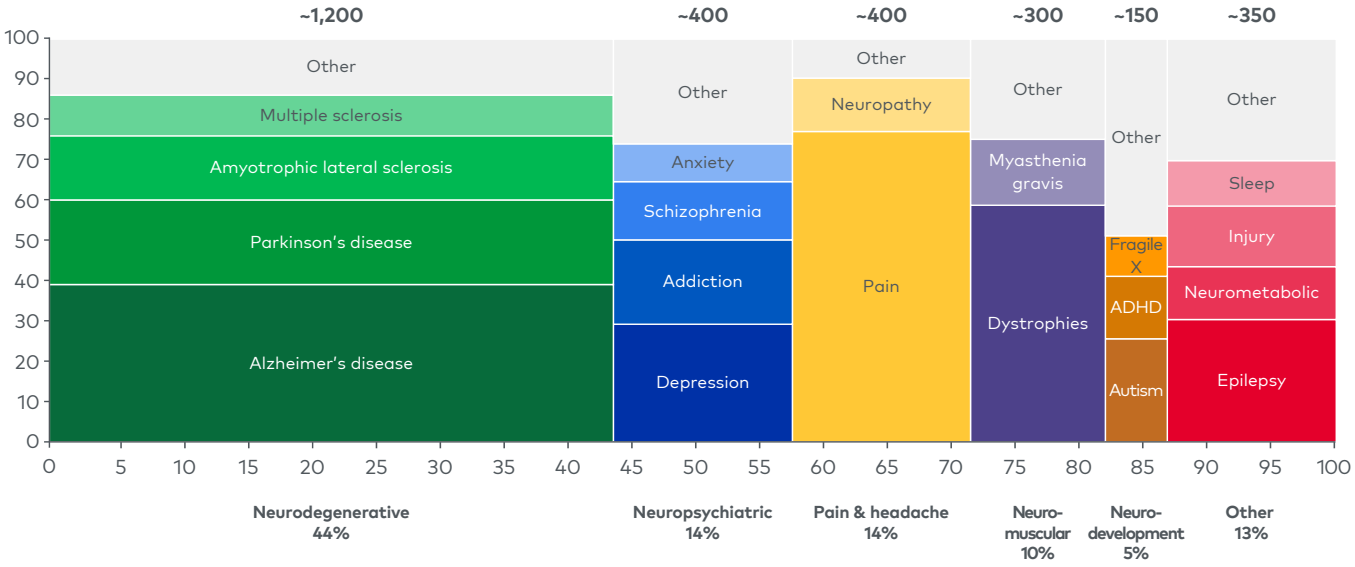
In Alzheimer's disease, R&D activities have expanded beyond the classic hallmarks of amyloid beta and phosphorylated tau to include additional targets such as glial-neuronal cross-talk, oxidative stress and proteostasis. In parallel, developers are innovating on existing amyloid approaches with subcutaneous or oral delivery forms (e.g., Eli Lilly's remternetug, Annovis's buntanetap), improved blood-brain barrier delivery (e.g., Roche's blood-brain barrier shuttle), and combination trials investigating multi-target approaches, which are gaining traction as understanding of disease biology broadens.

Alongside innovation in MOAs and delivery technology, biomarker development is expanding to include blood-based, imaging-based and digital tools; for example, Johnson & Johnson is investigating ways to use machine learning to measure changes in speech patterns that may be predictive of early Alzheimer's. These approaches reflect the continued centrality of amyloid and tau, complemented by a broader, multi-pathway understanding of disease biology and the technologies needed to target mutation more effectively as well as identify it earlier in the disease course.

Figure 6

Neurodegenerative-related assets make up almost half of the neuroscience R&D pipeline, driven primarily by Alzheimer's disease and Parkinson's disease

Total neuroscience pipeline (excl. reformulations) by sub-TA and indication (2025)
Percentage, # of assets*



Note: * Includes pipeline assets (does not include launched assets or reformulations) in neurological indications from Pharmaprojects. Assets in multiple indications were assigned to their most advanced indication where possible. Assets that could not be assigned to any indication (e.g., early preclinical assets for "unspecified neurological indication" and no other public information) were excluded from analysis (~380 assets)
Source: Pharmaprojects

Strategic planning for neuroscience R&D

Neuroscience drug development has long been regarded as one of the most challenging areas in biopharma. While historical failure rates remain high, novel MOAs, precision approaches and evolving regulatory pathways have revitalized interest in neuroscience development, offering new hope for patients with neurological and psychiatric disorders.

An opportunity exists to capitalize on today's unmet need "through" by advances in precision medicine (patient identification/evaluation), improved drug delivery and a growing understanding of the molecular pathology underlying heterogeneous diseases. Achieving success will require focused investment in the right biological target, modality and supporting diagnostic/enabling technology. The upside for a realized investment may be significant, as companies see opportunities to reach patient populations with limited therapeutic options and become a leader in a constantly evolving marketplace.

Editor's note: L.E.K. helps biopharma organizations evaluate white space opportunities and determine the most attractive areas for investment based on an individual organization's expertise, resourcing, and ambition. This includes developing a well-laid, long-term strategic roadmap that outlines developmental plans, investment and capability requirements, and timing for key inflection points. Our approach helps organizations consistently make better decisions, deliver improved business performance and reach critical areas of patient unmet need. To find out more and for further discussion, please contact Sean Dyson and Delia Silva.

For more information, please **contact us**.

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