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Beyond the single asset: The rise of combination and synergistic innovation in neurology drug development

Introduction

Historically, drug development within the neurology space has been characterized by the search for individual therapies that can arrest complex neurodegenerative or neurotoxic processes. However, as our understanding of the multi-faceted pathophysiology of central nervous system (CNS) disorders deepens, innovation in this disease space is moving towards the development of therapies that can be sequenced, layered, or combined to treat diseases more holistically.¹ Whilst this transition has the potential to achieve improved patient outcomes, it also brings with it several risks and strategic hurdles for pharmaceutical manufacturers to overcome for optimized commercial success.

Key takeaways:

- **Neurology is shifting from single-drug treatments to combination and multi-mechanism approaches**, driven by advances in systems biology, precision medicine, AI, biomarkers, and the emergence of disease-modifying therapies that can serve as treatment backbones.
- **Spinal muscular atrophy and Alzheimer's disease highlight this evolution**, with developers increasingly exploring ways to layer complementary therapies to address multiple disease pathways and improve outcomes beyond what standalone treatments can achieve.
- **Commercial success will increasingly depend on a therapy's role within broader treatment ecosystems**, requiring manufacturers to demonstrate incremental value, navigate more complex evidence and reimbursement requirements, and build strategies for partnerships, sequencing, and combination use.

Drivers of multi-mechanism innovation

The expanding role of multi-mechanism innovation in neurology is being accelerated by several converging clinical and scientific advances (**Table 1**).²⁻⁵ While these drivers are not necessarily unique to the neurology space, oncology treatment, for example, previously underwent a similar evolution toward combination-based care, there are several distinctive CNS considerations. Single-target approaches have struggled in neurology due to the biological complexity and heterogeneity of associated diseases, where a single clinical diagnosis often reflects diverse genetic, molecular, and environmental drivers rather than a unified pathology.

The brain operates as a highly interconnected and adaptive system, with redundant and compensatory pathways that can bypass inhibition of any single molecular target, limiting the durability and magnitude of therapeutic effect. As a result, targeting one node within a broader disease network frequently fails to meaningfully alter disease progression, highlighting the limitations of the “one target, one drug” paradigm in complex neurological disorders.¹

Table 1: Scientific advance supporting the rise of combination and multi-mechanism CNS therapeutic approaches²⁻⁵

Scientific advance	Relevance to neurology drug development
Systems biology and network-based understanding of CNS disease	Advances in basic neuroscience research, genomics, and translational biology have significantly expanded mechanistic understanding of the complex pathophysiological processes underlying CNS disorders.
Advances in biomarkers, diagnostics, and precision medicine	Fluid biomarkers, imaging, genomics, and digital tools are enabling earlier disease detection, patient stratification, and more precise characterization of disease biology, supporting the rational sequencing of therapies targeted to complementary mechanisms across the disease continuum.
Computational biology, AI, and multi-omics integration	Artificial intelligence, systems pharmacology, and multi-omics approaches are increasingly being used to identify novel targets, predict synergistic combinations, optimize patient selection, and accelerate discovery through the integration of genomic, proteomic, transcriptomic, and clinical datasets.
Expansion of novel therapeutic modalities and mechanisms of action	The transition from traditional small molecules, toward cell, gene, and RNA-targeted medicines, as well as emerging technologies for delivery of therapeutics across the blood-brain barrier, create new opportunities for layered and complementary mechanisms to enhance disease modification and functional outcomes.
Emergence of disease-modifying backbone therapies	The first validated disease-modifying therapies in neurology are beginning to establish foundational treatment backbones, upon which add-on and complementary therapies can be layered, creating the structural basis for future combination treatment paradigms.

Significantly, the transition toward combination-based care may also prove inherently more complex in neurology than in oncology. In oncology, combination strategies are often introduced in later-line or incident treatment settings, allowing manufacturers to demonstrate incremental benefit relatively rapidly before moving therapies earlier in the treatment pathway. By contrast, many neurological diseases are chronic, progressive conditions in which patients remain on therapy for prolonged periods, creating greater complexity around treatment layering, switching, sequencing, and the demonstration of an additive benefit on top of established long-term standards of care. Furthermore, progression and degeneration in these diseases are often irreversible, which constrains the ability to introduce and validate combinations in later lines. The recent emergence of the first validated disease-modifying backbones has created a platform upon which add-on and complementary therapies can now be developed, as illustrated in the following case studies in Spinal Muscular Atrophy (SMA) and Alzheimer's Disease (AD).

Case studies from the clinical pipeline

Spinal muscular atrophy

Spinal muscular atrophy (SMA) provides one of the clearest early examples of how neurology is evolving beyond single-agent treatment paradigms toward layered and potentially combination-based disease modification. Traditionally, SMA was associated with rapid and irreversible motor neuron degeneration, with treatment limited to supportive care and poor long-term outcomes, particularly in infantile-onset disease. The emergence of survival motor neuron (SMN) protein-targeted therapies, including the antisense oligonucleotide nusinersen, the oral splicing modifier risdiplam, and the AAV gene replacement therapy onasemnogene ABEPRV001, transformed the field by demonstrating that restoration of SMN protein can significantly alter disease trajectory, especially when initiated early.^{6,7} These treatments have changed the natural history of disease, giving rise to patient types who were not traditionally observed in SMA. The unique needs of these patients, such as residual weakness, impaired motor function, or plateauing clinical benefit, introduce new opportunities to improve clinical outcomes by enhancing SMN restoration with complementary add-on approaches.

As a result, SMA is increasingly being viewed not as a fully corrected monogenic disease, but as a chronic neuromuscular disorder where multiple biological processes may need to be addressed to maximize long-term outcomes. This has created growing interest in sequencing or layering therapies with complementary mechanisms of action. In addition to strategies combining gene replacement and chronic SMN-enhancing therapies, the next wave of innovation is expanding beyond SMN restoration alone toward muscle-directed and neuroprotective approaches designed to amplify functional gains. One of the most prominent examples is myostatin inhibition, which aims to enhance muscle growth and strength independently of motor neuron rescue, thereby complementing upstream SMN-targeted therapies. Myostatin inhibitors, such as recently approved apitegromab, have demonstrated encouraging improvements in motor outcomes when added to standard SMN-directed treatment backbones, supporting the broader concept that future efficacy gains in SMA may increasingly come from combination approaches targeting both neuronal rescue and peripheral muscle function.⁶ Longer term, additional mechanisms including neuromuscular junction stabilization, mitochondrial support, and neuroprotection may further expand the combination landscape.

Alzheimer's disease

Alzheimer's disease (AD) illustrates both the challenges and the inflection point facing many CNS drug development programs. Early waves of anti-amyloid monoclonal antibodies were characterized by repeated late-stage clinical failures, reflecting the difficulty of modifying a biologically complex, slowly progressive disease with a single intervention. More recently, however, antibodies such as lecanemab and donanemab have demonstrated reproducible amyloid clearance alongside measurable clinical benefit in selected early-stage patient populations, leading to regulatory approvals worldwide.⁸ While reimbursement remains challenging, growing evidence and real-world experience are helping to clarify their value and long-term impact. As the first validated disease-modifying treatments in AD, they have transformed expectations and established the foundation for the next generation of Alzheimer's innovation.

Building on this foundation, the logical next phase of innovation is the pursuit of combination strategies designed to address complementary disease pathways beyond amyloid alone. AD is understood as a network disorder involving tau propagation, neuroinflammation, synaptic dysfunction, vascular pathology, and metabolic stress, creating a strong mechanistic rationale for layered or combination approaches. As a result, combination therapy is becoming a prominent topic of discussion across scientific publications, congresses, and expert forums. Although the clinical pipeline for combination therapy remains at an early stage, interest is growing.

The leading example is Eisai's lecanemab + tau mAb E2814 program, which aims to maximise the disease modifying effect by consecutively targeting two key pathogenic proteins.³ The combination was initially advanced in familial AD populations, where predictable disease progression and earlier identification of at-risk individuals provide an opportunity to explore intervention before substantial pathology is established. Building on this foundation, a subsequent trial was launched in early sporadic AD, reflecting growing confidence in the potential of multi-target approaches across broader patient populations.⁹ Compared with other neurological diseases, where combination strategies often emerged years after the first disease-modifying therapies reached the market, the AD field appears to be progressing relatively quickly toward evaluating how established treatment backbones may be enhanced through complementary mechanisms.

Implications

As the neurology drug development landscape transitions from competition among standalone therapies toward increasingly complex, multi-mechanism treatment paradigms, the commercial success for future therapies will depend not only on demonstrating efficacy of an individual asset, but on securing a durable role within the evolving standard of care, whether as a backbone therapy, add-on agent, or complementary mechanism within a broader regimen. This shift creates significant strategic opportunities for manufacturers who are able to build or access portfolios spanning multiple disease pathways, extend lifecycle value through combination use, and differentiate assets based on compatibility with emerging treatment algorithms rather than standalone performance alone (**Table 2**).

At the same time, the transition introduces substantial scientific, developmental, regulatory, and commercial complexity. Future therapies will increasingly need to demonstrate meaningful incremental benefit over established backbones, requiring more expensive and sophisticated trial designs, biomarker strategies, and evidence generation capable of capturing additive or synergistic

effects. Manufacturers will also face growing challenges around treatment sequencing, pricing and reimbursement of innovative high-cost combinations, and coordination across development and commercialization pathways, particularly as cross-company combinations become more common. As seen previously in oncology, companies that proactively align portfolio strategy, partnership models, and evidence generation in this evolving ecosystem are likely to be best positioned to shape future standards of care and capture long-term value in the CNS space.

Table 2: Key opportunities and risks associated with strategic shifts in neurology drug development

Strategic shift	Key opportunities	Key risks
1. Shift from standalone therapies toward treatment ecosystems and combination paradigms	• Opportunity to secure a durable role within evolving treatment ecosystems and combination paradigms • Lifecycle expansion through sequencing, layering, and add-on use	• Payer resistance to “stacked” high-cost therapies and need to prove incremental benefit • Dependency risk on partner assets and increased negotiation complexity in cross-company combinations
2. Shift toward more complex and evidence-intensive clinical development models	• Potential for stronger efficacy and differentiated positioning through multi-mechanism approaches • Opportunity to shape future standards of care and regulatory expectations	• Larger, longer, and more complex trials with more difficult attribution of effect • Regulatory uncertainty around co-development, endpoints, and combination evidence requirements
3. Shift from drug-level efficacy toward system-level value demonstration	• Greater potential to demonstrate system-level value through improved long-term outcomes and reduced disease burden • Stronger health economic narratives beyond drug-level efficacy alone	• More challenging value attribution within combinations • Need for more sophisticated evidence generation and economic modelling to demonstrate system-level value across treatment combinations
4. Shift toward earlier intervention and pathway-driven patient identification	• Earlier intervention can allow for improved outcomes and increase long-term treatment value • Opportunity to shape diagnostic and screening pathways	• Commercial value shifts earlier in the patient journey • Requires investment in diagnostics, screening infrastructure, and HCP education

Conclusion

Neurology is rapidly evolving from a single-asset market to a multi-mechanism ecosystem, where commercial success may depend less on owning the best standalone therapy and more on securing a durable, differentiated role within increasingly complex treatment paradigms. To compete effectively, pharmaceutical companies must act now to understand and develop strategies to overcome the risks associated with this transition, as well as invest in biomarker and evidence

strategies that demonstrate incremental value. They will need to build flexible partnership and access models that mitigate dependency and pricing risks. Companies that proactively align portfolio, clinical, and commercial strategy to this new reality will be best positioned to shape future standards of care and capture long-term value in this evolving therapy area.

Drawing on deep neurology therapeutic knowledge, significant experience navigating the opportunities and pitfalls associated with launching combination and add-on therapies, and expertise drawing parallels and implications across therapy areas,¹⁰⁻¹² CRA can provide an objective and pressure-tested perspective on how to balance development risk with long-term commercial opportunity and pricing and market access success, as treatment paradigms continue to evolve in the CNS space.

For more information and support on navigating this evolving environment, please reach out to CRA.

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