White Paper

Mind over matter: The growing momentum of CNS innovation

How innovators are beating the odds in a high-stakes therapeutic area

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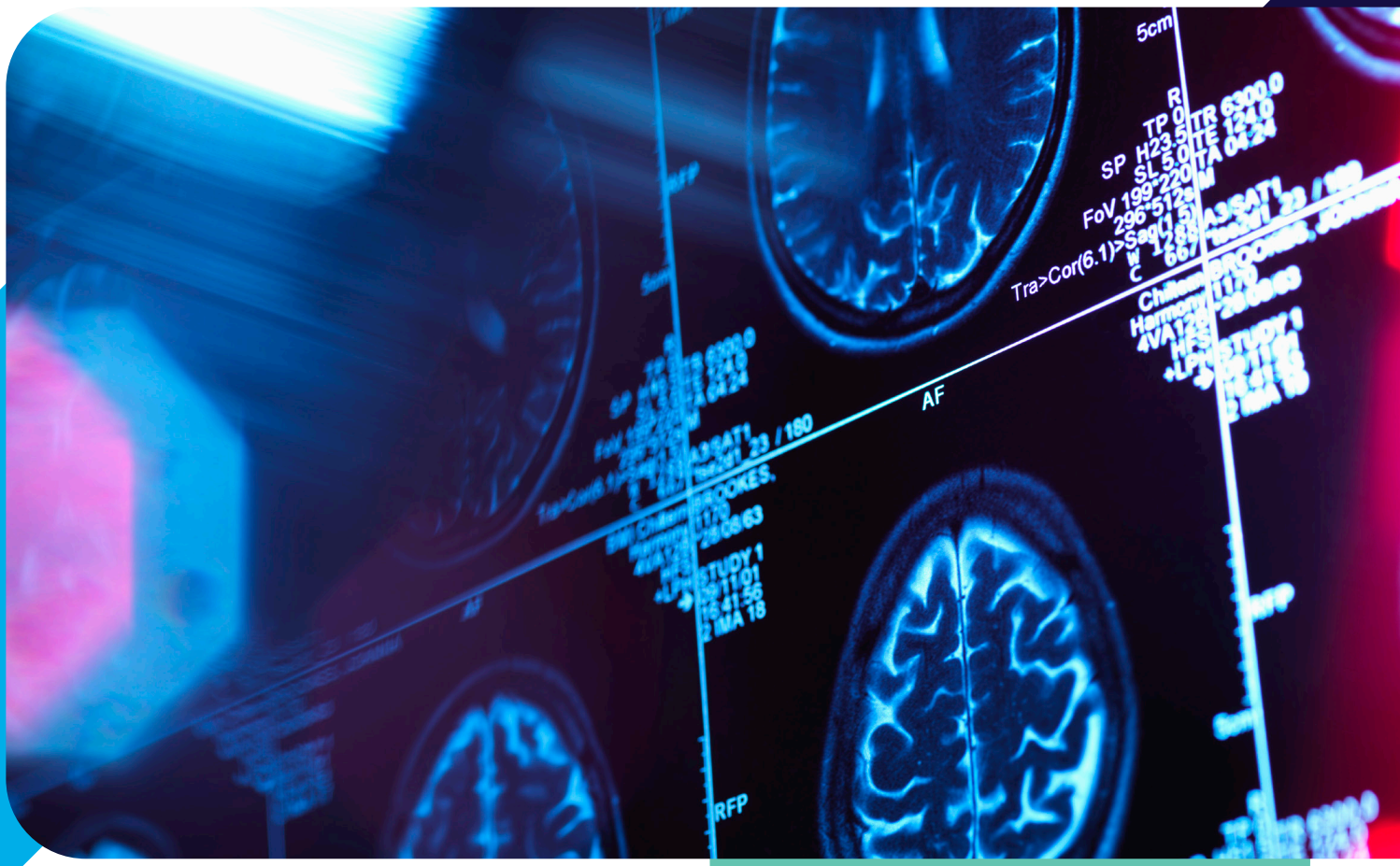

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Introduction

The global burden of illness related to Central Nervous System (CNS) disorders keeps rising unabatedly, with huge economic implications. By 2030, the global economic cost of mental health conditions alone is projected to reach $6 trillion,[1] for example, while the economic burden of Alzheimer's and related dementias is estimated to rise to $4.7 trillion.[2]

These extraordinary numbers reinforce the urgent need for novel therapeutic interventions to treat CNS disorders, however, the title of our previous publication from 2023, "Two steps forward, one step back: The long road to success in CNS"[3] still rings true today, as innovators continue to navigate the high-stakes roller coaster of developing and commercialising new CNS therapies.

Notwithstanding well publicised setbacks, numerous examples illustrate the significant progress made in expanding CNS therapeutic options to give hope to patients, their families and caregivers.

For example, the approval of Cobenfy represents the first new approach for treating schizophrenia in over 30 years, by targeting cholinergic receptors as opposed to dopamine receptors; NMDA-targeting Spravato (esketamine) for treatment-resistant depression and major depressive disorder with suicidal ideation is well on its way to reach blockbuster status in 2025 and signifies a case in point for the potential of psychedelics as valuable, and commercially viable, CNS therapies; while the approvals of amyloid-targeting therapies Leqembi and Kisunla, and the Lumipulse G test, as the first blood test for diagnosing Alzheimer's,[4] highlight the ongoing, albeit slow, progress in tackling this devastating disease.

In this white paper, we will explore the latest trends in CNS innovation, including a deep dive into selected therapeutic breakthroughs, and provide an outlook on the competitive landscape and the CNS market opportunity.

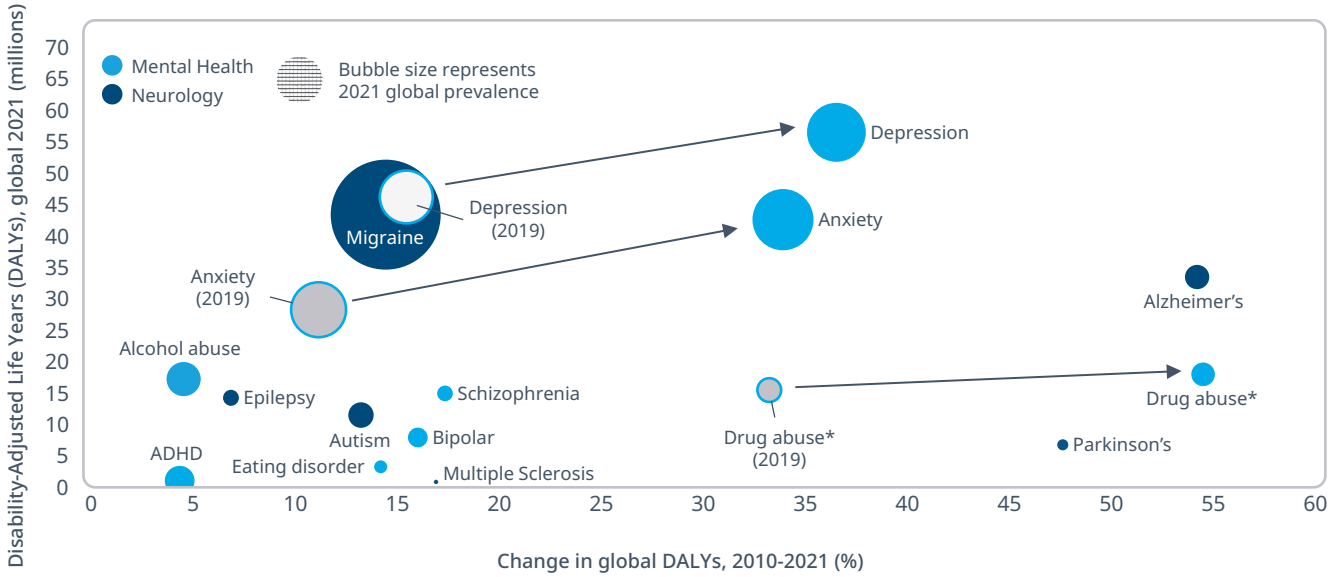
Unmet need is accelerating

The global burden of illness caused by mental health and neurological disorders is significant and continues to rise sharply. For 2021, the WHO[5] estimated the combined long-term impact on health-related quality of life of non-communicable mental health and neurological conditions as 304 million disability-adjusted life years (DALYs) globally, an increase of 26% since 2010. For context, this burden considerably exceeds the 2021 estimate of 270 million DALYs globally for all malignant neoplasms.

Consistent with our previous analysis based on 2019 data, Alzheimer's continues to be a major driver of the future global disease burden with a 54% increase in DALYs between 2010 and 2021.

However, between the 2019 and 2021 data sets from the WHO, several conditions have seen dramatic acceleration in their respective burden of illness when comparing change in DALYs for the time periods of 2010-2021 vs. 2010-2019: 47% for Parkinson's, up from 35%; 54% for drug abuse, up from 33%; 36% for depression, up from 16%; and 34% for anxiety, up from 11% (see Figure 1).

Figure 1: The disease burden of CNS is high and growing fast



* Includes use disorders of amphetamines, cannabis, cocaine, opioids and other substance abuse excluding alcohol
Source: WHO, Global Health Observatory; The Lancet, Global Burden of Disease Study 2021; IQVIA EMEA Thought Leadership analysis

The particularly pronounced acceleration in the disease burden of depression, anxiety and drug abuse between 2019 and 2021 overlaps with the beginning of the COVID-19 pandemic as a likely important contributor to this dynamic, and it highlights the scale of the growing global mental health crisis.

It is important to note that 80% of people affected by mental illnesses live in Low- and Middle-Income Countries (LMIC), with LMICs representing 9 of the top 10 countries ranked by absolute burden of illness (total DALYs) related to mental health disorders.[6,7] Among the top 20 non-communicable diseases, depression and anxiety rank 12th and 15th by disease burden, respectively, in Upper-Middle Income Countries (UMICs), while depression ranks 17th and 18th in Lower-Middle Income Countries (LrMICs) and Low-Income Countries (LICs), respectively.[8] At the same time, the World Health Organization estimates that over 75% of the population with mental health disorders in LMICs do not have access to the right care, with the provision of mental health services held back by a combination of factors, including health policy, funding and resources, but also cultural barriers and social stigma.[9]

Addressing the high and growing unmet need related to CNS conditions presents an attractive opportunity, however, innovators face serious challenges during both development and commercialisation of novel CNS therapies, for example:

- Limitations in translational animal models and validation of CNS drug targets, resulting in historically higher failure rates in CNS drug development compared to other therapy areas.
- Patient identification and recruitment for clinical trials, especially at asymptomatic, early-stage disease; for example, the median enrolment duration for CNS trials increased by over 40% between 2019 and 2024, from 9.5 to 13.4 months.[10]
- Measuring clinically meaningful, objective endpoints in clinical trials, beyond subjective assessments reliant on rating scales with limited relevance in routine clinical practice.
- Adoption of innovation by overwhelmed health systems facing growing capacity constraints, including a shortage of qualified staff as well as care pathway and infrastructure bottlenecks.
- Intensifying healthcare budget pressures resulting in increasingly stringent criteria to restrict market access and reimbursement for novel therapies.

However, the prospects for CNS innovation have been improving significantly, as we are beginning to reap the benefits of decades of foundational research , e.g., in the field of genomics, biomarkers, diagnostics and imaging techniques or regenerative medicine, while the growing burden of neurological and mental health conditions is being increasingly recognised as a public health concern.

"The prospects for CNS innovation have been improving significantly, as we are beginning to reap the benefits of decades of foundational research"

Pushing the frontiers of CNS innovation

Many of the scientific enablers we highlighted in past analyses — ranging from improved understanding of disease biology to genomic stratification tools — are beginning to deliver tangible advances in CNS R&D. At the same time, new platforms are expanding what is possible: AI is accelerating drug discovery and repurposing, while brain organoid models are redefining how we study disease mechanisms and drug responses in human-relevant systems. Together, these advances are fuelling a new era of modality-driven innovation in CNS, spanning neuroinflammation, the gut-brain axis, psychedelics and digital therapeutics. The focus across these domains is shifting firmly towards durable, disease-modifying outcomes driven by mechanistic insight and translational relevance.

Neuroinflammation

Neuroinflammation is now widely seen as a key contributor to the onset and progression of many brain diseases. It refers to the brain's own immune response, involving support cells like microglia and astrocytes, as well as immune cells entering from the bloodstream. While this response may initially help clear damage or toxins, it can become harmful when it stays active too long — fuelling further injury and long-term degeneration. Recent studies across conditions like Alzheimer's, Parkinson's, multiple sclerosis, and stroke show that this ongoing inflammation forms a vicious cycle with tissue damage reinforcing disease progression[11]. These insights have led to a major shift in thinking: controlling inflammation within the brain — especially with treatments that can reach into the central nervous system — is now seen as a critical strategy to change the course of a disease.

One of the most promising developments in this area is the emerging role of GLP-1 receptor agonists — originally developed for type 2 diabetes — as potential disease-modifying therapies in Alzheimer's disease (AD). Agents such as semaglutide and liraglutide are now in mid- to late-stage trials, showing potential to reduce neuroinflammation, improve insulin signalling in the brain, and slow cognitive decline. These hopes are supported by growing real-world evidence, including large observational datasets from U.S. Veterans Health Administration studies, which suggest a lower incidence of dementia among patients with type 2 diabetes treated with GLP-1s.[12] On the clinical front, Novo Nordisk is leading the way with the global phase 3 EVOKE and EVOKE+ trials in early Alzheimer's disease. These trials are evaluating once-daily oral semaglutide (14 mg) over a treatment period of 3 years in approximately 1,840 participants. Both trials are expected to complete in 2025, with top-line results anticipated in late Q4. Experts in the field are watching closely, with many noting that a positive outcome would not only validate GLP-1s as a scalable intervention in AD but also signal a major advance in targeting metabolic-inflammation pathways in neurodegeneration. If successful, they may offer the first scalable, orally available anti-inflammatory strategy in Alzheimer's disease.

In Parkinson's Disease (PD), however, the data are more mixed. While several early-phase trials of GLP-1 analogues like exenatide and liraglutide have shown signals of benefit in motor and cognitive function, results have not been consistently replicated in larger studies.[13] Although exenatide was well-tolerated, there was no significant difference in motor scores between placebo and treatment groups. Minimal weight loss was seen in the trial, raising the possibility

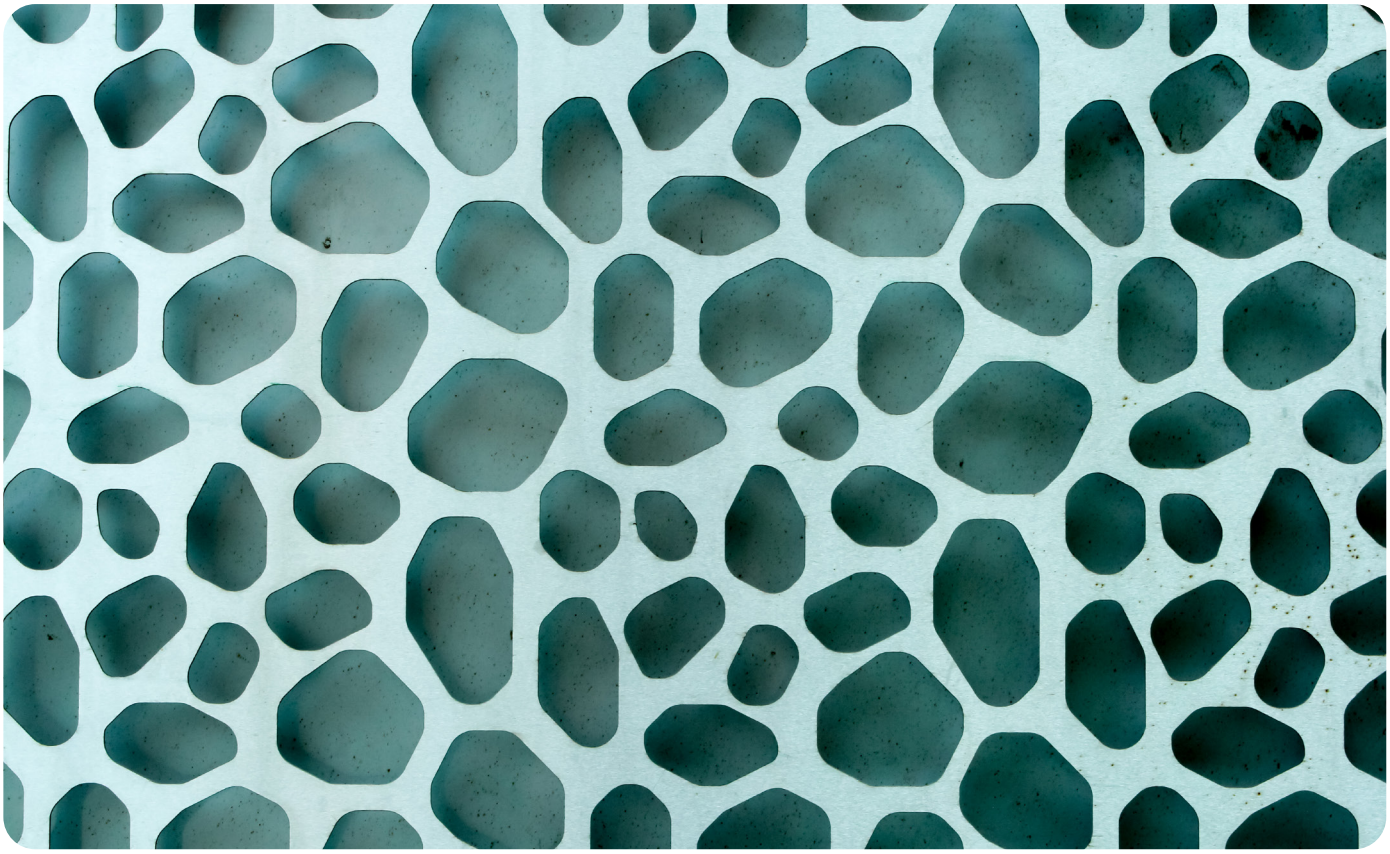
of insufficient dosing. This is particularly relevant in Parkinson's disease, where weight loss, and specifically loss of lean muscle mass, can worsen clinical outcomes. Despite this setback, the biological rationale for GLP-1s remains intact. Future research may carve out a role for next-generation agents, including obesity medicines that preserve muscle mass and have improved brain penetration.

Beyond GLP-1s, other innovative modalities are targeting neuroinflammation through distinct mechanisms. TREM2 agonists aim to activate microglia's protective functions, although the recent failure of the AL002 Phase 2 INVOKE-2 trial in Alzheimer's disease highlighted the need for refined targeting strategies, as the TREM2 agonist failed to demonstrate clinical benefit despite a strong mechanistic rationale.[14] Other clinical programs exploring TREM2-targeting therapies remain ongoing and may help clarify whether modulation of this pathway can deliver clinical value with improved compound design or patient selection.

Decades of experience in multiple sclerosis have shown that precise immune targeting can modify disease progression. These insights are now influencing how we approach conditions like Alzheimer's and Parkinson's, where the immune system may play a more active role than previously thought. While differences in underlying pathology remain, lessons from MS offer a valuable roadmap for how immune-modulating therapies might help slow or prevent neurodegeneration when applied with optimal timing and specificity.

The gut-brain axis

Increasingly, scientists are finding that what happens in the gut can influence what happens in the brain. The gut microbiome is emerging as both a contributor to, and potential early marker of neurodegenerative disease risk. In Alzheimer's and Parkinson's disease, shifts in microbial populations — including elevated levels of *Streptococcus, Actinomyces*, and oral pathogens like P. gingivalis—have been linked to inflammation and cognitive decline.[15, 16] Additionally, certain microbial byproducts, such as metabolites and bile acids, appear to affect disease progression, highlighting a functional gut-brain connection. These discoveries not only point toward novel therapies but also suggest opportunities for early diagnosis and risk stratification.



In response, companies are developing microbiome-based therapies aimed at brain health. These range from live biotherapeutics and engineered microbial consortia (custom blends of beneficial bacteria), to oral agents that neutralise gut-derived neurotoxins. These therapies seek to correct microbial imbalances, reduce systemic inflammation, and influence brain function through immune and neural pathways, including the vagus nerve. Innovators like Axial Therapeutics, Ultimate Medicine, and Piton Therapeutics are pioneering these approaches, especially in Autism Spectrum Disorder (ASD), Alzheimer's, and Parkinson's. While still in early stages, the field is gathering momentum, with growing support from translational science and clinical observations. The idea that gut-targeted interventions could modify brain disease is no longer speculative. It could quickly become a new frontier in neurology.[17]

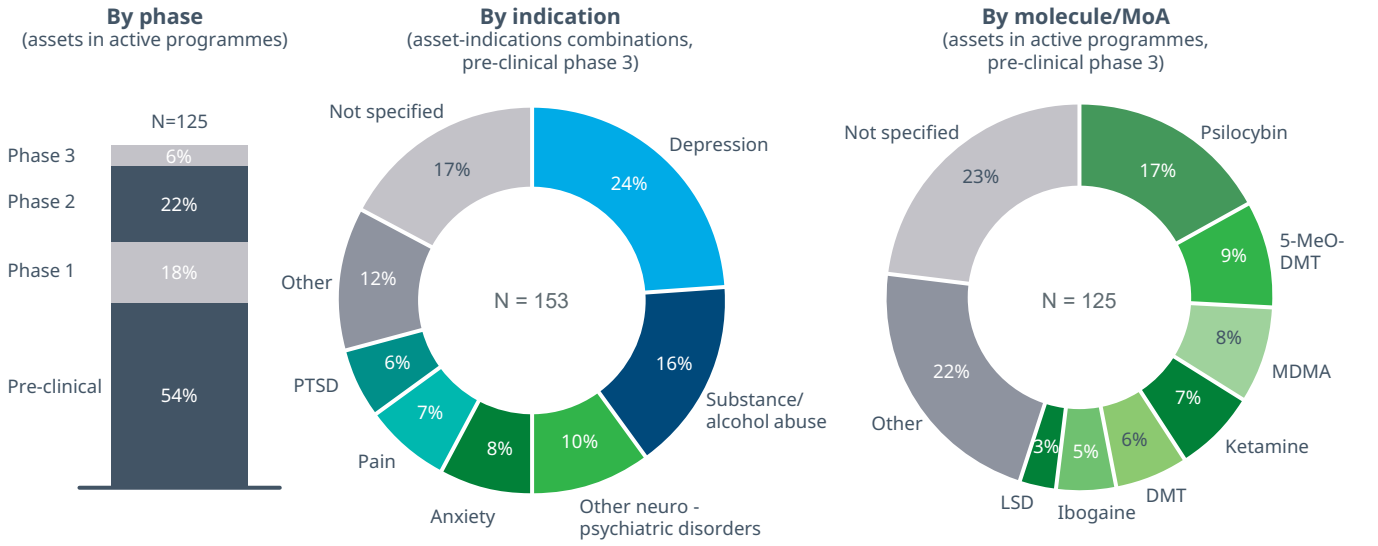
Psychedelics

Interest in psychedelics-derived therapeutics has increased significantly in recent years, as a novel, potentially disease-modifying approach to treat CNS conditions, in particular mental health disorders. Psychedelics' potential to induce or enhance neuroplasticity,[18] the nervous system's ability to reorganise its structure and function, is assumed to be at the centre of their ability to deliver durable clinical improvements, including in challenging conditions, e.g., treatment-resistant depression or PTSD.[19,20]

The current pipeline of psychedelics-derived therapeutics comprises 125 assets, of which 54% are at preclinical stage, 18% in phase 1, 22% in phase 2 and 6% in phase 3.

These assets are being investigated across a range of mental health conditions, with depression (24%), substance/alcohol use disorders (16%), other neuro-psychiatric disorders (10%), anxiety (8%), pain (7%) and PTSD (5%) the top indications in focus (see Figure 2).

Figure 2: Pipeline of psychedelics-derived therapeutics



Source: IQVIA Analytics Link; Clinicaltrials.gov; company reports, press releases, desk research; IQVIA EMEA Thought Leadership analysis

Seven molecules, including their derivatives, account for 55% of the pipeline: psilocybin, 5-MeO-DMT, MDMA, ketamine, DMT, ibogaine and LSD, with psilocybin the most investigated psychedelic, at 17% share.

A significant pipeline share of 22% attributed to 'other' reflects innovators' quest for novel approaches to overcome challenges often faced by traditional psychedelics, e.g., hallucinations, addictive potential, time-consuming administration with accompanying psychotherapy and need for monitoring, or potential side effects such as nausea, cardiovascular risks or seizures.[21]

Companies like Psilera, Seaport, Transneural or Gilgamesh are developing a new class of non-hallucinogenic neuroplastogens, with some of them deploying AI-assisted drug design to optimise candidates' pharmacological profile[22], while Negev Labs specifically focuses on building neuroplastogen-developing biotechnology companies.[23] In May 2025, Gilgamesh reported impressive top-line results from its phase 2a study of GM-2505, an experimental 5-HT2A receptor agonist and 5-HT releaser for major depressive disorder, showing a rapid and sustained antidepressant effect: 18.5-point drop in Montgomery-Åsberg Depression Rating Scale (MADRS) scores within 24 hours of the first dose, and a 94% remission rate one month after just two treatment sessions.[24]

The field of psychedelics-derived therapeutics has not been without setbacks, however. In August 2024, the FDA rejected Lykos' MDMA-assisted PTSD therapy after an earlier advisory committee raised questions about safety and efficacy.

This regulatory decision provides important lessons for innovators developing psychedelics-derived therapeutics.

It highlights the criticality of robust clinical trial design, in particular controlling for functional unblinding which presents an inherent challenge when studying therapeutic interventions with hallucinogenic properties. Ensuring phase 3 trials use a dose-response study design involving multiple dose strengths arms, including one for a low dose, for example, can help mitigate being challenged on functional unblinding being a main driver of the observed therapeutic effect.

"Robust clinical trial design to control for functional unblinding is critical when studying therapeutic interventions with hallucinogenic properties."

Furthermore, it is prudent to follow a more traditional development path focused on the pharmacotherapy in its own right, instead of embedding psychotherapy alongside pharmacotherapy as the combined intervention being investigated in a clinical trial.

Psychedelics-derived therapeutics may enjoy political tailwinds from a more supportive U.S. administration, which could help destigmatise this field or even lead to rescheduling of some of the psychedelics drugs being studied, e.g., psilocybin, to recognise their therapeutic potential and remove significant barriers to conducting research.

As a case in point for the changing political climate, in June 2025, Texas announced a $50 million public investment into psychedelic research to study the potential of ibogaine. The bill, which received bipartisan support, marks one of the largest government investments in psychedelic research to date.[25]

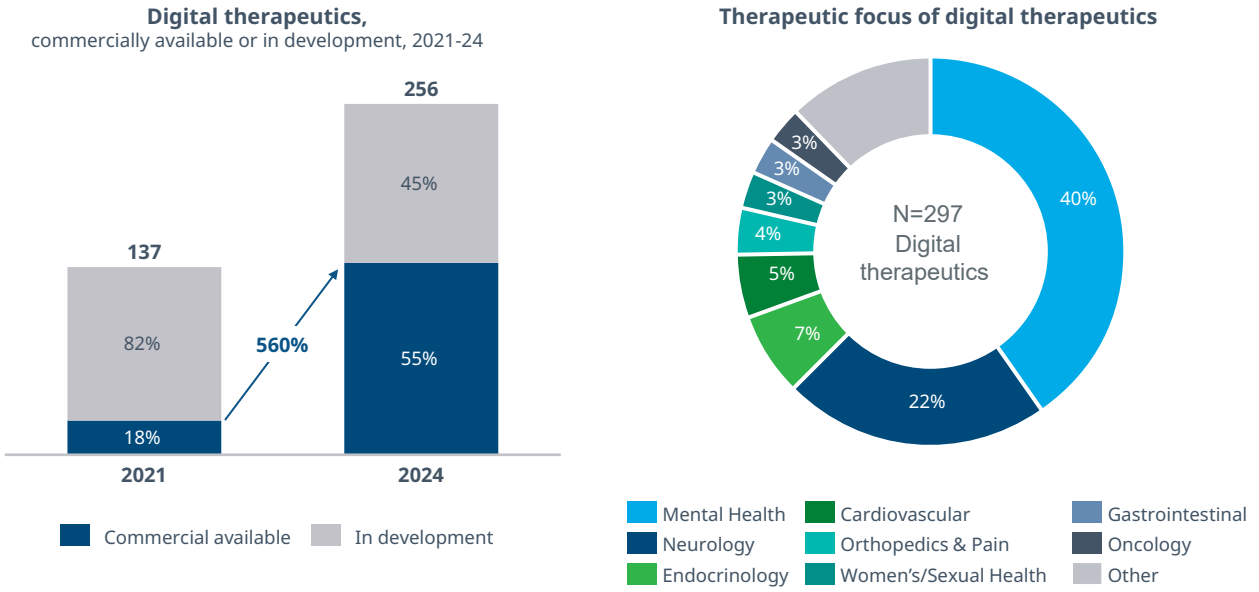
Digital health

Growing workforce shortages across healthcare — including limited availability of trained professionals in mental health, neurology, and primary care — are driving demand for scalable, technology-enabled solutions that can extend access and reduce system strain. In this context, digital interventions in CNS care span a continuum, from emerging platforms like chatbots to more established prescription Digital Therapeutics (DTx). While differing in maturity and regulatory status, both aim to complement the work of clinicians, support patient care across the journey, and help meet growing demand for digital interventions around the clock.

Chatbots, which are conversational agents powered by artificial intelligence, are increasingly used by individuals to explore health concerns, including mental health. These interactions often occur without medical supervision, proven effectiveness, or adequate attention to data privacy. Despite this unregulated use, formal evaluation of these tools is beginning to emerge. In a clinical trial published in March 2025, participants using Dartmouth's AI-powered "Therabot" reported average symptom reductions of 51% for major depressive disorder, 31% for generalised anxiety disorder, and 19% for eating disorders. Participants often described their experience as comparable to working with a therapist[26]. While these results are promising, the field remains nascent, with further validation and long-term outcome studies still developing.

In parallel, digital therapeutics (DTx) — software-based medical interventions that deliver evidence-based therapeutic outcomes — continue to capture attention as an exciting class of treatments. Pharmaceutical companies are playing a key role: Click Therapeutics' collaborations with Otsuka (for depression) and Boehringer Ingelheim (for schizophrenia) exemplify how DTx are being co-developed as adjuncts to pharmacotherapy. These alliances reflect pharma's growing confidence in the scalability and clinical value of software-based treatments. According to the IQVIA Institute's Digital Health Trends 2024 report, the number of commercially available DTx products has surged by 560% to 141, while the total number of DTx commercially available or in development has grown from 137 in 2021 to 256 in 2024.[27] Significantly, 62% of this pipeline is focused on mental health and neurology, reflecting a dynamic response to rising healthcare demands (see Figure 3).

Figure 3: Digital therapeutics are expanding with CNS leading



Source: IQVIA Institute, Oct 2024; IQVIA AppScript Digital Medicine Database, Apr 2024, updated manually through Oct 2024.

Recent FDA approvals and pivotal trial results have amplified excitement. Click Therapeutics' CT-132 received FDA clearance in 2025 as the first digital therapeutic for episodic migraine prevention, demonstrating a significant reduction in monthly migraine days.[28] Additionally, new mental health apps like DaylightRx (for generalised anxiety disorder) and SleepioRx (for insomnia) underscore the strong clinical validation digital therapeutics are achieving. These digital solutions, offering structured cognitive and behavioural therapies, are increasingly viewed not just as adjunctive options, but as essential components that both enhance modern healthcare and address critical gaps in access and continuity of care.

Policy is also gaining traction. In the U.S., the reintroduction of the Prescription Digital Therapeutics (PDT) Act in 2025 signals growing bipartisan support to establish dedicated reimbursement pathways for FDA-authorised digital therapies under Medicare. Complementing this legislative push, the Centers for Medicare and Medicaid Services (CMS) proposed new billing codes in its 2025 Physician Fee Schedule for digital behavioural therapy devices, thus enabling providers to be reimbursed for the setup and ongoing clinical monitoring of FDA-cleared DTx.

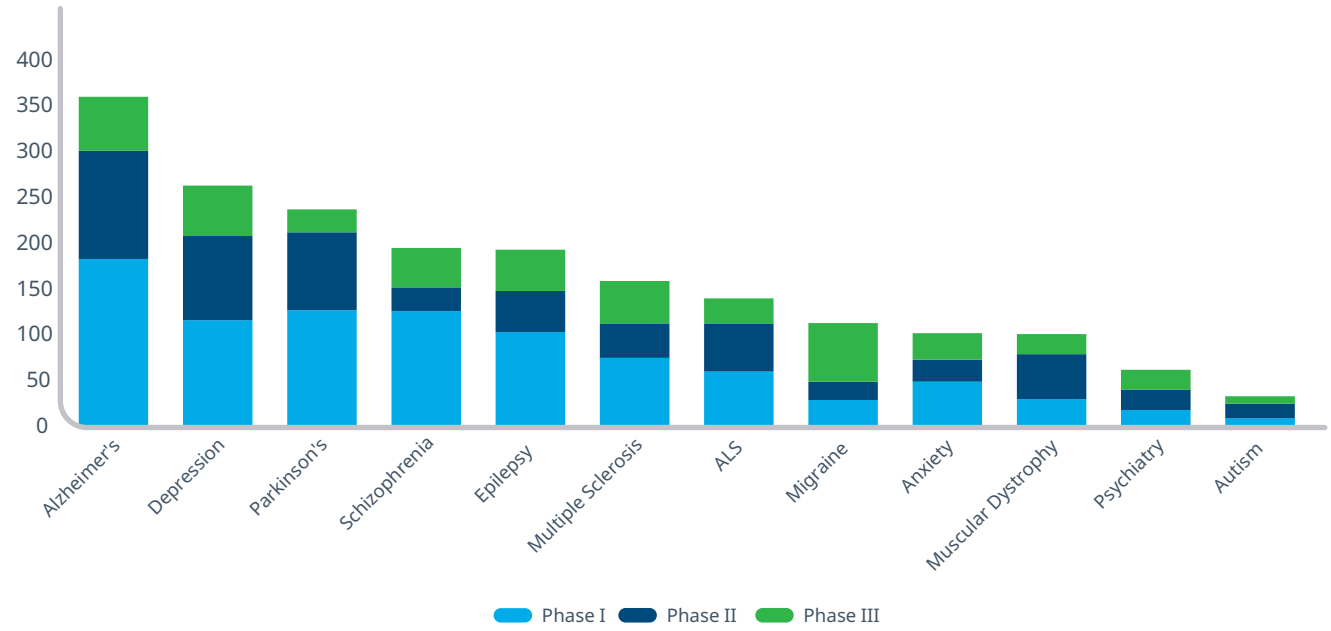
Meanwhile in Europe, national frameworks to regulate and fund DTx are advancing. Germany's DiGA programme became the first in Europe to offer full reimbursement for digital health applications. According to the DiGA-Report 2024 (published April 2025), by December 31, 2024, nearly 870,000 activation codes had been redeemed, with mental health apps leading by approvals.[29] Several other European countries, such as France, Belgium or Austria have followed suit or are piloting their own reimbursement models. These evolving policies aim to bridge the gap between innovation and patient access, accelerating integration of digital therapeutics into mainstream care pathways.

Innovation momentum and the competitive landscape in CNS

In 2024, 605 clinical trials were started with focus on CNS, representing 11% of total trial starts across the industry, the same share as in 2020. This puts CNS in third place in the ranking of therapy areas by clinical trial activity, behind oncology and immunology.

Over the past five years, Alzheimer's, depression and Parkinson's each saw over 200 clinical trial starts as the top 3 CNS indications, while schizophrenia, epilepsy, MS, ALS, migraine, anxiety and muscular dystrophy complete the top 10 CNS indications, with over 100 clinical trial starts each (see Figure 4).

Figure 4: CNS clinical trial starts by indication, 2020-2024



Source: Citeline Trialtrove; Global Trends in R&D: Overview through 2024. Report by the IQVIA Institute for Human Data Science.

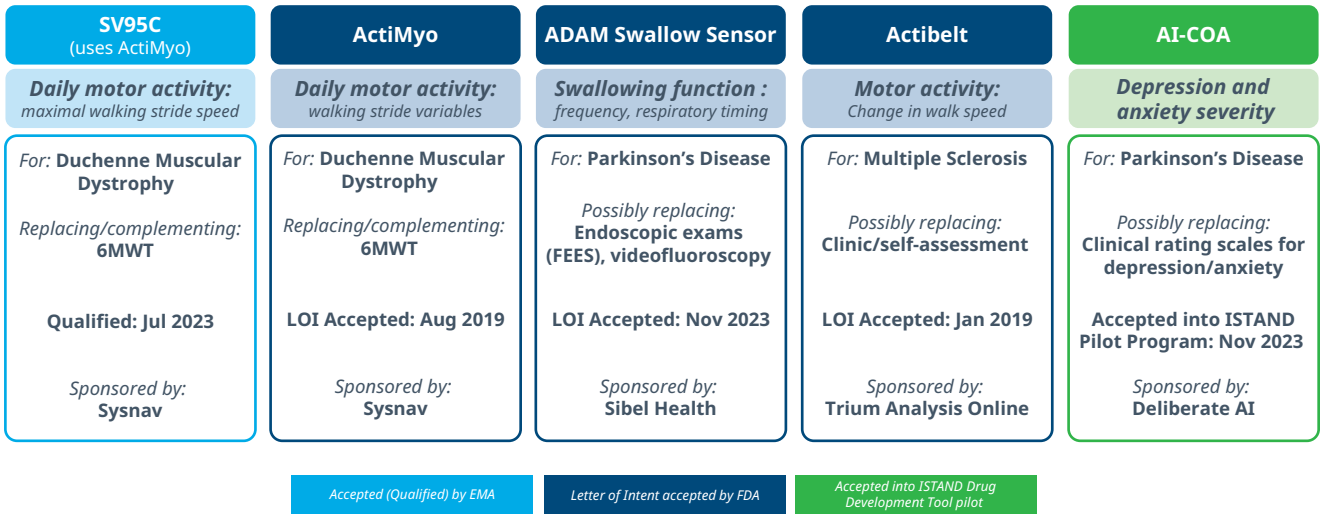
Clinical development of novel CNS therapies is at the forefront of embracing technology-enabled remote, virtual or decentralised (RVD) trials, with CNS accounting for 27% of total RVD trials over the past 5 years, the highest share among all therapy areas.

CNS innovators are also showing increasing willingness to explore digital measures captured via digital health tools, including wearables. As of July 2025, the Digital Medicine Society (DiMe) identified 29 CNS clinical trials in its Library of Digital Endpoints, collectively incorporating 91 digital endpoints, with multiple endpoints per trial.[30] The majority of these, 70%, were secondary endpoints, while 23% were primary endpoints, with exploratory endpoints accounting for the remainder.

Digital endpoints require regulatory "qualification" to be deemed adequate for use in research studies. Several digital measures have been submitted to the FDA and EMA for qualification as digital endpoints validated on wearables and other sensors (see Figure 5).

Figure 5: Digital endpoint submissions to FDA and EMA

CNS-relevant examples



Source: Digital Health Trends 2024: Implications for Research and Patient Care. IQVIA Institute for Human Data Science, December 2024.

Stride Velocity 95thCentile (SV95C) was the first-ever fully digital endpoint to be qualified in July 2023 by the EMA for use in studies of Duchenne Muscular Dystrophy.[31] It also became the first to be permitted as a primary endpoint, to be used for regulatory decision making and in pivotal trials.

As a sensor-based clinical outcomes assessment, SV95C allows continuous monitoring over relatively long periods in a home-setting, making it less sensitive to the timing of the assessment (e.g., day and time of test) while relying less on patient motivation or subjective assessment compared with established tests. Furthermore, the measure was found to be highly correlated to the 6-minute walk test (6MWT), the gold standard endpoint, but proved to be more sensitive to change and was considered more representative of a Duchenne Muscular Dystrophy patient's real ambulatory capability.

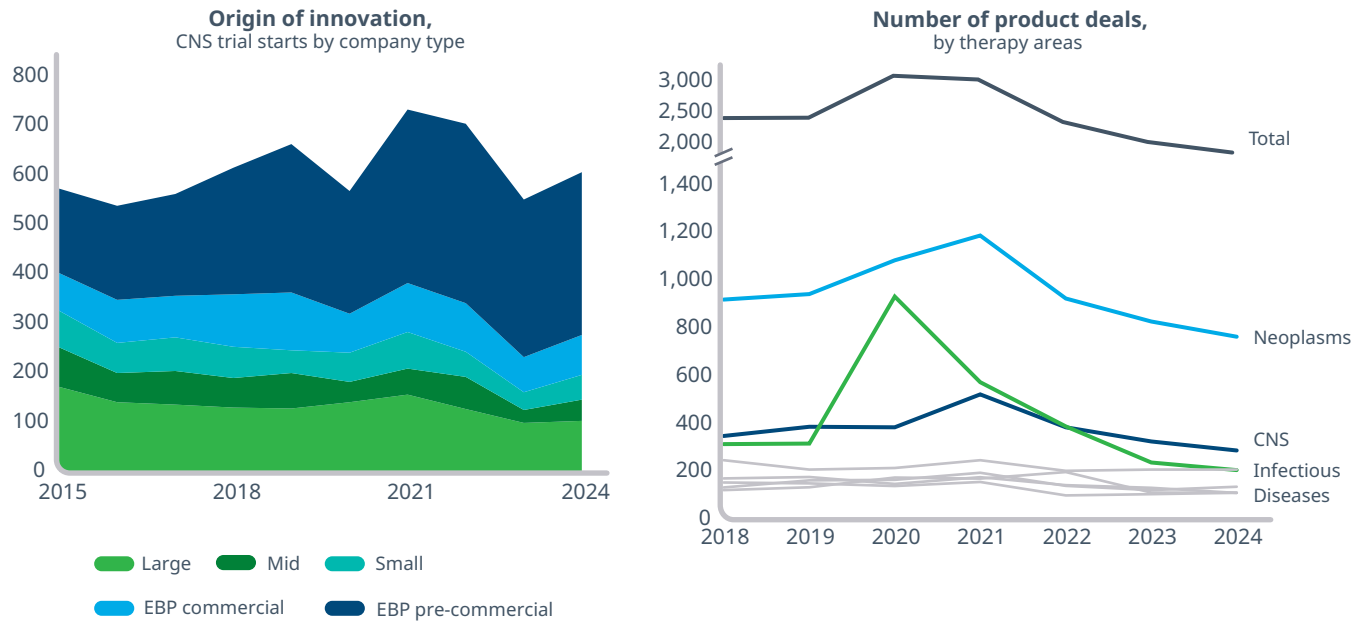
THE COMPETITIVE LANDSCAPE IN CNS

Emerging biopharma companies (EBPs)* dominate CNS innovation. Many of these companies are developing cutting-edge therapeutic approaches, e.g., Neurona Therapeutics exploring pluripotent stem cell-derived therapy to replace dysfunctional neurons in drug-resistant epilepsy for durable reduction in seizures;[32] or Kyverna deploying CAR T-cell therapies for deep B cell depletion to achieve a durable, treatment-free remission in neuroinflammatory conditions such as MS or Myasthenia Gravis.[33]

Over the past 5 years, EBPs expanded their share of all CNS trial starts from 58% to 68% in 2024, of which pre-commercial EBPs account for 55% and commercial-stage EBPs for 13%. Meanwhile, established pharma companies started 32% of all CNS trials in 2024, which breaks down into 17% by big pharma and 15% for small-to-mid size companies (see Figure 6).

*Emerging Biopharma Companies (EBPs) — defined as those with less than an estimated $200Mn in R&D spend per year, including those 'pre-commercial' companies with no revenue as well as smaller emerging companies with up to $500Mn per year in annual revenue. Large and-mid-sized companies — those with more than $10Bn and more than $5Bn, respectively, in global revenue.

Figure 6: Emerging biopharma companies lead as CNS innovators



Source: Citeline Trialtrove; IQVIA Institute, Jan 2025; Global Trends in R&D report 2025; IQVIA PharmaDeals Jul 2025

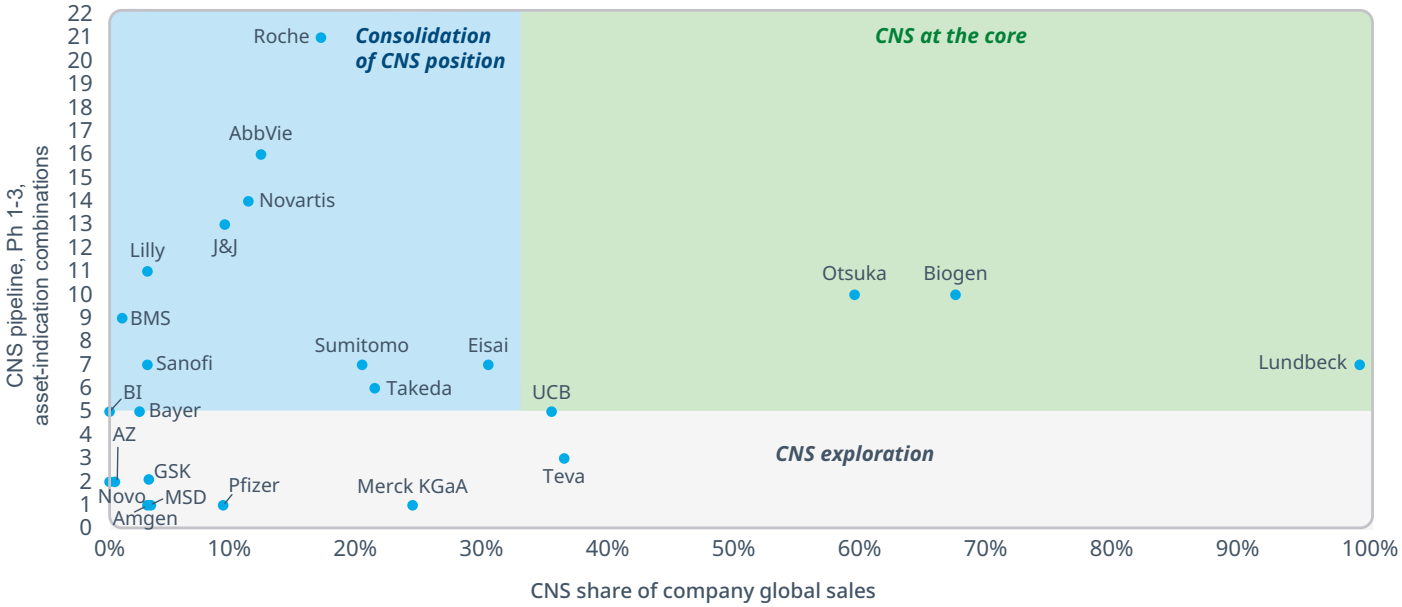
As major originators of CNS innovation, EBPs make attractive targets for partnering, licensing and acquisitions, which is reflected in high levels of deal activity in CNS.

Since 2018, CNS has consistently accounted for 15-16% of all product-focussed transactions each year, except for 2020 when the start of the COVID pandemic elevated infectious diseases as a deal-making priority. In 2023, CNS regained its pre-pandemic #2 spot in the therapy area ranking by absolute transaction volume, behind only oncology (see Figure 6).

Notable CNS deal examples include J&J's $14.6 billion acquisition of Intra-Cellular Therapies, still the largest pharma M&A deal of the year as of August 2025, adding Caplyta to J&J's neuroscience portfolio, an in-line brand which is approved for schizophrenia and as the first and only treatment for depressive episodes associated with bipolar I or II disorder[34]; Lilly licensing Sangamo Therapeutics' neurotropic adeno-associated virus capsid technology to develop a gene therapy for CNS diseases, in a deal worth up to $1.4 billion[35]; AbbVie entering the Alzheimer's arena with its $1.4 billion acquisition of Aliada Therapeutics to gain access to lead asset, ALIA-1758, an antibody targeting amyloid plaques[36]; while some of the largest transactions in previous years focused on CNS, e.g., the $12.7 billion acquisition of Karuna by BMS[37] and the $8.7 billion acquisition of Cerevel Therapeutics by AbbVie,[38] both centred on schizophrenia assets KarXT, now marketed as Cobenfy, and emraclidine, respectively.

The competitive field of mid-size and larger pharma companies with an active therapeutic focus on CNS divides into three archetypes of different strategic intent (see Figure 7):

Figure 7: Emerging competitive CNS landscape



Source: IQVIA EMEA Thought Leadership; IQVIA Analytics Link; IQVIA MIDAS MAT Q1 2025.

CNS at the core: Companies like Lundbeck, Biogen or Otsuka not only have a strong legacy in neurology and mental health, with a significant or dominant share of their revenue generated in CNS markets, these players also continue to invest in a CNS pipeline to secure the future of their franchises. For example, Biogen has a strong neurology-focused pipeline comprising 10 projects (asset-indication combinations), while CNS pure-player Lundbeck is exploring different therapeutic approaches, e.g., neuropeptide signalling, neuronal biology, protein aggregation, folding and clearance, and neuroinflammation, with 7 assets across a range of CNS indications.

Consolidation of CNS position: Companies like Roche, AbbVie, Novartis, J&J and Lilly recognise the promising long-term potential of CNS and are intensifying their commitment by investing into extensive CNS pipelines, with the goal to establish themselves as leading CNS players. For example, Roche has built an industry-leading CNS pipeline of 21 projects with focus on neurodegeneration and rare neurological diseases; followed by AbbVie with a 16-project strong CNS pipeline across a range of mental health, neurodegeneration and rare neurological diseases.

CNS exploration: This segment is represented by a diverse group of companies comprising some legacy players and newcomers to this therapy area that take, or retain, an exploratory stake in CNS. They typically hedge their CNS bets with a light pipeline, sometimes consisting of a single asset. Notable examples include Boehringer Ingelheim with a pipeline focused on mental health and comprising a combination of pharmacotherapeutics and DTx; Bayer exploring the potential of cell- and gene therapies in neurology, with rare diseases a particular focus; Novo Nordisk studying the potentially anti-neuroinflammatory properties of GLP-1 receptor agonist semaglutide in the EVOKE and EVOKE+ trials against Alzheimer's and a cell therapy in Parkinson's; or GSK investigating Alector-partnered, sortilin receptor-targeting antibodies latozinemab and AL101 in frontotemporal dementia and Alzheimer's, respectively.

As we discussed earlier, many of these mid-size and larger pharma companies look to external sources of innovation to advance their CNS ambitions.

Deep dive: CNS indication highlights

In this section we will elaborate in more detail on two disease areas — Alzheimer's disease and mental health — to illustrate the promise of cutting-edge CNS innovation.

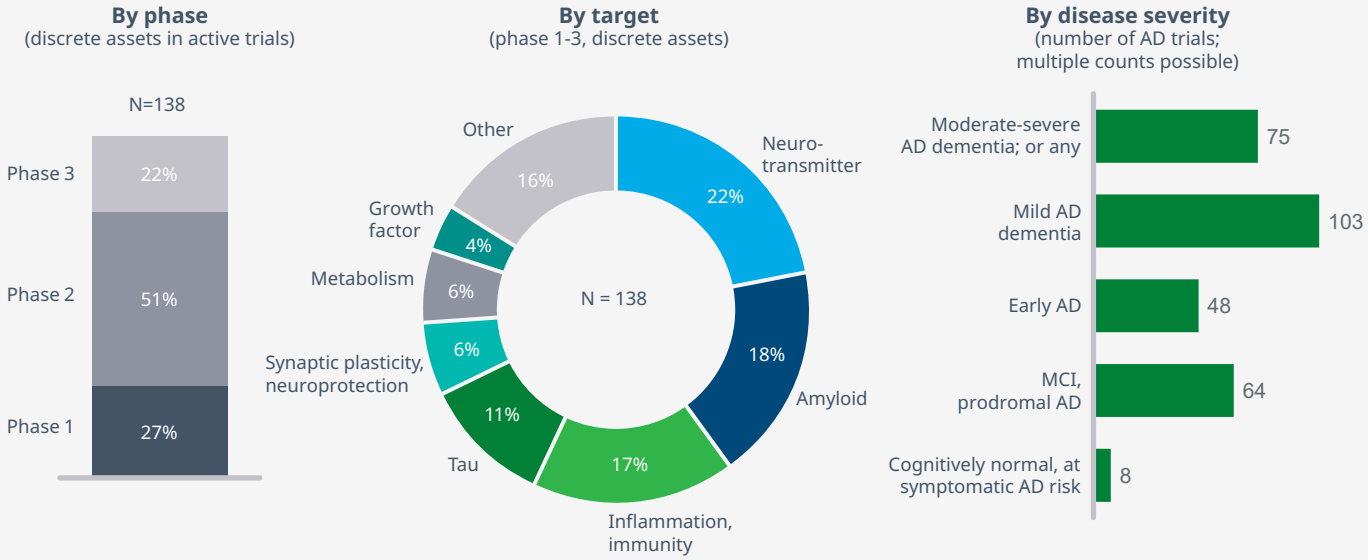
I. Alzheimer's disease

INNOVATION LANDSCAPE

Alzheimer's continues to be a major focus of innovation activity and accounted for 361 clinical trial starts over the past 5 years, the highest number of all CNS indications.

The current Alzheimer's pipeline comprises 138 discrete, clinical-stage assets, of which 27% are in phase 1, 51% in phase 2 and 22% in phase 3. These candidates are investigated across the full spectrum of disease severity, with the largest number of clinical trials focused on mild Alzheimer's dementia, followed by moderate-to-severe Alzheimer's dementia and mild cognitive impairment or prodromal disease (see Figure 8).[39]

Figure 8: Clinical-stage Alzheimer's pipeline



Note: Assets counted at highest phase; no double counting if assets are in multiple trials or combinations; AD: Alzheimer's disease, MCI: mild cognitive impairment
Source: Jeffrey L. Cummings et al., Alzheimer's disease drug development pipeline: 2025; https://doi.org/10.1002/trc2.70098

The amyloid hypothesis — which identifies the abnormal accumulation of amyloid-beta (Aβ) protein in the brain as a primary driver of Alzheimer's — has been guiding much of recent innovation efforts which culminated in the approval of 3 amyloid-targeting Alzheimer's therapies, one of which, Aduhelm, was later withdrawn from the market.

However, the Alzheimer's development pipeline spans a diverse range of targets, including neurotransmitters (22%), amyloid (18%), inflammation/immunity (17%), tau (11%), synaptic plasticity/neuroprotection (6%), metabolism (6%) and growth factors (4%), as the most explored approaches.

Noteworthy examples of other disease-modifying approaches beyond amyloid include phase 2 assets posdinemab (J&J), BIIB080 (Biogen), bepranemab (UCB), or Eisai's phase 3 candidate E2814 which target the tau pathology; inflammation-focused AB Science's phase 3 candidate, tyrosine kinase inhibitor masitinib,[40] Tiziana Life Sciences' phase 2 asset, intranasal-administered anti-CD3 foralumab,[41] and Novo Nordisk's GLP-1 receptor agonist semaglutide;[42] while synaptic plasticity and neuroprotection are in focus of Cognition Therapeutics' phase 2 candidate zervimesine, a neuroprotective agent shielding neurons and synapses from Aβ oligomer binding;[43] or Spinogenix's synaptic-regenerative phase 2 asset SPG302.[44]

"Crossing the blood brain barrier represents a major challenge for directly targeting therapeutics at the central nervous system."

Crossing the blood brain barrier (BBB) represents a major challenge for directly targeting therapeutics at the central nervous system, especially monoclonal antibodies.

Several innovators are developing novel BBB-crossing technologies to overcome this issue, for example, Aliada Therapeutics, acquired by AbbVie for $1.4Bn in December 2024, utilises transferrin to deliver its phase 1, anti-pyroglutamate amyloid beta antibody ALIA-1758 to the brain;[45] or Roche using an anti-transferrin receptor 'brain shuttle' conjugated to its anti-amyloid antibody trontinemab, which demonstrated rapid, deep clearance of amyloid plaques in its phase 1 Brainshuttle AD trial in patients with mild to moderate Alzheimer's disease.[46]

ON-MARKET THERAPIES: REGULATORY AND COMMERCIAL REALITIES

The two disease-modifying therapies currently marketed for the treatment of Alzheimer's experienced very different regulatory approaches by the FDA vs. the EMA.

In January 2023, the FDA granted accelerated approval for Leqembi (lecanemab), followed by full approval in July 2023 for patients with Alzheimer's and mild cognitive impairment or mild dementia. A year later, in July 2024, the FDA approved Kisunla (donanemab) for adults with early symptomatic Alzheimer's disease, including mild cognitive impairment or the mild dementia stage of Alzheimer's disease.

In contrast, the EMA adopted a more cautious approach. Safety concerns about amyloid-related imaging abnormalities (ARIA) initially prompted the EMA to refuse marketing authorisation for both Leqembi and Kisunla. In a reversal of its negative earlier opinion, the EMA later approved both products, Leqembi in November 2024 and recommending marketing authorisation for Kisunla in July 2025, but in a restricted population: patients with only one or no copy of the ApoE4 gene.

While Leqembi and Kisunla are both anti-amyloid monoclonal antibodies, their respective manufacturers, Biogen/Eisai and Lilly, have been focussing on differentiating their profiles:

- In January 2025, the FDA approved monthly maintenance dosing for Leqembi, following bi-weekly infusions during the 18-month induction period. In August 2025, the FDA approved a once-weekly subcutaneous maintenance dose of Leqembi IQLIK, allowing at-home administration following the initial 18-month biweekly intravenous treatment.

- Kisunla offers once-monthly dosing from the start, with a 30-minute infusion duration vs. Leqembi's 1 hour. Furthermore, Kisunla has the potential for finite dosing — with treatment discontinuation once amyloid plaques have been cleared. Recent data from the TRAILBLAZER-ALZ 2 Long-Term Extension showed that in patients who stopped Kisunla re-accumulation of amyloid plaque remained slow at up to 2.5 years of follow up.[47]

- In July 2025, the FDA approved a modified dosing schedule for Kisunla that significantly reduces the risk of brain swelling while preserving the drug's efficacy. Data from the TRAILBLAZER-ALZ 6 phase 3b trial showed more gradual dose escalation led to a 41% reduction in amyloid-related imaging abnormalities with oedema (ARIA-E) at 24 weeks, and a 35% reduction at one year, vs. the original dosing schedule.[48]
- Both Leqembi and Kisunla are aiming to expand into the earlier disease stage of preclinical Alzheimer's with their respective AHEAD 3-45 and TRAILBLAZER-ALZ 3 clinical trials.

To date, uptake of both products has been slow. For Q2/2025, Biogen/Eisai reported $160 million global sales for Leqembi after 2.5 years since its initial FDA approval, whereas Lilly reported $49 million quarterly global sales for Kisunla after 1 year on the market.

Apart from navigating reimbursement, therapy adoption has been hampered by a number of practical barriers:

- **Patient eligibility** must be determined via cognitive assessment, along with a PET scan, or MRI, which are expensive and require specialist facilities, or highly invasive cerebrospinal fluid (CSF) analysis to confirm the presence of beta-amyloid plaques. In addition, testing for APOE4 presence will be needed to establish patient eligibility in Europe.
- **Infusion capacity** has proven a bottleneck causing delays for patients.
- **Data collection** for a CMS maintained patient registry when prescribing the two therapies and ongoing monitoring for ARIA throughout treatment add to the administrative burden of providers.

THE FUTURE OF DIAGNOSING ALZHEIMER'S: BLOOD-BASED BIOMARKER TESTS

Minimally invasive testing based on accurate, blood-based biomarkers has the potential to transform the diagnosis of Alzheimer's, eventually enabling widespread population screening in a primary care setting and early disease detection at the preclinical or prodromal stage.

In May 2025, the FDA approved the first in vitro diagnostic device to test blood in aid of diagnosing Alzheimer's disease.[49] Fujireio's Lumipulse G pTau217/ß-Amyloid 1-42 Plasma Ratio test is for the early detection of amyloid plaques associated with Alzheimer's in adult patients, aged 55 years and older, exhibiting signs and symptoms of the disease.

Further blood-based biomarker tests are in development, several of which received FDA breakthrough device designation, e.g.,

- Roche's Elecsys Amyloid Plasma Panel, which demonstrated high negative predictive value (NPV) of 96.2% in a recent clinical trial,[50]
- Roche's Elecsys pTau217 plasma biomarker essay, developed in collaboration with Lilly,[51]
- Spear bio's pTau 217 blood test,[52]
- Quanterix's Simoa ALZpath p-Tau 217 assay.[53]

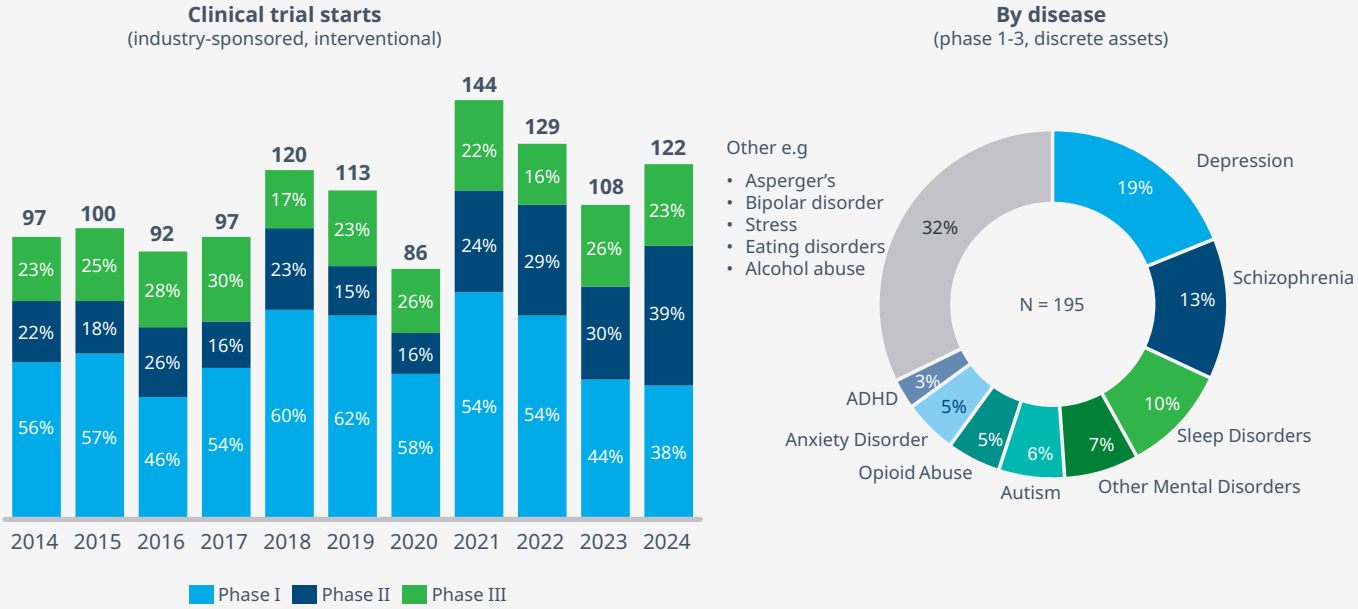
To realise the promise of innovation for Alzheimer's patients, their families and carers, different disciplines, and stakeholders, must converge.

II. Mental health

INNOVATION LANDSCAPE

Mental health clinical trial activity declined during the onset of COVID-19 in 2020 but rebounded to an average of 126 trial starts per year — about 20 more than the 2014–19 average (Figure 9, left panel). Mental health trials accounted for approximately 20% of all CNS trial starts in 2024, a proportion that has remained stable over recent years and is in line with the long-term average within CNS research.

Figure 9: Mental health clinical trial activity and pipeline



Note: No double counting if assets are in multiple trials or combinations; ADHD: Attention Deficit Hyperactivity Disorder.
Source: Citeline Trialtrove; IQVIA Pipeline Link; IQVIA EMEA Thought Leadership.

The current mental health pipeline comprises 195 clinical-stage assets across phases 1 to 3 (Figure 9, right panel). Depression remains the most active area, accounting for 19% of these candidates, followed by schizophrenia (13%) and sleep disorders (10%). Approximately one in five assets are exploring novel targets, reflecting a gradual shift away from legacy mechanisms. Despite dopamine continuing to dominate as the most frequently pursued target, the growing share of first-in-class approaches indicates meaningful diversification in the underlying biology being pursued.

Innovation in mental health is experiencing a notable shift, moving beyond monoaminergic antidepressants and anxiolytics toward novel mechanisms and modalities that aim to deliver faster, more durable, and more personalised outcomes. A new generation of therapies is targeting pathways such as synaptic plasticity, neuroinflammation, hormonal and metabolic signalling, and sleep regulation.

The approval of KarXT (xanomeline-trospium) by BMS for schizophrenia marked the first new non-dopaminergic mechanism for treating psychosis in over 30 years. This milestone exemplifies how first-in-class therapies can break through after years of stalled innovation and clinical trial setbacks in mental health. They demonstrate that despite the inherent challenges of psychiatric research, such as subjective endpoints, high placebo response rates, and heterogeneous patient populations, it is now possible to bring forward differentiated, mechanistically novel treatments that address previously untapped biological pathways.

Both early-stage biotech and big pharma are re-engaging in mental health R&D with renewed confidence, drawn by these proof points and the potential for platform approaches to cut across multiple psychiatric and neurological conditions.

Depressive disorders remain a critical focus of psychiatric innovation, with several novel therapeutic strategies emerging in recent years. The approval of esketamine (Spravato) marked a turning point, offering rapid antidepressant effects through NMDA receptor antagonism and receiving approval for both Major Depressive Disorder (MDD) and Treatment-Resistant Depression (TRD). More broadly, there is growing interest in fast-acting, non-traditional treatments for depression, including psychedelic therapies, which were discussed in greater detail earlier in this paper.

Among other promising avenues, pramipexole, a dopamine agonist approved for Parkinson's disease, has demonstrated potential neuroprotective and mood-regulating properties. In a study led by the University of Oxford, pramipexole was found to be more effective than placebo in reducing symptoms of TRD; however, head-to-head trials comparing it to current standard treatments are still needed. Kappa opioid receptor antagonists such as navacaprant, have also shown promise. Although it did not meet its primary endpoint in a recent trial, navacaprant demonstrated significant improvements in depressive symptoms among patients with moderate-to-severe MDD. Its favourable safety profile further supports continued investigation.[55]

Additionally, repurposed anti-inflammatory drugs such as celecoxib and minocycline are being explored as adjunctive therapies in depression, based on evidence showing how long-term inflammation in the body can interfere with brain chemistry and mood regulation.[56] However, despite some promising clinical findings, this approach faces challenges due to safety concerns and the need for better patient stratification to identify those most likely to benefit.

The recent breakthrough of KarXT sent waves of enthusiasm through the industry by achieving antipsychotic efficacy without the usual side effects of dopamine-blocking drugs including sedation or weight gain. Muscarinic-targeted treatments have become an appealing therapeutic approach. In 2024, AbbVie completed the acquisition of Cereval for $8.7bn to strengthen its neuroscience pipeline and had high hopes for muscarinic receptor modulator. However,

the asset failed to meet its endpoint in a phase 2 study later the same year.[57] TAAR1 agonism was another promising approach that ultimalely failed in the clinics. Another promising strategy involves modulating glutamate release through sodium channels. Newron Pharmaceuticals announced the approval for a pivotal phase 3 study of evenamide as an add-on therapy in treatment-resistant schizophrenia.[58]

Sleep disorders, long underrepresented in Central Nervous System (CNS) drug development compared to conditions like depression or schizophrenia, are now gaining recognition as a primary therapeutic target — rather than merely a comorbidity. At the forefront of this shift are orexin-targeted therapies, which for the first time allow clinicians to treat the underlying orexin deficiency directly. Takeda's oral orexin receptor agonist, TAK-861, reported positive phase 3 results in narcolepsy type 1, marking an inflection point after years of setbacks in orexin-focused drug development and carrying an anticipated peak sales potential of $3 billion[59]. Alkermes moreover has also announced encouraging results for its own orexin-based candidate.[60]

Insomnia has a high unmet need and is not only a nighttime issue but affects both physical and mental health 24 hours a day. Key advances were the approval of dual orexin receptor antagonists (DORAs), which target both orexin-1 and orexin-2 receptors. While effective, dual blockade can lead to next-day sedation in some patients. Selective orexin-2 receptor antagonists (SORAs), such as seltorexant, aim to deliver similar sleep benefits with a cleaner side-effect profile, as shown in patients with MDD and insomnia.[61] Excitingly, self-guided Cognitive Behavioural Therapy for Insomnia (CBT-I) apps bring sleep health into the broader healthcare mainstream. CBT-I alone, or combined with medication, can support adherence and improve patient outcomes. Digital tools, including CBT-I apps or chatbots, can become the first-line choice for mild cases in a stepwise care model for insomnia.

THE FUTURE OF MENTAL HEALTH

To fully realise the potential of recent advances and address the considerable unmet needs in mental health, coordinated efforts are required across clinical innovation, health system transformation, and equitable access to ensure meaningful improvements in patient outcomes.

PRECISION PSYCHIATRY

Tailoring mental health treatments to a person's biological and genetic profile can improve outcomes, reduce side effects, and minimise trial-and-error prescribing. In clinical trials, this precision approach supports more targeted patient selection using biomarkers such as inflammatory signals or genetic markers, increasing the chances of detecting true treatment effects. To further strengthen trial design, researchers are moving beyond subjective rating scales and exploring objective endpoints like digital and physiological measures. While these tools still require validation, they hold promise for reducing placebo response rates and advancing more personalised, effective treatments in psychiatry.

PARTNERING FOR IMPACT

Pharmaceutical companies must become a partner to the especially resource-constrained mental healthcare system. Patient support programmes address a patient's overall wellbeing and guide them and their caregivers throughout their treatment journey. Innovative pricing and subsidy models could open doors for those who would otherwise struggle to afford care. Moreover, while public attitudes around mental health are improving, pharma can further advance awareness by collaborating directly with patient advocacy groups and engaging more actively with communities on social media.

INTEGRATED PRIMARY CARE MODEL

Digital therapeutics, chatbots, in-person therapy, and pharmacotherapy work best when they complement one another to meet diverse patient needs. Primary care providers must be trained in identifying mental health conditions early and to deploy evidence-based digital solutions as indicated, so patients are not left waiting to see a specialist.

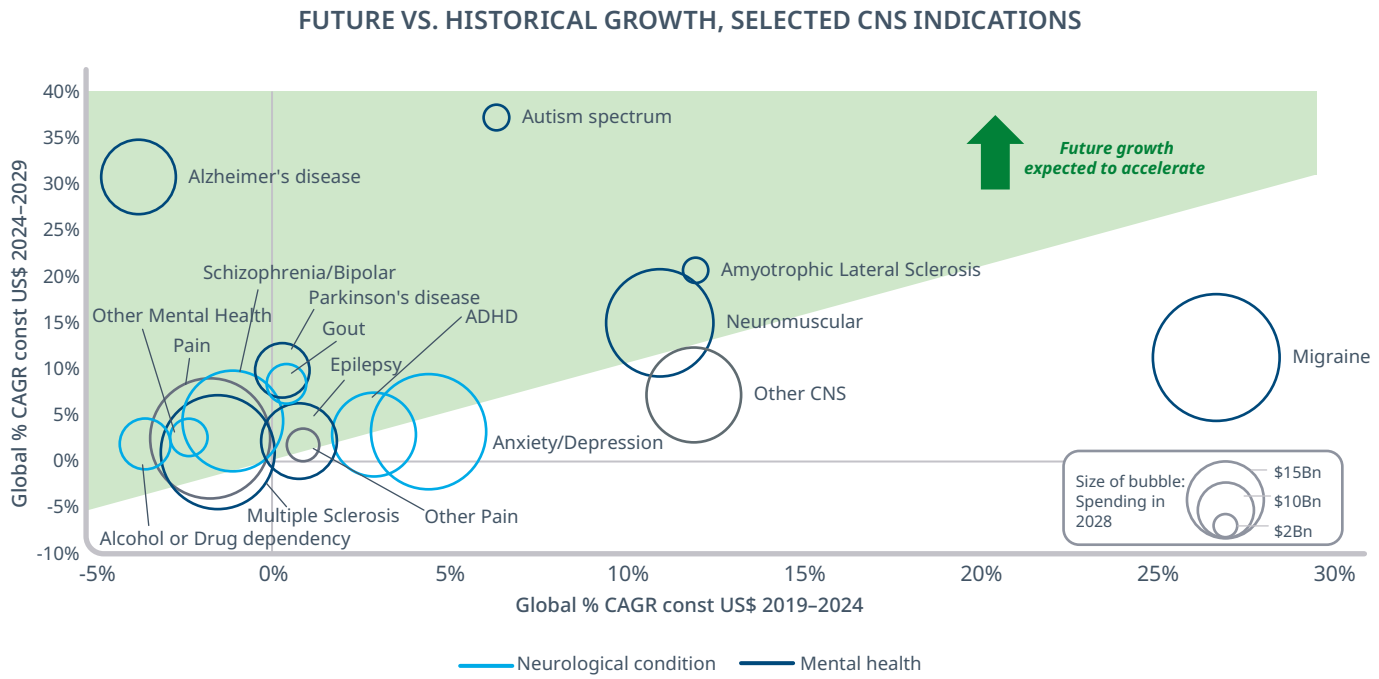
CNS market outlook

In 2024, the global CNS market, including neurological conditions, mental health and pain, was worth $146 billion, at ex-manufacturer prices. This compares to 2024 global market sizes of $250 billion for oncology, $198 billion for immunology and $183 billion for diabetes, making CNS collectively the fourth largest therapy area by global sales.

Over the past 5 years, the CNS market delivered growth of 3.6% CAGR (2019-2024) which we expect to accelerate to 6-8% future CAGR (2024-2029) driven by recently launched innovative therapies and those yet to enter the market in the next 5 years. Accordingly, by 2029, the global CNS market is forecast to reach $195-215 billion.

A closer look beyond these aggregate figures reveals a more nuanced picture, with a range of growth dynamics playing out at indication level, where pockets of high growth potential co-exist with less dynamic, stagnant or even declining CNS market segments (see Figure 10).

Figure 10: Innovation is driving growth acceleration in many CNS indications



Source: IQVIA Forecast Link, May 2025; The Global Use of Medicines 2024: Outlook to 2028. Report by the IQVIA Institute for Human Data Science.

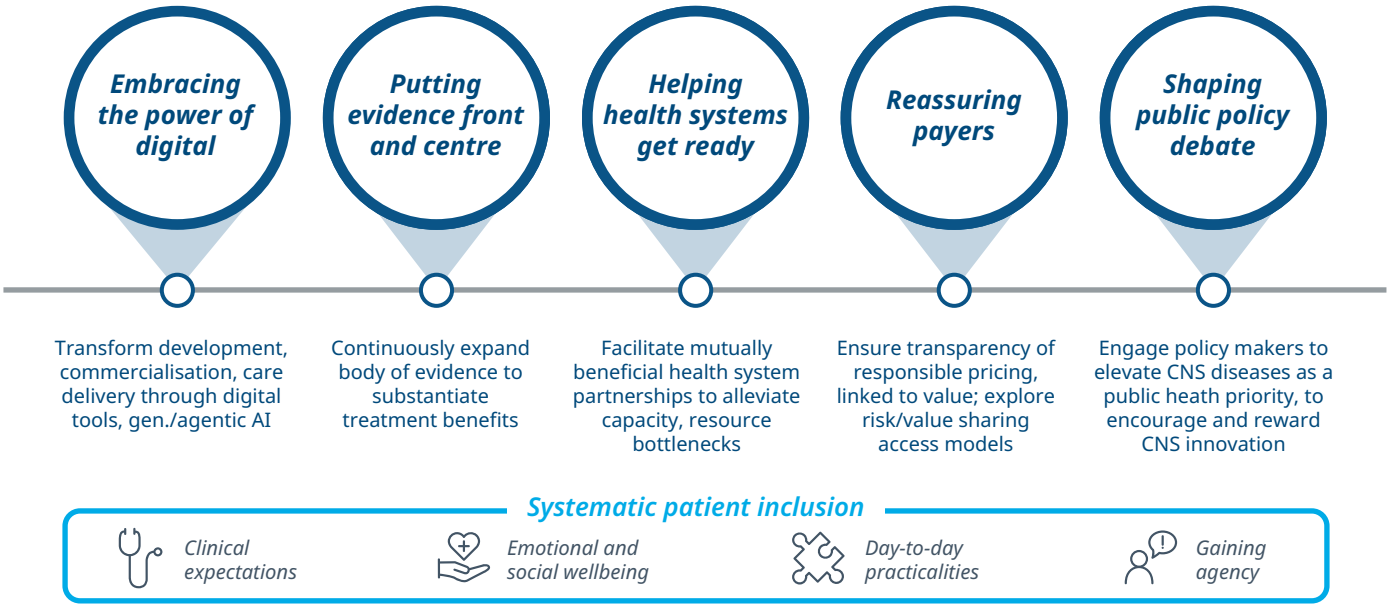
These growth dynamics are a reflection of differences between indications in the complex interplay of several market drivers; for example, long-term epidemiological trends, wide variations in the effectiveness of the respective, existing standard of care and the resulting unmet need, the extent of generics utilisation weighing down a market segment, and the differentiation and breadth of novel therapies: Are they addressing unmet need in specific patient sub-segments, as a narrow first-line treatment, or possibly in later line? Or will they fundamentally transform the existing treatment paradigm, by introducing a breakthrough, disease-modifying therapy, to set a new standard of care for all?

To define their asset and commercialisation strategies, CNS innovators will need a deep and granular understanding of these dynamics and the underlying drivers that determine how the commercial opportunity manifests itself and what it takes to seize it.

How to succeed as a CNS innovator

In our previous publication from 2023, we identified five priorities for the successful development and commercialisation of CNS innovation.[62] Fundamentally, these priorities still hold, but we have updated them to reflect the latest trends in the healthcare environment (see Figure 11).

Figure 11: How to succeed as a CNS innovator



1. **Embracing the power of digital**: Transforming development, commercialisation and care delivery through digital tools continues to be critical. Beyond tremendous gains in efficiency and speed, the rise of generative and agentic AI opens unprecedented opportunities for deeper, real-time insight to inform all stages of a CNS asset's lifecycle; the mass-personalisation in patient and HCP engagement, and optimal care delivery powered by advanced clinical decision support tools.

2. **Putting evidence front and centre**: A lifecycle evidence strategy remains key to optimise asset development and positioning, and to continuously substantiate treatment benefits, especially post-approval in routine practice and in patients' day-to-day life. Harnessing integrated data networks, e.g., IQVIA's Neurodegenerative Diseases (NDD) network for RWE, a pan-European initiative designed to accelerate real-world research in Alzheimer's and Parkinson's disease by integrating clinical expertise, pre-profiled data sources, and site-based solutions, offers faster access to novel types of insights and evidence, contextualised within the relevant local standard of care.

3. **Helping health systems get ready**: Health systems' capacity for adopting innovation is stretched to breaking point as they are pulled in two opposite directions: Simultaneously having to deliver ever more sophisticated, highly specialised therapeutic innovation targeted at small (often rare) disease populations while facing a renaissance of innovation directed at high prevalence conditions, e.g., cardiometabolism. Against this backdrop, CNS innovators must embrace mutually beneficial partnerships with health systems to co-develop solutions that alleviate capacity and resource bottlenecks and streamline care pathways, to facilitate the broad adoption of novel CNS therapies.

4. **Reassuring payers**: CNS innovators must address payer uncertainty around clinical outcomes and budget impact of novel therapies, with clearly defined target populations that are identifiable in real world clinical practice, transparent pricing linked to value and by exploring innovative ways of sharing both risk and value, e.g. flexible pricing strategies or access models that align incentives around shared objectives, e.g., outcomes-based contracts.
5. **Shaping public policy debate**: The surge of novel anti-obesity medications, and a wider cardiometabolic renaissance, dominate the current public health debate. Therefore, it is critical to effectively engage policy makers to ensure CNS diseases do not lose out and are elevated as a public health priority to create an environment that encourages and rewards CNS innovation. Beyond traditional clinical evidence, quantifying the heavy humanistic burden on patients and caregivers, and the huge economic cost of CNS diseases will be crucial for shaping this policy debate.

Faced with formidable challenges, being a CNS innovator is not for the faint hearted, with the stakes remaining uncomfortably high. However, as we elaborated in this white paper, there are good reasons to be optimistic about CNS innovation fulfilling its promise.

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