White Paper

Two Steps Forward, One Step Back: The Long Road to Success in CNS

Why CNS innovators should feel emboldened to stay the course

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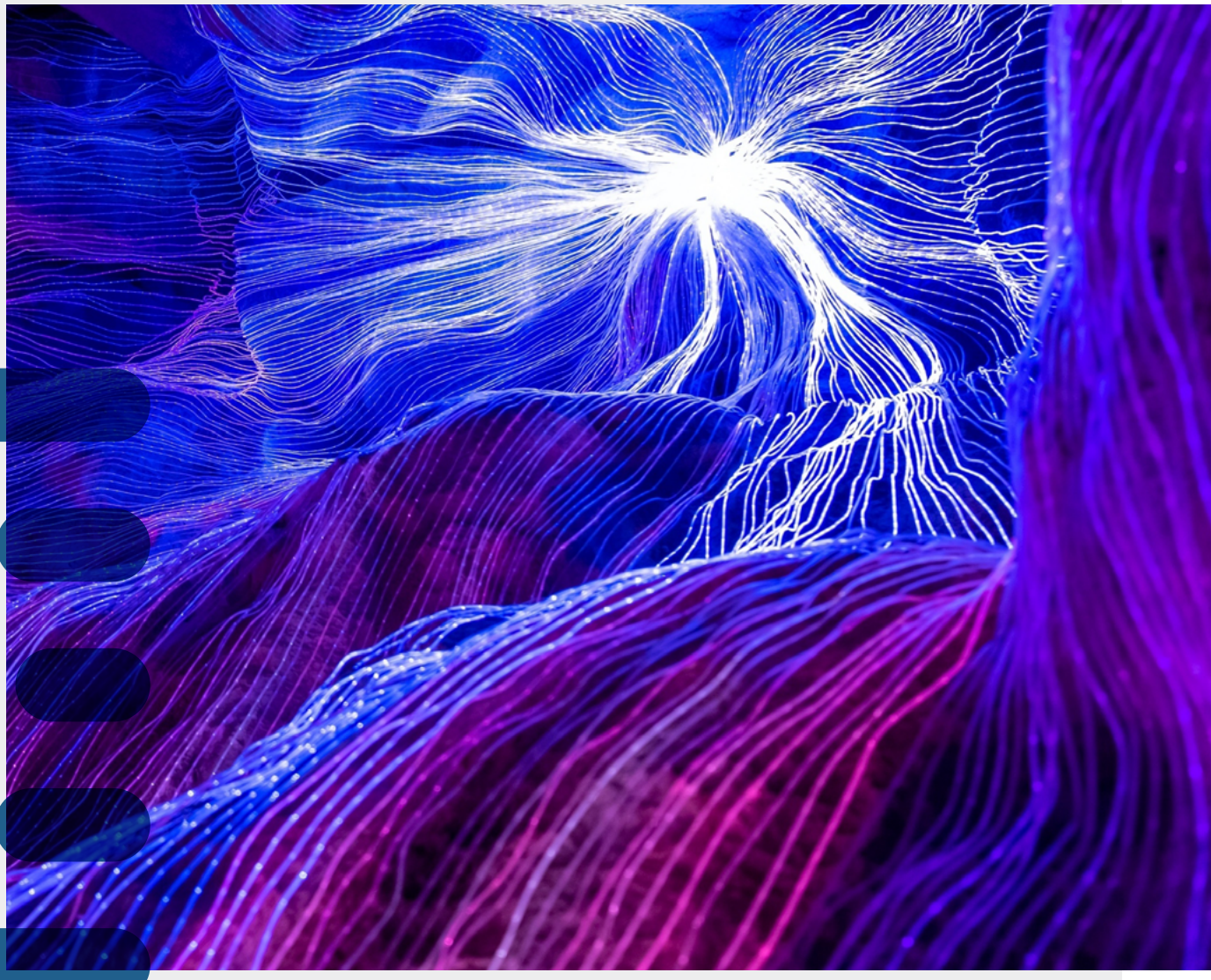

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Introduction

The development and commercialisation of innovative treatments for central nervous system (CNS) disorders have proved yet again not to be for the faint hearted. While we are seeing encouraging progress, for example, advances in understanding the complex biology of these conditions, the identification of new drug targets or a raft of novel late-stage candidates for treating serious CNS disorders progressing through the development pipeline and entering the market, CNS innovators have suffered numerous, high-profile setbacks, including Aduhelm as one of the most prominent in recent history.[1]

Nevertheless, despite some daunting and very real near-term challenges, we believe there are good reasons to be optimistic for CNS innovation to fulfil its promise in the medium term.

As we highlighted in our previous publication on the outlook for CNS in 2021[2], the fundamentals of CNS innovation are improving dramatically, with many of the catalysts that we identified then maturing, e.g., digital biomarkers, AI tools, novel trial designs or diagnostics. At the same time, unmet need and the burden of illness in CNS continue to be high, while the COVID-19 pandemic has aggravated the situation. For example, it exacerbated mental health challenges and added numerous neurological and mental health manifestations of post-/long-COVID, but it has also helped raise general awareness of the debilitating impact CNS conditions have.

In this white paper, we will revisit the enablers of CNS breakthrough innovation, provide a latest outlook on the CNS competitive landscape and market opportunity, and take a deep dive into four 'hot areas' — Alzheimer's, Parkinson's, psychedelics and digital therapeutics — as exemplars of the promise of cutting-edge CNS innovation.

Despite some daunting and very real near-term challenges, there are good reasons to be optimistic for CNS innovation to fulfill its promise in the medium term.

256m DALYs*

Global disease burden for CNS, 2019

$169 billion

Global CNS market size forecast, 2027

* Disability-Adjusted Life Years (DALYs)

A bumpy ride for CNS innovators: Opportunity, barriers and improving fundamentals

The global burden of illness caused by mental health and neurological disorders is significant and continues to grow. For 2019, the WHO[3] estimated the combined long-term impact on health-related quality of life of non-communicable mental health and neurological conditions as 256 million disability-adjusted life years (DALYs) globally, an increase of 16% since 2010. For comparison, this exceeds the 2019 estimate of 242 million DALYs globally for all malignant neoplasms.

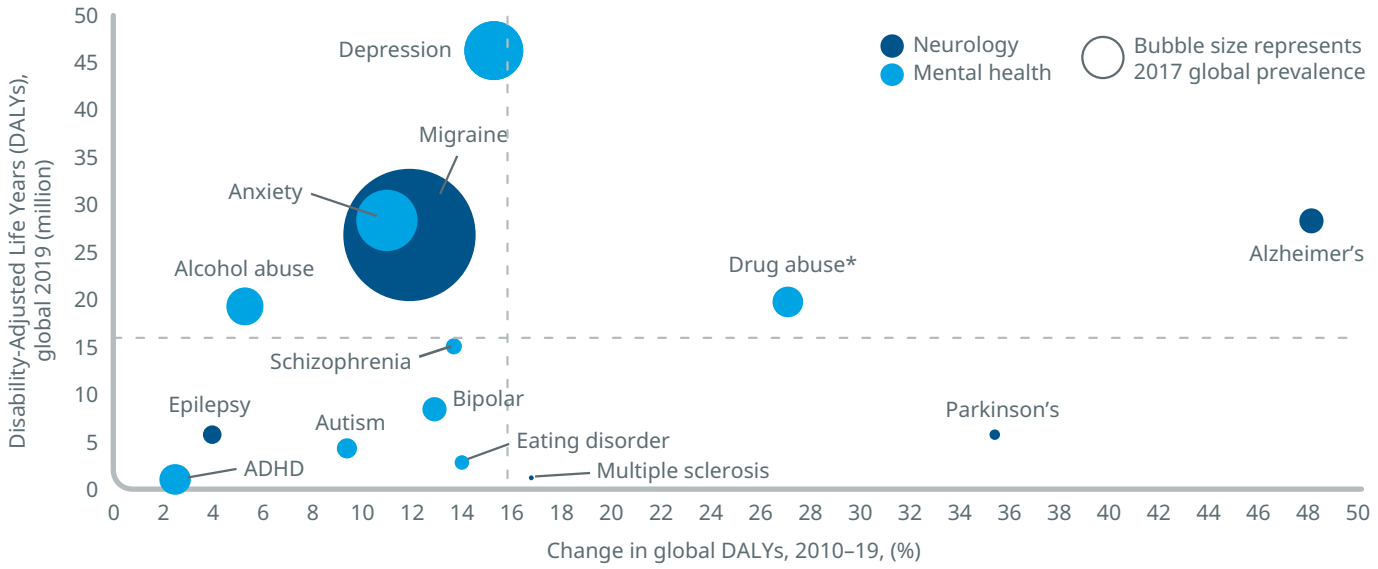
Highly prevalent conditions such as migraine, depression and anxiety have a huge impact on people's quality of life and accounted for over 102 million DALYs globally in 2019, while neurodegenerative disorders Alzheimer's and Parkinson's are driving the future global disease burden with increases in DALYs of 48% and 35% between 2010 and 2019, respectively (see Figure 1).[3,4]

Unmet need continues to be high, because despite intensifying innovation activity many debilitating CNS conditions still lack disease-modifying treatments (DMT), e.g., Parkinson's, or rare neurological diseases. In Alzheimer's, the recently approved anti-amyloid DMT Leqembi has yet to show its real-world benefits for patients' quality of life. Poorly controlled patient populations still exist even in CNS conditions with well-established pharmacotherapy options, e.g., treatment-resistant depression or epilepsy.

The COVID-19 pandemic has further contributed to the global burden of CNS conditions. Lockdowns and social distancing, especially during the early phase of the pandemic in 2020, adversely impacted population mental health.[5] Furthermore, increasing evidence suggests a significant proportion of 20-30% of patients experience a range of post-COVID conditions persisting or even presenting months after the initial COVID-19 infection, of which neuropsychiatric conditions account for a third.[6,7] Depression, anxiety, sleep disorders, fatigue and cognitive deficits are among the most commonly reported manifestations.[8]

Despite significant unmet need in CNS, addressing it through innovation has proven challenging due to a combination of scientific, practical and financial barriers:

Figure 1: The global 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 2017; IQVIA EMEA Thought Leadership analysis.

1. Our understanding of the underlying, complex biology of many CNS conditions is still less advanced than in other therapy areas, e.g., oncology or immunology. The continuing discussion about the validity of the amyloid hypothesis in Alzheimer's is a case in point. As a consequence, over the past 5 years composite success rates for CNS assets spanning phase 1 through regulatory submission declined from 13% to 5-6% in 2022.[9]

2. Sponsors conducting clinical trials in CNS conditions face numerous practical challenges, e.g., identifying and recruiting patients, especially early-stage, asymptomatic ones, or defining and measuring clinically meaningful and objective endpoints.

3. Health systems struggle to accurately diagnose and treat patients in a timely manner for many CNS conditions, e.g., due a lack of diagnostic infrastructure, such as MRI or PET scanners, a shortage of qualified practitioners or limited treatment capacity, e.g., for administering biologics or therapies derived from re-purposed controlled substances.

4. Health systems fail to adequately reward innovation in effective preventatives or treatments for chronic, high prevalence conditions, including many CNS ones. Alzheimer's is a case in point. As the example of Leqembi shows, many barriers related to funding, expanding access and broader health system readiness must still be overcome to reach a true inflection point in the wider adoption of this novel therapy, even after clinical development and regulatory hurdles have successfully been taken.[10,11]

Numerous CNS innovators have been caught up in those barriers and suffered high-profile setbacks. However, the fundamentals of CNS innovation are changing dramatically for the better and provide reason for optimism.

THE FUNDAMENTALS OF CNS INNOVATION ARE IMPROVING

Many of the catalysts for successful CNS innovation are maturing. For example, an improving understanding of the underlying disease biology is opening up new MoAs, such as non-amyloid targets or vaccines in Alzheimer's; the wider availability of next-generation sequencing (NGS), growing public recognition of the value of genomic databases combined with the emergence of liquid biopsies will support better diagnoses, e.g., using genetic factors to stratify patients by risk of developing neurodegenerative diseases; or enabling precision medicine by understanding patients' likely responsiveness to different treatments.

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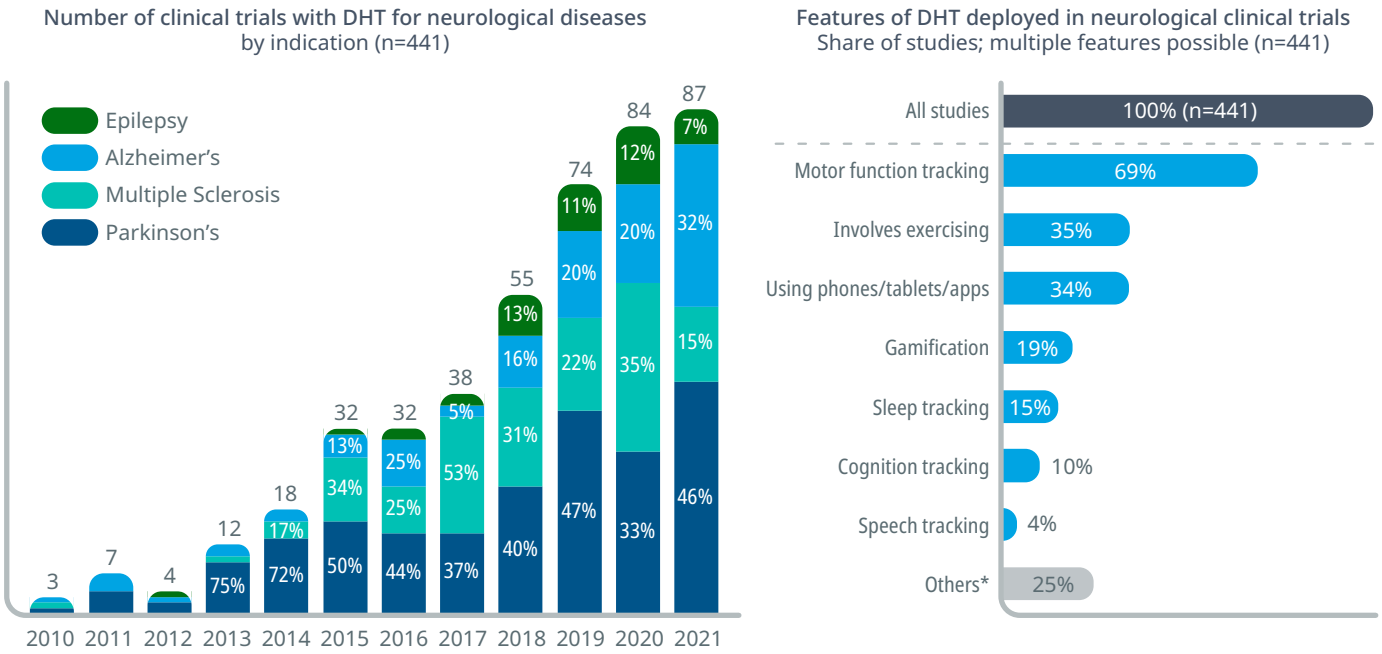
However, it is the area of digital health technologies (DHT) where we have seen the most dramatic developments, with the potential to fundamentally transform the prospects of CNS innovation.

DHT enable the capture of digital biomarkers (dBMs) — quantifiable measures of e.g., physiology, patient behaviour, mood and cognitive function that can inform diagnosis as well as prognosis.[2] Using dBMs, a patient's condition can be monitored continuously in a real-life setting instead of capturing a series of snapshots at regular check-ups. Utilising DHT in clinical trials has been increasing sharply. For example, Masanneck et al. identified a total of 441 clinical trials utilising DHT since 2010 with focus on Alzheimer's, Parkinson's, MS and epilepsy, while the annual number of trials with DHT in these indications has grown at ~36% CAGR between 2010 and 2021. Motor tracking is amongst the well-established measurements and most deployed in clinical trials of neurological diseases; more advanced dBMs, e.g., to monitor sleep, cognition or speech have been used less often to date (see Figure 2).[12]

Progress has been made in overcoming technological barriers around measuring and analysing large amounts of data via dBMs, while patients increasingly

Figure 2: Digital health technology usage in clinical studies increases



* Others include exercise with gaming consoles, caregiver support, medication adherence
Source: Masanneck, L., Gieseler, P., Gordon, W.J. et al. Evidence from ClinicalTrials.gov on the growth of Digital Health Technologies in neurology trials. npj Digit. Med. 6, 23 (2023). https://doi.org/10.1038/s41746-023-00767-1.

accept use of DHT. However, challenges remain to fully implement dBM innovation in clinical research as clinically meaningful endpoints and regulator-grade evidence. Generally, dBMs are more accepted where clinical analogues exist, e.g., heart rate or blood pressure measurements. In CNS, regulators consider dBMs on a case-by-case basis at an indication level. There is a clear need to harmonise regulation internationally, which will require collaboration between the pharmaceutical industry, academia, patient groups, tech companies and regulators.[13] RADAR CNS is an example of such collaborative initiative aimed at improving patients' quality of life through wearables and smartphone technology.[14]

Another example is The Digital Medicines Society (DiME) which has published guidelines for assessing whether digital measurements are fit-for-purpose.[15]

Digital health technology has the potential to better understand the manifestations and day-to-day impact of CNS conditions, beyond the limitations of scale-based endpoints; it allows monitoring disease progression in a real-life setting to inform treatment decisions and facilitate the development of novel therapies for better patient outcomes.

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Innovation momentum and the competitive landscape in CNS

As the fundamentals of CNS innovation keep improving, pipeline momentum continues to build. Over the past 5 years, the CNS pipeline has expanded by 31% and now accounts for 14% of the overall industry R&D pipeline, making it the second largest therapy area after oncology by number of assets in development.[9]

Its focus is split roughly 80/20 between neurological conditions and mental health, with major neurodegenerative diseases Alzheimer's and Parkinson's accounting for 25% of the industry's CNS pipeline across all phases. Rare neurological disorders, such as Huntington's, ALS or Duchenne muscular dystrophy, represent a sizable share of the CNS pipeline at 14%, which reflects the high levels of unmet need in these debilitating conditions (see Figure 3).

Pipeline highlights include psychedelics-derived treatments being investigated in a wide range of CNS conditions; or next generation biotherapeutics, such as cell and gene therapies, which represent 12% of the CNS pipeline, to target neurodegenerative and neuromuscular diseases with potentially disease-reversing or even curative outcomes.[9,16]

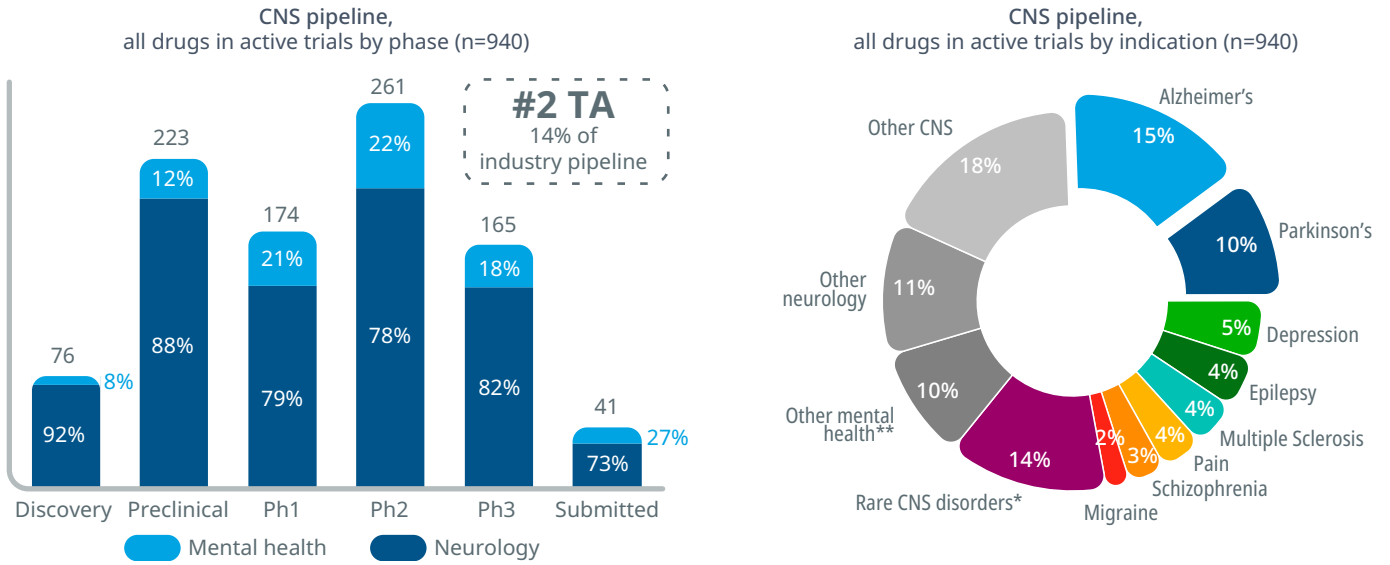
At this stage it is worth noting that innovation in non-pharmacological interventions holds great promise for treating numerous CNS conditions, for example, digital therapeutics (DTx) as enablers of cognitive behaviour therapy for mental health illnesses, or medical devices, such as neurostimulators, for movement disorders, epilepsy or Parkinson's disease.[17]

In our deep dive section further below we will elaborate in more detail on four areas — Alzheimer's, Parkinson's, psychedelics and digital therapeutics — to illustrate the remarkable pace and breadth of CNS innovation.

THE COMPETITIVE LANDSCAPE IN CNS

Innovation in CNS is predominantly driven by smaller companies, which account for 84% of the CNS industry pipeline today. Notable examples include, Argenx with neonatal FcRn antagonist efgartigimod, now approved as Vyvgart for generalized myasthenia gravis (gMG)[18]; Karuna Therapeutics with novel schizophrenia treatment KarXT, which delivered impressive results in its phase 3 EMERGENT-2 trial, setting it on course for blockbuster sales potential[19]; or the partnership of Capsida Biotherapeutics and Prevail Therapeutics to develop non-invasive gene therapies for CNS diseases.[20]

Figure 3: CNS represents 14% of the total industry pipeline



*Includes rare neurological, neuromuscular and neurodegenerative disorders; **includes insomnia, anxiety disorders,, drug abuse and other psychiatric illnesses.
Notes: Neurology includes ATCs: L3B, N7A, N7X, N3A, N4A, N5B, N5C, N6C, N6D, N6E, N7D, N7X, N2C; Mental health includes ATCs: N5A, N6A, N7B, N7C, N7E, N7F.
Source: IQVIA EMEA Thought Leadership; IQVIA Pipeline Link Jan. 2023.

However, many mid-size and larger pharma companies are also increasingly focusing their attention on CNS as an area of high unmet need with promising long-term potential.

Some are established CNS players doubling down on their existing TA presence, e.g., Biogen/Eisai with Leqembi in Alzheimer's, or UCB with Zilucoplan and rozanolixizumab, both for generalized myasthenia gravis (gMG), while others are expanding and formalising their commitment to CNS, such as Lilly with the creation of a dedicated neuroscience business unit to house their migraine franchise and future neurodegeneration-focussed business. Among the emerging CNS players, we also find a few novices without any legacy in this therapy area, e.g., Boehringer Ingelheim with some pharmacological assets and DTx, both for mental health conditions, in their pipeline; or Novo Nordisk investigating semaglutide in Alzheimer's (see Figure 4).

Given big pharma's renewed interest in CNS, it is not surprising that this therapy area accounted for an average of 15% of all product-focussed transactions in four of the past five years, as larger players tapped into external sources of innovation to advance their CNS ambitions. Before the pandemic, this made CNS the second most important therapy area for deal-making, behind oncology. Only as the pandemic hit was it eclipsed by infectious diseases, which have since retreated from their COVID-driven peak in 2020, and CNS is poised to regain its spot as #2 therapy area in focus of deal-making (see Figure 5).

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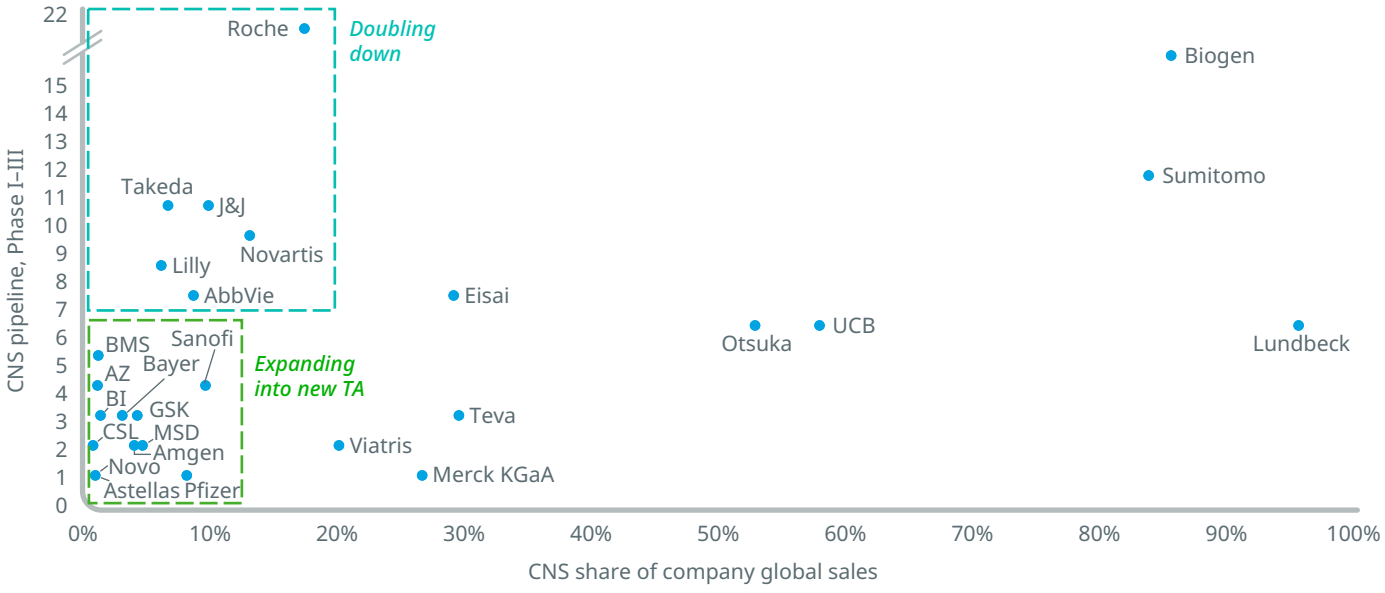
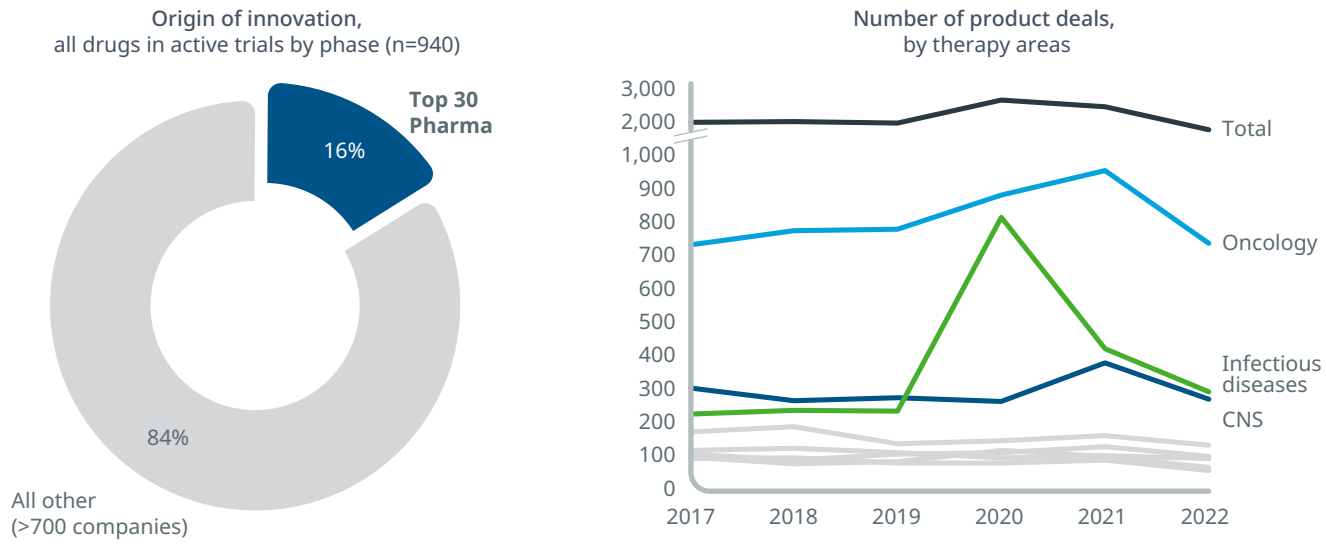
Figure 4: Emerging competitive CNS landscape



Source: IQVIA EMEA Thought Leadership; IQVIA Analytics Link; IQVIA MIDAS MAT Q3 2022.

Figure 5: Small players dominate the CNS pipeline and as targets fuel deal-making in this TA



Source: IQVIA EMEA Thought Leadership; IQVIA Pipeline Link; IQVIA PharmaDeals Jan 2023.

In fact, one of the largest deals in 2022, Pfizer's $11.6 billion acquisition of Biohaven, centred on a CNS portfolio of CGRP inhibitors, most notably marketed migraine treatment Nurtec.[21] Other examples include UCB's $1.9 billion acquisition of Zogenix, adding Fintepla which is approved for seizures associated with Dravet syndrome, with potential in other seizure disorders, e.g., Lennox-Gastaut syndrome.[22] AbbVie is also strengthening its CNS portfolio. In March 2022, they acquired Syndesi Therapeutics for $1 billion to gain access to Syndesi's portfolio of synaptic vesicle protein 2A.[23] Furthermore, AbbVie entered into a drug discovery collaboration, including an option to a license agreement, with the Sosei Group to leverage the company's structure-based drug design platform to target novel G protein-coupled receptors associated with neurological diseases.[24] Sosei received an upfront payment of $40 million with research milestone-dependent payments totalling up to $1.2 billion in the next three years.

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Deep dive: The promise of cutting-edge CNS innovation

In this section we will elaborate in more detail on four areas — Alzheimer's, Parkinson's, psychedelics and digital therapeutics — as exemplars of the promise of cutting-edge CNS innovation.

I. Alzheimer's disease

INNOVATION LANDSCAPE

Alzheimer's is a major focus of innovation activity and represents 15% of the overall CNS industry pipeline, its single largest indication and a direct reflection of the high unmet need in finding effective treatment options for this debilitating disease. Innovators need resilience to succeed in an area that has been beset by many unpleasant (late-stage) surprises, which makes two steps forward, one step back an apt description of the nature of progress seen.

The anti-amyloid antibodies are a case in point for the rollercoaster ride between hope and disappointment:

Aduhelm's short-lived run as the first FDA approved, disease-modifying Alzheimer's treatment[1] cast doubts on the validity of the amyloid hypothesis, which were dispelled by the positive readout of its successor lecanemab's CLARITY-AD trial[25] and its subsequent accelerated approval by the FDA in January 2023 as Leqembi. Meanwhile, Roche's anti-amyloid candidate gantenerumab failed to improve the rate of cognitive and functional decline in its GRADUATE I and II trials[26], while in January 2023 the FDA denied Lilly's accelerated approval application for its anti-amyloid contender donanemab, citing insufficient safety data.[27] Pending readout of its confirmatory TRAILBLAZER-ALZ 2 trial, FDA submission for donanemab is now expected in the second half of 2023. And so, the amyloid story continues.

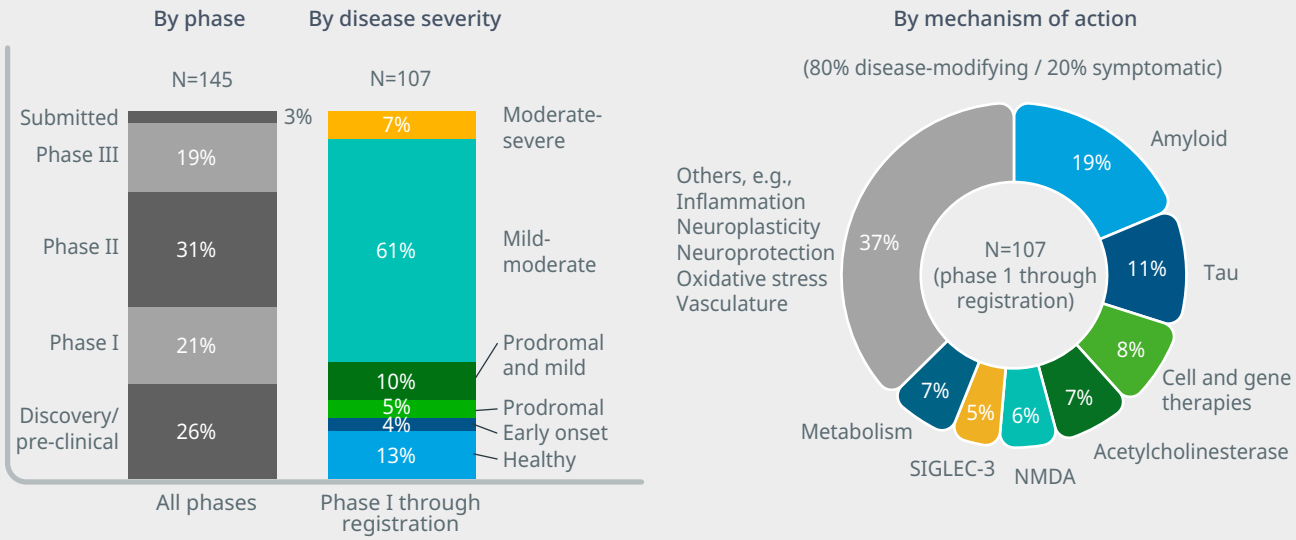
While amyloid-targeting drugs are a major focus for innovators, the Alzheimer's pipeline is diverse and roughly split 80/20 between other disease-modifying treatments (DMT) and symptomatic ones. It spans a wide range of mechanisms of action, e.g., targeting the tau pathway, SIGLEC-3 or cell and gene therapies to replace damaged cells and facilitate neuron regeneration, and many others, such as targeting inflammation, stimulating immunity, e.g., AC Immune's anti-amyloid vaccine[28], addressing metabolism, oxidative stress, vasculature, neuroprotection or restoring neuroplasticity, e.g., via small molecule SIGMAR1 agonists[29] (see Figure 6).

Several re-purposed drugs which are already marketed in other indications are also being trialled in Alzheimer's, e.g., daratumumab, on the market as Darzalex for multiple myeloma, to target inflammation, or semaglutide, marketed as Ozempic/Rybelsus and Wegovy for diabetes and obesity, respectively, to target the underlying metabolism in Alzheimer's.

Sixty-one percent of clinical-stage candidates are being investigated in mild-to-moderate Alzheimer's, with the aim of slowing progression. This focus is also a reflection of the practical challenges of identifying patients for clinical trials in earlier disease, e.g., prodromal and early onset.

Innovators need resilience to succeed in an area that has been beset by many unpleasant (late-stage) surprises.

Figure 6: Alzheimer's development pipeline



Notes: Includes industry-sponsored trials only.
Source: IQVIA Pipeline Link, Jan. 2023; IQVIA Institute; clinicaltrials.gov; desk research; IQVIA EMEA Thought Leadership.

THE WAY FORWARD

The approval of the first disease-modifying treatment was undeniably a momentous milestone to provide a glimmer of hope to Alzheimer's patients and their families, however, we are still a long way away from defeating this debilitating disease.

Significant gaps must be addressed to advance the development and adoption of new Alzheimer's therapies and improve the continuum of care[30]:

- **Disease models**: Develop a deeper understanding of pathological mechanisms, molecular pathways, risk factors and biological causes of behavioural and psychological symptoms.
- **Diagnosis**: Develop highly sensitive, specific biomarkers, including imaging, blood, genetic and digital biomarkers, and improve clinical assessments of cognition and function to enable accurate, timely diagnosis, especially for prodromal stages.
- **Diversity**: Ensure participation of diverse populations in drug development, representing different ethnic, gender, socio-economic backgrounds, by utilising patient-centric designs, remote data capture and other trial innovations.
- **Speed and efficiency**: Establish global clinical trial networks and technology platforms linking trial sites around the world to facilitate patient recruiting and data sharing, for faster, less costly clinical development.
- **Equitable access**: Improve access along the care continuum from diagnosis, treatment to long-term care; recognising the societal burden of Alzheimer's to shape policies for adequate funding of research, ensuring health system readiness and to reward innovators.

Collaborations between industry, academia, governments and international organisations will play a critical role in closing these gaps[31], e.g., the Accelerating Medicines Partnership — Alzheimer's[32], the Alzheimer's Disease Neuroimaging Initiative[33], EU Joint Programme — Neurodegenerative Disease Research[34], or the Davos Alzheimer's Collaborative.[35]

II. Psychedelics-derived therapeutics

INNOVATION LANDSCAPE

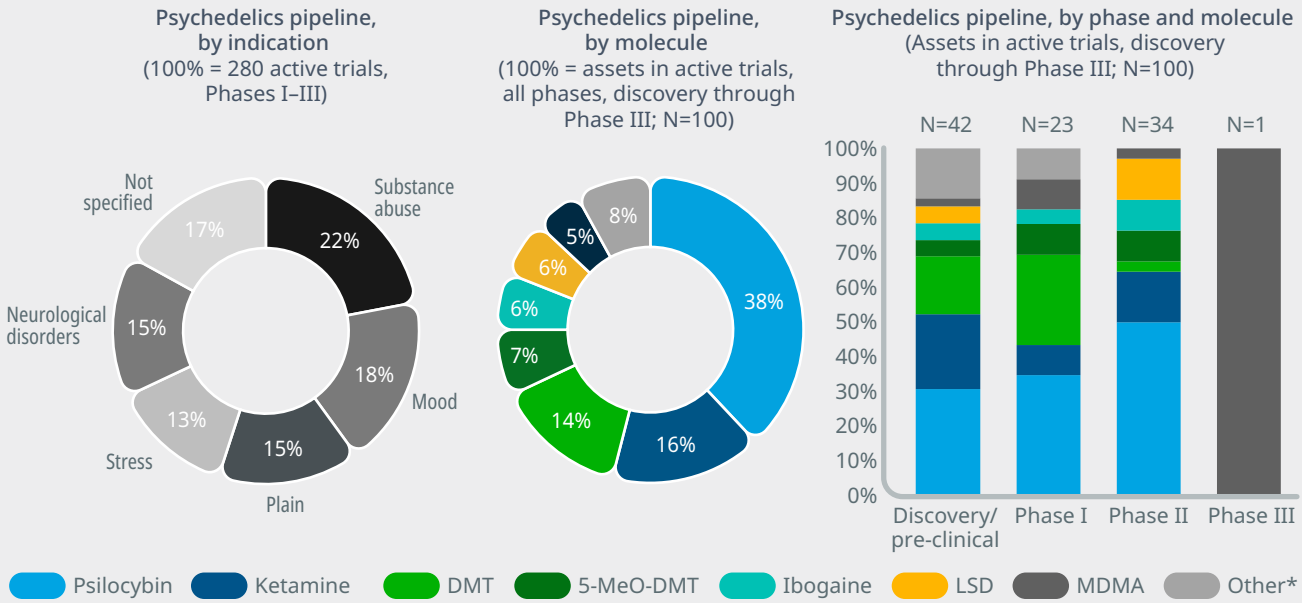
Research into psychedelics-derived therapeutics has gained significant momentum in recent years[36] after decades of being hamstrung by regulatory action, which classified many of these compounds under The Controlled Substance Act of 1970 as Schedule I drugs, i.e., high potential for abuse and no currently accepted medical use.[37]

Today, nearly 50 publicly listed companies and over 45 private companies, as well as numerous non-profit organisations such as the Multidisciplinary Association for Psychedelic Studies (MAPS)[38] or The MIND Foundation[39], are conducting research into psychedelics-derived therapeutics, while the non-profit organisations are also active in public education and shaping the policy debate. Meanwhile, regulators are adopting a more positive stance that recognises the potential of psychedelics, e.g., the EMA encouraging innovators to engage early to overcome challenges of developing psychedelics-derived therapeutics[40], as does the FDA[41]; the Australian regulator re-classifying psilocybin and MDMA to enable prescribing by authorised psychiatrists from July 2023[42], while the FDA granted breakthrough therapy status to psilocybin and MDMA.[43,44]

Four molecules, including psilocybin, ketamine, DMT and 5-MeO-DMT, account for two-thirds of active trials investigating psychedelics across a range of mental health and some neurological conditions, e.g., depression, anxiety, substance use disorders, PTSD, Parkinson's and Alzheimer's (see Figure 7).

Interestingly, substance use disorders are a major focus of clinical trials investigating psychedelics, with a share of 22%. Combined, alcohol and drug abuse accounted for 40 million DALYs globally in 2019, making it the second largest global burden of illness in mental health after depression (see Figure 1). Psilocybin used alongside CBT has shown promise in reducing alcohol dependency[45], illustrating the potential of psychedelics in difficult to treat addictions.

Figure 7: Pipeline of psychedelics-derived therapeutics



* Includes mescaline, salvinorin A, mitragynine, phenethylamine derivative.
Source: IQVIA Pipeline Link, Jan. 2023; clinicaltrials.gov; IQVIA EMEA Thought Leadership.

Psilocybin is the single most studied molecule within the psychedelics pipeline, representing 38% of all assets in active trials, and it was twice granted breakthrough therapy status by the FDA, first for treatment-resistant depression (TRD) in 2018, followed by major depressive disorder (MDD) in 2021.[43] Current late-stage pipeline candidates closest to FDA approval are MAPS-led MDMA for PTSD, and Compass Pathways' psilocybin for treatment-resistant depression[46], possibly in late 2023 and 2024, respectively.

A major milestone for psychedelics was reached in March 2019, when the FDA approved Janssen's nasal-spray Spravato (esketamine) as the first psychedelics-derived therapeutic for a mental health condition, as an add-on to oral antidepressants for TRD or MDD with suicidal ideation.

THE WAY FORWARD

Securing regulatory approval for psychedelics-derived therapeutics is only one of many hurdles that commercial players must overcome to capture their share of what IQVIA estimates could be a $10–15 billion market globally by the end of the decade. Specific challenges include:

- **Intellectual property (IP)**: Protecting their IP when new treatments are typically derived from natural products, e.g., psilocybin, mescaline, or old, post-LoE molecules such as MDMA and LSD, requires a clear strategy that ensures patentability. For example, by developing novel formulations, e.g., Spravato's ketamine-based nasal spray, oral formulations of psilocybin; or derivatives of naturally occurring compounds, e.g., deuterated DMT, or pure enantiomers.
- **Legalisation:** Regulatory approval does not mean a controlled substance is legalised for use in the general population. For example, Schedule I substances in the U.S., such as MDMA, would first need to be de-scheduled by the Drug Enforcement Administration (DEA) before they could be used in clinical practice following FDA approval. Furthermore, national laws typically regulate controlled substances, e.g., at member state level in the EU, and thus create complexity and opportunity fragmentation, with legal implications for choosing manufacturing locations and managing supply chains.
- **Access and reimbursement:** For safety and effectiveness, treatment with new psychedelics-derived therapeutics is integrated with extensive behavioural therapy – psychedelic-assisted therapy (PAT)[36] – often involving two therapists. The therapy component adds significant cost on top of reimbursing the drug itself, and it complicates the pre-and post-launch evidence burden. Furthermore, it creates capacity bottlenecks, e.g., available behavioural therapists qualified to deliver PAT or accredited facilities, which affects equitable patient access and limits adoption of novel therapeutics.

Securing regulatory approval for psychedelics-derived therapeutics is only one of many hurdles that commercial players must overcome to capture their share of the market.

Overcoming these challenges will require a multi-stakeholder effort which looks beyond typical barriers for drug commercialisation and instead must focus holistically on re-defining the model for delivering mental health services.

III. Parkinson's disease

INNOVATION LANDSCAPE

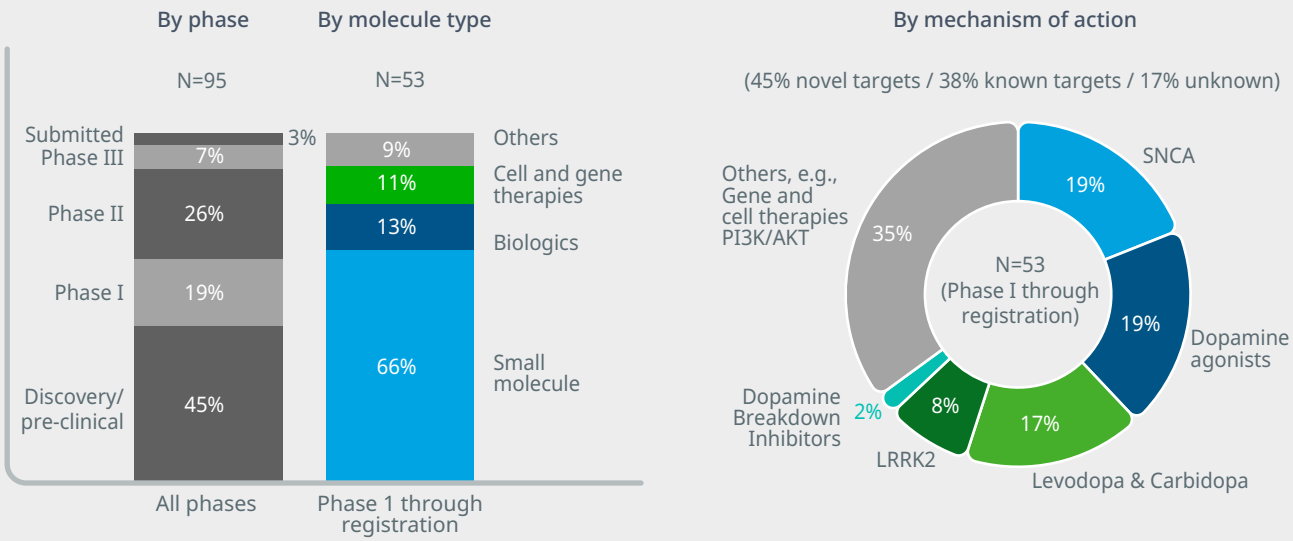
The global disease burden of Parkinson's is growing rapidly (Figure 1) and will continue to do so driven by an ageing population. Currently available pharmacotherapies only treat symptoms in the absence of approved DMTs. Pharma is focusing on this growing unmet need, with 10% of the CNS pipeline dedicated to Parkinson's disease (see Figure 8).

Small molecules that either compensate for the loss of dopamine or block its breakdown dominate symptom management. However, this therapeutic window narrows and treatments get less effective over time, resulting in patients suffering from off episodes. To address this challenge, AbbVie designed its ABBV-951 to continuously administer foscarbidopa/foslevodopa under the skin to deliver stable dopamine levels. In 2022, AbbVie filed a new drug application with the FDA for advanced Parkinson's disease based on positive phase 3 data and is gearing up to launch later in 2023.[47]

In search of DMTs, pharmaceutical companies are also exploring novel targets which account for 45% of the late-stage Parkinson's pipeline. Mutations in the LRRK2 gene are a known cause for the rare hereditary form of Parkinson's but research suggests that targeting LRRK2 could impact disease biology and slow disease progression.[48] Biogen and Denali Therapeutics collaborate on the development of a small molecule inhibitor of LRRK2 – BIIB122 (DNL151) and recently announced the initiation of a phase 3 study.[49]

Alpha-synuclein protein aggregates in the brain of Parkinson's patients are considered a biomarker for the disease. Prasenizumab, a monoclonal antibody designed to break up those aggregates recently failed to slow down Parkinson's Disease progression.[50] Yet, Roche and Prothena did not

Figure 8: Parkinson's development pipeline



Notes: Includes industry-sponsored trials only.
Source: IQVIA Pipeline Link, Jan. 2023; IQVIA Institute; clinicaltrials.gov; desk research; IQVIA EMEA Thought Leadership.

conclude this was the end of alpha-synuclein as a drug target for DMT. As an alternative approach, AC immune is testing its vaccine ACI-7104 to generate clinical proof-of-concept data in early stages of the disease.[51]

Cell and gene therapies account for 11% of the clinical-stage Parkinson's pipeline, but progress to date has been erratic. For example, Voyager's VY-AADC, a gene therapy aimed at restoring the treatment benefits of oral levodopa, was put on clinical hold and later terminated over MRI abnormalities, despite promising results.[52] Conversely, MeiraGTx started dosing patients to deliver a healthy copy of a gene in the hope of improving motor control of Parkinson's patients.[53]

THE WAY FORWARD

Parkinson's disease is a complex disorder with challenges from diagnosis to pharmaceutical intervention and patient monitoring. Therefore, a patient-centric, multi-disciplinary approach is needed to enable breakthrough innovation in managing this disease:

- **Disease model, clinical trials and access challenges** as described in the Alzheimer's section are very relevant and must be addressed for Parkinson's disease too.
- **Diagnosis**: The accuracy of Parkinson's disease diagnosis at ~80% is not satisfying.[54] There is a lack of easy-to-use biomarkers e.g., from blood samples, and their limited translatability warrants caution. Early detection of motor and non-motor symptoms using wearable sensors may lead to earlier diagnoses and better patient outcomes.
- **Precision medicine**: Though most Parkinson's cases are non-hereditary, the genetic makeup is linked to the idiopathic form of the disease. As companies explore genes like SNCA or LRRK2 as drug targets, genomic testing will become important to identify patients who will most benefit from these treatments.
- **Patient support programmes**: A Parkinson's diagnosis is life-changing for patients and their families. In addition to the well-known motor symptoms, patients very often suffer from depression, dementia and anxiety. A holistic treatment approach must go beyond standard pharmacotherapy aimed at Parkinson's and address broader co-morbidities, including mental health.

Defeating Parkinson's disease will require a collaborative approach involving all stakeholders to tackle barriers along the innovation process and the entire patient journey.

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IV. Digital therapeutics

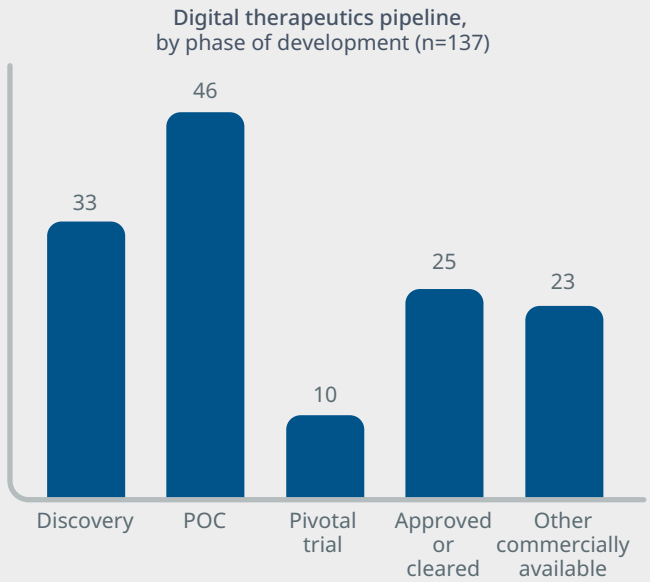
INNOVATION LANDSCAPE

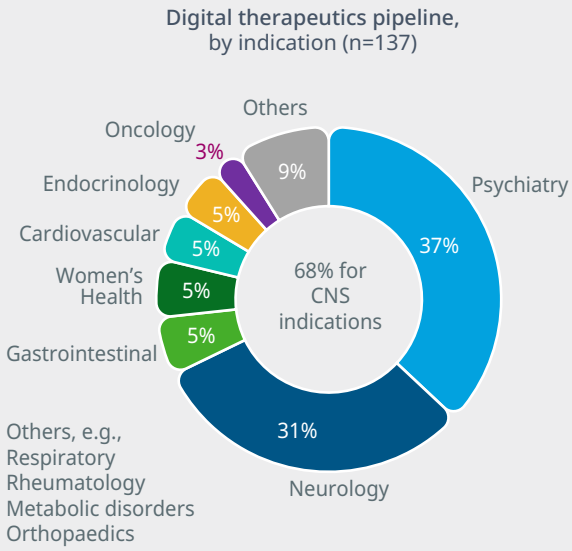
Digital therapeutics (DTx) typically focus on specific clinical indications, follow a development path that involves generating clinical efficacy data, require market authorisation by regulatory bodies, and sometimes they need a prescription.[55] Germany passed the Digital Care Act ('Digitale Versorgung Gesetz', DiGA) in 2019 and created a DTx approval and reimbursement pathway to serve its 73 million publicly-insured patients. Today, a total of 43 apps are fully or temporarily approved in Germany – most for mental health conditions using cognitive behavioural therapy (CBT).[56] Germany's DiGA serves as a blueprint which other countries start emulating, while in the U.S. the 'Access to Prescription Digital Therapeutics Act' was introduced to extend Medicare coverage to prescription-bound DTx.

DTx can improve access to CBT as demand far exceeds the availability of qualified therapists. CNS is a key focus area of DTx development, accounting for 68% of the DTx pipeline (see Figure 9).

Pharmaceutical companies are also looking at combining DTx with pharmacotherapeutics. For example, Boehringer Ingelheim recently expanded its collaboration with Click Therapeutics to develop and commercialise a second prescription-bound DTx.[57] Already in 2020, the large pharma secured the exclusive rights for Click's CT-155.[58] This DTx has achieved all development milestones to date and could potentially be prescribed alongside Boehringer Ingelheim's pharmacological pipeline asset for Cognitive Impairment Associated with Schizophrenia (CIAS).

Figure 9: Digital therapeutics (DTx) development pipeline





Source: IQVIA Digital Health Trends 2021; IQVIA Digital Solutions Database, Jun 2021; IQVIA Institute, Jun 2021.

THE WAY FORWARD

DTx have the potential to be widely adopted as complementary or even alternative options to pharmacotherapeutics in CNS. To ensure DTx innovation reaches patients, some barriers and challenges must be addressed:

- **Value proposition**: The benefits of digital solutions are often not understood by patients or prescribers. Developers of DTx must clearly articulate the value of their product to all healthcare stakeholders, supported by robust evidence.
- **Market access**: Regulatory approval is a prerequisite for DTx reimbursement in many countries. Generating evidence through clinical trials is challenging for this start-up dominated sector. DTx developers should thus explore partnerships with experienced CROs or pharmaceutical companies while engaging early with regulatory bodies.
- **HCP education**: While numerous DTx have been approved for mental health conditions, awareness among prescribers is typically limited. Therefore, DTx developers must focus on building wider awareness alongside traditional promotional efforts.

As health systems face unprecedented financial and operational pressures, unlocking the full potential of DTx is crucial to alleviate the growing CNS burden.

- **Business model**: DTx developers face a fundamental choice of how to monetise their product.

  Even where DTx meet the high evidence standards for regulatory approval, commercial success is not guaranteed, as examples of lower-than-expected reimbursement prices in Germany show. Therefore, DTx developers must carefully consider if commercialisation via the prescription route is the most viable option vs. alternatives such as direct-to-consumer or companion apps.

As health systems face unprecedented financial and operational pressures, unlocking the full potential of DTx is crucial to alleviate the growing CNS burden.

Outlook for the CNS market

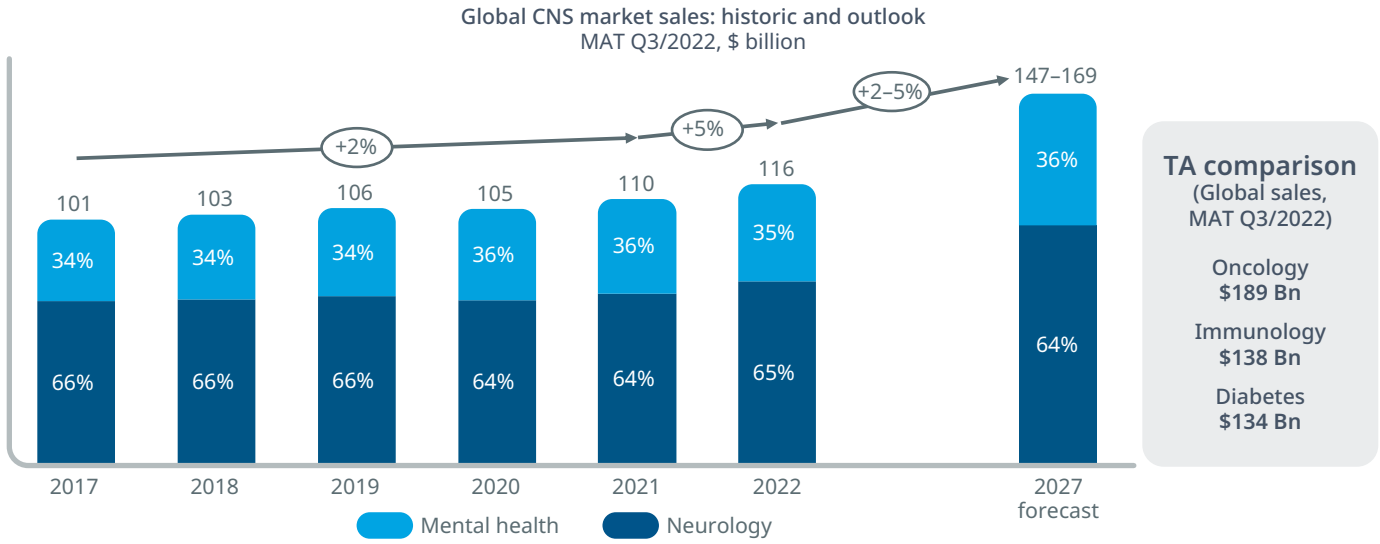
Collectively, CNS disorders represent a sizeable market worth $116 billion globally in 2022, at ex-manufacturer prices. This compares to 2022 global market sizes of $189 billion for oncology, $138 billion for immunology and $134 billion for diabetes, which makes CNS the fourth largest therapy area. As the fundamentals of CNS innovation keep improving, we expect growth will accelerate over the next 5 years, from 2–3% historical 5-year CAGR (2017–2022) to 2–5% future 5-year CAGR (2022–2027), with the CNS market set to reach $147–169 billion globally by 2027 (see Figure 10).

However, these modest headline growth figures understate the true impact of novel future therapies on the CNS market and reflect a legacy of decades of stalled innovation. Consequently, a high share of generics volume utilisation in many CNS indications is weighing on the market, e.g., at 85%, 76% and 86% in Alzheimer's, Parkinson's and depression, respectively.[59]

Nevertheless, the combination of long-term epidemiological trends, including a growing burden of illness, and the absence of effective treatment options in many CNS indications creates an attractive commercial opportunity for innovators. Where breakthrough innovation is targeting high unmet need to set a new standard of care by introducing disease-modifying treatments, we will see rapid sales growth in pockets of high potential over the next 5 years, for example, in Parkinson's, rare neurological diseases and notably Alzheimer's, which is poised to reverse a historical double-digit decline into double digit market growth (see Figure 11).

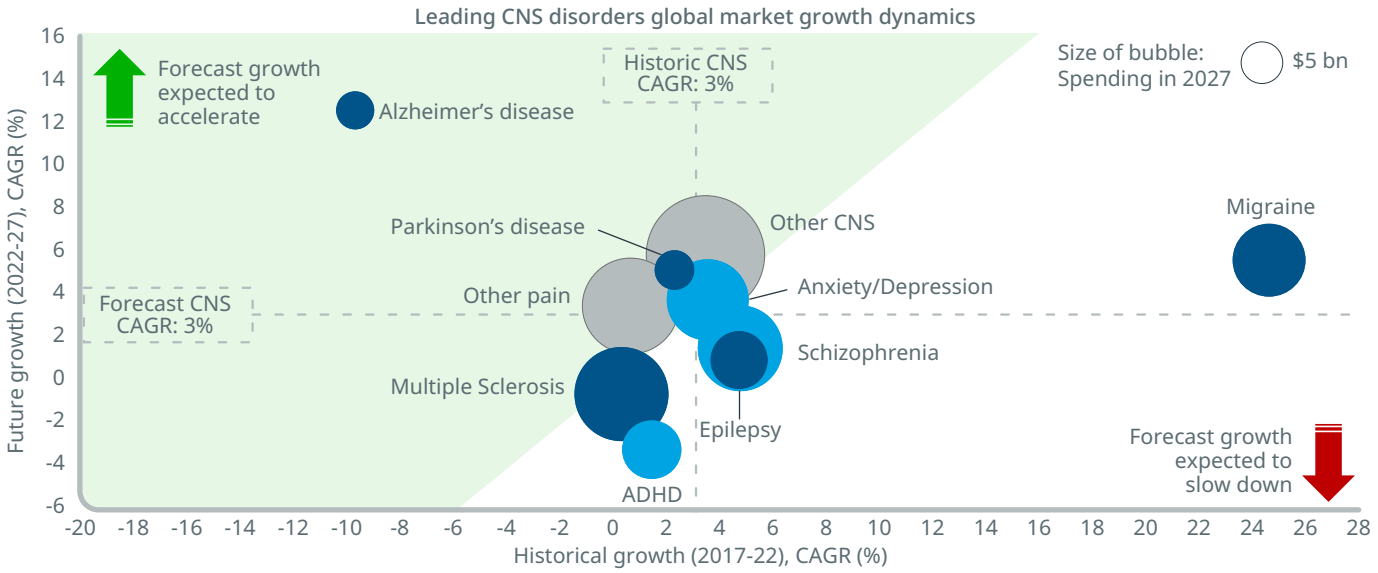
Where breakthrough innovation is targeting high unmet need to set a new standard of care by introducing disease-modifying treatments, we will see rapid sales growth in pockets of high potential over the next 5 years.

Figure 10: Collectively, CNS disorders represent a sizeable market



Note: Neurology includes ATCs: L3B, N7A, N7X, N3A, N4A, N5B, N5C, N6C, N6D, N6E, N7D, N7X, N2C; Mental health includes ATCs: N5A, N6A, N7B, N7C, N7E, N7.
Source: IQVIA EMEA Thought leadership; MIDAS MAT Q3 2022, Rx only; IQVIA Forecast Link, January 2023.

Figure 11: Disease-modifying treatments are driving CNS growth dynamics



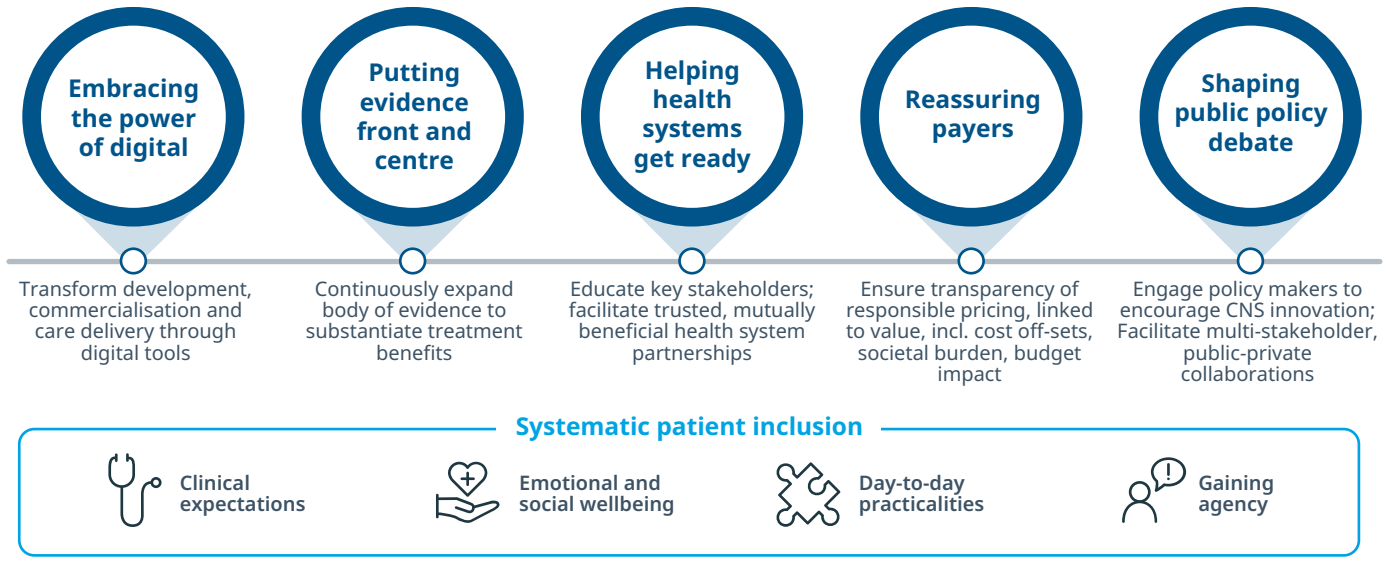
Source: IQVIA Forecast Link, IQVIA Institute – The Global Use of Medicines 2023.

How to succeed as a CNS innovator

Shepherding pipeline assets through the development process and bringing them to the market is only part of success as a CNS innovator. Its ultimate measure is the wide adoption of novel therapies to benefit all eligible patients, which is a challenge along the disease prevalence spectrum, e.g., accurate and timely diagnosis of patients with rare neurological disorders, adequate infrastructure and capacity for treating chronic, high prevalence conditions, or funding models that reward innovation, provide broad patient access while ensuring health systems' financial sustainability.

To overcome the barriers to the development and commercialisation of CNS innovation and to reach a true inflection point in the wider adoption of breakthrough therapies, CNS innovators must address five critical priorities (see Figure 12):

Figure 12: How to succeed as a CNS innovator



Source: IQVIA EMEA Thought Leadership.

1. **Embracing the power of digital:** Transform development, commercialisation and care delivery through digital tools, e.g., digital biomarkers and connected devices for clinical trial innovation; data-driven, highly tailored patient programmes offering continuous support; real-world patient outcomes and experience tracking via digital biomarkers; or care pathway analytics and AI-powered clinical decision support tools to ensure health system readiness.

2. **Putting evidence front and centre:** Continuously expand the body of evidence to substantiate treatment benefits, especially post-approval in routine practice and patients' day-to-day life.

3. **Helping health systems get ready:** Educate key stakeholders on requirements for the optimal adoption of new therapies. Facilitate trusted, mutually beneficial health system partnerships to optimise patient journeys, care pathways, capacity and resource utilisation to broaden patient access and ensure the sustainable delivery of cutting-edge CNS innovation.

4. **Reassuring payers:** Ensure transparency of responsible pricing, linked to value, including quantified cost off-sets, patient and societal burden and budget impact[60]; explore new access models that align incentives around shared objectives, e.g., outcomes-based contracts.

5. **Shaping public policy debate:** Engage policy makers to create an environment encouraging CNS innovation, especially for treating high prevalence, chronic conditions like Alzheimer's. Facilitate multi-stakeholder, public and private collaborations for novel, sustainable health system solutions.

Innovation in CNS continues to be a high-stakes endeavour. However, the odds for success are improving considerably as key enablers fall into place.

CNS innovators should therefore feel emboldened to stay the course and seize the ultimate prize.

Systematic patient inclusion throughout these five priorities is fundamental to success. This means holistically engaging with patients across multiple dimensions: (i) understanding their clinical expectations, disease and therapy burden, and preferred outcomes; (ii) supporting patients, their families and caregivers to ensure their emotional and social wellbeing; (iii) supporting patients in dealing with the practicalities of day-to-day living with the condition and receiving treatment; and (iv) helping patients to gain agency, e.g., by engaging patient communities as experts on their condition.[61]

Innovation in CNS continues to be a high-stakes endeavour. However, the odds for success are improving considerably as key enablers fall into place, as we have shown here.

CNS innovators should therefore feel emboldened to stay the course and seize the ultimate prize.

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