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A New Era for CNS Therapeutics

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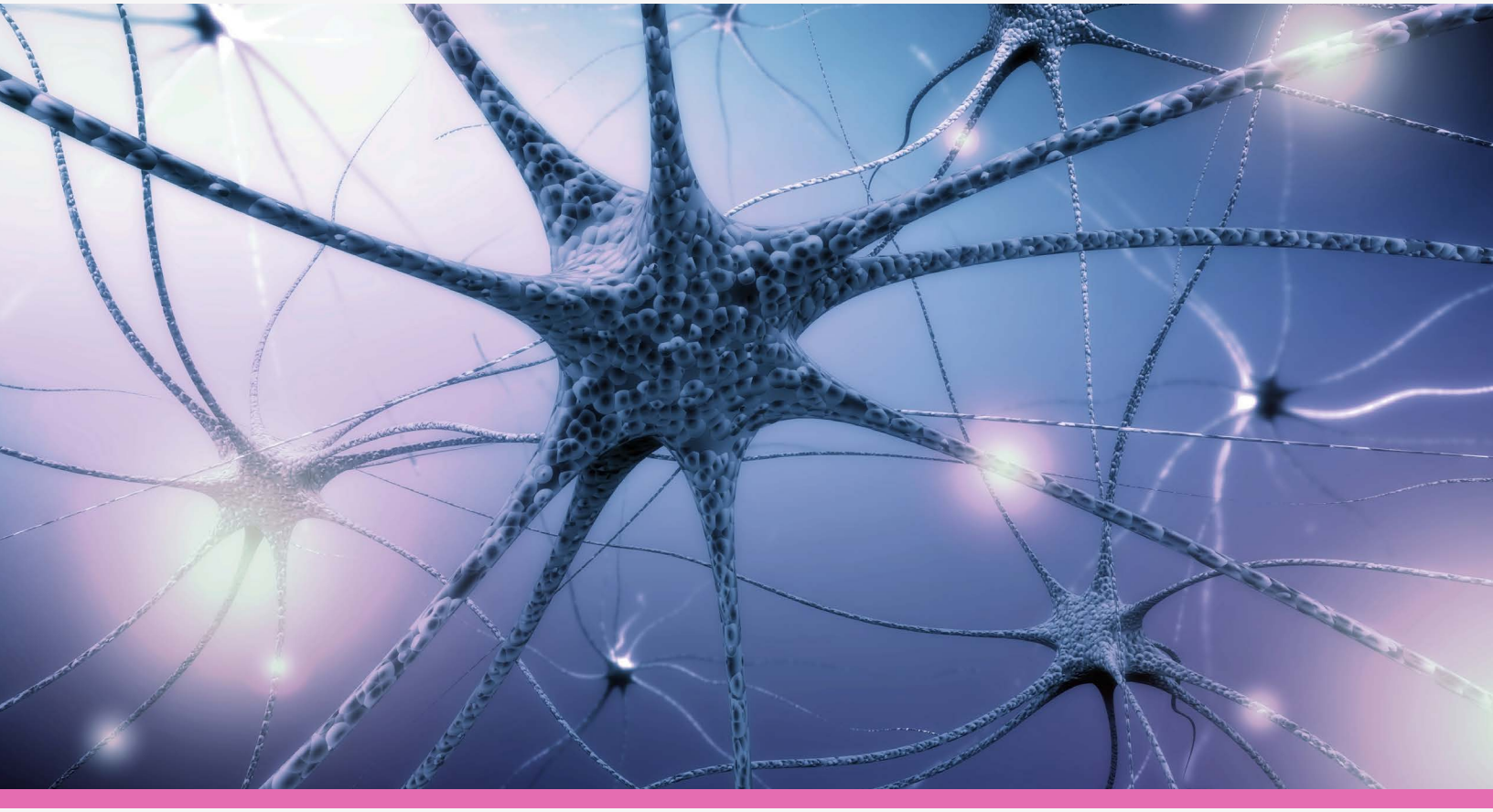

In collaboration with ICON BIOTECH

Foreword

This eBook takes the pulse of the latest biotech research on CNS therapeutics. Researchers and scientists are problem-solvers. They are aware that while the challenges they face are difficult, they pale in comparison to the challenges CNS disorder patients contend with every day.

Improving the quality of life for patients with CNS conditions is the driving force for many Biotech companies. To do so they must balance innovation with regulation, and cost-effectiveness with commercialisation. Added to this is the triple challenge of every clinical trial: patient recruitment, retention and safety.

All of this can trigger delays. But patients with progressive neurological conditions can't afford to wait, new treatments can't come soon enough. As an article in this eBook observes, in one CNS treatment trial by the time the Investigational New Drug (IND) had been approved all of the selected study participants had died.

Yet against this stark reality there are some "sparks in the darkness," another article notes. Biotech companies are developing new approaches with promising results. From repurposing existing drugs, to treating the single gene defect responsible for the CNS disorder, biotech continues to break new frontiers. Through novel trial designs and new partnerships, they are developing new treatments for mental health disorders that have had limited treatment options for generations.

Of course, clinical trials cannot take place without willing participants. Patients may be highly motivated to contribute to new treatments that will improve their lives or give hope to the newly diagnosed. However, participant drop-out rates in phase 3 clinical trials can exceed 30%.[1] One promising development in this new era for CNS therapeutics is digital therapeutics. This intuitive technology is easy for participants to use and can help maximise data collection while keeping the participant burden low.

We hope that you find these articles helpful and inspire new approaches for your research endeavours.

Nina Samra
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CNS Therapeutic Area Head, ICON Biotech

1. Alexander W. The Uphill Path to Successful Clinical Trials: Keeping Patients Enrolled. Pharmacy and Therapeutics. 2013;38(4):225

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Pioneering Partnerships And Novel Trial Design Are Reshaping Repurposing In The CNS Space

Major Repurposing Projects Are Underway Across Multiple Disease Areas

Chloe Kent
19 Jul 2023

Executive Summary

Repurposing licensed drugs can be an affordable and effective way to bring new treatments to market, but initial efforts tend to lack funding from big pharma. In Vivo takes a closer look at repurposing projects across the central nervous system space, what it is that drives the work forward and how innovative trial design is changing the game.

Highly anticipated results from the US National Institutes of Health's Drug Repurposing for Effective Alzheimer's Medicines (DREAM) initiative proved disappointing for the research community in October last year, as the study revealed that sildenafil and tadalafil were not suitable candidates for treating dementia.

NIH researchers examined the risk of Alzheimer's and related dementias using two groups of Medicare beneficiaries with pulmonary atrial hypertension; those who were being treated with sildenafil or tadalafil and those treated with another class of drugs. They also tested whether sildenafil had effects on cell culture models of Alzheimer's.

The findings indicated PDE5 inhibitors, the drug class both compounds belong to, did not reduce patients' risk of Alzheimer's and related dementias, nor did they correct molecular abnormalities associated with Alzheimer's. These findings were a stark contrast to research reported during 2021 from the Cleveland Clinic, which found that patients taking sildenafil were 69% less likely to develop Alzheimer's disease over a six-year period than those who did not take the drug.

DREAM is a multidisciplinary initiative to identify candidate treatments for Alzheimer's and related dementias by repurposing drugs that are approved by the US Food and Drug administration for other indications. Previous results from DREAM studies have indicated that some arthritis drugs may reduce Alzheimer's risk in patients with heart disease. It is just one of many repurposing projects underway in the central nervous system (CNS) disease space.

Sildenafil itself is perhaps the most well-known repurposed drug, initially investigated by Pfizer as a potential antihypertensive medication but now most well-known as an erectile dysfunction treatment. Thalidomide, an anti-nausea drug indicated for use during pregnancy which was pulled from the market after causing birth defects, is now used to treat leprosy and multiple myeloma. A catalogue of compounds have been repurposed to treat COVID-19, reigniting a degree of market interest in repurposing across the board. Now, academic teams across the CNS space are investigating the use of pre-approved drugs to treat these illnesses.

Biomarkers As A Basis For Repurposing Opportunities

PrecisionLife, a UK biotech focused on identifying precise treatment options for chronic disease patient subgroups, published a study in June last year identifying 477 potential repurposing opportunities in over 35 secondary disease indications across the development and marketed drug pipelines of 177 companies.

Steve Gardner, PrecisionLife CEO and co-founder, said: "That was the first bit of triage, trying to find genetic associations that would link the drivers of disease biology that were modulated by those drugs to particular patient subgroups where they were clinically prevalent enough to be interesting."

He continued: "We've extended that pipeline a little bit and now we go in and also check things like modality, the route of administration and whether dosage required would create additional toxic effects in the second indication. We also assess whether there's freedom to operate with a good regulatory package, what the commercial landscape that they would be repurposing into would look like and whether that's viable or not. If all of those things hold through, then we feel that we do have a very strong opportunity to take those medicines forward."

Gardner said that around 250 of the opportunities PrecisionLife identified have now been through this level of analysis. "We have the mechanistic patient stratification biomarkers that allow us to really look across multiple disease areas for common pathophysiology and therefore start to identify potential repurposing targets," he explained.

The company has also partnered with venture capital funds that support company creation around repurposed assets.

In May this year, PrecisionLife announced a partnership with medical research charity LifeArc as part of the latter's Motor Neurone Disease Translational Challenge, which will see it focus on repurposing in this area. While partners will primarily work together to select and validate multiple novel targets and their accompanying patient stratification biomarkers, PrecisionLife will also work to identify opportunities that might exist for repurposing existing medicines for MND.

"The obvious mantra with repurposing is it's faster and cheaper, but there are lots of caveats involved in that statement," Gardner said. "There are ways of de-risking and adding value to repurposing opportunities that make them a very viable strategy going forward, over and above novel target discovery or molecular design."

He explained: "Even if you have proven your compound is safe, tolerated, deliverable and manufacturable, it's perfectly possible to fail in Phase III just because you haven't chosen the right people to put in the clinical trial population. It doesn't mean that drug isn't still going to work for a bunch of patients, maybe 25% of your target population. That's where repurposing really wins out, I think, because those assets are good to go apart from that last piece."

Essentially, if a company managing a Phase III trial can utilize mechanistic biomarkers to select for the patient population where a drug is more likely to prove effective, it becomes more realistic to start considering the compound as a potential market asset.

Repurposing In The Age Of The Inflation Reduction Act

"The other thing that repurposing offers is a view of maybe two or three additional indications that you might want to repurpose your medication into, built off that same underlying data and regulatory package," said Gardner. "I think that strategically it offers some new opportunities to think about how to ameliorate the effects on innovation coming from the Inflation Reduction Act."

Gardner notes that the way secondary indications are currently set to be treated under the IRA, especially with respect to orphan status, can be seen as problematic. "This potentially creates the need to identify and evaluate all of the potential markets and pursue the most lucrative indication first, and perhaps only ever use the drug in that indication, rather than bring it to market in secondary indications, which would disqualify the drug from orphan status and open it up in all indications to price negotiation," he explained.

He continued: "This would work to incentivize selection of the largest single market first rather perhaps than the one with most unmet medical need or bringing innovation to multiple diseases. Obviously in this context several players will be tempted to pick a single market and will need to have very good insight into prevalence, market size and competition in that space. Of course, the law may well change here to avoid such negative consequences on innovation."

However, several key provisions of the IRA in the US will contribute directly to revenue losses for biopharmaceutical companies and may see them forced to make cuts to research and development. By investigating repurposing opportunities, pharmaceutical companies may discover new avenues through which to relaunch existing intellectual property, bringing new treatment options to the market while saving on time and money.

"Identifying secondary indications for assets that you are not currently developing creates the option for finding lucrative out-licensing opportunities, which increases return on investment on the sunk R&D costs, especially if you don't have the complication of an existing on-market indication for the asset," said Gardner.

"Innovation is still really important from a novel target and novel molecule discovery perspective," he added. "But by the same token, there's a whole bunch of drugs out there that could really, really help people and would make very significant revenues for pharma companies if they are able to get over that hurdle of designing clinical trials that demonstrate significant efficacy."

LifeArc's Toolkit

The partnership with PrecisionLife is not the only initiative LifeArc is involved in which focuses on repurposing. The firm has also launched a toolkit for researchers working on repurposing projects, to help signpost them to various resources that can help them plan their projects from lab to clinic.

"We focus on preclinical and early-stage clinical projects, we don't fund later stage clinical trials and we don't take products all the way to market adoption ourselves," said LifeArc business manager Joanna Davidge. "The toolkit was put in place to bolster the data packages coming out of Phase II, for repurposed therapeutics."

LifeArc has also worked in partnership with the National Health Service England Medicines Repurposing Programme, which has been set up to take generic repurposed medicines forward for new indications. The program, described by Davidge as a "matchmaking service," puts out market authorizations to tender for generic manufacturers, with the aim of taking drugs which have an initial proof-of-concept in the clinic forward, toward market authorization and a reliable route to patient access.

"They told us that they are not seeing anything like the number of programs they expected to see with strong enough data to be accepted," Davidge said. "They asked us to try and bolster those earliest stages with our online resource." After all, commercial opportunities cannot come to fruition at all without the successful completion of early-stage research projects.

Davidge added that while the established safety profile of repurposed drugs can make the R&D process more straightforward for researchers and manufacturers, a lack of commercial incentive can be a key hurdle to securing drug approval after the fact.

"If it's a generic medicine, there aren't many incentives for commercial partners to pick those up and take them toward market authorization, because the profits are just not there," she said. This issue can apply across the board but is particularly prevalent in the rare and ultra-rare disease space and can lead to drugs being prescribed off-label. (Also see "FDA's Peter Stein On Hitting The 'Persuasive Evidence' Bar For Rare Disease Drug Repurposing" - Pink Sheet, 14 Feb, 2023.)

"In the academic sector, there is definitely an uptick in interest in repurposing," Davidge said. "I think

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COVID-19 really helped the optics, people have seen things in the public domain that have been repurposed." (Also see "Clinical Trials: Have We Finally Reached The New Normal?" - In Vivo, 1 Dec, 2022.)

Repurposing Projects Lack Big Pharma Funding

Major repurposing projects are now moving to later stages of development across the CNS space.

The ASPro-PD trial is a world-first, aiming to establish the potential of ambroxol – a compound that breaks up phlegm and is typically found in cough syrups – to slow progression of Parkinson's disease. The research follows work led by Anthony Schapira, head of clinical neurosciences at University College London.

For this study the drug is being dosed in a tablet form at a higher concentration than would be found in a cough medicine. Ambroxol has been found to increase the activity of glucocerebrosidase (GCase) in the body, an enzyme involved in the breakdown and clearance of waste proteins. Low GCase activity in the body can lead to a buildup of proteins such as alpha-synuclein that can contribute to the neurodegeneration associated with Parkinson's disease.

The trial is being run in two patient cohorts of up to 180 in each arm: those with mutations in the CBA1 gene, the most common genetic risk factor for Parkinson's, and those who do not have this mutation. Around 10% to 15% of Parkinson's patients have CBA1 mutations.

GBA1 mutations can cause problems with production of GCase, but many people with Parkinson's who do not have the GBA1 mutation can still have lower levels of GCase production. This suggests that a GCase-enhancing drug, like ambroxol, could be beneficial to a very wide number of Parkinson's patients.

> **"Repurposing projects need to source their funding through either charitable or government funding to test out these compounds, there doesn't tend to be pharmaceutical money driving the process."**

Parkinson's UK director of research David Dexter expressed confidence that if Phase III trial meets its endpoints a product could be brought to market very quickly, through working with the NHS Accelerated Access Collaborative.

"If this Phase III shows positive effect, then we would work with one of the generic manufacturers of ambroxol to gain a license for its use in Parkinson's," he said. "The AAC will actually pay for the licensing of this if we have one of the manufacturers actually willing to do all the paperwork for it, so that actually covers about £20,000 ($26,221) worth of cost. This could be in clinical use quite shortly after the trial closes, the data is published and it's looked at by the Medicines and

Healthcare products Regulatory Agency. Repurposing compounds is quite attractive for that point, really."

Dexter said there are currently "more novel drugs coming through than repurposing candidates" in the Parkinson's space, and that while government and charitable assistance can be beneficial pharmaceutical companies often are not involved in funding this sort of work.

He said: "Traffic to clinical use is not necessarily straightforward. Ambroxol is a component in cough mixture, so it's in a syrup and not a tablet, so we'd have to find manufacturers that are willing to make the tablets and then go through the licensing approach. Repurposing projects need to source their funding through either charitable or government funding to test out these compounds, there doesn't tend to be pharmaceutical money driving the process."

That said, manufacturing a tablet form of ambroxol for Parkinson's disease "should be quite an attractive market" for whichever generic manufacturer decides to pick it up, according to Dexter.

Novel Design Can Shave Years Off Trial Timelines

Meanwhile, research likewise spawning from UCL has allowed the Octopus trial to launch. The multi-arm, multi-stage (MAMS) trial will test several treatments with the aim of slowing down or stopping disease progression in people with primary or secondary progressive multiple sclerosis. The trial is starting by repurposing metformin, a first-line type II diabetes drug, and alpha lipoic acid, a medication used to manage and treat chronic diseases associated with oxidative stress. Octopus is the first MAMS trial to be launched in the space.

"Ultimately having a MAMS trial is exciting because it allows us to test potential treatments more quickly and more effectively," said MS Society research communications manager Catherine Godbold.

MS progression is a slow process, meaning it can take years to say for sure whether a drug has effectively slowed the gradual worsening of disability. To bypass this wait, patients enrolled in initial phases of the Octopus trial will undergo MRI scans many months before an effect on disability progression could be expected to show itself, to get a preview of whether the drug is having an effect inside the brain.

"If there's no effect at the MRI stage, we can stop testing the drug without waiting for the end result," said Godbold. "Then we can focus our resources on drugs that still have a chance of making a difference. Equally, if a drug is successful at that interim analysis stage, it can then move seamlessly through, and hundreds more people can join the current participants. Then those data that's already collected from the first people feeds into the final results. You're condensing what would normally be two successive multi-year trials into one."

She continued: "In traditional trials, you compare a group of people taking a new treatment with a group of people taking a placebo or an existing treatment. In Octopus, several drugs can be tested at once and compared against a single control group – that's what makes it multi-arm."

Octopus is far from the first repurposing effort in MS, or even the first multi-arm trial. The MS-SMART trial, which explored the use of fluoxetine, riluzole and amiloride in patients with secondary progressive MS, failed to meet its endpoints in 2020. Godbold explained that through its multi-arm design the MS-SMART trial took just five years but would have taken around 15 years if conducted as three separate clinical trials.

There are other repurposing trials in the MS space that will report sooner than the Octopus trial, which is not expected to deliver any concrete results until at least 2028. MS-STAT2, the largest academic-led progressive MS trial to date, is testing the use of cholesterol-lowering drug simvastatin to slow disability progression in secondary progressive MS and is expected to report in 2025. The ChariotMS trial, which is estimated to complete in 2027, is a Phase II trial testing whether Mavenclad (cladribine), a drug already licensed for highly active relapsing MS, can slow worsening of arm and hand function in people with advanced MS.

Godbold explains that researchers have a three-pronged approach when it comes to trialing new drugs for MS, looking at protecting nerves, repairing myelin and preventing attacks. "If you're someone with MS, you want to know that it's being tackled from all angles," she explained.

"We're using this repurposing and novel trial design to come at it in all the ways that we need."

Novel molecule development, compared to repurposing, entails a far higher cost and a much longer time spent in development – time that patients with certain progressive neurological conditions cannot always afford to wait. In the CNS space, the growing body of repurposing research could prove to be particularly vital.

CGT Is In Its Infancy For CNS Disorders, But Technical Strides Being Made

David Wild
18 Mar 2024

Executive Summary

Technical challenges and lackluster investor sentiment about the near-term commercial potential of cell and gene therapies in neurological disorders may be holding the field back.

Neurological disorders account for roughly 45% of rare diseases; and 85% of rare and ultra-rare disease trace back to a single gene defect. Given this, the potential for regenerative therapies to benefit patients with central nervous system-based disorders is vast.

But the task at hand for companies in the CNS cell and gene therapy space is formidable.

As Cory Nicholas, co-founder and CEO of Neurona Therapeutics, a CNS cell therapy company told In Vivo, "We're combining two historically difficult areas – treating the central nervous system and using cell therapy. There aren't many successes that you can easily point to in the space."

The Spinal Muscular Atrophy Race

The limited commercial successes in the CGT market for neurological diseases to date have been most notably focused on the treatment of spinal muscular atrophy (SMA), an inherited neurological disorder that affects motor neurons controlling movement and skeletal muscle activity.

Biogen, Inc.'s antisense (ASO) therapy Spinraza (nusinersen) was first to market, approved in 2016,

and was eventually overtaken by Novartis AG's adeno-associated virus (AAV)-based treatment, Zolgensma (onasemnogene abeparvovec), approved in 2019.

Then came Roche Holding AGwith its once-daily, orally administered survival motor neuron (SMN)-2 RNA splicing modifier Evyrsdi (risdiplam), developed initially by PTC Therapeutics, Inc.. Now, Biogen is trying to regain its market position in the SMA gene therapy space by returning to its Spinraza partner, Ionis Pharmaceuticals, Inc., and licensing BIIB115, a next generation, longer-acting ASO, for $60m upfront. (Also see "Biogen Acquires Ionis' Spinal Muscular Atrophy Candidate As Spinraza Loses Its Shine" - Scrip, 5 Jan, 2022.)

The few other CNS regenerative therapies include bluebird bio's Skysona (elivaldogene autotemcel), a gene therapy for boys with early-active cerebral adrenoleukodystrophy, PTC Therapeutics' Upstaza (Eladocagene exuparvovec), for the treatment of aromatic L-amino acid decarboxylase deficiency, and Sarepta Therapeutics, Inc.'s Elevidys (delandistrogene moxeparvovec), for Duchenne's muscular dystrophy.

All told, CGT products for CNS indications have generated $5.3bn in sales through the end of 2023, according to Evaluate data.

Investor Concerns

For CGT companies interested in treating CNS disorders, finding funding is a challenge. Pamela Spicer, therapy are director for CNS and I&I at Citeline's Datamonitor Healthcare, said the cost and complexity of developing and administering these products, as well as the logistical and regulatory hurdles and market access challenges, were at the top of the list of investor concerns.

"We remain in the infancy of developing the infrastructure needed to support these drugs on the market," she said.

For example, the number of specialized providers and treatment centers that can authorize use of these drugs and monitor for safety concerns after an AAV infusion are limited.

Additionally, strict CMC requirements create bottlenecks for producing these therapies, while regulation around CNS clinical trials of CGTs can slow down testing. "In one example, a developer identified patients for a study and by the time the Investigational New Drug for the trial had cleared, all of the patients had passed away," Spicer noted.

Once a product is on the market, market access can be slowed by reimbursement processes, again delaying treatment in patient populations for whom time is of the essence. "The speed of Medicaid coverage seems to vary, though there have been reports of it taking over a year to determine coverage criteria and prior authorization from when a treatment was approved," said Spicer.

For these and other reasons, "short-term enthusiasm around some neurological conditions has been dampened," lamented Michael Lehmicke, senior vice president of science and industry affairs at the Alliance for Regenerative Medicine (ARM), an international advocacy group for CGTs.

Lehmicke contrasted the initial funding boom that helped finance the development and commercialization of CNS CGTs like Zolgensma with the current cautious approach investors are taking. Like other biotechs, CGT companies looking at CSN indications need to do much more with less these days.

While regulatory and reimbursement hurdles need to be worked out – and many of them overlap with the broader CGT field – Lehmicke said important technical advances were being made.

Important CGT Technical Advances For The CNS

There is an "explosion of work looking at different ways of using gene therapy in the central nervous system," echoed Deborah Phippard, chief scientific officer of Precision for Medicine, a global contract research organization.

"Where I get particularly excited is how you might use CRISPR/Cas9," Phippard told In Vivo.

Research into CRISPR/Cas9 approach is primarily being conducted in academia, so it could be a while before that modality appears in corporate pipelines. But other companies are developing nearer-term technical improvements.

For example, South San Francisco-based Neurona Therapeutics is a clinical-stage cell therapy startup developing a genetically modified cell type that can carry "complex payloads, have better cell and dose specificity, and superior targeting" within the CNS, Nicholas, the company's CEO, told In Vivo.

"It's all about the cells for us, and cell quality is what's behind our success in the clinic," he said.

That success is most apparent with the company's

lead program, NRTX-1001, a treatment consisting of human myelinating glial cell-type inhibitory GABAergic interneurons that the company is studying as a one-time therapy for patients with drug-resistant epilepsy. This subgroup comprises about one-third of the overall epilepsy population.

Emerging data from the first five participants who received the therapy are encouraging. Two individuals reported a 95% drop in overall seizure counts more than one year after receiving NRTX-1001, while three-month data from another two patients treated more recently showed a 76%-87% reduction in seizure frequency after the first month. The fifth patient still needs to be evaluated but Neurona has already started a higher-dose five-patient arm of the same study and plans to begin a 30-patient randomized controlled trial in 2025.

Aside from the convenience of one-time administration, the treatment has several advantages over current epilepsy treatments. GABA-receptor agonists, for example, can cause sedation and addiction, while surgery or ablation carries the risk of damaging adjacent brain tissue and causing permanent cognitive deficits or vision loss.

"It's on both these counts that we think a regenerative cell therapy could potentially do better," said Nicholas.

The company is also examining NRTX-1001 for other types of epilepsy that originate in clearly-defined areas of the brain and can thus be approached with the same therapeutic strategy. Interestingly, Neurona is planning to study the therapy in a sub-group of Alzheimer's disease patients with subclinical temporal lobe electrical discharges, similar to what happens in the brains of individuals with epilepsy. Nicholas said new research suggests that a third of Alzheimer's patients have this silent feature. And those that do suffer faster disease progression and steeper cognitive decline. The Alzheimer's disease program is in the preclinical phase.

Neurona, which bucked the difficult funding trend and raised $120m in private financing in February, also has an innovative approach to manufacturing. They can produce off-the-shelf products using allogeneic human pluripotent stem cells in a slightly different way than competitors in the same space, Nicholas explained.

"Most other groups work with progenitor cells that are still dividing when they're administered, and that leads to more heterogenous grafts," he said. "We decided to take the cells one step further in the manufacturing process to where they are fully differentiated and their fate is completely locked before they're administered."

This technical advancement helps address a historical barrier in the cell therapy field: controlling and directing stem cells into an exact cell type in a consistent and reproducible manner.

Other Cell Therapy Research

A few other companies are developing advanced cell therapy approaches for neurological disorders. For example, BlueRock Therapeutics LP, a Bayer AG subsidiary, is studying allogeneic pluripotent stem cells to replace dopamine-producing neurons that are lost in Parkinson's disease. It recently released up to 18 months of Phase I data in 12 participants receiving a high or lower dose of the treatment and showed the surgically implanted therapy had no major safety issues. Transplanted cells survived and engrafted in the brain and F-DOPA levels increased even after stopping immune suppression therapy at 12 months. The company is set to begin enrolling patients in a Phase II trial this year.

While investors watch and wait for the CGT CNS space to evolve, government agencies are providing important funding for the field. For example, the National Institutes of Health's National Institute of Neurological Disorders and Stroke (NINDS) launched the Ultra-rare Gene-based Therapy (URGenT) network in 2021 with the goal of developing state-of-the-art gene therapies for ultra-rare neurological and neuromuscular diseases, both through in-house research and external funding. They support Investigational New Drug-enabling studies and plan activities for first-in-human clinical testing of gene-based or transcript-directed therapeutics.

Parkinson's Disease:

- MeiraGTx Holdings plc is evaluating AAV-GAD, designed to increase production of GABA via delivery of the glutamic acid decarboxylase to the subthalmic nucleus.
- Eli Lilly and Company is studying LY3884961, an asset it obtained with its purchase of Prevail, as a treatment administered sub-occipitally intra cisterna magna in Parkinson's disease patients with GBA1 mutations.
- Bayer subsidiary Asklepios BioPharmaceutical, Inc. is evaluating bilateral intraputaminal infusions of AB-1005 (AAV2-GDNF). The glial-cell line-derived neurotrophic factor (GDNF) is intended to improve survival of dopamine neurons.
- Voyager Therapeutics, Inc and Neurocrine Biosciences, Inc. are studying GBA1 gene-

replacement therapy using a blood-brain barrier-penetrant AAV vector delivered intravenously.
- Novo Nordisk A/S is participating in the STEM-PD trial in Sweden and the UK, studying the effects of human embryonic dopamine stem cells for Parkinson's disease.
- Hope Biosciences is conducting Phase II studies evaluating allogeneic and autologous adipose-derived mesenchymal stem cells in Parkinson's disease

Alzheimer's Disease:
- Stemedica Cell Technologies, Inc. is studying intravenously administered ischemia-tolerant allogeneic human mesenchymal stem cells in patients with mild-to-moderate disease.
- Longeveron, Inc.'s allogeneic mesenchymal stem cell formulation, Lomecel-B, produced an encouraging signal in a small Phase IIa trial.
- Regeneration Biomedical has initiated a trial evaluating intracerebroventricular injections of ex vivo expanded, autologous adipose-derived stem cells.
- NKGen Biotech, Inc. is studying SNK01, a cryopreserved autologous, non-genetically modified natural killer cell therapy.
- Lexeo Therapeutics is investigating LX-1001, a serotype rh.10 AAV gene transfer vector expressing the complementary deoxyribonucleic acid coding for human apolipoprotein E2, to reduce the known APOE4 homozygote risk for Alzheimer's disease by modifying the CNS with APOE2.

Amyotrophic Lateral Sclerosis:
- Kadimastem Ltd. is evaluating AstroRx, a treatment composed of allogeneic healthy human astrocytes derived from human embryonic stem cells.
- Coya Therapeutics, Inc. is studying COYA-101, an off-the-shelf, autologous, expanded T-reg cell therapy.
- Cellenkos, Inc. is developing CK-0803, an umbilical cord blood-derived T-regulatory cell therapy.
- uniQure N.V. and Apic Bio, Inc. are evaluating AMT-162, a recombinant AAV vector-based treatment containing complementary deoxyribonucleic acid encoding the SOD1 gene.

Reaching The Brain With Gene Therapies

For gene therapy developers, the primary challenge to date has been safely and effectively delivering these treatments past the blood-brain barrier. Barrier integrity prevents most large molecules, including gene therapies, from entering the brain.

Researchers have been trying different approaches to improving CNS penetration, from simple mechanical adjustments like patient positioning during therapy administration to the use of ultrasound to temporarily disrupt the blood-brain barrier and facilitate transduction of AAV gene therapy.

Others are examining novel modes of administration, like intra cisterna magna injection, which places the treatment directly into the cerebellum, brainstem, or spinal cord, or intracerebroventricular injections, which bypass the blood-brain barrier. The challenge with complex treatments like these is that they require a highly specialized procedure that health care systems may not have the resources to provide.

"If you're dealing with a condition like Parkinson's, which affects around 100,000 people in the US, that might be a much larger number of surgical procedures than the system can handle," said ARM's Lehmicke.

Voyager's Sought-After Capsids

Boston-based Voyager Therapeutics has developed a tracer-derived capsid delivery system they say can overcome some of the challenges of existing AAVs, and their approach has been attracting big pharma and biotech partners. Their capsids provide better brain penetration and can deliver payloads more efficiently and in a more targeted manner, reducing the need for higher doses and limiting the risk of exposure to other tissues.

"Gene therapy has gone through periods of great excitement and periods of concern, and I think one concern now is that we've hit limits on toxicity profiles as we keep pushing the dose higher," CSO Todd Carter told In Vivo. "We can screen millions of potential capsid variants and pull out those that deliver thousands of times better to the brain using much less payload, so we can have reduced delivery to off-target tissues."

The company was founded with a focus on direct cerebral injections of AAV-based treatment but started developing its novel technology in 2021 after seeing that "conventional capsids really weren't up to the task of delivering therapies to the brain, in most cases."

The company has preclinical programs targeting Alzheimer's and Parkinson's diseases as well as amyotrophic lateral sclerosis and Friedreich's Ataxia. Although the pipeline only has early-stage programs, Voyager has garnered some notable partnerships.

The company signed a strategic collaboration and capsid license agreement worth up to $1.2bn with Novartis Pharma AG in 2023 to advance potential gene therapies for Huntington's disease and SMA, and the big pharma has also licensed other capsids from Voyager.

Voyager has also licensed capsids to Alexion Pharmaceuticals Inc., AstraZeneca PLC and Sangamo Therapeutics, Inc., and it has four CNS gene therapy programs partnered with Neurocrine Biosciences, Inc..

The partnerships are an encouraging sign that despite the challenges in regenerative medicine in the CNS space, the right innovation can garner financial support.

Other companies pioneering the gene therapy CNS space include New York City-based Neurogene Inc., which has a small pipeline of clinical and preclinical gene therapies for rare monogenic neurological diseases. They claim their transgene regulation platform facilitates delivery of therapeutic levels of genetic payloads while limiting transgene toxicity associated with conventional gene therapy.

Along with Neurona, Neurogene is another one of the few companies in the CNS CGT space that has had recent fundraising success. After a reverse merger and concurrent $95m private financing in 2023, it reported a cash balance of approximately $200m in December 2023, enough to fund operations through the second half of 2026. (Also see "Deal Watch: Sangamo Inks Significant Option Deal With Prevail After Losing Tie-Ups With Novartis, Biogen" - Scrip, 18 Jul, 2023.)

Its lead program is NGN-401, a one-time AAV9 gene therapy treatment for Rett syndrome, a rare monogenic neurological and developmental condition beginning in the first year of life. Unlike conventional AAVs, AAV9 can fit in larger amounts of material, in this case delivering the entire human MECP2 gene. Interim Phase I/II clinical data for this indication are expected later this year, as are interim Phase I/II clinical data for their experimental gene therapy for CLN5 Batten disease, an inherited nervous system disorder that manifests around age 5.

Additional Genetic Innovations

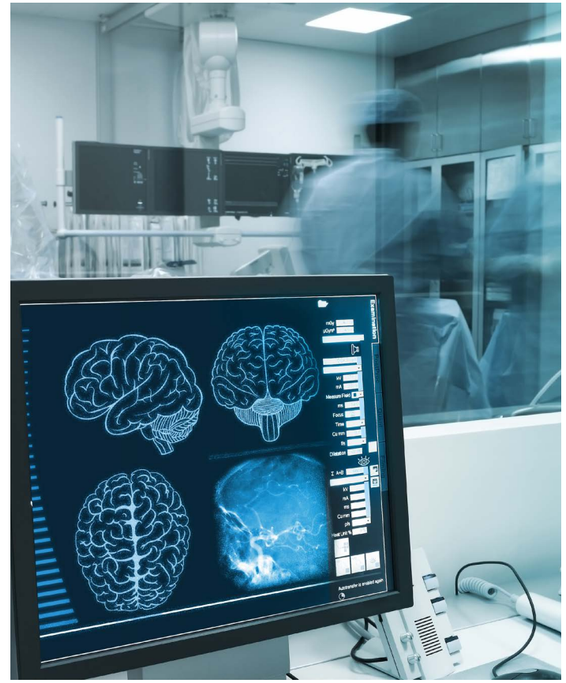
Other technical improvements that could expand use of CGT in neurological indications are a few years away. These include not only novel capsids, but cell- and tissue-specific promoters that could expand the reach of gene therapies to specific dividing and non-dividing cells, from astrocytes to neurons.

Immunogenicity could also become less of a concern if researchers successfully employ optimized codons, another area of research. Furthermore, lentivirus-mediated gene delivery approaches are being investigated to package larger amounts of genetic material.

Novel non-viral delivery systems are also under development. These include lipid polymers and nanoparticles, which are particularly useful for packaging RNA-based modalities, such as small interfering RNAs (siRNAs) and ASOs. They have also yielded promising laboratory results for targeted delivery of CRISPR-Cas9, helping to facilitate in vivo gene editing in neural cells for conditions like viral keratitis and Leber congenital amaurosis inherited blindness.

A Matter Of Time

While CGT is still in its infancy when it comes to neurological disorders, the plethora of research efforts underway could push the field towards maturity sooner than onlookers may anticipate. As the improvements come to fruition, more financing will be directed to companies with compelling advances, overcoming a key barrier to the field's progress. And once that happens, allow regenerative medicine will be able fulfill the potential that many believe it has: alleviating the burden of illness for so many individuals with currently untreatable CNS conditions.



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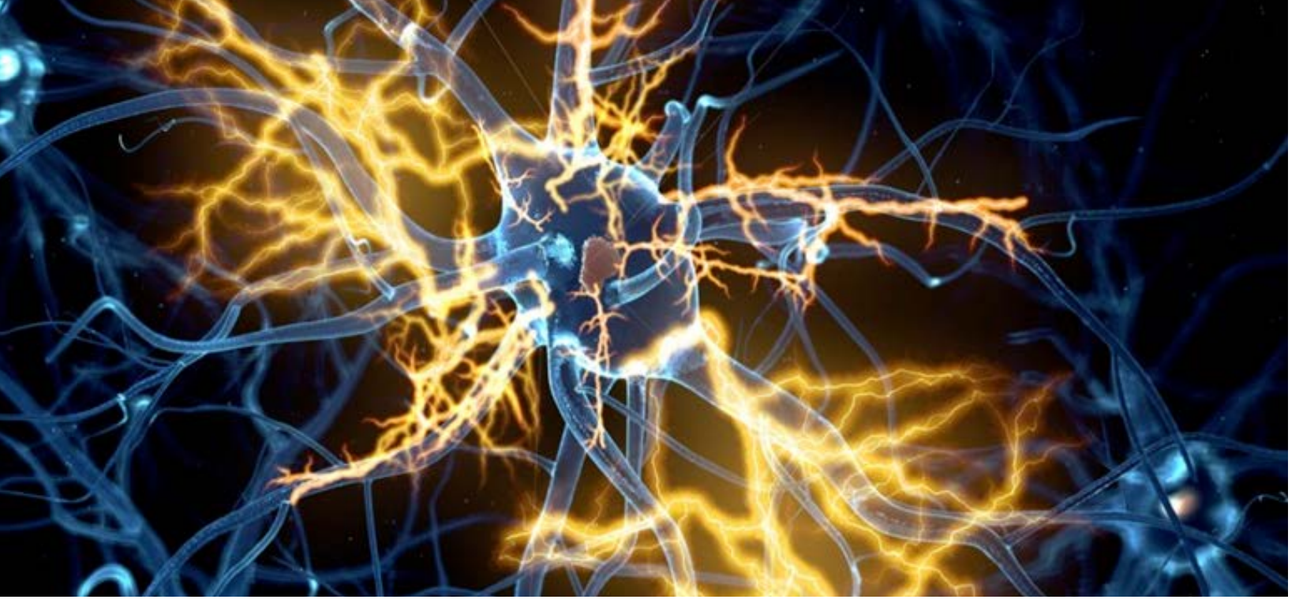

Schizophrenia, Depression And Neuropathy: What's Coming In 2024

Elizabeth Cairns
08 Sep 2023

Executive Summary

The following four neurological products are likely to reach market next year. Carving out sales will be an entirely different problem.

Drugs that act on the nervous system are notoriously difficult to bring to market, with unpredictable placebo responses scuppering many a late-stage trial. But there are some sparks in the darkness, and Biomedtracker has pinpointed four psychiatric or neurological products that are likely to buck the trend and reach market next year.

Some of the most emphatic victories seen in the extremely hard to treat indication of schizophrenia have been won by Karuna Therapeutics, Inc.'s combo therapy KarXT, and if it is approved next year, as is expected, it would usher in the first new mechanism to treat the disease in decades.

KarXT is a coformulation of the M1/M4-preferring muscarinic agonist xanomeline with trospium chloride, a peripheral muscarinic receptor antagonist. The idea is that trospium cancels out xanomeline's peripheral side effects but, since it cannot cross the blood-brain barrier, does not hamper xanomeline's effect in the brain.

PANSS down

In its two pivotal trials, EMERGENT-2 and -3, both in acutely psychotic hospitalized adult patients with schizophrenia, KarXT produced statistically significant reductions on the Positive and Negative Syndrome Scale (PANSS) total score of 9.6 and 8.4 points, respectively (Also see "Karuna Three-For-Three As Another KarXT Schizophrenia Trial Hits Primary Endpoint" - Scrip, 20 Mar, 2023.).

This compares well with many other antipsychotics. The label for Johnson & Johnson's now-generic Risperdal (risperidone) claims simply that it was "generally superior to placebo on several PANSS measures" in its pivotal trials. The label for the current biggest-selling branded schizophrenia product, J&J's long-acting pill Invega Sustenna (paliperidone palmitate), just says that it was "superior to placebo on the PANSS at all doses".

Karuna plans to submit an NDA for KarXT in schizophrenia in the next few months, so an FDA approval decision ought to come in 2024. Data from two Phase III long-term safety and tolerability trials are also expected next year.

Another Phase III trial, ARISE, will evaluate the safety and efficacy of KarXT as an adjunctive treatment in adults who have an inadequate response to their current antipsychotic therapy, which is likely to better reflect how the drug would be used in the real world, if approved.

The agent has a drawback in its twice-daily administration versus the once-daily or longer schedules of available schizophrenia therapies. But it is still considered biopharma's most valuable unpartnered asset, with Evaluate Omnium placing its net present value at $8.3bn.

Sleepless Nights

A new mechanism could make its debut next year in depression, too. J&J is developing seltorexant, a hypocretin/orexin 2 receptor antagonist, for patients with major depressive disorder and insomnia.

Two Phase III trials are ongoing, one head-to-head against AstraZeneca PLC's Seroquel XR (quetiapine extended-release tablets) in 720 patients and another, 588 patients strong, against placebo. Data from both could come this year.

However, another Phase III trial was terminated in 2022 after an interim analysis, though J&J did not say whether this was due to concerns over efficacy or safety.

In a Phase IIb trial in MDD patients with sleep disturbances, seltorexant allowed a statistically significant reduction in Montgomery-Asberg Depression Rating Scale (MADRS) score at week three but not at week six, suggesting that effects could taper over time. Although seltorexant showed only modest efficacy as an adjunctive treatment in this study – specifically at the lowest dose – the drug's target population is SSRI/SNRI-inadequate responders, a challenging population to treat.

In a smaller Phase IIb study versus Seroquel, J&J's therapy permitted greater improvement in MADRS score and a lower treatment-related discontinuation rate than the control after six months' treatment. Discontinuation rates were similar in the two arms.

Should the two ongoing Phase III studies come up trumps, J&J could submit an NDA before the end of 2023, with the intention of a 2024 launch. But the terminated study remains a mystery, and therefore, perhaps, a red flag.

Expansion

Intra-Cellular Therapies, Inc. first obtained approval for Caplyta (lumateperone) in schizophrenia, in 2019, and expanded into bipolar disorder, specifically bipolar depression, two years later. Now it hopes to add a claim for MDD, and much will depend on the three near-identical placebo-controlled Phase III trials currently underway.

Like other atypical antipsychotics, Caplyta modulates both serotonin and other monoamines, particularly dopamine, although its exact mechanism of action is unknown.

In the Phase III Study 403 trial, Caplyta was explored as a monotherapy in MDD as well as bipolar I and II. In this combined patient population, Caplyta demonstrated a statistically significant reduction of 5.7 points on the MADRS total score compared with placebo at week six, and a 5.9-point reduction over placebo in the MDD subpopulation.

Interestingly, despite the drug's success as a monotherapy in MDD, the three Phase III studies are assessing Caplyta as an adjunctive treatment. Each is in 470 patients who have not responded well to other antidepressants; all are assessing MDRS score change at six weeks. Two of these trials, known as 501 and 502, are set to finish this year, with the third, 505, likely to read out towards the end of 2025. A larger, longer, open-label study in MDD will conclude in the middle of next year.

Intra-Cellular has indicated that it plans to file an sNDA in 2024, and an approval decision could come the same year. Bearing in mind the trials' design, however, Caplyta could well be relegated to refractory patients.

Convenience

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare disorder of the peripheral nerves characterized by increasing sensory loss and weakness associated with loss of reflexes.

Takeda Consumer Healthcare Co. Ltd.'s HyQvia is a formulation of recombinant human hyaluronidase and immunoglobulins, which is infused under the skin into fatty subcutaneous tissue. It is intended as a maintenance therapy in adult patients with CIDP, and if it is approved, as it cold be next year, it will become the first monthly subcutaneous immunoglobulin injection on the market. It employs Halozyme Therapeutics, Inc.'s ENHANZE technology to enable high levels of the immunoglobulins to enter the bloodstream.

In the pivotal Phase III ADVANCE-CIDP 1 trial, HyQvia, administered every four weeks to most patients, showed a significant reduction in relapse rate compared with placebo, and the product is now filed with regulators.

Takeda's argument is convenience. The current standard of care for CIDP is intravenous immunoglobulin, which must be administered over several hours every three weeks and carries the risk of side effects including injection site reactions, nausea, and headaches. But the immunoglobulin market is long established and dominated by CSL Limited and Grifols, S.A., and convenience – plus, Takeda hopes, better efficacy thanks to the concentrated formula – might not be enough to take share from the entrenched players.

For Psychedelics, US FDA Is Open To Creative Thinking But Firm On Approval Standards

Bridget Silverman
21 Feb 2024

Executive Summary

Flexible thinking and rigorous standards will both be needed to develop psychedelics as drug therapies in order to surmount the many complicating factors, from unique 'set and setting' aspects to functional unblinding, speakers at Reagan-Udall Foundation meeting agree.

Psychedelic drugs present unique challenges to the conventional drug development paradigm, so it is fitting that a more unconventional or creative package of clinical trials could make for a more successful NDA than the traditional ideal of two replicate randomized pivotal trials.

"Our regulations are inherently flexible, and the exact types of studies that are needed to provide this data aren't specified," FDA Center for Drug Evaluation and Research Division of Psychiatry director Tiffany Farchione told a recent Reagan-Udall Foundation for the FDA meeting on psychedelic clinical study design.

"The standard for substantial evidence for psychedelics is the same as it is for any other drug," Farchione emphasized as she described the agency's June 2023 draft guidance "Psychedelic Drugs: Considerations for Clinical Investigations." (Also see "US FDA Outlines Psychedelic Drug Trial Principles, But It Won't Be An Easy Trip" - Pink Sheet, 28 Jul, 2023.)

However, "substantial evidence doesn't have to mean two trials designed exactly the same," she said. "I guess this is the bottom line."

Key Takeaways

- From dose response to maintenance assessment, trials for psychedelic drugs will likely be very different from other psychiatric drugs, even if the approval standards are the same.
- Even if the value of psychological support can be measured, an integral role as part of drug treatment regimen poses stark challenges to FDA's regulatory authority, though it does have safety powers.
- EMA is wrestling with the same quandaries as it updates 10-year-old guidance on major drug depression to address psychedelics; comments are due by 31 March.

"We don't have a specific recommendation for how to do these studies the right way," Farchione observed. "That's why we describe trial design elements for sponsors to consider rather than characterizing them as best practices or standards in the guidance."

"You're going to have different designs within a given program," CDER Division of Psychiatry deputy director Bernard Fischer noted.

"Instead of having just two placebo-controlled studies, it may be the case that we would want to see a placebo-controlled study to really characterize the safety of an intervention, but then we might want to see something else for a second kind of study … like a dose response study," he explained.

Or "we might want to see something with an active control, where we wouldn't necessarily be looking at safety per se" because the study "would be primarily to look at efficacy."

"Treatments with novel mechanisms of action and new dosing paradigms will require unique clinical development plans to inform labelling and clinical use," Johnson & Johnson Innovative Medicine VP neuropsychiatry clinical development Carla Canuso advised.

J&J's Spravato (esketamine), a single-isomer nasal spray formulation of the dissociative anesthetic ketamine, is usually considered the first – and still the only – psychedelic therapy approved by the FDA, although the FDA is reviewing an NDA for midomafetamine (MDMA) for post-traumatic stress disorder from Lykos Therapeutics (formerly known as MAPS Public Benefit Corporation).

Regulators in the European Union are wrestling with the same quandaries facing psychedelic drug development. The European Medicines Agency is updating a 10-year-old guidance on major drug depression to address the repurposing of psychedelics and rapid-acting antidepressants, issuing a draft in September 2023 that advises that different types of products may require separate trial design strategies.

At the October RAPS Convergence meeting, EMA senior scientific specialist in psychiatry, mental health and digital health Florence Butlen-Ducuing sounded similar concerns to the Reagan-Udall panelists about the importance of setting, the role of psychotherapy, and the need for unconventional thinking about trial design. (Also see "Psychedelic Drugs: Regulators Still Unsure On Development Path, But Willing To Listen" - Pink Sheet, 10 Oct, 2023.)

The EMA is seeking comments on its draft MDD guidance until 31 March 2024. (Also see "EMA Addresses Rapid Acting Therapies, Psychedelics In Updated Guidance On Depression Treatments" - Pink Sheet, 20 Sep, 2023.)

Thinking About Dose, From Response…

"The dose response relationship for most psychedelics is really poorly understood," Farchione noted, so "it's important to characterize this in your clinical studies, both for safety and for efficacy."

Dose response trials could be "another type of adequate and well controlled study" to support a psychedelic NDA, she said.

A dose response trial design "really offers a potential alternative to some of the traditional models with placebo or with having an active comparator," Farchione suggested. Even if there is no placebo group, a study with multiple different doses "can serve as one of the adequate and well-controlled trials," with an application rounded out by studies using "different complementary designs."

In such a scenario, one placebo-controlled trial could "help us assess safety," and then a dose response trial could "help with the efficacy assessment," Farchione said. "That could be one strategy to demonstrating substantial evidence."

...To Maintenance

Canuso highlighted the importance of maintenance of effect data in psychedelic applications based on J&J's experience with Spravato, which was first approved in treatment-resistant depression in 2019 and for rapid reduction of depressive symptoms in MDD patients with active suicidal ideation with intent in 2020.

"Oral antidepressants, at least those that were approved to modern times, completed the maintenance of effects study post approval," the J&J exec noted. "Short-term studies were sufficient for the initial FDA approval."

With esketamine, however, the FDA told J&J that "due to its uniqueness (e.g. safety concerns, questions of how to maintain response), we view esketamine very differently than the previously approved oral antidepressants. We would therefore need to see maintenance data at the time of filing."

"Given the great importance of the maintenance-of-effect data with this drug," the FDA said it "would consider one positive short-term study along with a positive maintenance-of effect-study to be sufficient for NDA submission," Canuso reported.

Ultimately the FDA approval of Spravato for treatment-resistant depression in 2019 rested on five completed Phase III trials that addressed different concerns, Canuso summarized, including three short-term acute induction studies (TRANSFORM-1, -2 and -3); SUSTAIN-1, an integrated acute/maintenance trial using a randomized withdrawal design; and the SUSTAIN-2 open-label safety study.

Ongoing trials included a US-only short-term Phase III and SUSTAIN-3, which provided patients from prior studies access to esketamine nasal spray while assessing long-term individualized dosing.

The FDA approval carried an enhanced Risk Evaluation and Mitigation Strategy and long-term postmarketing safety study.

The decision also marked the first time the Division of Psychiatry had considered a randomized withdrawal trial as one of two adequate and well-controlled trials to demonstrate substantial evidence of effectiveness. (Also see "Janssen's Spravato Enters US Market With Enhanced REMS And Plans For A Monotherapy Trial" - Pink Sheet, 6 Mar, 2019.)

Single-Dose Therapy But Chronic Disorders

"Even though current psychedelic drug development programs are exploring mostly single dose or intermittent dose treatment paradigms, most of the conditions that are being studied, at least in psychiatry, are for chronic disorders like major depressive disorder and PTSD," Farchione stated. "Bear this in mind when we talk about durability of treatment response."

"Until we know how long a treatment effect lasts ... we don't know yet whether chronic quality studies are going to be required for these programs," she noted. "This is a major unanswered question."

"Our a priori assumption is that ... the symptoms will come back when you don't continue to treat," she said. "We need to be able to write a label information about more than just the first dose or two."

"Durability of effect becomes an even greater factor in the overall benefit-risk assessment of novel therapeutics with safety and abuse liabilities," J&J's Canuso stated.

During Spravato's development, the FDA advised that "in order to approve such a product, we would need to be able to advise clinicians on how best to use the product after an initial response," she reported.

"We are interested in understanding the dose response with regards to the efficacy and how that might or might not affect the psychedelic effects," FDA psychiatry division clinical team lead Martine Solages told the Reagan-Udall meeting.

"We're still in the phase of gathering data, but if any of these products were ever to get to the point where we're talking about labeling" the agency will want to describe for practitioners what doses might be useful and what the associated safety concerns might be.

Currently, "we don't have information to guide whether a lower dose would still be effective, or potentially mitigate risk," Solages said. "We don't have information to understand whether a higher dose could be used, including in different populations that might have differential responses."

"It's a very heavy regulatory challenge for us," she stated. "We certainly want as much information as we can to help us with those decisions."

Lykos Therapeutics chief scientific officer Berra Yazar-Klosinski emphasized the work the company put into designing and justifying an empirical dosing regimen for midomafetamine (MDMA) for PTSD. "We need to understand what's the relationship between drug dose and various intrinsic factors such as weight when determining what dose to study for MDMA."

"We really had to learn from empiric recommendations from clinicians in order to design this development program," she said. MDMA does not have a linear dose response curve, but it did show a threshold effect – and it does have extensive use outside of conventional medicine.

"Essentially, we reverse engineered what the clinicians were telling us was most beneficial, utilizing PK studies," Yazar-Klosinksi said. The company used a fixed-dose paradigm in Phase II/III, not based on weight, in a split dose approach with dose escalation.

Standardizing Set And Setting

Under Lykos' pending NDA, midomafetamine is given at three medication sessions, at least 21 days part, administered in combination with psychological intervention provided a qualified healthcare provider.

"We've described the therapy component of these sessions as a psychological intervention to reflect the intensive nature of these sessions, which go beyond a standard talk therapy session," Yazar-Klosinski emphasized. "They involve the intentional use of the effects of the medication."

"We've intentionally not characterized the risk of use of MDMA without adequate psychological support due to the seriousness of the underlying disease," PTSD, she explained.

Lykos' perspective on the importance of set and setting to the success of midomafetamine treatment is a majority position.

COMPASS Pathways' psilocybin therapy COMP360 includes "psychological support," chief medical officer Guy Goodwin noted. "And the reason we provide psychological support is essentially for the reasons of safety."

"We need to further standardize psychological support," Goodwin continued, to "ensure we're clearly measuring the drug effects and not ... differential behavior by therapists."

"The issue at stake here is whether preparation and integration should be best considered psychological support, or supportive psychotherapy," David Yaden, Johns Hopkins University, said.

"I think going forward more and more standardization is ideal, mostly for scientific reasons," Yaden suggested. A set of concepts could be provided in the psychological support model "to cut down on the variability of what facilitators are drawing on."

Many non-mainstream therapies are used in the psychedelic community, he pointed out, but "the main issue is the lack of safety testing related to concepts. There's minimal careful research done on these concepts."

Cognitive behavioral approaches are a more realistic source of therapeutic concepts suitable for supportive psychotherapy, Yaden said. CBT and its ideas about cognitive beliefs, mindfulness and emotional regulation are "relevant and resonant with the psychedelic experience" while giving facilitators "a common constellation of concepts to draw from."

"We're seeing a lot of psychedelic scientific and ethical exceptionalism," Yarden observed, "and they do have distinct qualities." However, "rather than treating psychedelics as something new under the sun, I think we can apply existing concepts, guidelines and standards in psychedelic research and perhaps in clinical applications," he concluded.

eBook - A New Era for CNS Therapeutics

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MindMed Aims For Standard Endpoints

MindMed is taking a stand against psychedelic exceptionalism in its development of MM-120 (lysergide D-tartrate), an LSD therapy in Phase IIb for generalized anxiety disorders. “We decided that really what needs to be done here is a standard drug development, standard clinical trials and standard endpoints and to the greatest extent possible, to treat patients and our protocol the exact same way that we would treat any other CNS drug,” CEO Robert Barrow said.

In contrast to the other late-stage psychedelic sponsors, “we were not going to do any sort of therapeutic intervention other than administration of the drug,” he said. “We’re not going to do any assisted therapy or therapeutic intervention prior to treatment.”

Patients in MindMed’s trials are under observation by staff who are qualified under FDA’s draft guidance on psychedelic development, Barrow emphasized, and have follow up visits and comprehensive informed consent.

When MindMed read out four-week primary Phase II results in December 2023, “we were very happy to have seen that even when we remove any of those other [therapy] elements that have been used historically, we saw a drastic reduction in anxiety symptoms,” Barrow said.

A Placebo Wrapped In A Complex Therapeutic Milieu?

“The combined use of drug and therapy in an intervention ultimately complicates our assessment of the drug’s effectiveness, and presents a challenge for future labeling,” Farchione observed.

Even if the value of psychological support can be measured, an integral role as part of drug treatment regimen poses stark challenges to the FDA’s regulatory authority. “We don’t regulate psychotherapy,” Farchione reminded the Reagan-Udall meeting. “And we don’t regulate the practice of medicine.”

The FDA’s ability to regulate the circumstances around drug administration is pegged to safety. Farchione noted a few examples of psychological support in labeling, emphasizing that “the descriptions of the therapy type intervention that are in labeling are very abbreviated and very general”:

- Naltrexone extended-release injectable suspension for alcohol and opioid dependence, where the Indications and Usage section of labeling states that “treatment … should be part of a comprehensive management program that includes psychosocial support.”
- Bupropion extended-release tablets for smoking cessation, where the Dosage and Administration section that that “it is important that patients continue to receive counseling and support throughout treatment … and for a period of time thereafter.”
- Buprenorphine sublingual tablets for opioid dependence, where the Clinical Studies section of labeling reports that “all trials used buprenorphine in conjunction with psychosocial counseling as part of a comprehensive addiction treatment program. There were no clinical studies conducted to assess the efficacy of buprenorphine as the only component of treatment.”

“We can mandate certain credentials for clinical studies,” Farchione noted, but “we do not have the authority to say that similar credentials will be needed for similar roles in the post-market setting.”

From a regulatory and labeling perspective, another major problem with psychotherapy-assisted psychedelic therapy “is the lack of a rigorous definition of what the psychotherapeutic interventions are,” she said.

“Overall, the therapy is not just a confounding factor in the overall treatment model” for psychedelics, Farchione noted. “It appears to be integral to the treatment as a as a safety feature, and in order to maximize the treatment effect. But we don’t know what major components of this psychotherapeutic intervention are necessary to ensure safety.”

“Identifying what is really the active component in this paradigm will help us come up with better designs and better controls,” Fischer commented.

The FDA will want to know “which features are critical for efficacy and what are the minimum components necessary to control safety,” Division of Psychiatry associate director Javier Muniz added. “This is ultimately extremely important to write a label.”

“A factorial study would be highly informative, and allow us to write a better label, but we just haven’t seen that,” Farchione said. “These are big and expensive.”

“But each of these elements can impact the therapeutic response, so it’s important to tease out the contribution from these various issues in order to avoid ultimately approving a placebo that’s just wrapped in a complex therapeutic milieu,” Farchione stated.

The Role Of Digital Therapeutics In Central Nervous System Clinical Trials

Maureen Glynn PsyD LMFT, is global head of Medical Device Regulatory Services at ICON.
Louisa Steinberg MD PhD, is senior director, Drug Development and Consulting Services at ICON.

Executive Summary

Louisa Steinberg and Maureen Glynn from ICON consider the role of digital therapeutics in the treatment of central nervous system conditions and how they can be used to improve clinical trials.

The circumstances surrounding the COVID-19 pandemic increased the number of patients faced with mental health challenges. At the same time, providers and patients became more adept at using online and digital care frameworks. These two factors combined to accelerate the development of digital therapeutics to prevent, manage and treat central nervous system (CNS) conditions.

The promise of digital therapeutics for CNS conditions has coincided with the increasing popularity of wellness apps. However, digital therapeutics are distinct from these apps, since they provide an evidence-based therapeutic intervention and must be clinically evaluated – in many cases, requiring a clinical trial to demonstrate safety and efficacy. There are a number of aspects to these clinical trials that differ from traditional therapeutics trials, of which – due to the relative newness of digital therapeutics – sponsors may not be aware.

The majority of digital therapeutics in the CNS space are not intended to be used as stand-alone treatments. Instead, they may aim to improve daily functioning

for people suffering from a severe illness, or provide ongoing, additional support for patients who have experienced some improvement to a condition following treatment but continue to experience impairment. Examples of digital therapeutics in the psychiatric space include bringing cognitive behavioural therapy (CBT) modalities to patients — for example, exercise modules on cognitive restructuring — and contingency management, which recognises and reinforces individual positive behavioural change. In neurology, some available digital therapeutics have focused on managing mood and anxiety symptoms associated with a specific neurologic indication, or providing physical and occupational therapy components to improve daily functions such as walking or writing.

Here, we explore how the present regulatory and payer landscape for digital therapeutics in CNS treatments impacts clinical trial design and additional elements of clinical trial design for digital therapeutics, which sponsors may need to consider.

CNS digital therapeutic regulatory and payer landscape

All digital therapeutic products must demonstrate clinical evidence of safety and efficacy and, therefore, demonstrate clinical value. However, a digital therapeutic's classification within the regulatory landscape will guide the requirements for a clinical trial. Within the US Food and Drug Administration's (FDA) Center for Devices and Radiological Health, digital therapeutics are classified under 'software as a medical device.' Under the FDA, digital therapeutics are then classified as Class I, II or III medical devices.

Since Class I medical devices pose minimal risk to patients, nearly all of these devices do not require clinical trials for safety, and are excused from the regulatory process.[1] In behavioural health, digital therapeutics are most often categorised as Class II medical devices, which are described as having a moderate risk to user safety.[2] Finally, Class III medical devices pose a high risk to patient safety, encapsulating medical technologies such as life-supporting devices and implants.[1] Digital therapeutics may also be grouped into one of three categories that describe intended purpose: disease treatment, disease management or health function improvement.[3] Digital therapeutics must always administer a therapeutic intervention and support the claims of a product using clinical endpoints, regardless of the intended purpose.[3]

Meanwhile, payer coverage of digital therapeutic interventions can pose unique challenges as a result of contrasting evidence standards between disparate regulatory bodies, such as the Centers for Medicare and Medicaid Services (CMS) and the FDA. For example, the CMS requires that intervention be 'reasonable and necessary,' whereas the FDA demands that products be 'safe and effective.' Oftentimes payers follow CMS decisions because of its exacting formulary guidelines. Clinical trials should be designed to maximise data collection to ensure payer coverage, while also striving to minimise the length of the trial to keep participant burden low.

Aligning clinical trial evidence with regulatory and payer requirements

When designing clinical studies, it is important to account for the type of evidence that should be generated to ensure CMS and payer coverage. This often requires more granular or specific information, such as pinpointing exactly which populations might benefit from the intervention and including evidence of the long-term effects of a therapeutic.

Taking into consideration the need for evidence generation for regulatory review and payer reimbursement decisions, the specific type of data used to quantify endpoints should be carefully selected. Primary, secondary and exploratory endpoints measure the positive or negative impacts that a therapeutic may have on a participant of a clinical trial. When assessing these endpoints in CNS clinical trials for digital therapeutics, it is important for healthcare professionals to consider the various types of reported outcomes – patient-reported outcomes, performance outcomes, clinician-reported outcomes, observer-reported outcomes and even ecological momentary assessments – and which ones are appropriate to use for evaluating the different levels of study endpoints. For example, clinician-reported outcomes should be used with primary endpoints, which are generally efficacy measures that address the main research question.

To get long-term efficacy and safety data, sponsors may benefit from using tokenisation. Participant tokenisation links different sources of patient-level, real-world evidence – while, at the same time, protecting patient privacy – thereby giving researchers invaluable insights into new data trends. Tokenisation may offer a deeper understanding of patient journeys, providing past and current data on a participant's medical history, medical events, concomitant medications and ongoing endpoint evaluation. Furthermore, tokenisation can integrate wider populations into the data set, improving sample diversity and overall comparative accuracy.

Data considerations

Data strategies are vital when designing a clinical trial with digital devices. The use of digital therapeutics in decentralised clinical trials (DCTs) often produces larger data sets than traditional trials, requiring a data infrastructure that is robust, adaptable and scalable. For example, a phase 2 clinical trial for CNS disorders that uses a 50Hz mobile sensor for movement data from a few dozen patients can easily approach one billion data points per day. The complexity of data sets in CNS trials is multilayered, since data is often combined with electronic patient-reported outcome software. Therefore, data will need to be integrated from a variety of different sources, making it necessary for companies to implement a strong cybersecurity plan to ensure that data coming from disparate sources is equally protected.

Participant recruitment and retention

Without a sufficient number of willing participants, a clinical trial cannot run. In fact, in phase 3 clinical trials, participant drop-out rates can exceed 30%.[4] Digital therapeutics' capabilities are flexible and can be used in hybrid and fully decentralised trials. This has the potential to ease costs and enhance participant recruitment, retention and diversity with its remote options, introducing flexibility in trial participation and removing location as a limiting factor. For example, a DCT on a drug for heart failure symptoms recruited 52% more women and 17% more non-Caucasian people when compared to traditional chronic heart failure trials.[5]

While hybrid or fully decentralised trials for digital therapeutics may increase participant engagement by reducing a patient's travel burden, decentralised elements of a clinical trial can also present challenges for engagement or compliance if patients feel ill-prepared or confused. To ensure patient support is fully embedded in decentralised or hybrid trials, patients should have access to an intuitive, end-to-end digital platform that creates a unified interface between the participant and the clinical trial, including apps that consider user experience and have features that reinforce study compliance. Patients should also be supported by dedicated concierge services, which complement the digital platform and collectively reduce patient burden. For example, a digital platform can provide patients with reminders and monitor compliance and concierge services can directly reach out to patients via text message when non-compliance occurs.

Additionally, sponsors should aim to incorporate digital therapeutics that are intuitive, easy to use and require minimal actions from the participant, allowing for seamless data collection. Providing staff contact information, such as phone number or email, within the digital therapeutic product can also help ensure patients will reach out if they encounter an issue.

Safety considerations

Of course, safety should be paramount when conducting any clinical trial. This is magnified in digital therapeutic clinical trials, especially decentralised ones, in which participants will have far more interaction with the therapeutic than with investigators and healthcare providers, imposing further safety considerations, such as data protection. As such, when designing a CNS trial using digital therapeutics, it is important to consider safety monitoring, which should influence the type of data collected, frequency of data collection and the review of this data.

Additionally, in these trials, symptom severity should be assessed, enabling appropriate monitoring for decompensation. Both criteria and steps for intervention should be included in the protocol, in the event that a participant's symptoms worsen. For example, in a trial for patients with major depressive disorder, suicidality assessment should be assessed at baseline and regular intervals, giving investigators, monitors and sponsors insight into the participant's risk.

Conclusion

To ensure their widespread use moving forward, digital therapeutics will have to demonstrate their usefulness, namely through improvements to clinical outcomes and healthcare savings. Moreover, they must address underserved needs in healthcare, including insufficient access to care. This is of the utmost importance in the CNS space, in which it is often harder to find success in clinical trials.[6] As such, establishing the utility of CNS digital therapeutics in clinical trials will prove critical to their long-term adoption in patient care.

References

1. Visit: fda.gov/medical-devices/ consumers-medical-devices/learn-ifmedical-device-has-been-cleared-fdamarketing
2. Substance Abuse and Mental Health Services Administration. Digital Therapeutics for Management and Treatment in Behavioural Health. Publication No. PEP23- 06-00-001. Rockville, MD: National Mental Health and Substance Use Policy Laboratory. Substance Abuse and Mental Health Services Administration, 2023
3. Visit: dtxalliance.org/understandingdtx/
4. Alexander W. The Uphill Path to Successful Clinical Trials: Keeping Patients Enrolled. Pharmacy and Therapeutics. 2013;38(4):225
5. Case study "Fully decentralised clinical trial in heart failure. Study team improves patient compliance and diversity" (ICON, 2022, not on website)
6. Gribkoff VK, Kaczmarek LK. The need for new approaches in CNS drug discovery: Why drugs have failed, and what can be done to improve outcomes. Neuropharmacology. 2017;120:11-19. doi:10.1016/j.neuropharm.2016.03.021

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