Drill Down & Catch Up: Psychiatric Disorders

A New Era of Neuroscience Series

August 2024

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Advances in Psychiatric Disorders

Psychiatric Disorders

Welcome to our first installment of our “Drill Down & Catch Up” series, part of the broader “A New Era of Neuroscience” initiative.

In our initial post, we expressed cautious optimism about transformational changes in various areas of neuroscience over the next 1-5 years. Here, we highlight a few key August 2024 data readouts and regulatory decisions in psychiatric disorders and list select upcoming events in the back half of 2024, including:

- A new wave of antidepressants
- Psychedelics
- Novel mechanisms of action for schizophrenia

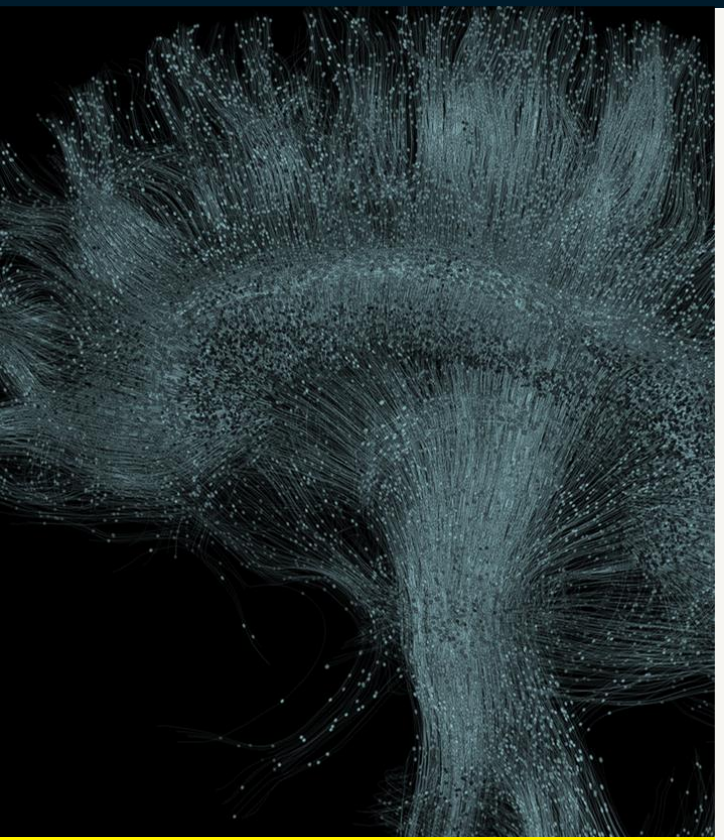
Neuro-degenerative Disorders

Pain and Migraine

Sleep Disorders

Neuro-inflammatory Diseases

Epilepsy



A few of the "Still to Come" Data Readouts for Depression in 2024

- Boehringer Ingelheim BI1358894 Phase 2 in MDD
- Beckley Psytech BPL-003/5-MeO-DMT Phase 2 in Treatment-Resistant Depression (TRD)
- Neurocrine NBI-1065845 Phase 2 in TRD

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Major Depressive Disorder (MDD)

The treatment of depression is on the precipice of transformational change as companies move from a one-size-does(n't)-fit-all approach to targeting specific subpopulations to address patient needs not currently satisfied by cheap generic including treatment-resistant depression, suicidality, rapid-acting symptom control, specific symptoms such as anhedonia, and comorbid conditions such as sleep disturbance and pain.

Recent News in Depression:

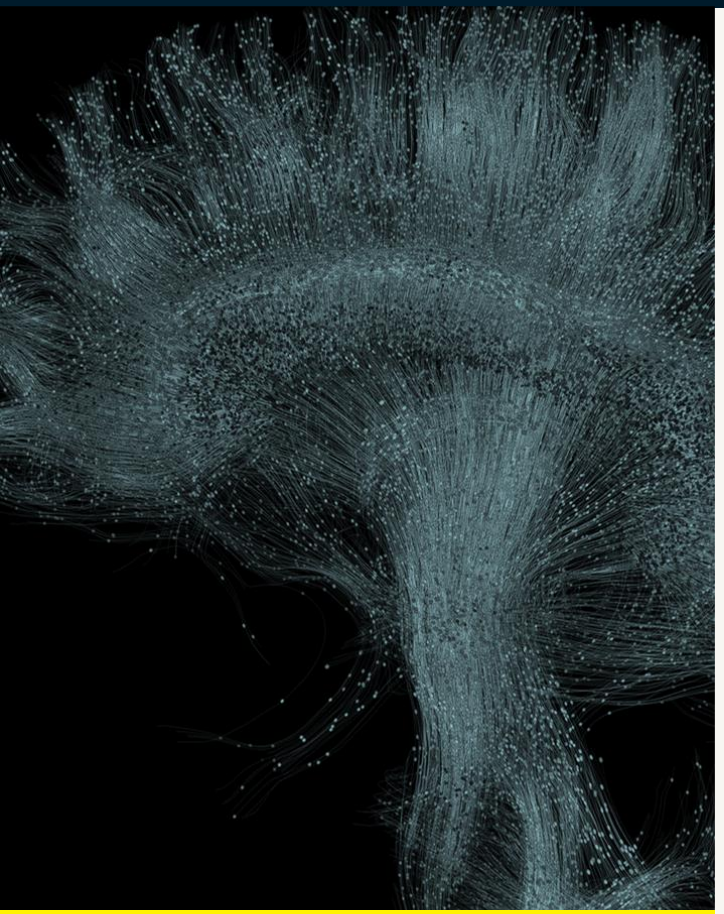
JNJ/Cerecor and **Neumora Therapeutics** are both conducting pivotal studies with novel **kappa opioid receptor (KOR) antagonists (aticaprant and navacaprant**, respectively), that promise to address the symptoms of anhedonia (reduced ability to experience pleasure) of MDD patients which can lead to longer time to remission, reduce chances of achieving full recovery and increase chances of recurrence. Thankfully, KOR antagonists have no pharmacological properties associated with opioid-related abuse.

- Phase 2 results for **JNJ/Cerecor's aticaprant** published in Nature in April 2024.
- **Neumora's navacaprant** is in Phase 3 trials for MDD and announced initiation of Phase 2 trials for treatment of mood and adhedonia in bipolar depression in May 2024.

In May 2024, **JNJ** announced positive results for Phase 3 studies **for seltorexant (selective antagonist of the orexin-2 receptor)** as an **adjunctive therapy for MDD patients with insomnia symptoms**. Selorexant demonstrated statistically significant and clinically meaningful improvement in depressive symptoms and improved sleep disturbance outcomes in patients who had a prior inadequate response to SSRI/SNRI antidepressants alone. While these results should come as no surprise, as depression and sleep disturbance are inextricably linked, they offer much-needed relief to the estimated 60-75% of people with depression who have trouble falling or staying asleep.

The first prescription digital therapeutic was authorized in the US for the adjunctive treatment of **MDD** in April 2024. **Otsuka Pharmaceutical, Co. Ltd. (Otsuka) and Click Therapeutics, Inc.**, received FDA clearance for **Rejoyn®,** a smartphone-based six-week treatment program designed to help enhance cognitive control of emotion through a combination of clinically-validated cognitive emotional training exercises and brief therapeutic lessons. Otsuka started selling Rejoyn® in August at a low introductory cost of $50 out-of-pocket cost plus the cost of optional Wheel consultation. To date, no insurers have agreed to cover Rejoyn®.

https://www.nature.com/articles/s41386-024-01862-x
https://ir.neumoratx.com/news-releases/news-release-details/neumora-therapeutics-announces-initiation-phase-2-study
https://www.jnj.com/media-center/press-releases/johnson-johnson-pivotal-study-of-seltorexant-shows-statistically-significant-and-clinically-meaningful-improvement-in-depressive-symptoms-and-sleep-disturbance-outcomes
https://www.otsuka.co.jp/en/company/newsreleases/2024/20240402_1.html



"It's not, 'Oh my god, this can't be done,'" she said. "It's 'Well, Lykos made some important misjudgments, and those are fixable misjudgments'". – Holly Fernandez-Lynch, Professor of medical ethics, University of Pennsylvania

Psychedelics

There has been significant recent activity around the potential for psychedelics (e.g., **ketamine, psyilcybin, midomafetmine (MDMA)**, as much-needed next generation treatments for **indications including depression, anxiety, addiction, pain, post-traumatic stress disorder (PTSD), and even palliative care.** Investment, partnership and acquisition dollars have been pouring into companies like **Lykos Therapeutics, Compass Pathways, Gilgamesh Pharmaceuticals and Mindset Pharma**. There is now a clinical roster of over 50 psychedelics in various stages of development. The August 9th FDA rejection of Lykos' submission for approval of MDMA as a complement to psychotherapy in patients with PTSD (MDMA-assisted therapy) have impacted the class, though the lessons from this rejection may not be applicable to other compounds as reasons for the rejection included, but are not necessarily limited to, an earlier advisory board panel's conclusion that benefit did not outweigh risk, the inability to mask active drug from placebo in clinical studies, requirement for use in combination with psychotherapy, lack of diversity among participants, addictive potential of the drug and failure to disclose a serious and disturbing case of trial misconduct.

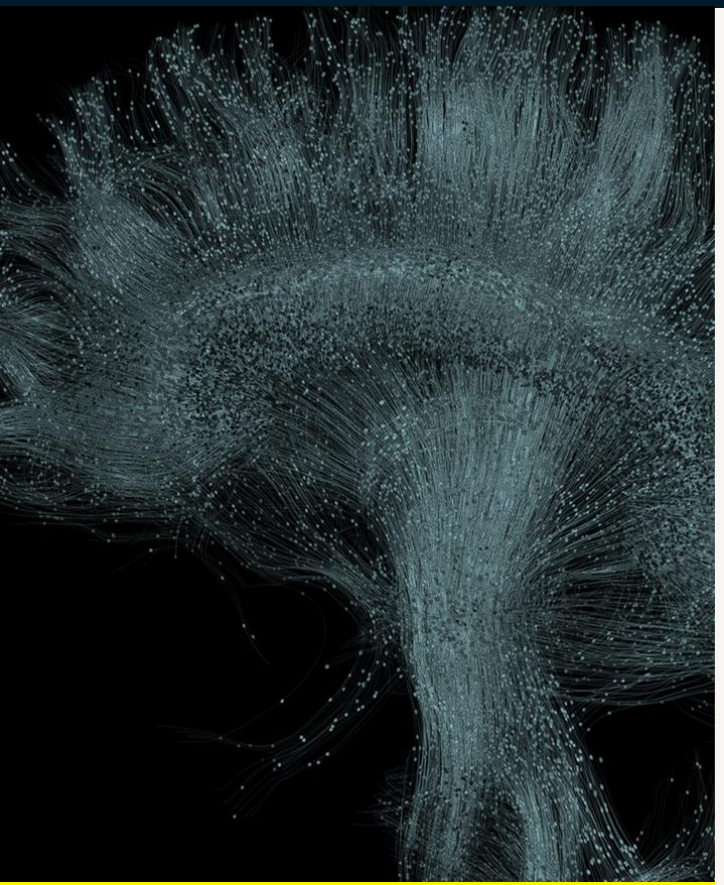
Holly Fernandez-Lynch, a professor of medical ethics at the University of Pennsylvania, clearly sees this as an educational speed bump for the psychedelic space overall, but not an impassable roadblock – as outlined in a quote from a recent Rollcall article, "It's not, 'Oh my god, this can't be done,'" she said. "It's 'Well, Lykos made some important misjudgments, and those are fixable misjudgments.'"

Next up on the clinical roster for psychedelics

The FDA may have rejected Lykos' MDMA-assisted psychotherapy, but the overwhelming unmet need is driving other players to continue. Next up for regulatory review is likely to be **Compass Therapeutics**' lead product candidate, COMP360 psilocybin treatment. Phase 2 data for treatment-resistant depression was published in The New England Journal of Medicine in November 2022 and Phase 3 trials are currently recruiting. COMP360 is also being studied for the treatment of PTSD, anorexia nervosa and a wide range of neuropsychiatric studies in investigator-initiated trials.

- After a single 25mg dose of COMP360 psilocybin, in combination with psychological support, 29.1% of participants with TRD were in remission by week 3 ($p<0.002$) - this is higher than the response rates seen for equivalent lines of treatment in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study*, a large prospective clinical trial of major depressive disorder conducted to determine the effectiveness of different treatments for depression.

https://rollcall.com/2024/08/12/fda-rejects-mdma-therapy-for-treatment-of-ptsd-whats-next/
https://ir.compasspathways.com/news-releases/news-release-details/compass-pathways-announces-publication-phase-2b-study-comp360



Real-world impact of a more effective and/or better-tolerated drug for schizophrenia (including considerations such as improved personal care and social functioning, returning to work, or continuing education) will be critical as patients and clinicians choose therapy in this evolving market.

Schizophrenia

In schizophrenia all eyes are on **muscarinic receptor targeting therapies** as the highest profile new mechanism, with **Karuna Therapeutics** (acquired by BMS for $14B earlier this year) being front and center.

Muscarinic modulators have been of interest in treating schizophrenia and other CNS disorders for some time but have been plagued by peripheral side effects including dry mouth, blurred vision, constipation and urinary retention. M1 and M4 receptors, in particular, are believed to have the potential to address positive (e.g., hallucinations, delusions) and negative (e.g., withdrawal from others, difficulty enjoying life) symptoms of schizophrenia, as well as cognitive deficits. Muscarinic agents offer a novel, non-directly dopaminergic approach to treatment of schizophrenia with potential for improved efficacy over currently available therapies without the safety and side effect issues (e.g., weight gain, metabolic syndrome, tardive dyskinesia).

Pairing a M1/M4-preferring muscarinic agonist with a peripherally-acting muscarinic antagonist promises to provide the therapeutic benefits of activating these receptors in the CNS while blocking the potential side effects outside of the CNS. The clinical success of targeting M1/M4 could de-risk earlier-stage programs, such as **MapLight Therapeutics** and **Neurocrine Biosciences** (both Phase 1). **AbbVie's/Cerevel's emraclidine** also targets muscarinic receptors, but specifically blocks the M4 subtype which led to a better gastrointestinal side effect profile in a Phase 1b study.

"By selectively targeting the M4 receptor, emraclidine resulted in infrequent gastrointestinal side effects, with rates similar to placebo," Dawn Carlson, AbbVie's vice president of neuroscience development, wrote in an email to PharmaDive/PharmaVoice. Topline data for emraclidine Phase 2 studies is expected later in 2024.

Other novel approaches specifically targeting the cognitive symptoms of schizophrenia include **Neurocrine Biosciences's luvadaxistat, a selective d-amino acid oxidase (DAAO) inhibitor** in Phase 2 and **Boehringer Ingelheim's, iclepertin (selective glycine transporter 1 inhibitor**, Phase 3), both seeking an indication for cognitive impairment associated with schizophrenia.

Real-world impact of a more effective and/or better-tolerated drug for schizophrenia (including considerations such as improved personal care and social functioning, returning to work, or continuing education) will be critical as patients and clinicians choose therapy in this evolving market.

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https://www.biopharmadive.com/news/bms-karxt-schizophrenia-approval-abbvie/724555/

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