IS PRECISION PSYCHIATRY READY FOR PRIME TIME?

Reflections from the 2025 American Psychiatric Association (APA) Annual Meeting

Edward Shorter, a pre-eminent historian of psychiatry, once remarked:

"Many psychiatrists are extraordinarily effective clinicians. They can make their patients reliably better which is something you could say of no other medical specialty with the possible exception of radiation oncology. But psychiatrists are able to do this in a way that has relatively little scientific underpinning."

Dr. Shorter's pointed, but indisputable, assertion relates both to the field's nosology and its approach to treatment. With many psychiatric diagnoses in the DSM (Diagnostic and Statistical Manual of Mental Disorders) being based on symptom clusters, not underlying biological mechanisms, it's often difficult to match patients to effective treatments without relying on a trial-and-error approach. This stands in contrast to cardiology or oncology, where validated biomarkers are available to guide both diagnosis and treatment selection. One might argue that psychiatry's broad and heterogeneous diagnostic categories have also hampered drug development; this branch of medicine has certainly not been blessed by an abundance of therapeutic breakthroughs in recent decades!

This year, I returned to the APA's annual meeting for the first time in 8 years to assess the field's progress in achieving precision psychiatry. From Freud to fluoxetine (ie, psychoanalysis to the first SSRI) may have taken 8 decades, but the past 8 years have given us the first antidepressant and schizophrenia therapies with genuinely novel mechanisms in

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decades, the first prescription digital therapeutics (PDTs) for mental health conditions, and significant adoption of telepsychiatry (due to a "once in a century" pandemic).

Moving beyond monoamines: new mechanisms and medications

At this year's meeting, Bristol Myers Squibb's muscarinic receptor-targeting therapy Cobenfy (xanomeline-trospium) made its historic debut as the first-ever medication indicated "for the treatment of schizophrenia" that is not described as an "antipsychotic." Despite high levels of interest in Cobenfy across several sessions, its disappointing failure as adjunctive therapy in the recent phase 3 ARISE study was the "elephant in the room" that only served to accentuate the ongoing need for a shift away from dopamine-based treatments to novel therapies. Thankfully, other innovative mechanisms are gaining traction, including TAAR1 agonism (ulotaront), sigma2 and adrenergic antagonism (roluperidone), and PDE10A inhibition (CPL'36). Regarding the latter, Celon Pharma presented promising phase 2 data with CPL'36 in the treatment of acute exacerbations of schizophrenia.

In depression, the mechanistic diversity is even greater. Actinogen presented positive phase 2 data in moderate MDD with their selective 11β HSD1 inhibitor Xanamem (emestedastat), which decreases CNS cortisol synthesis. Biogen and Sage Therapeutics' Zurzuvae (zuranolone), a $GABA_A$ receptor positive allosteric modulator (approved for postpartum depression [PPD]) was shown, in a post-hoc analysis, to effectively treat anhedonia in those patients.

As the first antidepressants to signal a major move away from monoamines in MDD, the success of ketamine and Spravato (esketamine) has laid the groundwork for a neuroplasticity-based conceptual framework of depression. Interestingly, the mechanistic emphasis on neuroplasticity has relevance for other novel MDD therapies, including Otsuka's prescription digital therapeutic for MDD, Rejoyn (CT-152), and psilocybin.

Psilocybin appears to be the next promising psychedelic candidate for treatment-resistant depression. Previously, Compass Pathways presented promising data on their synthetic psilocybin in patients with treatment-resistant depression, demonstrating significant clinical improvement and effect sizes comparable to esketamine. Few areas in psychiatry have ignited as much interest and curiosity in recent memory as psychedelics. Though there were little new data at this year's annual meeting, psychedelics remained prominent due to numerous sessions at which experts presented critical appraisals of progress.

The FDA's rejection of Lykos Therapeutics' MDMA-assisted therapy for post-traumatic stress disorder (PTSD) in 2024 is provoking considerable introspection. The serious methodological flaws forming the basis of Lykos's denial—inadequate blinding, rater bias, and difficulty determining the respective contributions of drug and therapy—are unresolved issues that may be common to several investigational psychedelics. Dr. Roger McIntyre identified two additional issues that complicate the development and commercialization of psychedelics: (1) understanding whether the psychedelic experience (ie, the "trip") is necessary for the clinical benefit; and (2) practical challenges in moving therapy from trial settings to real-world psychiatry. As an example of the latter, a psilocybin experience typically lasts 6 to 8 hours and requires a therapist to be present throughout the session.

One concern with the rapid expansion and diversification of therapeutic options is that

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some mental health professionals may struggle to understand the underlying science and this could slow the uptake of important new therapies. Several pharmaceutical company representatives confided to me that some clinicians are indeed finding it challenging to understand the role of novel targets and the rationale for targeting them. In addition, the audience's response to polling questions at several industry-supported product showcases was illuminating. At a Cobenfy product showcase, more than half of attendees reported being "*not familiar*" with Cobenfy. (Figure 1A). Perhaps more startling was the audience's response to the question, "Which hypothesis do you believe best explains the pathophysiology of major depressive disorder?" at a Boehringer Ingelheim-supported event on major depressive disorder. One-quarter of the respondents selected the option *"Monoamine neurotransmitter hypothesis: imbalances in monoamine levels in the brain."* (Figure 1B). Though monoamine neurotransmitters play a role in MDD, psychiatry has been trying to move away from the oversimplified, inaccurate, and misleading concept of "chemical imbalance" for many years.

The distance between the luminaries of academic psychopharmacology and frontline clinicians may be greater in psychiatry than in any other specialty. Targeted education must be a priority to bridge this divide.

Digital psychiatry: new tools, new terrain

Large language models (LLMs): From scribes to symptom detection to therapy?

Psychiatry is a discipline deeply rooted in language—both diagnostically (eg, through interviews, mental status exams, and narrative history-taking) and therapeutically (eg, in cognitive-behavioral therapy). This makes it fertile ground for LLMs as generative AI becomes ever more sophisticated.

LLMs are already being used as "AI scribes"—transcribing and summarizing sessions and even suggesting treatment plans. But their clinical potential is much broader. Researchers from Emory University used LLMs to identify individuals at high risk for psychosis, by analyzing their speech patterns, word choice, and commonly communicated themes.

One of the more intriguing—and controversial—uses of LLMs, however, is in therapeutic chatbots. A landmark randomized controlled trial of *Therabot*—an LLM-based chatbot grounded in cognitive-behavioral therapy (CBT) and motivational interviewing—showed significant reductions in depression and anxiety symptoms—benefits that persisted for 4 weeks post-intervention. In a separate session, however, John Torous—a pioneer in the field of behavioral informatics—cautioned against overhyping generative AI tools (such as

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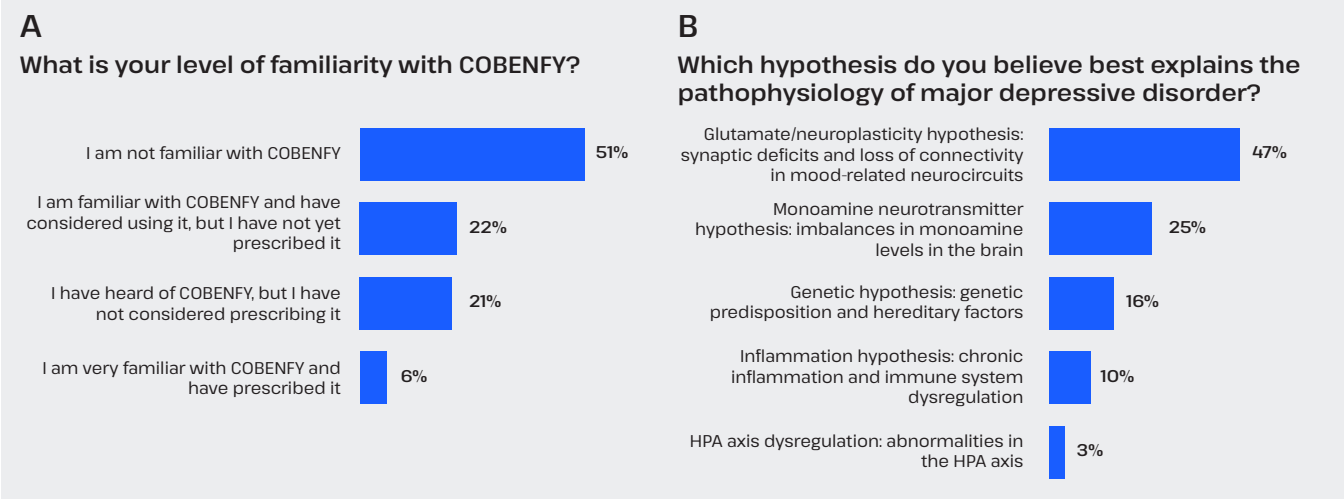

Figure 1. Audience responses to polling questions at: (A) Bristol Myers Squibb–supported product showcase ("Learn About a Different Treatment Option for Adults with Schizophrenia: Where Does It Fit in Your Practice?") and (B) Boehringer Ingelheim–supported product showcase ("Beyond the serotonin deficit hypothesis: communicating a neuroplasticity framework of major depressive disorder")

chatbots), which he believes are not ready to deliver therapy, noting that many studies compare chatbots to waitlists or no treatment, which exaggerates their impact. Other concerns include (1) the potential for bias and health inequities; (2) inaccuracy and hallucinations that could put patients at risk; and (3) context insensitivity.

Advances in digital phenotyping to drive precision psychiatry

Dr. Torous also showcased the promise of digital phenotyping, an approach that uses data from smartphones and wearables to monitor behavior and mental states in real time. Unlike traditional clinical assessments that rely on periodic, self-reported symptoms, digital phenotyping provides continuous, objective insight into a patient's lived experience by collecting both passive data (eg, *mobility* – via accelerometry and GPS; *sleep patterns* – via phone activity and app use; *social connectedness* – via number of calls and messages) and *active data* (eg, mood and anxiety levels – via self-reported surveys).

In a compelling example from his recent research, passive smartphone sensor data (eg, screen time, mobility) were used to identify 3 distinct behavioral clusters among people with schizophrenia. These findings have major implications for precision psychiatry because they suggest the potential for scalable smartphone-based digital phenotyping to help define clinically meaningful subtypes.

Progress in establishing a biological foundation for psychiatry

Arguably, the major obstacle to precision psychiatry comes from the current psychiatric nosology, with diagnostic manuals (DSM and ICD) that provide a rich system of categorical diagnoses largely based on observed symptoms and behaviors, not the underlying biology.

Reason for hope, however, comes from the APA's Future DSM Strategic Committee, which is defining a forward-looking roadmap for the next iteration of the DSM that aligns with contemporary neuroscience, precision medicine, and the real-world complexities of mental health care. Members of the committee acknowledged the limited validity, categorical rigidity, and lack of biological grounding of the DSM, and presented a new diagnostic framework with the following features:

- Contextual factors: Social determinants of mental health, life experiences, and co-existing medical conditions will be included
- Biological factors: Various modalities of biomarkers (including genetic, neuroimaging, and digital phenotyping) will be incorporated, with the potential to predict risk, monitor disease progression, guide treatment selection, and improve early detection
- More-dimensional diagnoses: Categorical disorders will be retained but with greater nuance (eg, stratified subtypes, clear severity scales)
- Transdiagnostic dimensions: Cognitive function and cross-cutting symptoms (eg, anxiety) that affect multiple conditions will be included

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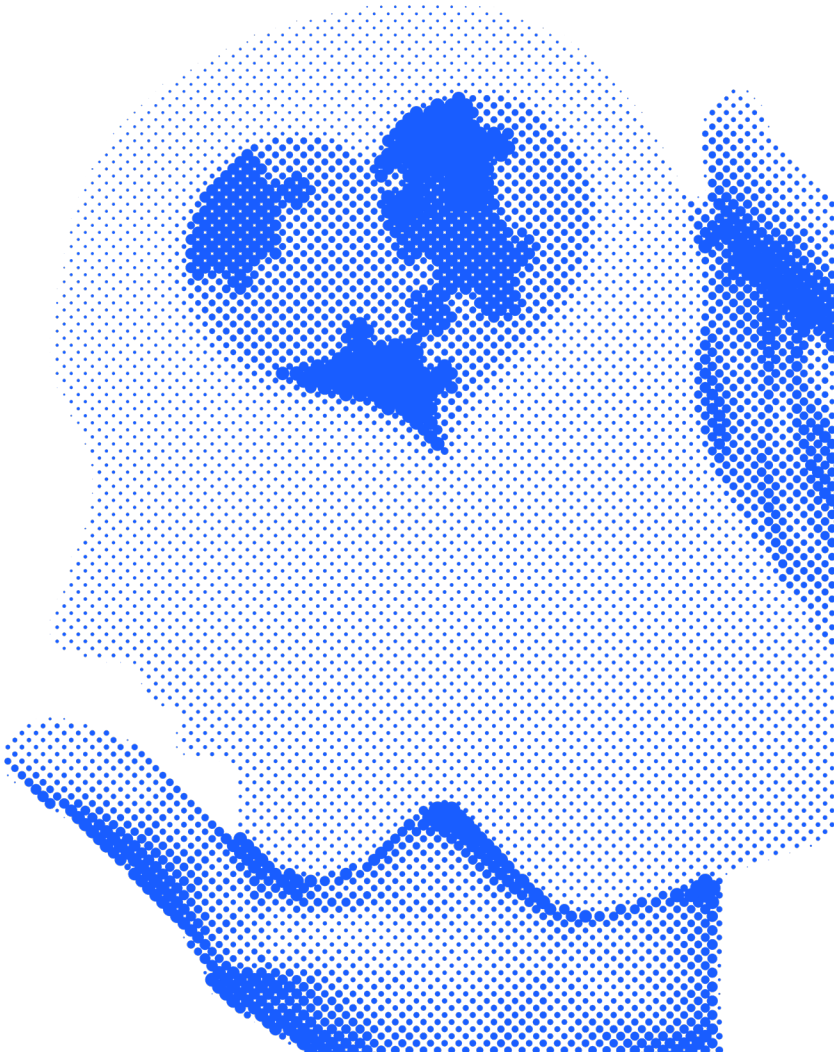

What this means for the pharmaceutical industry

After many years characterized by a relative lack of innovation, the rapid emergence of powerful digital tools and new therapeutic mechanisms is expanding what's possible. In the years to come, psychiatrists may have the opportunity to break decades-long stalemates in treating schizophrenia, depression, and other serious mental illnesses. If psychiatry is to fully embrace its "translational era," however, strenuous efforts must be made to eliminate barriers to integrating new breakthroughs into clinical practice.

As a pioneering healthcare communications agency, HCG has played a critical role in helping to bring the fields of precision oncology and precision cardiology to fruition from the early 2000s onward. We know that the success of precision medicine in any field relies on so much more than R&D spend and robust data. Our large team of strategists and psychiatry and neuroscience experts (PhDs, PharmDs, and MDs) has identified several imperatives for all pharmaceutical companies working in mental health:

- Orchestrate comprehensive educational campaigns that leverage storytelling, striking visuals and animations, and innovative formats, and deploy content via channels that meet HCPs where they are—whether in a community practice or an academic setting
- Tailor content to diverse provider types (psychiatrists, psychologists, social workers, primary care). This is particularly important given only 5% of US mental health professionals are psychiatrists. Specialty-specific content should be carefully planned across publication plans, medical education plans, and all promotional messaging
- Foster greater interdisciplinary leadership that harnesses the unique contributions of all specialties; examples include cross-disciplinary advisory boards, content co-creation, and speaker pairs on every webinar or symposium to model real-world collaboration
- Increase HCP understanding and adoption of novel therapeutics by creating modular, mechanism-focused training content with striking visuals and animations that can be adapted to different audiences
- Promote digital psychiatry and PDTs by integrating education into broader clinical workflows and co-creating implementation playbooks
- Enhance literacy around biomarkers with educational approaches that emphasize clinical relevance and include real or simulated case studies showing how biomarkers might stratify patients or predict treatment response
- Accelerate adoption of measurement-based care (MBC) by framing it as a shared decision-making tool that empowers providers and patients, and developing specialty-specific toolkits to support implementation. ■

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