

Schizophrenia research grapples with trial design hurdles in hunt for new treatments

A sector plagued by drug failures is looking to optimise study methodology, site selection, and patient recruitment.

Jam Bensilum | October 9, 2026

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Growing placebo response rates in schizophrenia trials can make treatment benefits harder to detect, potentially contributing to the sector's drug development challenges. Credit: 9dream studio/Shutterstock.com.

Placebo response in acute schizophrenia trials has been rising for decades. At the same time, the observed treatment benefit is in decline.

In 2020, amidst mounting concerns, the US Food and Drug Administration (FDA) published [a review of](#) schizophrenia trials submitted as part of New Drug Applications (NDAs) over 18 years. The analyses revealed that the pre- and post-2009, mean placebo response scores increased from -6.4 to -10.5 on the Positive

and Negative Syndrome Scale (PANSS)—the gold standard for schizophrenia research. Meanwhile, study success rates fell from 78% to 57%.

At the time, the agency conceded that “close attention to trial conduct and re-examination of design elements for future trials may be warranted”.

Yet, several years later, experts continue to raise the same concerns. A strong placebo response is a common and increasing issue in schizophrenia trials, says Dr Dan Siskind, head of Physical and Mental Health Research Stream, Queensland Centre for Mental Health Research, Australia.

Experts say this difficulty in designing schizophrenia trials may also be thwarting drug development, and a wider reform of the neuropsychiatric trial ecosystem that can also tackle fraudulent behaviour is needed.

Strong placebo response stymies drug development

A high placebo response narrows the gap between active treatment and placebo, making it more difficult to demonstrate statistical superiority, says Christine Moore, PhD, senior vice president, Scientific Solutions, at the contract research organisation (CRO) Worldwide Clinical Trials. From a drug development perspective, this is a major issue, as an effective therapy may fail simply because the study could not reliably detect its effect, she adds.

Dr Amit Etkin, CEO of precision neuropsychiatry-focused biopharmaceutical Alto Neuroscience, says this is likely common, especially within biotech. “We don’t know how many false negatives are out there,” he says.

Indeed, the field has seen a catalogue of drug failures due to this issue. Notably, AbbVie’s [emraclidine flunked](#) a pair of Phase II trials in late 2024, due, in part, to unexpectedly high placebo response rates. In an investor call, the company later pointed to variability in placebo effect across sites, saying certain sites showed a clearer efficacy signal.

What is driving the trend in placebo response?

The industry has been wrestling with this question for years and the consensus seems to attribute the trend more to how trials are conducted than a genuine increase in the biological placebo response, Moore explains.

Over the last 20–30 years, trials have gotten bigger and more complex, with studies now typically involving more sites, raters, and outcome measures, says Moore. This introduces more variability, making it harder to distinguish a true drug effect from background noise, she adds. Clinicians, known as raters, use structured interviews to assess schizophrenia symptoms and assign a PANSS score.

Other important factors include treatment expectations among patients and study staff, the tendency for raters to inflate baseline scores at study entry, more interaction between patients and clinicians becoming overly therapeutic in itself, and measurement variability associated with subjective endpoints like the PANSS, adds Moore.

While acknowledging their impact, Etkin argues these challenges have not changed substantially over time. Instead, he lays responsibility at the door of a clinical trial ecosystem dominated by specialist clinical research sites and a tendency to attract patients who enrol in multiple trials—so-called “professional patients”.

Elsewhere, a [study conducted in the UK](#), which compared a small randomised cohort of patients with schizophrenia or psychosis to anonymised patients

undergoing schizophrenia treatments in the UK health service, found that patients in randomised trials resemble those in real-world scenarios in terms of disease severity. Moore says that it is always a balancing act between ensuring the study population reflects real-world patients and preserving the ability of the trial to detect treatment effects, if they exist.

A call for reform

Across psychiatry, a core issue stems from diagnoses that rely on subjective assessment rather than lab or imaging tests, says Etkin. As such, the field is prone to seeing “professional patients”, often attracted by financial incentives for enrolling, who misrepresent their symptoms or history, he elaborates.

What’s more, the system can exacerbate rather than ameliorate the issue. Unlike oncology trials that recruit patients largely from academic medical centres, psychiatry research is not embedded within clinical systems, says Etkin. Instead, professional research sites are employed that often rely heavily on social media for participant recruitment, he says.

Moreover, Etkin notes that the sites may be incentivised by financial return on enrolment, sometimes to the detriment of the quality and rigour of the study. Siskind similarly acknowledges this incentive in industry-sponsored trials, which may affect quality control.

Meanwhile, Dr Joseph McEvoy, professor of psychiatry and health behaviour at Augusta University, Georgia, US, goes a step further, describing the clinical trial apparatus in schizophrenia research as “completely corrupt”, due to enrolment of participants with questionable diagnosis or symptom severity.

According to Etkin, the COVID-19 pandemic opened the public’s eyes to what clinical trials entail. Participants who discovered the system during this period form the bulk of the recruitment pool for professional research sites, he says.

How to optimise trial design

There is no “silver bullet” to overcoming the persisting challenges in neuropsychiatry, says Etkin. Ultimately, the goal should not be to totally eliminate placebo response but to maximise detection of the true treatment effect, explains Moore.

One important aspect is how symptom severity is assessed, says Moore. Limiting investigators’ visibility of enrolment thresholds can reduce the risk of inadvertent inflation of baseline measures at screening. For this, centralising eligibility review and independently assessing baseline severity can help, she advises.

For depression research, Alto has developed its own large language model (LLM) to score patients on the Montgomery-Asberg Depression Rating Scale (MADRS),

a widely used clinical assessment tool, during rater-conducted interviews in close to real time, effectively acting as a re-rater, says Etkin.

Additionally, recruitment processes must ensure that participants truly meet the intended and carefully considered disease-state definition, says Moore. Ideally, patients should be well known to the site or a referring psychiatrist with reliable access to their clinical history, she says. Moore also recommends the use of patient registries to identify potential “professional patients” and support enrolment integrity.

Etkin echoes the importance of participant verification. In 2024, a Phase IIb trial (NCT05712187) with Alto’s major depressive disorder (MDD) candidate ALTO-100 failed to meet its [primary endpoint](#). Upon detailed study analysis, it was revealed that patients in an adjunctive treatment arm were 100% compliant versus just 56% in a monotherapy arm, the company stated in its FY 2024 results. Etkin hypothesises that “professional patients” cropped up in this study. Subsequently, the company has leaned into the adjunctive route across its programmes, not only because it made clinical and commercial sense but because, on a basic level, it confirms diagnosis and permits use of medical records and lab tests to verify existing treatment adherence, he explains.

Study site identification is another critical piece of the puzzle. When it comes to site selection, sponsors should prioritise not only recruitment capacity, but also demonstrated experience, endpoint quality, and commitment to scientific rigour, says Moore.

The 2020 FDA review found the trend in placebo response to be particularly pronounced in North America. While sponsors may be tempted to move studies outside of the region, active monitoring of individual site quality throughout the trial may offer a better approach, says Moore.

Can we predict placebo response?

Placebo response prediction models may be a promising area for future research, according to Moore. While numerous factors associated with placebo response, such as young age and shorter illness duration, have been identified, the field is some distance from establishing a reliable “placebo responder” profile, she adds. Leveraging artificial intelligence (AI) to develop models incorporating participant characteristics, biomarkers, symptom trajectories, site-level performance metrics, rater behaviour, protocol adherence, and expectation-related measures may be particularly valuable, says Moore.

Alto has developed and validated a predictive placebo response model for multiple prospective trials, utilising electroencephalogram (EEG) data, says Etkin. While not yet mathematically reliable enough for routine use, he anticipates that in the next five to 10 years, predictive models could be incorporated into trial design as a statistical covariate, akin to baseline symptoms.

Predictive models, however, cannot compensate for poor trial design; rather, they should be viewed as supplementary to quality execution, notes Moore.

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