International
CLINICAL TRIALS

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STARTS ON PAGE 57

TRIALS-TO-GO

How can direct shipping-to-consumer models be applied to clinical trials to ease patient burden?

A BEAUTIFUL MIND

What are the best ways to overcome challenges in Alzheimer's disease and dementia trials?

AN ALL-INCLUSIVE TRIP

Psychoactive trials are gaining popularity. Now, study designers need to make sure they're diverse

SPOTLIGHT

In need of an all-inclusive trip: socio-demographic diversity in psychedelic research

Psychedelic treatments are gaining traction for the treatment of psychiatric disorders, but to what extent can the results be generalised to apply to the wider population? Questions persist about whether psychedelic researchers are doing enough to recruit a representative proportion of minority groups in their clinical trials to prove efficacy for all

Adrienne Rivlin at L.E.K. Consulting

Psychedelic clinical trials are pushing the frontiers of modern psychiatric research. Six primary psychedelic categories are being investigated for therapeutic use – psilocybin, ketamine, MDMA, DMT, LSD and 5-MeO-DMT – and are currently being trialled for substance use disorders (SUDs), depression and post-traumatic stress disorder (PTSD).

Levels of interest and investment to support development of psychedelics have increased in recent years. Psychedelics are at a critical inflection point, with increasing investment, a growing body of clinical evidence and evolution of regulatory pathways driving strong growth in clinical development activity (see **Figure 1**).

What diversity issues exist in trial populations?

Positive momentum behind development in this space must continue in order to generate clinical evidence that is both robust and generalisable to the broader population, to support regulatory approval and subsequent reimbursement. The intentional inclusion in trials of a diverse patient population – defined as participants who differ from one another based on factors such as race, ethnicity and gender – is crucial for ensuring this generalisability.[1]

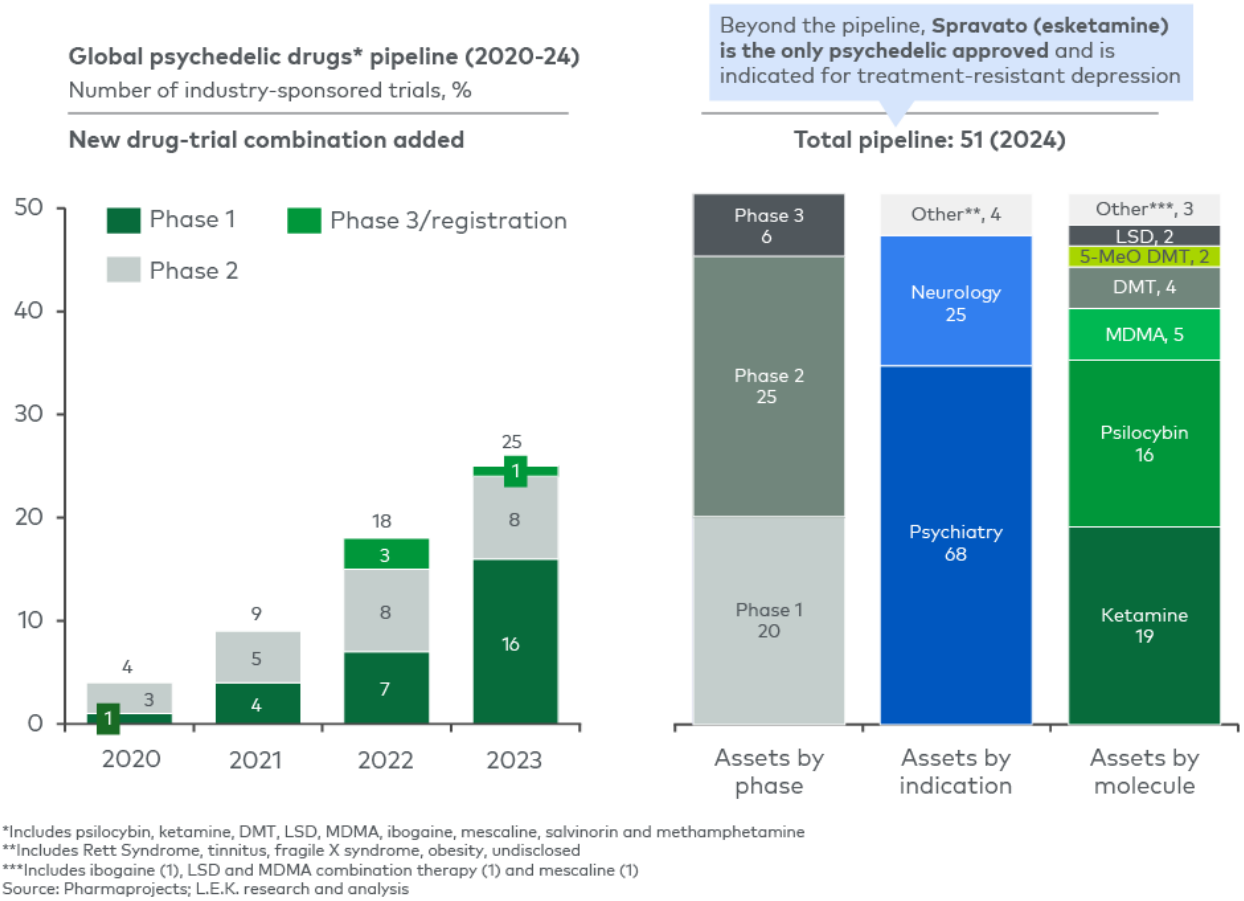
A deep dive into psychedelic clinical trial data reveals that trial populations consistently fall short of being representative of the broader population with respect to race and ethnicity, potentially limiting the applicability of results. It is worth noting that the same issue is not present with respect to male and female representation, which is broadly equivalent.

The American Psychiatric Association recognised this shortfall in 2024, and released a public letter stating a need for a more diverse group of patients in Lykos's clinical trials of MDMA for the treatment of PTSD. The letter also expressed caution to the US Food and Drug Administration (FDA) about generalising the results of the clinical trials to populations not represented adequately in the study.[2]

Why is this important?

Race, ethnicity, sex and gender can all significantly impact the way different people respond to the same medication. In fact, over the past few decades, several drugs have been withdrawn from the market because of adverse sex-based effects that were not accounted for in clinical trials. Furthermore, compelling examples exist of variation in drug metabolism and toxicity due to race and ethnicity.[3]

With a wave of new psychedelic treatments reaching the later stages of clinical trials and nearing regulatory approval, the scientific community must keep a watchful eye on how generalisable these studies claim to be. Without showing evidence of clinical efficacy and safety for an appropriately diverse sample that reflects the real-world population, how well these promising assets will work once approved and available to all cannot be guaranteed.



*Includes psilocybin, ketamine, DMT, LSD, MDMA, ibogaine, mescaline, salvinorin and methamphetamine
**Includes Rett Syndrome, tinnitus, fragile X syndrome, obesity, undisclosed
***Includes ibogaine (1), LSD and MDMA combination therapy (1) and mescaline (1)
Source: Pharmaprojects; L.E.K. research and analysis

Figure 1: Global psychedelic drugs pipeline

Racial diversity

Minority and ethnic groups are underrepresented in psychedelic medicine studies. An analysis of the ethnic breakdown of trial participants in 20 psychedelic-assisted psychotherapy studies from 2006-2023 revealed that almost 80% were non-Hispanic, white individuals.[4] Of the c.22% of participants who were ethnic minorities, c.12% were either Black, Asian or Hispanic/Latino, and the remainder were either mixed, of Indigenous descent or another race (see **Figure 2**). These figures appear to suggest that trial populations to date have fallen short of providing a representative sample of the general population, with minority groups generally underrepresented in psychedelic studies.

Deep dive: US clinical trials

Examining the picture in the US in more detail, the representation of minority groups in psychedelic studies is found to be lower than in the general population, and in psychiatric drug trial participants overall (see **Figure 3**).[5] This suggests that any structural issues in trial recruitment are specific to psychedelics rather than a function of the disease space.

What are the causes, and what can be done?

Issues with diagnostic approach

The existing diagnostic paradigm for psychiatric disorders, such as the DSM-5, inadequately considers the cultural nuances that significantly influence the clinical manifestation of psychopathology in individuals of colour. For example, the current diagnostic criteria for PTSD do not include race-based trauma.[6] Without these culturally inclusive diagnostic criteria, minorities often do not qualify for treatment studies, reducing their overall representation relative to the general population in some studies.

Unlike in many other psychiatric drug trial designs, researchers in psychedelic studies have not accounted for this inherent bias, and thus far have been unable to recruit participant groups that represent greater ethnic diversity.

Ineffective and narrow recruitment methods

Many trial participants are referred from outpatient providers, including physicians and mental health clinicians. These centres typically

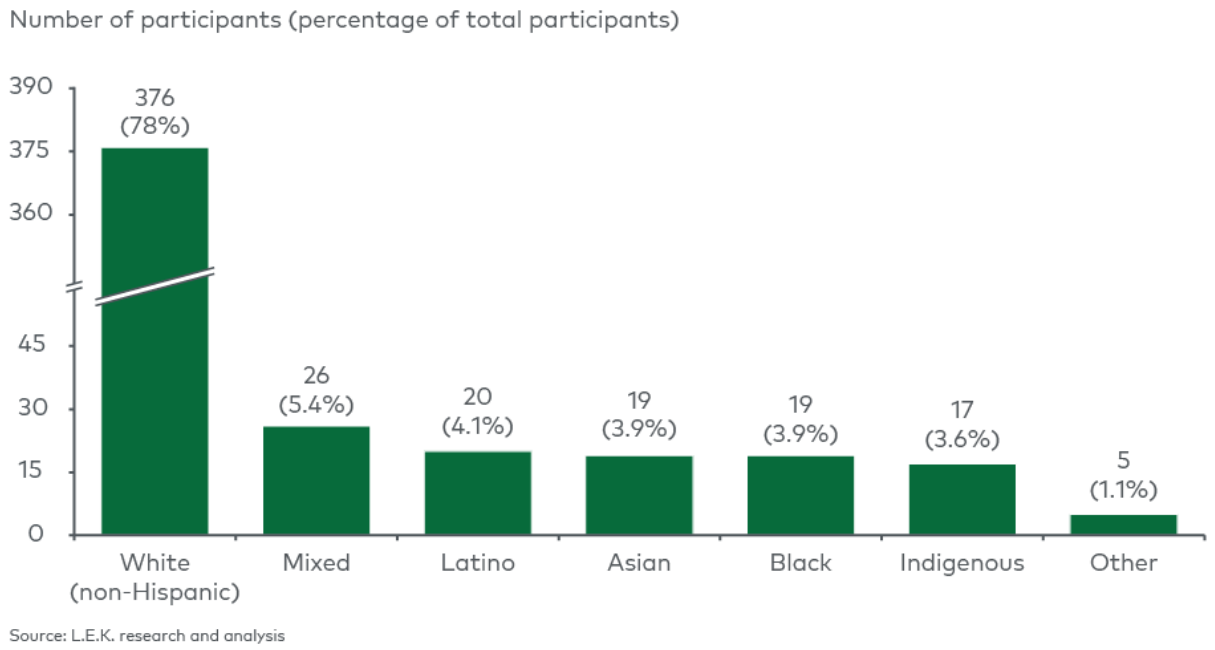


Figure 2: Participants in 20 psychedelic trials, by ethnicity (2006-2023)

treat a lower proportion of patients from diverse ethnic backgrounds, as certain factors – eg, cultural and social stigma regarding seeking medical help, the cost of physician fees – might prevent individuals in marginalised groups from reaching care.

If researchers in psychedelic trials sought referrals from providers that accept Medicaid and other forms of affordable healthcare in the US, they would likely experience greater success in recruiting minority ethnic groups.[7] Researchers with specific expertise in areas of cultural diversity and the recruitment of people of colour should be included in trial teams, and efforts should be made to recruit more researchers from minority groups into the psychedelic field.

Increasing the diversity of therapists involved in clinical trials would improve participant recruitment, as well as the research itself. Sunstone Therapies, based in Rockville, Maryland, US, is a clinical trial centre for psychedelic-assisted therapy in the medical setting, and keen to promote more diverse therapist populations. Manish Agrawal MD, chief executive officer at Sunstone Therapies, says: "Having clear sightlines for understanding perspectives, and investing in diversity, equity and inclusion (DEI) for therapists, is crucial to the

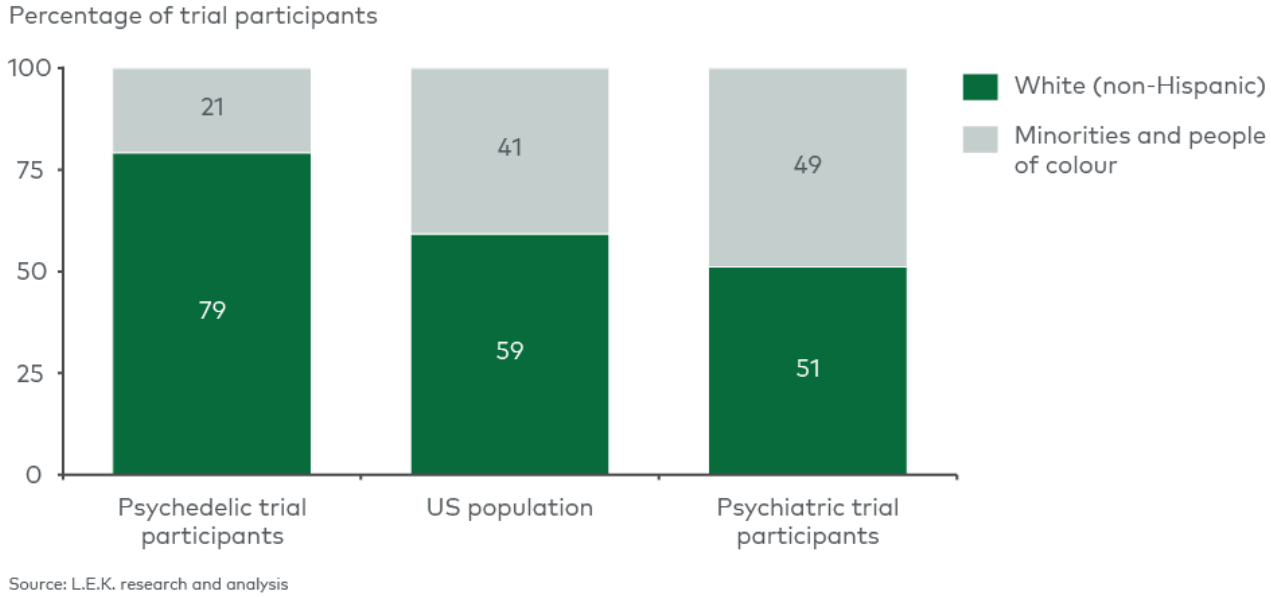


Figure 3: Ethnic breakdown for psychedelic trial participants, whole population and psychiatric trial participants in the US (2006-23)

overall health and foundation of research into psychedelic-assisted therapies. We have funded a project with Dana-Farber to identify and understand the opportunities and barriers for Black therapists to engage in this field. We need more initiatives like this across the industry so that we develop culturally informed research designs, training programmes and funding opportunities – and can accelerate the diversification and equity of psychedelic research."

Insufficient incentivisation to overcome hurdles

Many recent psychedelic studies in the US have been privately funded, which means they were not required to conform to National Institutes of Health (NIH) diversity guidelines.

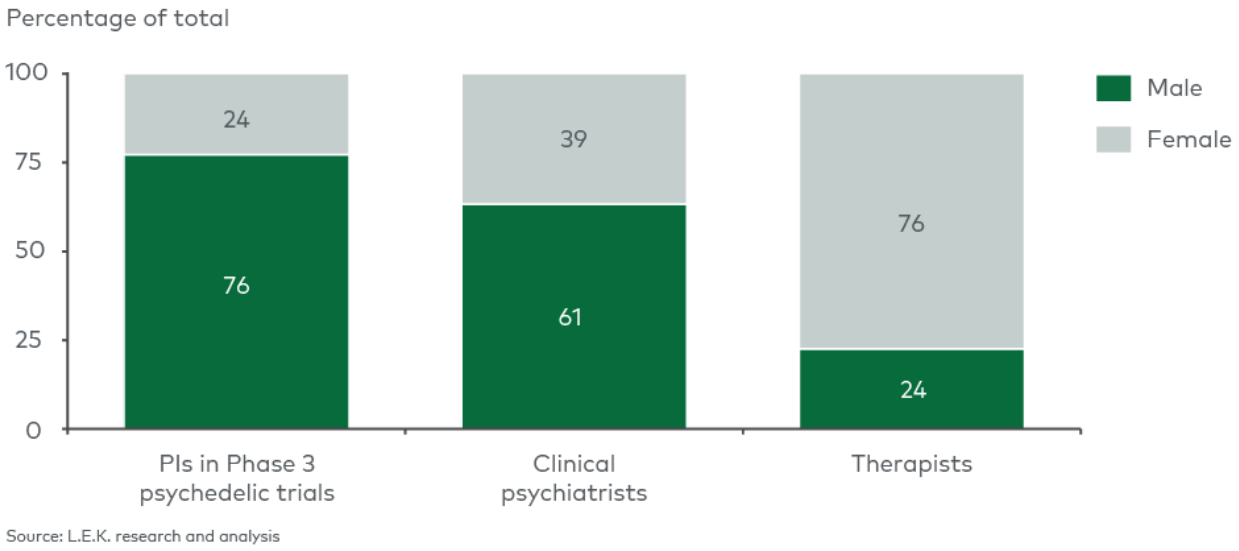


Figure 4: Sex-based comparison of principal investigators (PIs) in phase 3 psychedelic trials, clinical psychiatrists and therapists in the US

The NIH Revitalisation Act of 1993 mandated that all studies supported by NIH funding must carefully consider the proportions of ethnic minorities and women in a study population, and provide a rationale for its overall composition.[8] However, regulatory focus on diversity in clinical trials is increasing, and the Food and Drug Omnibus Reform Act (FDORA) that was passed in 2022 required the FDA to develop guidance to enhance diversity within clinical trial populations. In June 2024, the FDA issued its draft guidance on the subject, which states that participants in clinical trials should be representative of the patients who will use the medical product. It requires sponsors of phase 3 and other pivotal clinical studies to submit a Diversity Action Plan outlining their rationale, goals and intended approach for clinical study enrolment.

Similarly, in the UK, the Health Research Authority (HRA) has been working with groups of researchers, public contributors and research ethics committees to develop supporting guidance for researchers to consider when designing clinical trials, so that they develop a better understanding of the most effective treatments for different groups of people. As government funding and focus increase, further emphasis on recruitment criteria and appropriate demographic representation is anticipated.

Sex and gender diversity

From a sexual diversity perspective, trial recruitment has historically been more balanced. Of the 20 psychedelic studies whose demographics were analysed, 58% of the trial participants were female, and the most recent MDMA study contained more females in its sample than males – accurately representing the demographics of the PTSD patient pool.[9] Greater female representation in clinical trials will support increased confidence in the safety profile for women, an issue that has historically arisen in trials with disproportionately low female representation.[10]

However, the historical underrepresentation persists in PTSD research with transgender and gender-diverse people, who experience trauma and PTSD at higher rates than the general population.[11] Including gender-diverse participants in such studies is important for understanding the efficacy of psychedelic therapies for those suffering from gender-based trauma. The issue relating to gender extends beyond the recruitment of trial participants and lies more fundamentally in the people leading the psychedelic movement in psychiatry. Of the 46 principal investigators leading phase 3 psychedelic clinical trials, 76% are male and 24% are female. Unfortunately, this type of imbalance is common across many scientific research fields. When compared with the percentage of female clinical psychiatrists in the US overall, the psychedelic field comes up short once again (see **Figure 4**). The disparity

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is even greater when comparing the trial investigators to the number of therapists in the US, where 76% are female.[12] Addressing this disparity will likely facilitate a more balanced interpretation of clinical results, ensuring they are more applicable to the wider population.[13]

Conclusion

With psychedelic-assisted psychotherapy coming to the forefront of novel psychiatric medicine, the spotlight is on clinical trials to assess whether the drugs are efficacious and safe for the wider population. Although many of these trials have demonstrated clinical efficacy, questions remain over the extent to which the trial results are applicable to the wider, more diverse population at large.

When it comes to representing ethnic and racial minorities, psychedelic trials have not effectively demonstrated compliance with population-level demographics. To ensure confidence in the potential of psychedelic-assisted psychotherapies – their real-world efficacy and safety applicable to the entire general population – psychedelic trials must focus on increasing DEI within their sample populations, especially with respect to race and ethnicity. As the psychedelic movement continues to grow and gain momentum, regulatory boards and clinical researchers should consider improving representation to be imperative.

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Dr **Adrienne Rivlin** is a partner in **L.E.K. Consulting**'s Life Sciences practice, based in the London office. She advises private- and public-sector organisations across the pharmaceutical, biotech, medical device and consumer healthcare sectors on critical commercial challenges. Adrienne is passionate about addressing some of the most challenging issues facing the healthcare sector today, including treatment access, affordability and discrimination in medicine, all of which affect the mental health of patients and caregivers. Before beginning her career in consulting, Adrienne was a researcher, public policy consultant and tutor at the University of Oxford, UK. During this time, she worked with the Home Office, the Ministry of Justice and the Department of Health to research and review health policy in prisons. She holds a DPhil in psychiatry from the University of Oxford.

a.rivlin@lek.com