

# Psychedelic Use and Placebo Response

Robert Morlock, PhD<sup>1</sup> and Karin Blakolmer, MD<sup>2</sup>

<sup>1</sup>YourCareChoice, Ann Arbor, MI USA. <sup>2</sup>BYAS-PEB, Chicago, USA.

## Background

- Placebo (PBO) response is an undesirable outcome that can make the demonstration of efficacy difficult. An assessment administered at screening can serve as a measure of potential PBO response providing important information when assessing the true therapeutic impact of a novel treatment.
- The Placebo Response Probability Scale (PRPS) is an instrument that has been developed to identify placebo responders. It is a measure of the propensity for PBO response that can be used to retrospectively assess, or prospectively to minimize, PBO response within clinical trials, increasing confidence in the therapeutic value of compounds in development.
- Previous studies have demonstrated the ability of the initial version of the PRPS to identify PBO responders.<sup>1</sup> It is unknown if self-reported psychedelic use in the last 12 months is related to PBO response.
- In the last 5 years, there has been renewed interest in the use of psychedelics and a significant acceleration in research activity, leveraging their neuroplastic effect as a novel approach for the treatment of psychiatric disorders.<sup>2</sup>

## Objective

- Previous work demonstrated the proportion of PBO responders as measured with the PRPS increased with disease severity.<sup>3</sup> This work used the PRPS to classify the proportion of potential PBO responders by disease severity in those with and without psychedelic use.

## Methods

- Data was collected through an online, cross-sectional survey of US adults aged ≥18 years old. Participants were recruited 2Q 2021.
- Participants completed demographic background questions, comorbid conditions to calculate the Charlson Comorbidity Index (CCI)<sup>4,5</sup> score, the Generalized Anxiety Disorder 7-item<sup>6</sup> (GAD7) and the Patient Health Questionnaire 9-item<sup>7</sup> (PHQ9) screening questionnaires, the PRPS and were asked to self-report psychedelic use in the last 12 months.
- The proportion of PBO responders by psychedelic use were identified in those with no/mild, moderate, and severe anxiety and depression and summarized using descriptive statistics.

## Results

### Characteristics of Psychedelic Use

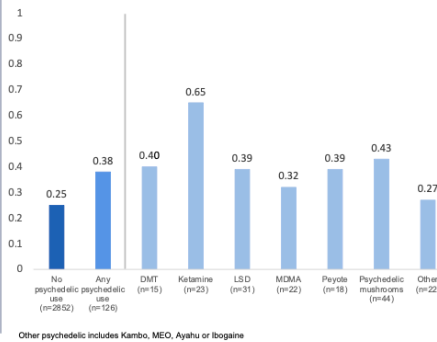
- Of the 2978 participants, 4.2% (n=126) reported using a psychedelic in the last 12 months.
- Relative to those not using a psychedelic, those reporting use of a psychedelic were younger (33.5 vs. 44.5 years; p<0.001), more likely to be male (60.7% vs. 47.5%; p=0.006), had a lower body mass index (BMI) (26.63 [SD 7.15] vs. 28.00 [SD 7.23] lbs/in<sup>2</sup>; p=0.038), and had a higher proportion of potential PBO responders based on the PRPS scores (38.10% vs. 25.42%; p=0.001). (Table 1, Figure 1)

**Table 1. Characteristics of No Psychedelic Use vs. Psychedelic Use in the Last 12 Months**

	No Psychedelic Use n=2852	Any Psychedelic Use n=126	Sig.
PRPS PBO Responder*, %	25.4	38.1	0.001
Male, %	47.8	60.3	0.006
Age, mean (SD)	45.57 (17.57)	33.41 (10.86)	<0.001
African American or Black, %	8.8	10.3	
White, %	78.6	77.0	0.844
Other, %	12.6	12.7	
Northeast, %	17.4	17.5	
Midwest, %	21.4	19.0	
South, %	37.7	37.3	0.869
West, %	23.4	26.2	
CCI score, mean (SD)	0.51 (1.09)	0.54 (1.00)	0.760
BMI (lbs./in <sup>2</sup> ), mean (SD)	28.00 (7.23)	26.63 (7.15)	0.038
Median household income, mean (SD)	69,491 (28,846)	66,215 (29,617)	0.213
Education > high school, %	78.6	79.4	0.840
Employed ≥ 32 hours/week, %	35.7	39.7	0.357

\* PRPS ≥ 50 higher likelihood of PBO response.

**Figure 1. Proportion of Population with PRPS Scores above PBO Response Threshold by Psychedelic Use**



Other psychedelic includes Kambo, MEO, Ayahu or Ibogaine

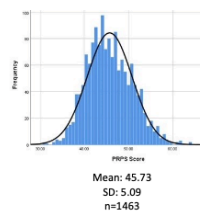
## Anxiety and Depression by Psychedelic Use

- Across all disease severity classifications, using the GAD7 for anxiety and the PHQ9 for depression, the propensity for PBO response was highest in those reporting psychedelic use. (Figures 2A-7B)

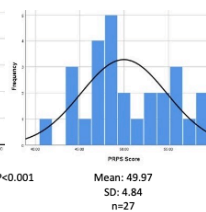
### No/Low Anxiety

- Psychedelic users had higher PRPS scores.
- Comparing means we see higher PRPS scores for psychedelic users vs. those with no use.

**Figure 2A. No Psychedelic Use**



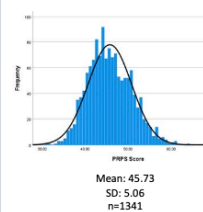
**Figure 2B. Any Psychedelic Use**



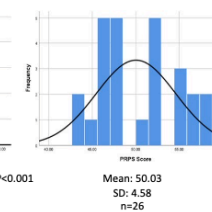
### No/Low Depression

- Psychedelic users had higher PRPS scores.
- Comparing means we see higher PRPS scores for psychedelic users vs. those with no use.

**Figure 5A. No Psychedelic Use**



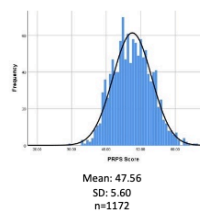
**Figure 5B. Any Psychedelic Use**



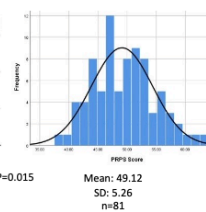
### Mild Anxiety

- Psychedelic users had higher PRPS scores.
- Comparing means we see higher PRPS scores for psychedelic users vs. those with no use.

**Figure 3A. No Psychedelic Use**



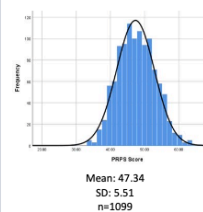
**Figure 3B. Any Psychedelic Use**



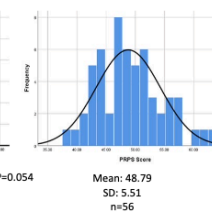
### Mild Depression

- Psychedelic users had higher PRPS scores.
- Comparing means we see higher PRPS scores for psychedelic users vs. those with no use.

**Figure 6A. No Psychedelic Use**



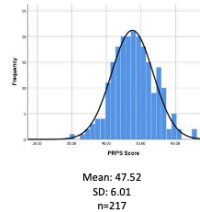
**Figure 6B. Any Psychedelic Use**



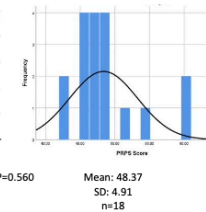
### Moderate/Severe Anxiety

- Psychedelic users had higher PRPS scores.
- Comparing means we see higher PRPS scores for psychedelic users vs. those with no use.

**Figure 4A. No Psychedelic Use**



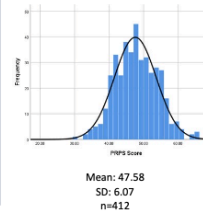
**Figure 4B. Any Psychedelic Use**



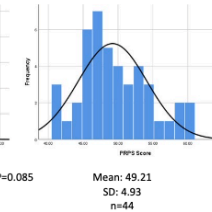
### Moderate/Severe Depression

- Psychedelic users had higher PRPS scores.
- Comparing means we see higher PRPS scores for psychedelic users vs. those with no use.

**Figure 7A. No Psychedelic Use**



**Figure 7B. Any Psychedelic Use**



## Conclusion and Discussion

- Adequately assessing efficacy signals in psychiatric trials may be complicated by PBO response.
- The potential for PBO response is higher in those that report using psychedelics overall and across all disease severity classifications relative to those not using psychedelics.
- Including measures of potential PBO response within trials allows assessment of results with and without those with a high propensity for PBO response allowing for more confidence when trying to establish a true signal of efficacy.
- This may be particularly important in trials testing psychedelic compounds.

## Limitations

- Data were self-reported and subject to recall bias.
- Participants were limited to those with computer access.
- The study was undertaken during the COVID-19 pandemic, which may have impacted the results.
- It is not known if psychedelic use in the last 12 months (by self-report) is related to the propensity for placebo response.
- The small sample size limits may limit generalizability of results.
- Results indicate those that use psychedelics are more likely to be placebo responders, it does not answer the question if they are placebo responders.

## References

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## Disclosures

- YourCareChoice holds the copyright for the Placebo Response Probability Scale (PRPS).

Email: rmorloc1@yourcarechoice.com

One or more of the authors report potential conflicts which are described in the program.