Diverse Predictors of Treatment Response to Active Medication and Placebo in Gambling Disorder

Nathan T.M. Huneke1,2,3, Samuel R. Chamberlain1,2,3,4, David S. Baldwin1,2,3,5, Jon E. Grant6

1. Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, UK

2. University Department of Psychiatry, University of Southampton, UK

3. Southern Health National Health Service Foundation Trust, Southampton, UK

4. Department of Psychiatry, University of Cambridge, UK

5. University Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa

6. Department of Psychiatry & Behavioral Neuroscience, University of Chicago, Pritzker School of Medicine, Chicago, IL, USA

Corresponding author: Nathan TM Huneke, University Department of Psychiatry, Academic Centre, College Keep, 4-12 Terminus Terrace, Southampton, SO14 3DT, UK. Email: n.huneke@soton.ac.uk

# Abstract

Gambling disorder creates a significant public health burden. Despite decades of clinical trials, there are no licensed pharmacological treatments for gambling disorder. Contributing factors to this are the high placebo response rates seen in clinical trials, the heterogeneity of the disorder and high rates of psychiatric comorbidities. Indeed, a number of demographic and clinical variables have previously been associated with altered responses to pharmacotherapy, psychotherapy and placebo. Which variables are likely to predict response to one modality over another remains uncertain. We carried out multiple linear regression analyses in a pooled dataset from six treatment studies in gambling disorder with the aim of identifying predictors of treatment response. Potential predictors were identified *a priori* through hypothesis and entered into models including all patients, and subsequently for those randomized to active medication or placebo separately. We found that baseline severity of gambling symptoms and number of weeks completed in a trial were predictors of active medication response, while decreased baseline symptoms of anxiety, increased baseline symptoms of depression, and non-Caucasian ethnicity were associated with placebo response. Sensitivity analyses showed that these associations were robust to choices made during the analysis. Further research is required to understand whether controlling for these variables, or using enriched samples, improves assay sensitivity in placebo-controlled clinical trials for gambling disorder.

# Keywords

Gambling disorder, Treatment response, Clinical trials, Placebo response

# Introduction

Gambling can be a normal recreational activity; however, in some individuals, gambling behavior can become persistent, recurrent and maladaptive, leading to problems with relationships, employment and financial difficulties (Grant et al., 2010b). The prevalence of subclinical problem gambling behaviors is approximately 3-4%, while a further 1% experience a gambling disorder (Black and Shaw, 2019; Buchanan et al., 2020). Patients with gambling disorder additionally often experience comorbid psychiatric disorders, such as substance use, depression or anxiety disorders (Black and Shaw, 2019; Kessler et al., 2008). Therefore, gambling disorder creates a significant public health burden.

At present there are no licensed pharmacological treatments for gambling disorder despite decades of clinical trials. One contributing factor to this is the large placebo response rate seen in clinical trials for gambling disorder, sometimes surpassing 70% (Kraus et al., 2020). As a result, it can be challenging to demonstrate medication benefits over placebo. Furthermore, gambling disorder is heterogeneous in nature, with differing behavioral subtypes and (as noted) high rates of comorbidity with other psychiatric disorders (Black and Shaw, 2019; Kessler et al., 2008). uncertainies Understanding who is more or less likely to respond to treatment is therefore crucial.

Predictors of treatment response to pharmacotherapy, placebo, and psychotherapy have been explored in gambling disorder. A systematic review of 33 studies of psychosocial interventions showed that male gender and low depression levels were consistent predictors of successful treatment (Merkouris et al., 2016). Other less consistent but nonetheless important predictors of positive outcomes included older age, being employed, Asian American ethnicity, lower pre-treatment gambling symptom severity, and being in the action stage of change (Merkouris et al., 2016). These findings are supported by similar associations seen in other studies. For example, younger age, lower education level, and higher baseline symptom severity have been linked with poorer treatment outcomes (Granero et al., 2020; Jimenez-Murcia et al., 2015). Conversely, a study conducted in a gambling service in Singapore found that increased seriousness of the patient’s gambling problem at baseline was associated with *improved* outcome (Manning et al., 2014). Higher treatment satisfaction and playing strategic games (e.g. poker), as opposed to non-strategic games (e.g. slots), have also been associated with improved psychological treatment outcomes (Guo et al., 2014; Manning et al., 2014; Moragas et al., 2015).

Compared with this literature, predictors of improved outcomes with pharmacotherapy or placebo has received relatively little attention in the context of gambling disorder. In a pooled analysis of two double-blind placebo-controlled trials of opiate antagonists (naltrexone or nalmefene), younger age was associated with placebo response, while a family history of alcoholism and intensity of gambling urges were important in medication response (Grant et al., 2008b). In another study of 152 patients assigned to placebo in multiple randomized-controlled trials, placebo responders stayed in treatment significantly longer, were more likely to support ‘enjoyment’ and less likely to support ‘loneliness’ or ‘boredom’ as triggers for gambling, and were more likely to be non-Caucasian. Interestingly, there was no difference in age between placebo responders and non-responders in this study (Grant and Chamberlain, 2017). However, it is unknown whether these findings are specific to their respective studies or can be generalized to the gambling disorder population as a whole. The first study included only a single class of medication (opiate antagonists) (Grant et al., 2008b). It therefore remains to be determined whether family history of alcoholism and intensity of gambling urges are specific predictors of response to opiate antagonists. The second study did not include patients assigned to active medication, meaning it is unclear whether the predictive factors identified are specific to placebo response or are non-specific predictors of improvement in symptoms (Grant and Chamberlain, 2017; Huneke et al., 2020).

In this study, we aimed to identify predictors of treatment response in gambling disorder, and then to explore whether response predictors for pharmacotherapy and placebo differed. We pooled data from treatment studies carried out in patients meeting diagnostic criteria for gambling disorder by the same group of researchers. A number of different pharmacological agents were tested in these trials with either an open-label or double-blind, placebo-controlled design. We hypothesized that some variables measured in all studies would transcend study design and treatment modality to predict treatment response in gambling disorder. Specifically, based on the above reported relationships between predictor variables and treatment outcomes, we hypothesized that demographic (age, gender, and ethnicity) and clinical variables (baseline severity, symptoms of anxiety or depression, comorbid psychiatric illness, and non-strategic gambling) would predict response to treatment. Previous treatment experience is also known to affect subsequent treatment outcomes (Colloca and Benedetti, 2006; Kessner et al., 2013; Zunhammer et al., 2017). We therefore also hypothesized that previously seeking gambling treatment and number of weeks spent in the trial might be important. Our secondary hypothesis was that significant predictors of response to active medication and to placebo would differ. The information gleaned from this analysis might inform study design in future clinical trials for gambling disorder.

# Method

## Characteristics of Included Trials

We included data from six treatment studies in gambling disorder all carried out by the same group of researchers. We included three double-blind, randomized, placebo-controlled trials:

1. A 16-week trial of paroxetine in 76 outpatients with gambling disorder in five centres across the USA and Spain. Patients who did not respond during a 1-week placebo run-in phase were randomized to paroxetine or placebo. Paroxetine was initiated at 10mg/day, and increased to 20mg/day during week 2 with flexible dosing up to 60mg/day. Response rate did not significantly differ between groups (59% in the paroxetine group, 49% in the placebo group, p = 0.390) (Grant et al., 2003).
2. An 18-week trial of naltrexone in 77 patients. Patients who did not respond during a 1-week placebo run-in phase were randomised to one of four conditions: naltrexone 50mg/day, 100mg/day, 150mg/day, or placebo. Outcomes did not differ significantly between the doses of naltrexone. Patients randomized to naltrexone exhibited significantly greater reductions in gambling severity (p = 0.0094), gambling urges (p = 0.0053), and gambling behavior (p = 0.0134) compared with patients on placebo (Grant et al., 2008a).
3. A 12-week trial of N-acetylcysteine in 28 patients with co-occurring nicotine dependence and gambling disorder. Patients were randomized to either N-acetylcysteine 1200mg/day (increased to 3000mg/day based on clinical judgement) or placebo. For the first 6 weeks, patients additionally received smoking cessation treatment, and in weeks 6-12, patients received imaginal desensitization plus motivational interviewing therapy for pathological gambling. Following this, all treatments ceased and patients were followed up 3 months later. There was no significant additional benefit of N-acetylcysteine over placebo during the treatment period. However, at the 3-month follow-up after treatment had ended, patients randomized to N-acetylcysteine exhibited significantly reduced severity of gambling symptoms (p = 0.043) (Grant et al., 2014). For the purposes of this study, data for the 6-week period of treatment for gambling disorder are included.

We also included three open-label treatment studies:

1. A 12-week open-label pilot study of escitalopram in 13 patients with co-occurring anxiety and gambling disorders. Patients completed a 1-week placebo run-in phase, after which escitalopram was initiated at 10mg/day, increasing at fortnightly intervals to 30mg/day (unless clinical improvement was seen at a lower dose). During the 12-week treatment period, there was a significant decrease in gambling symptom severity (p = 0.002) (Grant and Potenza, 2006).
2. A 14-week pilot study of N-acetylcysteine in 36 patients. N-acetylcysteine was initiated at 600mg/day for 2 weeks and increased fortnightly to 1800mg/day (unless clinical improvement was seen at a lower dose). There was a significant decrease in gambling symptom severity at the end of treatment (p < 0.001) (Grant et al., 2007).
3. A 10-week pilot study of open-label memantine in 29 patients. All eligible patients were started on 10mg/day for 2 weeks, and the dose was increased fortnightly to 30mg/day (unless clinical improvement was seen at a lower dose). There was an unusually high retention rate in this study, with 28 of 29 patients completing the entire 10-week treatment period. Gambling symptom severity significantly improved over the treatment period (p < 0.001) (Grant et al., 2010a).

An assessment of these trials’ quality is available in supplementary material. All trials were carried out in accordance with the protocol and provisions of the Declaration of Helsinki. All study procedures and accompanying literature were approved by The Institutional Review Boards of the University of Minnesota and the University of Chicago. All patients provided informed, written consent to participate.

## Study assessments

Data were gathered for all eligible patients regarding general demographics and problems due to gambling. Additionally, patients completed the following measures at baseline:

1. Structured Clinical Interview for Gambling Disorder (SCI-GD) – a clinician-administered, nine-item instrument that assesses gambling symptoms over the past 12 months according to the DSM criteria for gambling disorder (modified to reflect DSM-5) (Grant et al., 2004).
2. Structured Clinical Interview for DSM-IV (SCID-I) – to assess for the presence of psychiatric comorbidity (First et al., 1994).
3. Gambling Symptom Assessment Scale (G-SAS) – a validated, reliable self-report measure of gambling symptom severity over the past week. This scale consists of 12 items, each scoring 0-4, with a maximum score of 48 (Kim et al., 2009).
4. Hamilton Rating Scale for Depression (HAM-D) – a validated, reliable clinician-administered measure of depression severity over the past month (Hamilton, 1960).
5. Hamilton Rating Scale for Anxiety (HAM-A) – a validated, reliable clinician-administered measure of anxiety symptom severity over the past month (Hamilton, 1959).

In all trials, change in G-SAS (post-treatment G-SAS subtracted from baseline G-SAS) was an outcome measure of improvement in gambling disorder symptoms, and was therefore chosen as the primary outcome measure for this analysis.

## Statistical Analysis

All statistical analyses were carried out using Jamovi version 1.6.23.0 (<https://www.jamovi.org>) (The jamovi project, 2021). Descriptive statistics were calculated for demographic and baseline measures. A one-way ANOVA demonstrated that there were no significant differences between studies in mean change in G-SAS (F(5,200) = 1.65, p = 0.147). Data were therefore pooled from all studies for subsequent analyses.

Potential predictors of treatment response were assessed through multiple linear regression analysis. We chose a linear analysis to reduce the risk of bias that can be introduced by transforming linear outcome and/or covariate variables into categorical groups (Ritz, 2021). Since the placebo response rate in gambling disorder trials is high (Kraus et al., 2020), it is common practice to exclude patients with mild disorder from these trials to prevent floor or ceiling effects interfering with detection of medication effects (Whitlock et al., 2019). Therefore, to ensure external validity of our analyses, we excluded patients with a baseline G-SAS of less than 20 (classified as ‘mild’ severity of symptoms). We entered the following predictors into the model, based on reported relationships in the literature between predictor variables and treatment outcomes and *a priori* hypotheses : age, gender, ethnicity (dichotomized to Caucasian and non-Caucasian), weeks completed in the trial, whether the patient had previously sought gambling treatment, baseline G-SAS, baseline HAM-D, baseline HAM-A, presence of psychiatric comorbidity, and whether the patient preferred strategic or non-strategic games. All predictors were entered simultaneously. We initially ran this model on all patients as a single group. Next, to identify whether predictors of treatment response differ for active medication or placebo, we ran the same models separately in patients randomized to active medication and in those randomized to placebo. Each model was applied only to the pooled sample of patients in which all entered variables had been measured. Where data were missing, these participants were excluded from the model via listwise deletion.

We assessed the robustness of our findings to choices made through two sensitivity analyses. First, we carried out the same regressions but included those with mild G-SAS scores at baseline to ensure we had not introduced selection bias by excluding these patients. Second, although patients with mild disorder were excluded, it is possible that in a regression analysis involving a change score as the dependent variable, that predictor variables could reach significance through floor or ceiling effects in the remaining sample. We therefore ran a sensitivity analysis with percentage reduction in G-SAS as the dependent variable, rather than absolute change in G-SAS, to identify whether any predictors reached significance due to remaining floor or ceiling effects. Percentage reduction in G-SAS was calculated as follows:

# Results

## Baseline Characteristics

The final intent-to-treat sample size was n = 279 patients, which reduced to n = 235 patients after excluding those with a G-SAS of less than 20 at baseline. Of these, 168 patients (71%) were assigned to active medication arms and 67 (29%) were assigned to placebo. The patients’ mean age was 47.76 ± 11.11 years. The majority of patients were single or divorced (n = 129, 55%), and 32 (18%) had a previous history of alcohol dependence. On average, patients started gambling aged 37.82 ± 12.52 years, and mean time to gambling becoming a problem was 10.07 ± 9.61 years. Forty-two percent of patients had previously sought treatment for gambling disorder. Across all studies, mean baseline G-SAS was 31.51 ± 6.42 (severe), which on average reduced to 19.28 ± 10.78 (mild). Baseline characteristics are summarized in Table 1.

## Predictors of treatment response

Predictor variables associated with response to treatment in all patients, and with active medication or placebo response, are summarized in Table 2.

### All patients

When pooling all patients, the regression model was significant and explained 18% of the variance in change in G-SAS (adjusted R2 = 0.18, *F*(11,119) = 3.60, *p* = 0.00021). Significant positive predictors of treatment response included baseline G-SAS (β = 0.37, t = 4.26, p < 0.0001), number of weeks completed in the trial (β = 0.19, t = 2.33, p = 0.0215), and baseline HAM-D score (β = 0.36, t = 2.29, p = 0.0235). Baseline HAM-A score was the only significant negative predictor of treatment response (β = -0.52, t = -3.32, p = 0.0012).

### Active arms only

For patients receiving active medication, the regression model was significant and explained 22% of the variance in change in G-SAS (adjusted R2 = 0.22, *F*(11,85) = 3.46, *p* = 0.00051). The only positive predictors of treatment response in this model were baseline G-SAS (β = 0.43, t = 4.17, p < 0.0001) and number of weeks completed in the trial (β = 0.30, t = 3.20, p = 0.0020). Baseline HAM-A score approached significance as a negative predictor (β = -0.35, t = -1.87, p = 0.0643).

### Placebo arms only

For patients receiving placebo, the regression model was significant and explained 30% of the variance in change in G-SAS (adjusted R2 = 0.30, *F*(11,22) = 2.29, *p* = 0.04725). Baseline HAM-A score was a negative predictor of placebo response (β = -1.03, t = -3.88, p = 0.0008), while baseline HAM-D score positively predicted placebo response (β = 0.62, t = 2.32, p = 0.0299). Finally, being non-Caucasian was a significant positive predictor of change in G-SAS scores following placebo treatment (β = 0.97, t = 2.50, p = 0.0203).

## Sensitivity analyses

To assess the robustness of our findings against choices made during analysis, we modified the regression models detailed above with: 1. Patients with mild G-SAS scores (< 20) included and 2. Percentage reduction in G-SAS as the dependent variable. The results of these sensitivity analyses are summarized in supplementary Tables S1 and S2.

All models including patients with baseline G-SAS score of less than 20 remained significant. In patients assigned active medication, baseline HAM-A score was an additional significant negative predictor of treatment response (β = -0.37, t = -2.11, p = 0.0379). In patients assigned placebo, baseline G-SAS score was an additional positive predictor (β = 0.50, t = 3.11, p = 0.0048), while baseline HAM-D score was no longer a significant predictor.

When percentage reduction in G-SAS was the dependent variable, the only change in predictors in all 3 models was that baseline G-SAS score was no longer significant in the model that included all patients, instead approaching significance (β = 0.17, t = 1.87, p = 0.0638). Baseline G-SAS remained a significant predictor of response to active medication (β = 0.25, t = 2.30, p = 0.0240).

# Discussion

We aimed to identify predictors of treatment response, and whether the predictors for pharmacotherapy and placebo response differed, in gambling disorder. Through multiple regression analyses, we identified that baseline severity of gambling symptoms, number of weeks completed in a trial, and baseline anxiety and depressive symptoms were significant predictors of subsequent response to treatment. Importantly, these associations appeared to be driven by opposing effects in patients assigned to active medication and those assigned to placebo. In those randomized to active medication, higher baseline severity of gambling symptoms and number of weeks completed in the trial were predictors of greater treatment response, while decreased baseline symptoms of anxiety, increased baseline symptoms of depression, and non-Caucasian ethnicity were associated with improved response to placebo. Our sensitivity analyses showed that these associations were robust to choices made during the analysis.

## Predictors of response to active medication

We found that the number of weeks a patient spent in a trial was positively predictive of response to active medication. It is plausible this represents a dose-effect of medication, i.e. taking it for longer leads to greater improvement. However, there could be other explanations for this association. For example, previous studies have shown that ‘treatment satisfaction’ can be associated with symptom improvement following cognitive behavioral therapy (CBT) for pathological gambling (Guo et al., 2014; Manning et al., 2014). It is conceivable the effect of weeks completed might represent ‘treatment satisfaction’ in that patients could be more likely to withdraw from a clinical trial if they are unsatisfied. Counter to this, number of weeks completed was not a predictor of reduction in G-SAS in the placebo arms. Indeed, the beta coefficient for this predictor was negative in the placebo arms. Not only does this suggest that the effect of number of weeks in the trial is not a ‘treatment satisfaction’ effect, this also potentially suggests that trials of longer duration might reduce placebo response rate. In a previous analysis of placebo response in gambling disorder, patients who responded to placebo had, on average, spent a greater number of weeks in the trial compared with those who did not respond (Grant and Chamberlain, 2017). This analysis involved a dichotomous definition of response (greater than 35% reduction in G-SAS) that possibly obscures some nuance in the data. Further, it is not known whether a 35% reduction in G-SAS is an appropriate cut-off for defining “response” (Grant and Chamberlain, 2017). The effect of study duration on both active medication and placebo response requires further study.

We also found a positive association between baseline severity and response to active medication. This remained significant when percentage reduction in G-SAS was the dependent variable, suggesting this was not the result of a ceiling effect. A previous systematic review exploring predictors of treatment response in gambling disorder found that lower baseline symptom severity was predictive of improved outcome (Merkouris et al., 2016). However, all the studies included in that review involved psychosocial interventions, and none involved medication. Instead, increased baseline severity might be predictive of improved outcome with medication. Supporting this, baseline G-SAS score was not a predictor of placebo response in this sample. This is potentially similar to conditions such as depression where increasing severity is associated with greater benefit of medication over placebo (Fournier et al., 2010). Baseline symptom severity could be a useful clinical indicator to help identify who might derive benefit from medication or psychotherapeutic interventions in those with gambling disorder.

## Predictors of placebo response

Increased anxiety symptoms at baseline was associated with lower change in G-SAS over time. Anxiety is often comorbid with gambling disorder, and there is evidence that anxiety disorders precede the onset of gambling disorder (Kessler et al., 2008), and stress is predictive of relapse (Buchanan et al., 2020). It is possible therefore that those entering a trial with increased anxiety symptoms at baseline are at risk of deteriorating, or minimally improving, over the course of a trial. The effect of baseline anxiety on the progression of gambling disorder symptoms within a clinical trial should be considered during analysis.

Another intriguing possibility is that anxiety reduces the placebo effect in these patients. Anxiety is known to reduce placebo and increase nocebo effects on pain (Colloca et al., 2010; Corsi and Colloca, 2017; Morton et al., 2009; Staats et al., 2001), and has also been correlated with nocebo effects on itch (Bartels et al., 2016). It is noteworthy that the opioidergic and dopaminergic systems have been implicated in both gambling disorder and placebo effects (Benedetti et al., 2011; Grant et al., 2016; Huneke et al., 2020). Further investigation of the neurobiology of placebo and nocebo effects in gambling disorder, and how anxiety symptoms might interact with these, is needed.

HAM-D scores at baseline positively predicted placebo response. Gambling disorder is associated with symptoms of depression, and these have been hypothesized to be important in the pathogenesis of the disorder (Hodgins et al., 2005; Kim et al., 2006; Valleur et al., 2016). However, in treatment studies of depression, higher baseline depressive symptoms have been linked to *reduced* placebo response rates (Stein et al., 2006), which makes the present result puzzling. It should be noted that in the treatment studies included in the present analysis, high levels of depressive symptoms and the presence of other axis I psychiatric disorders were exclusion criteria. Indeed, in this sample the average HAM-D score was 7.11 (±4.08) suggesting no or mild depressive symptoms. It is unclear therefore whether the effect of baseline HAM-D score on treatment outcome is the result of depressive symptoms or an epiphenomenon not directly measured. Nevertheless, the effects of baseline depressive and anxious symptoms on treatment outcome in studies of medication for gambling disorder warrants further research.

We also found that non-Caucasian ethnicity was associated with greater reduction in G-SAS in the placebo groups. This replicates a previous finding that non-Caucasians receiving placebo in treatment studies for gambling disorder were more likely to be categorized as “responders” (Grant and Chamberlain, 2017). The reasons for this are unclear. It has been argued that non-Caucasians might experience *reduced* placebo effects that normally result from a clinical encounter due to inequalities in health services (Friesen and Blease, 2018), although we are not aware of any empirical data showing this to be the case. Interestingly, a study exploring predictors of treatment outcome in a US outpatient problem gambling service found that Asian Americans were more likely to benefit than Caucasians, while other ethnicities such as Native Americans were less likely to demonstrate a favorable outcome (Ingle et al., 2008). Ethnicity might be an important variable to consider in treatment studies of gambling disorder.

## Limitations

There are several limitations that need to be discussed. First, for a study of this kind, the sample size is relatively small. There is a risk therefore of false positives, although the findings were robust to different analysis choices as shown by our sensitivity analyses. Second, due to the nature of the linear regression model chosen, we could only include those individuals with data for all measures. The effect of missing data on the outcome has not been assessed. Third, the longest trial duration in this analysis was 18 weeks. It is unclear whether the predictors identified here are also associated with outcomes beyond this time. Fourth, in a linear analysis such as this, it could be argued whether statistically significant predictors are also predictive of clinically significant outcomes. In the present sample, mean baseline G-SAS was 31.51 (severe), which on average reduced to 19.28 (mild). Although the ideal assessment and threshold for clinical improvement in gambling disorder remains in doubt to some extent (Walker et al., 2006), this would generally be regarded as a clinically significant improvement. This suggests that the identified predictors are associated with clinically significant improvements in gambling symptoms. Finally, there are a number of potential factors that might be associated with treatment response that were not measured consistently or at all in these studies. For example, expectations of therapeutic benefit, which likely play a role in both active medication response and placebo effects (Huneke et al., 2020; Petrie and Rief, 2019; Rutherford et al., 2017). Triggers for gambling behavior have also been associated with placebo response in gambling disorder (Grant and Chamberlain, 2017), but were not measured consistently enough in the present studies to be included in the regression model. Predictors of response to psychological treatments for gambling disorder also include certain personality traits and being in the action stage of change (Merkouris et al., 2016). Additionally, predictors of response might differ for different classes of medication. Due to the small sample sizes of parent studies we were unable to assess this within this dataset. Further studies are needed to assess the effects of such factors in medication studies for gambling disorder, and whether they interact with the predictors identified here.

# Conclusion

We carried out a pooled analysis of medication studies in gambling disorder. We found that baseline severity of symptoms and number of weeks completed were significant predictors of active medication response. Conversely, baseline anxiety and depressive symptoms, and non-Caucasian ethnicity were significant predictors of placebo response. Further research is required to understand whether controlling for these variables, or using enriched samples, improves assay sensitivity in placebo-controlled clinical trials for gambling disorder.

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