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The Placebo Effect and Its Clinical Associations in Gambling Disorder

Jon E. Grant[a]

Samuel R. Chamberlain[b]

[a]Department of Psychiatry & Behavioral Neuroscience, University of Chicago, Pritzker School of Medicine, Chicago, IL, USA

[b]Department of Psychiatry, University of Cambridge, UK; & Cambridge and Peterborough NHS Foundation Trust, UK

Address correspondence to:

Jon E. Grant, J.D., M.D., M.P.H.

Department of Psychiatry & Behavioral Neuroscience

University of Chicago, Pritzker School of Medicine

5841 S. Maryland Avenue, MC-3077, Chicago, IL 60637

Telephone Number: 773-834-1325; Fax: 773-834-6761;

Email: jongrant@uchicago.edu

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Running title: Gambling and placebo

Abstract

Background: Gambling disorder is prevalent and functionally impairing, yet no FDA approved medications exist for its treatment. The ability of clinical trials to discriminate active treatment benefits has been hindered by the unusually high placebo response. Virtually nothing is known about baseline clinical characteristics that might be predictive of placebo response in gamblers.

Methods: 152 participants assigned to placebo were pooled from multiple double-blind trials in gambling disorder. Participants were classified as placebo responders or non-responders based on a cut-off of 35% reduction in symptom severity on the Gambling Severity Scale (GSAS). Baseline group differences were characterized using t-tests and equivalent non-parametric tests as appropriate.

Results: Fifty-one percent of individuals assigned to placebo treatment showed a significant clinical response to placebo. Placebo responders stayed in treatment for significantly longer, were more likely to endorse 'enjoyment' as a trigger for gambling, and were less likely to endorse 'boredom' or 'loneliness' as triggers for gambling. Placebo responders and non-responders did not differ significantly on age, gender, age at symptom onset, baseline symptom severity, comorbidities, or likelihood of having received a previous treatment.

Conclusions: Predictors of placebo response for gambling disorder appear markedly different from those reported for other mental health disorders.

Introduction

Gambling disorder is a potentially disabling global mental health problem in which individuals develop a maladaptive form of gambling behavior associated with impaired functioning, reduced quality of life, and high rates of bankruptcy and divorce (1). Many individuals with gambling disorder report intrusive thoughts and urges related to gambling that interfere with their ability to concentrate at home and at work, and work-related problems such as absenteeism and poor performance are common (2). Gambling disorder is also frequently associated with marital problems, diminished intimacy and trust within the family, as well as greater rates of health problems (e.g., hypertension, obesity, insomnia) (3-4). Thus, effective treatments for gambling disorder are needed.

After approximately three decades of pharmacological research, there are no Food and Drug Administration (FDA)-approved treatments for gambling disorder. Many of the double-blind, placebo-controlled pharmacological studies of this disorder have failed to separate from placebo. Interestingly, this has often been due to very high rates of placebo responders (i.e. 47% to 72%) (5-7). Understanding the complexity of the placebo response in gambling disorder has been challenging due to the limited sizes of the research samples. The present study seeks to overcome this limitation by using a relatively large data set, which combines participants from eight double-blind, placebo controlled pharmacological trials in gambling disorder (8-15).

As it is generally understood, a placebo is an inert substance with no direct peripheral or central nervous system effects. There is often a strong response to a placebo, however, and this may be due to multiple factors. Some research suggests that the placebo effect in clinical drug trials generally may influence as many as 49% of treated patients, that the effect may be unrelated to symptom severity, and that its duration may vary from minutes to years (16). The

placebo effect also appears to vary in strength based on different indications and what is being measured (for example, subjective versus objective endpoints) (17), and may further be influenced by factors such as genetics, patient expectations, and even the color and size of the placebo (18-21). In fact, there may be multiple placebo effects, or multiple mediators of the placebo effect, not simply a single factor contributing to this phenomenon (22-23).

Understanding the factors associated with the placebo effect in gambling disorder may allow for a more efficient examination of potentially beneficial pharmacological treatments for this disabling disorder. Here, we pooled data from studies conducted by the same group of researchers, in which all participants met diagnostic criteria for gambling disorder, took placebo-pills, and were seen regularly by a medical professional. Unlike studies of alcohol use disorders which involved combination treatments with therapy and therefore may have complicated the understanding of a placebo response (24-25), these studies were all comparative studies of medication versus placebo, in the absence of potentially confounding effects of concomitant psychotherapy. Based on the extant mental health literature, we hypothesized that the placebo effect in gambling disorder would be associated with younger age, shorter duration of illness, milder gambling illness severity at baseline, plus milder anxiety and depressive symptoms at baseline (26-30).

Methods

Subjects

Data from participants in gambling disorder treatment studies at the University of Chicago and the University of Minnesota, who were assigned to placebo during the clinical trial, were included in this study. A diagnosis of *gambling disorder* was confirmed by the primary

investigator, a board-certified psychiatrist, using the criteria set forth by the DSM-IV (31) and the diagnoses were later confirmed to be consistent with the current requirements for gambling disorder using the DSM-5 criteria (32). Exclusion criteria for these studies included current illegal drug use, any history of psychotic or bipolar disorder, any current psychotherapy, or inability to provide informed consent.

Data from eight, double-blind, placebo-controlled published trials were included (8-15). Of the eight studies, two examined naltrexone, two studied nalmefene, two focused on N-acetyl cysteine, and two involved paroxetine. Measures common to all studies included those analyzed in this study (see below). The studies differed in length with a range from 8 to 16 weeks.

All study procedures were carried out in accordance with the Declaration of Helsinki. The Institutional Review Boards of the University of Minnesota and of the University of Chicago approved the procedures and the accompanying consent forms. After all procedures were explained, all subjects provided informed written consent.

After providing informed consent, all participants in the trials completed a full psychiatric assessment using the Structured Clinical Interview for DSM-IV (SCID-I) (33). Subjects also completed general demographic questionnaires, self-report and clinician-administered severity measures, as well as information about symptom triggers.

Assessments

All participants underwent a semi-structured interview assessing gambling behavior: age at onset of gambling and problems due to gambling. In addition, all participants completed the following measures:

Gambling symptoms during the past 12 months were evaluated using the *Structured Clinical Interview for Gambling Disorder (SCI-GD),* a nine-item instrument covering the DSM-5 criteria (31; modified to reflect DSM-5).

Yale-Brown Obsessive-Compulsive Scale modified for Pathological Gambling (PG-YBOCS): The PG-YBOCS is a clinician-administered scale that assesses severity of urges and behaviors related to gambling during the past week, with higher scores indicating greater severity (34).

Gambling Symptom Assessment Scale (GSAS): The GSAS is a reliable self-report measure that assesses gambling symptom severity over the last week. Scores are based on ten questions, with each being scored from 0-4, with a maximum possible severity score of 40. The scale covers a range of symptoms related to gambling disorder, including the severity, duration, and frequency of both urges and behaviors related to gambling (35).

Hamilton Depression Rating Scale (HAM-D): The HAM-D is a clinician-administered scale which assesses a patient's level of depression during the past month (36).

Hamilton Anxiety Rating Scale (HAM-A): The HAM-A is a clinician-administered scale which assesses a patient's level of anxiety during the past month (37).

Sheehan Disability Scale (SDS): The Sheehan Disability Scale is a valid and reliable, three-item, self-report scale that assesses psychosocial functioning in work, social or leisure activities, and home/family life (38).

Data Analysis

Baseline characteristics of the placebo participants pooled from all of the studies were presented in terms of means and standard deviations for continuous variables and frequencies and percentages for categorical variables.

Patients were grouped as placebo responders (>35% reduction in GSAS total scores from baseline to end-point) or non-responders. The two groups were compared on pertinent demographic, clinical, and cognitive measures using independent sample t-tests or equivalent non-parametric tests as indicated in the text. This being an exploratory study, statistical significance was defined as $p<0.05$ uncorrected, two-tailed.

Results

Data from 152 participants with primary gambling disorder (N=63 [41.5%] female, mean age 45.9 ± 11.9 years) who were assigned placebo were included in the analysis. In the pooled analysis, 51.3% of participants assigned to placebo improved at least 35% on GSAS during placebo treatment.

Clinical variables of responders and non-responders are presented in Table 1, where it can be seen that the groups did not differ from each other in terms of age, gender, or educational level. The responder group had a significantly lower proportion of participants with White Caucasian ethnicity versus the other group.

The placebo responders group, compared to the non-responders group, showed significantly more weeks of study completion, were more likely to endorse 'enjoyment' as a trigger for gambling, and were less likely to endorse 'feeling sad' or 'loneliness' as triggers for gambling. State mood and anxiety, history of comorbid mental disorders, and previous treatment status did not significantly differ between the two groups.

Table 1. Clinical Variables of Participants with Gambling Disorder Who Did and Did Not Respond to Placebo

Variables	Those Who Responded to Placebo (n=78)	Those Who Did Not Respond to Placebo (n=74)	Statistical Test	P value
Age, years	46.4 (10.4)	45.5 (13.4)	t-test=-0.476 df=150	0.635
Gender, female, N [%]	31 [39.7%]	32 [43.2%]	LR chi-square = 0.192	0.662
Education level	2.8 (1.1)	3.3 (1.1)	t-test=1.705 df=78	0.092
Race, white Caucasian, N [%]	58 [74.4%]	65 [87.8%]	LR chi-square = 4.572	0.033
Age at onset of gambling	23.0 (12.2)	25.3 (11.9)	t-test=1.121 df=135	.264
G-SAS baseline score	36.3 (9.6)	33.6 (9.0)	t-test=-1.723 df=149	.087
PG-YBOCS				
Urge subscale	11.3 (2.7)	11.4 (2.6)	t-test=0.235; df=125	.815
Behavior subscale	12.1 (2.8)	11.9 (3.20	t-test=-0.387; df=125	.699
Total score	23.4 (4.8)	23.3 (5.2)	t-test=-0.107; df=125	.915
Weeks of study completed	13.2 (4.2)	10.6 (5.1)	t-test=-3.379 df=150	<.001

Previous treatment for gambling, yes, N[%]	29 [42.7%]	26 [46.4%]	LR chi-square = 0.178	0.673
Triggers to gambling, n {%]				
Enjoyment	4 [19.1%]	0 [0%]	LR Chi-square = 6.380	0.012
Having money	12 [84.0%]	12 [42.9%]	LR Chi-square = 0.141	0.707
Depression	4 [16.0%]	8 [28.9%]	LR Chi-square = 1.214	0.271
Feeling sad	0 [0%]	3 [10.7%]	LR Chi-square = 3.989	0.046
Loneliness	2 [8.0%]	10 [35.7%]	LR Chi-square = 6.263	0.012
Boredom	10 [40.0%]	6 [21.4%]	LR Chi-square = 2.173	0.140
Sheehan Disability Scale	17.1 (6.1)	16.7 (6.7)	t-test=-0.358 df=114	.721
HAMA	6.39 (4.35)	8.01 (5.13)	t-test=1.509 df=78	.135
HAMD	6.39 (3.96)	7.56 (4.99)	t-test=1.145 df=78	.256
Lifetime Psychiatric Comorbidity				
Mood Disorder	16 [23.5%]	15 [26.8%]	LR Chi-square = 0.173	0.677
Anxiety Disorder	5 [7.4%]	5 [8.9%]	LR Chi-square = 0.102	0.749
Alcohol Use Disorder	8 [11.8%]	8 [14.3%]	LR Chi-square = 0.173	0.678
Behavioral Addiction	2 [5.4%]	7 [15.9%]	LR Chi-square = 2.392	0.122

All values are mean (±SD) for continuous variables and N [%] for categorical variables. LR = likelihood ratio test.

Discussion

This is the first study we are aware of that examines clinical variables associated with the placebo response in the pharmacological treatment of gambling disorder. Given that the pooled placebo response in these studies was 51%, and that there is as of yet no FDA-approved medication, determining predictors of placebo response is crucial for the timely and cost-effective development of pharmacological interventions. Knowledge of variables associated with placebo response might also be useful for sample enrichment in clinical trials.

This study found that those who completed more weeks of treatment, those who endorsed 'enjoyment' as a trigger for gambling, and those who did not endorse 'feeling sad' or 'loneliness' as triggers for gambling, were more likely to be placebo responders. Contrary to our expectations, baseline symptom severity, gambling at a younger age, and previous treatment for gambling disorder did not differ between placebo responders and non-responders. The differences between our results and studies of other mental health conditions in which younger age and previous treatment were meaningful predictors of placebo response (28, 30, 39-40) could reflect the particular characteristics of our subject population or of the disorder itself.

Given the relative paucity of side effects associated with placebo, and the high rate of response to placebo observed in this pooled dataset, these findings raise the crucial question of whether placebo should be used for the treatment of gambling disorder. The ethical implications of this option have been debated for decades (41). In the case of gambling disorder, we know that in one of the studies, the placebo response was robust for the entire 4-month period of the study (10). Therefore, the placebo effect may not be transient for gambling disorder as it is for other health conditions (42). The current findings add another layer to the debate about the possible use of placebos in clinic settings.

This study suggests that few baseline clinical characteristics in gambling disorder distinguish placebo responders from non-responders, but there exist several limitations to the studies included in the pooled analysis. First, some data suggest that expectancy (i.e. an individual's beliefs about whether he or she will improve due to the treatment) may play a large role in a placebo response (41, 43). Expectancy was not measured in the studies analyzed here. Second, although the G-SAS scoring has demonstrated strong validity and reliability in previous trials as reflecting a response to medication (35), the ideal assessment of (and threshold for) gambling disorder response remains somewhat in doubt (44). Third, some clinical measures were available only for a subset of individuals in the pooled dataset (e.g., rates of behavioral addictions were not examined in the earlier studies). Fourth, the finding that placebo responders were more able to experience pleasure as a trigger and less likely to report sadness raises the question as to whether the affective state at the time of testing would affect the placebo response. Unfortunately this was no examined in these studied. Finally, this study did not examine baseline brain function (e.g. cognition, blood oxygen level dependent activation) that might be predictive of placebo response, nor such changes over the course of placebo treatment. This may in the future be a useful means of distinguishing placebo responders from non-responders before treatment, especially given that the placebo response can be linked with neural changes (45).

Placebo controlled studies are the gold standard for the examination of pharmacological interventions. Individuals with gambling disorder who respond to placebo appear to have different distributions of triggers for their gambling behavior – being disproportionately more likely to endorse enjoyment as a gambling trigger, and less likely to endorse feeling sad/lonely as a trigger. Furthermore, placebo responders may potentially benefit from longer interventions than non-responders. Given the global health problems associated with gambling disorder (1),

understanding the placebo response will be crucial for developing better pharmacological interventions for this disorder. Since opioid and dopamine pathways are implicated both in gambling disorder and in the placebo response (29, 46-47), gambling disorder may be a particularly fruitful condition with which to study the neurobiological basis of placebo response. In addition, this study suggests that those who were in the studies longer had a stronger placebo response, but we have no clear data regarding how long the placebo effect lasts. Future studies therefore may also wish to focus on several unanswered questions such as the duration of the placebo effect in gambling disorder, whether incentives that increase the time spent in the study increase the placebo response, and whether short studies of say two to four weeks may decrease the placebo effect and be more fruitful in finding beneficial pharmacological treatments for gambling disorder.

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