Silymarin Treatment of Pathological Gambling: A Double-Blind, Placebo-Controlled Study

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Jon E. Grant, M.D.

University of Chicago

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Project Goals

The goal of the proposed study is to evaluate the efficacy and safety of silymarin in individuals with gambling disorder. The hypothesis to be tested is that silymarin will be more effective and well tolerated in subjects with gambling disorder compared to placebo. The proposed study will provide needed data on the treatment of a disabling disorder that currently lacks a clearly effective treatment.

Specific Aims

The primary aim of this application is to conduct a randomized controlled pharmacotherapy trial in 80 individuals with gambling addiction. Participants with gambling disorder will be started and continued on medication during an 8-week treatment phase. The study will be the first to use a pharmacological intervention targeting stress response in gambling addiction and thereby has the potential to set a new standard of care for addictions. Impairments in prefrontally-mediated cognitive functions appear to underlie behavioral dysregulation, namely planning and inhibitory control. These impairments may increase the risk for making decisions that are impulsive, focused on short-terms gains and thereby place the individual at high risk for continued smoking and gambling. Relapse to addictions may therefore be related to less efficient prefrontal neural signaling and possible deficits in executive cognitive functioning. The antioxidant, milk thistle, offers a unique mechanism to address cognitive deficits associated with gambling disorder. By increasing dopamine in the prefrontal cortex, milk thistle may improve performance on tests of executive functioning and the efficiency of cortical information processing in healthy adults. Optimal dopamine modulation of prefrontal cortical networks appears to be necessary for a variety of cognitive functions, such as planning, response flexibility, and response inhibition. The proposed study will allow us to investigate baseline cognitive aspects of individuals with gambling disorder and examine the impact of drug treatment on tasks of cognitive control.

Aim 1: We will examine the effects of milk thistle versus placebo in individuals with gambling disorder. By targeting deficits in cognitive control, milk thistle may offer a unique mechanism to address addictive disorders. We hypothesize that milk thistle will be more effective than placebo in reducing gambling behavior during an acute treatment period.

Aim 2: Because lack of cognitive control may underlie a range of addictive behaviors, and improvement in addictive symptoms may be secondary to greater control, we will examine levels of cognitive control using cognitive tasks pre- and post-treatment. This study will examine cognitive deficits across a range of prefrontal-dependent domains which have been associated with gambling disorder - inhibition, working memory, cognitive flexibility and planning ability - as possible predictors of treatment and as possible biomarkers for underlying pathophysiology of addiction. We hypothesize that improvement in planning ability and inhibition will be greater in participants who receive milk thistle compared with placebo.

Background and Significance

Gambling disorder is a significant public health problem that often results in a distinctive pattern of persistent and disabling psychological symptoms. Although once thought to be

relatively uncommon, studies estimate that gambling disorder has a lifetime prevalence among adults of 1.6% and past-year prevalence of 1.1% (1-2). Patients with gambling disorder also experience significant social and occupational impairment as well as financial and legal difficulties (3).

Individuals with gambling disorder report chronically high levels of stress, and vulnerability to gambling addiction is enhanced by stressful events (4), particularly as stress may result in cognitive problems leading to impulsive and unhealthy decisions (5). A stress response is elicited when sensations and observations do not match existing or anticipated expectations. A primary endocrine response to stress is the secretion of glucocorticoids through the activation of the hypothalamic–pituitary–adrenal axis (6). Although their release serves to maintain homeostasis during acute episodes of stress, prolonged stress responses have been associated with structural brain damage both in humans and animals (6). In humans, stress also enhances addictive craving, and relapse to addiction is more likely to occur in individuals exposed to high levels of stress. Since oxidative stress may be implicated in the etiology of addictive behaviors, use of antioxidants to reduce relapse, improve cognitive functioning, and reduce addictive urges may be a sensible step.

Silymarin, a flavonoid and a member of the Asteraceae family, is extracted from the seeds of milk thistle (*Silybum marianum*) and is known to own antioxidative and anti-apoptotic properties. Silymarin has been reported to decrease lipid peroxidation. Furthermore, it has been demonstrated that its anti-oxidative activity is related to the scavenging of free radicals and activation of anti-oxidative defenses: increases in cellular glutathione content and superoxide dismutase activity. Milk thistle has been used for a range of psychiatric disorders including methamphetamine abuse and obsessive compulsive disorder, two psychiatric disorders with similarities to gambling disorder. The flavanoid complex silymarin in preclinical studies has been found to increase serotonin levels in the cortex (7), and ameliorate decreases in dopamine and serotonin in the prefrontal cortex and hippocampus associated with methamphetamine abuse (8). In the frontal cortex one of the functions of dopamine is to increase the signal to noise ratio, increased dopamine correlating with increased frontal performance (9). Studies have shown that the higher cortical dopamine levels are associated with improved frontal cortical cognitive performance (9). Cortical inhibition is felt to be the basis for top-down control of motivated behaviors. A recent randomized controlled study with milk thistle was conducted in Iran. Thirty five participants with moderate OCD were randomly assigned to 200 mg of milk thistle leaf extract or 10 mg of fluoxetine three times daily for eight weeks. Results revealed no significant difference in treatment effects between milk thistle and fluoxetine from baseline to endpoint as both interventions provided a highly significant reduction in symptoms (10).

Silymarin or Milk Thistle may therefore offer promise for the treatment of individuals with gambling disorder. Pharmacological management of gambling symptoms has produced mixed results, with some studies showing a superiority of medication to placebo (11).

The current pilot study examines the tolerability and efficacy of milk thistle in the treatment of gambling disorder. We hypothesize that milk thistle will reduce the severity of gambling symptoms and improve patients' overall functioning.

Methodology

The proposed study will consist of an 8-week double-blind, placebo-controlled trial of milk thistle in 80 subjects with gambling disorder. Sample size calculation, using baseline PG-

YBOCS total scores reported in a previous gambling study (mean score of 14.6 (SD 7.1)), is based on a simple test of mean differences. For this study, we assumed 30% and 60% decreases for placebo and for milk thistle, respectively, by week 8, leading to mean scores of 10.2 and 5.8. Normal distribution was assumed. To detect a mean difference of 4.4 with 80% power and 5% significance level in a two-sided test, 40 subjects per group are needed.

Subjects:

Inclusion criteria:

1) Men and women age 18-75;
2) Diagnosis of current gambling disorder based on DSM-5 criteria and confirmed using the clinician-administered Structured Clinical Interview for Pathological Gambling (SCI-PG) (12);
3) Gambling behavior within 2 weeks prior to enrollment;
4) Women of child bearing age are required to have a negative result on a beta-human chorionic gonadotropin pregnancy test;
5) Women of childbearing potential utilizing a medically accepted form of contraception defined as double barrier, oral contraceptive, injectable contraceptive, implantable contraceptive devices, and abstinence

Exclusion criteria:

1) Infrequent gambling (i.e. less than one time per week) that does not meet DSM-5 criteria for gambling disorder;
2) Unstable medical illness or clinically significant abnormalities on laboratory tests, EKG, or physical examination at screen as determined by the investigator;
3) History of seizures;
4) Myocardial infarction within 6 months;
5) Current pregnancy or lactation, or inadequate contraception in women of childbearing potential;
6) A need for medication other than milk thistle with possible psychotropic effects or unfavorable interactions as determined by the investigator;
7) Clinically significant suicidality (defined by the Columbia Suicidal Scale);
8) Lifetime history of bipolar disorder type I or II, schizophrenia, or any psychotic disorder;
9) Initiation of psychotherapy or behavior therapy within 3 months prior to study baseline;
10) Previous treatment with milk thistle

Study Design

The study is an eight-week, double-blind, placebo-controlled, pilot study of the safety and efficacy of milk thistle for individuals with gambling disorder. All eligible study subjects will begin milk thistle at 150mg twice a day or placebo at a 1:1 ratio of milk thistle or placebo for subjects who are randomized into the study. After 2 weeks, the dose can be increased to 300mg twice a day. Subjects will be seen for scheduled study visits every two weeks during the 8-week double-blind, placebo-controlled study. All efficacy and safety assessments will be performed at each visit. Subjects who are not compliant with their use of study medication (i.e. failing to take medication for three or more consecutive days) will be discontinued from the study. Patients who experience a clinically significant adverse event will also be discontinued from the study.

Screening Assessments

Subjects will be evaluated at entry into the study by the Structured Clinical Interview for Pathological Gambling (SCI-PG), a reliable and valid diagnostic instrument using criteria for DSM-IV PG. Psychiatric comorbidity will be assessed using the Structured Clinical Interview for DSM-5 (SCID) and SCID-compatible modules for impulse control disorders (13-14). Medical history, physical examination, electrocardiogram and routine laboratory testing will be obtained. Gambling symptom severity will be assessed using the PG-YBOCS (15) and the self-rated Gambling Symptom Assessment Scale (G-SAS) (16). Anxiety symptom severity will be assessed with the Hamilton Anxiety Rating Scale (HAM-A) (17). Depressive symptoms will be measured with the Hamilton Depression Rating Scale (HAM-D) (18). Psychosocial functioning will be evaluated using the Sheehan Disability Scale (SDS) (19). Personality will be assessed using the lie acceptability Scale, The Narcissistic Personality Inventory 16, and the Social Desirability Scale.

In addition, subjects will undergo cognitive assessments at baseline and study endpoint. **Cognitive Assessments:** Assessments of cognitive control will be comprised of several valid paradigms (Table 1). These tasks are designed to probe dissociable neural circuitry and cognitive processes likely to be implicated in the pathophysiology of addictions. Task order was chosen arbitrarily and will be applied consistently across subjects, to minimize possible confounding factors of differences in task order across participants.

Table 1. Neurocognitive Tasks

Task	**Neurocircuitry/Neurochemistry**
Stop-Signal Task of Inhibitory Control	Activates distributed circuitry including the right frontal gyrus
Intra-dimensional/Extra-dimensional Set Shift Task (ID/ED task)	Dependent on bilateral orbitofrontal cortices for reversal learning and bilateral lateral prefrontal cortices for extra-dimensional set-shifting
Tower of London Task	Tests frontal lobe integrity

Efficacy Assessments

The primary outcome measure will be the *Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS)* (15). The PG-YBOCS is a reliable and valid, 10-item, clinician-administered scale that rates gambling symptoms within the last seven days, on a severity scale from 0 to 4 for each item (total scores range from 0 to 40 with higher scores reflecting greater illness severity). Scores ranging from 0 to 10 reflect minimal or mild symptoms; scores from 11 to 20 suggest moderate symptoms; severe symptoms are associated with scores from 21 to 30; and scores greater than 30 reflect extreme gambling symptoms.

Secondary efficacy measures include the Clinical Global Impression Scale (CGI). *Clinical Global Impression-Improvement and Severity scales (CGI)* (20). The CGI consists of two reliable and valid 7-item Likert scales used to assess severity and change in clinical symptoms. The improvement scale will be used every visit after the screening visit. The scale ranges from 1 = “very much improved” to 7 = “very much worse.” The CGI severity scale was used at each visit and ranges from 1 = “not ill at all” to 7 = “among the most extremely ill.” The CGI has been used successfully for gambling trials previously.

Gambling Symptom Assessment Scale (G-SAS) (16). Subjects will complete the G-SAS at each study visit. The G-SAS is a 12-item, reliable and valid, self-rated scale assessing gambling

urges, thoughts, and behaviors during the previous seven days. Each item is rated 0 to 4 with a possible total score of 48. Higher scores reflect greater severity of PG symptoms.

Sheehan Disability Scale (SDS) (19). The SDS is a three-item, reliable and valid scale that assesses functioning in three areas of life: work, social or leisure activities, and home and family life.

Hamilton Anxiety Rating Scale (HAM-A) (17). The HAM-A is a reliable and valid, clinician-administered, 14-item scale that provides an overall measure of global anxiety.

Hamilton Depression Rating Scale (HAM-D) (18). The HAM-D is a valid and reliable, 17-item, clinician-administered rating scale assessing severity of depressive symptoms.

Perceived Stress Scale (PSS) (21). The 14-item PSS is a reliable and valid, self-report measure designed to assess the degree to which individuals find their lives to be unpredictable, uncontrollable, and stressful. Each question is answered on a 5-point scale (ranging from "never" to "very often") based on experiences of the previous month. Scores range from 0 to 40.

Quality of Life Inventory (QOLI) (22). The QOLI is a 16-item self-administered rating scale that assesses life domains such as health, work, recreation, friendships, love relationships, home, self-esteem and standard of living. Each item is rated according to importance in the respondent's life and the level of satisfaction perceived by the respondent in that area of life.

MINI International Neuropsychiatric Interview (MINI) (23). The MINI is a valid and reliable semi-structured interview, assessing the most prevalent psychiatric disorders.

Barratt Impulsivity Scale (*BIS*; 24). The BIS is a valid and reliable, self-report measure designed to assess the degree to which individuals are highly impulsive. While it is not a diagnostic assessment, it is key to understand the participant's entire psychiatric profile.

Alcohol Use Disorders Identification Test (AUDIT; 25*).* The AUDIT is a valid and reliable 10-item self-report questionnaire assessing problem drinking.

Fagerstrom Test for Nicotine Dependence (FTND; 26). The FTND is a valid and reliable 7-item self-report questionnaire assessing nicotine dependence.

Eysenck Impulsive Questionnaire (EIQ; 27*).* The EIQ is a valid and reliable 54-item self-report questionnaire assessing the degree to which individuals are highly impulsive. While it is not a diagnostic assessment, it is key to understand the participant's entire psychiatric profile.

Minnesota Impulse Disorders Interview (MIDI; 28*).* The Minnesota Impulse control disorders Interview (MIDI) is a diagnostic tool assessing compulsive buying, kleptomania, trichotillomania, intermittent explosive disorder, pyromania, pathological gambling (now known as gambling disorder), and compulsive sexual behavior.

Canadian Adolescent Gambling Inventory (CaGI; 29*).* The CaGI is a valid and reliable 44-item self-report scale assessing the avenues through which people engage in problem gambling over the past 3 months.

Structured Clinical Interview for Pathological Gambling (SCI-PG; 30*).* The SCI-PG a structured clinical interview to diagnose gambling disorder.

Columbia Suicide Severity Rating Scale (C-SSRS; 31*).* The Columbia Suicide Severity Rating Scale is a valid and reliable clinical assessment designed to assess an individual's suicide risk level and suicidal ideation.

Safety Assessments

Safety assessments (sitting blood pressure, heart rate, adverse effects, and concomitant medications) will be documented at each visit. In terms of vital signs, those subjects with abnormal blood pressures will be assessed for symptoms of hypo- or hypertension.

Asymptomatic subjects will be evaluated each visit for changes in vital signs. In the case of hypertensive emergencies (BP greater than 210/120), appropriate referral to the emergency room will be made. In the case of hypotension (BP less than 90/60), participants will be evaluated for symptoms of hypotension and if symptomatic, appropriate interventions will be made.

Suicidality will be assessed using the Columbia Suicide Severity Scale. The Columbia Scale will be performed at every visit. Subjects who endorse suicidal thoughts at any time during the study will be removed from the study and appropriate clinical intervention (e.g. hospitalization) will be arranged.

The investigator will record use of concomitant medications in terms of daily dosage, start and stop dates, and reason for use. Adverse events will be recorded at each study visit and as they become known to the study staff. Urine pregnancy tests will be performed only at screening. Medication compliance will be ascertained through weekly pill count of investigational medication.

Due to the pandemic of COVID19, study participants can perform their baseline and follow-up visits online using encrypted Zoom instead of in person visits. All inventories will be assessed.

Data Analysis

Demographic and baseline visit characteristics for milk thistle and placebo groups will be compared using chi-square and analysis of variance to determine if group differences existed at ranodmization. Primary and secondary measures will be examined using repeated-measures ANOVA modeling analyses (PROC MIXED, SAS/STAT Sofetware for Windows, Version8.2, SAS Institute Inc., Cary, NC, USA). The baseline value of the measure being analyzed will be used as a covariate. A time trend (linear) will be included in all models. The difference in the overall level of posttreatment values, the main effect for treatment, will be the test of primary interest. Analyses will be performed on all available data as well as for the completers. All available post-randomization data will be first analyzed and a secondary, supportive analysis of completers will be performed. All comparison tests will be two-tailed and an alpha level of .05 will be used to determine statistical significance.

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