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Treatment of Pathological Gambling with Naltrexone Pharmacotherapy and Brief Intervention: A Pilot Study

By Tuuli Lahti, Jukka T. Halme,
Maiju Pankakoski, David Sinclair, Hannu Alho

ABSTRACT ~ We explored the efficacy of the opiate antagonist, naltrexone, as a treatment for pathological gambling. Treatment seeking pathological gamblers ($n = 39$) (according to both South Oaks Gambling Screen and a screen based on the Diagnostic and Statistical Manual of Mental Disorders) participated into our treatment study during 2009. The subjects were instructed to use 50 mg of naltrexone before gambling or when feeling craving towards gambling.

The protocol contained one initial doctor visit with motivational brief intervention. During period that were free of gambling, the subjects were instructed to practice other healthy behavioral alternatives to gambling. The primary outcome measure was the Yale Brown Obsessive Compulsive Scale adapted for Pathological Gambling. The other outcome measurements were the EQ-5D quality of life survey, the Alcohol Use Disorders Identification Test, and the Beck Depression Inventory.

The average age of the subjects was 39 years; 80% were men. Highly significant ($p < 0.01$) decreases in reported obsessive-compulsive gambling and depressive symptoms and increases in the subjective quality of life developed in the study.

These positive changes suggest that this simple, inexpensive treatment helps pathological gamblers. The role of naltrexone in the treatment effect, however, needs to be determined with a larger, placebo-controlled study. *Psychopharmacology Bulletin*. 2010;43(3):35-44.

INTRODUCTION

Pathological gambling (PG) is characterized as an impulse control disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)

Dr. Lahti, PhD, Halme, MA (Psych), Pankakoski, B.Soc.Sci, Dr. Sinclair, PhD, National Institute for Health and Welfare, Department of Mental Health and Substance Abuse Services, Helsinki, Finland. Dr. Alho, MD, PhD, National Institute for Health and Welfare, Department of Mental Health and Substance Abuse Services and Research Unit of Substance Abuse Medicine, University of Helsinki, Helsinki, Finland.

To whom correspondence should be addressed: Tuuli Lahti, PhD, National Institute for Health and Welfare, P.O. Box 30, FO-00271 Helsinki, Finland. Phone: 020 610 8908; Fax 020 610 6111; E-mail: tuuli.lahti@thl.fi

[APA 1994]. PG is characterized by frequent gambling episodes and thoughts governed by gambling. Gambling replaces other activities of the pathological gambler and causes financial, social and emotional problems. PG shares many of the same diagnostic criteria as substance use disorders: repeated unsuccessful attempts to quit, disturbing impacts on life, tolerance, and withdrawal effects. The primary difference is that in PG no substance is present. Thus research on PG provides us a pure insight to the neurophysiologic features of addictive behavior and may guide the development and testing of effective treatments for other addictions, too.

The pathological gambling prevalence rate in the US is approximately 1%.¹ Similarly, in Finland approximately 1% of the adult population is estimated to be pathological gamblers.² Untreated PG can impair functioning at many levels; validated, effective treatments are, therefore, needed. Psychosocial treatment options are usually the first choice when treating PG's.³⁻⁶ Alongside with the psychosocial methods, pharmacological treatment may benefit the patient. Although PG is a relatively common disorder, only limited information on pharmacotherapy for PG exists. Changes in opioid, noradrenalin, serotonin, dopamine and glutamate neural systems seem to be related to PG, and most pharmacological approaches have been based on the hypothesis that balancing dysfunctional neurotransmission especially during the withdrawal process will reduce the urge to gamble.⁷⁻¹² Mood stabilizers have also been tested in the treatment of PG.¹³⁻¹⁵

Since endogenous opioids are important mediators of the reinforcement process of the nervous system, the blocking of opioid receptors with antagonists such as naltrexone and nalmefene may be a promising new form of pharmacological treatment option for PG.¹⁶ Despite their well-demonstrated efficacy in the treatment of alcohol dependence, few randomized controlled trials with naltrexone or nalmefene have evaluated their efficacy for the treatment of PG.¹⁷ In the naltrexone trials, the antagonist was administered on daily basis. However, some recent data indicates that targeted use—taking the antagonist only when drinking alcohol—may be effective for the treatment of heavy alcohol consumption.¹⁸⁻¹⁹ Our novel approach herein is to use the opiate antagonist naltrexone in a targeted manner in PG treatment, i.e., taking naltrexone only before the gambling or only when the patient feels craving for gambling. It has been suggested that the benefits from naltrexone in treating opiate addiction and alcoholism come primarily from the mechanism of extinction produced after the patient makes the response of taking opiates or drinking alcohol while reinforcement is blocked by the antagonist. We hypothesized similarly that naltrexone blocks the reinforcement that the patient gets from gambling and thus,

extinguishes the gambling behavior and the desire to gamble. Another novel idea herein was to motivate the patient to practice healthy alternative behaviors during the periods when they are not gambling and thus are not taking naltrexone.

METHODS

The volunteer participants in this study were recruited by announcements in gambling-related internet sites (www.ray.fi, www.pakkopeli.fi, www.a-klinikka.fi, www.peluuri.fi, www.suomi24.fi, www.paihdelinkki.fi) and by two announcements in a giveaway newspaper (Metro) during the first quarter of 2009. In the announcements, those who experienced gambling as a problem were advised to visit the study webpage (www.ktl.peli.fi) and fill in validated Finnish version of the South Oaks Gambling Screen (SOGS-R)²⁰ and DSM-IV screen for diagnostic criteria of PG.²¹ SOGS-R includes 16 questions about problems associated with gambling and is used to measure the pathology of gambling. The total score on the SOGS-R ranges from 0 to 20 (higher values are indicative of worse psychopathologic states: a value of 5 or more indicates probable pathological gambling). The lifetime version of SOGS-R was used in the present study. The DSM-IV screen for pathological gambling includes 10 questions of persistent and recurrent maladaptive gambling behavior. The total score of the DSM-IV ranges from 0 to 10 (higher values are indicative of worse gambling-related problems; a value of 5 or more indicates pathological gambling).

Those respondents who scored five or more on both SOGS-R and DSM-IV were informed about the possible suitability for the study and given the e-mail address to contact the research team. Those who contacted the research team were invited for a visit with study doctor where the suitability of the subject for the research was assessed. The inclusion criteria were: scores of 5 or more from SOGS-R and DSM-IV and ability to use internet and e-mail. The exclusion criteria were: acute hepatitis, severe liver or kidney dysfunction, suicide risk or severe depression or other untreated mental health problem, participation to other gambling research at the same time, the use of drugs (especially opiates), pregnancy; prisoners, retarded and mentally ill patients were also excluded. The ethics board of the Helsinki and Uusimaa hospital district gave permission for this study (permission # EudraCT # 2008-004102-14 and ethical permission # 259/13/03/00/2008).

All participants had to be able to read and understand the patient information sheet and sign the informed consent. All participants were free to stop being in the study whenever they wanted. The patients were not paid or reimbursed for participation. At the study visit, the subjects were given written instructions for the proper use of naltrexone. Subjects

were advised to take 50 mg naltrexone approximately one hour before gambling or feeling urges to gamble (and to refrain from taking naltrexone at other times). In this study the maximal daily dose was 50 mg of naltrexone. The medication was free for the subjects. The subjects were also given written instructions for practicing healthy alternative behaviors (physical exercise, reading etc.) at times when they were not gambling. The participants were given one visit including motivational brief intervention to reduce gambling along with a brief intervention booklet "Winning Within, a self help guide to changing gambling behaviors" (Finnish version edited by permission of Nova Scotia Health Promotion, Canada).

MEASURING THE TREATMENT OUTCOME

The study period consisted altogether 19 weeks: 3 weeks of retrospective gambling disquisition, and 16 weeks of the treatment period. At baseline the patients were interviewed by the study doctor with a timeline follow back method for determining the gambling quantity and quality during the last three weeks. The participants filled out the Yale Brown Obsessive Compulsive Scale adapted for Pathological Gambling (PG-YBOCS),²² the EQ-5D,²³ the Beck Depression Inventory (BDI),²⁴ and the Alcohol Use Disorders Identification Test (AUDIT)²⁵ self-report measures. These standardized questionnaires were used to measure the severity of gambling problem and different health variables among the subjects. After the baseline period, the subjects filled out the follow-up diaries and questionnaires via the internet using a secured software service Digium (Digium Oy, Helsinki, Finland). The primary outcome measure was the PG-YBOCS (questionnaire on weeks 0, 4, 8, 12 and 16) and the secondary outcome measures were the BDI (questionnaire on weeks 0, 8, 16), EQ-5D (questionnaire on weeks 0 and 16) and the AUDIT (questionnaire on weeks 0 and 16). No physical examination (blood tests, urine samples etc.) was done during the study period.

PG-YBOCS has been developed to measure the severity and change in severity of pathological gambling symptoms. PG-YBOCS includes 10 questions measuring the severity of PG over time. Each question is rated from 0 (no symptoms) to 4 (extreme symptoms). The total score of PG-YBOCS ranges from 0 to 40 (0–7 is subclinical, 8–15 is mild, 16–23 is moderate, 24–31 is severe, and 32–40 is extreme symptoms). Patients scoring in the mild range or higher should consider professional help to alleviate the symptoms. In our study PG-YBOCS was used as a self-report scale, which was filled out by the subjects themselves (not as a clinician-administered assessment tool).

EQ-5D is a standardised instrument for use as a measure of health outcome. The EQ-5D questionnaire includes 5 dimensions: mobility, self-care, usual activities pain/discomfort and anxiety/depression. Each dimension can be graded on three levels, reflecting “no health problems,” “moderate health problems,” and “extreme health problems.” The values for the five dimensions can be combined to describe the respondent’s overall health state ranging from 0 “Worst health state” to 1 “Best health state”.

The BDI is used to measure the severity of depression. The BDI includes 21-questions relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex. The total score of the BDI ranges from 0 to 63 (0–13 is the minimal range, 14–19 is mild, 20–28 is moderate, and 29–63 is severe depressive symptoms).

The AUDIT is a self-report screening tool sensitive to early detection of risky and high risk (or hazardous and harmful) drinking. It has three questions on alcohol consumption, three questions on drinking behavior and dependence, and four questions on the consequences or problems related to drinking. The total score of the AUDIT ranges from 0 to 40 (0–7 is low risk, 8–15 is risky or hazardous level, 16–19 is high-risk or harmful level, 20 and over is high-risk/almost certainly alcohol dependent).

STATISTICAL ANALYSIS

By the end of the study as much as 51 percent of the participants had dropped out from the study. We used multiple imputation to deal with this problem.²⁶ Missingness at random (MAR) is the principal assumption for multiple imputation: it assumes that the pattern of missing data can be explained by observed values in the sample but it is not dependent on any unobserved values. Changes in the imputed score variables (BDI, PG-YBOCS, EQ-5D, AUDIT) were examined using linear random effects modelling with restricted maximum likelihood estimation.^{27,28} The model is appropriate for the analysis of longitudinal data because it allows the existence of individual heterogeneity in the variables under examination, and thus provides subject specific inferences. Our models included a random intercept to account for individual differences in the mean levels of the sum score variables. A time indicator was used as a categorical variable, with dummy variables representing each time point. Logarithmic transformations were conducted for BDI, AUDIT and PG-YBOCS scores to reduce non-normality. Preliminary analyses and graphical examination

suggested that the change in the PG-YBOCS score was non-linear, declining quite dramatically until 8 weeks before stabilizing to a more constant level (see Figure 1). Hence, for the PG-YBOCS-variable, we estimated a piecewise linear random effects model with two slopes representing weeks 8 and 16, assuming that the change inside these time frames was linear. All analyses were performed in R statistical language²⁹ (version 2.9.2) by using the package “mi”(version 0.08-06) for the imputation process and “nlme” (version 3.1. -93) for the incomplete data random effects modelling.²⁶ A probability level of $P < 0.05$ was considered significant.

RESULTS

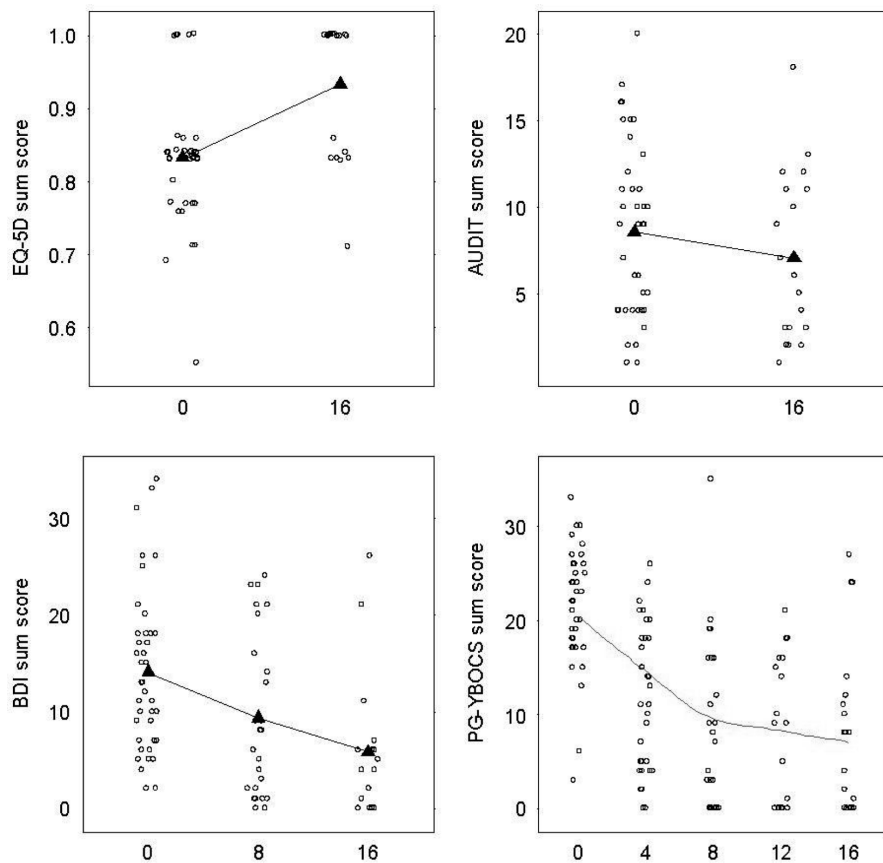
The subjects ($n = 39$) were Finnish Caucasian adults, aged 20–78 years (mean age 39 years), with 80% of the subjects being men (mean age 36 years, SD 15.49) and 20% women (mean age 51 years, SD 13.55). Most of the subjects were married (59%), lived with their family (64%), had at least a secondary education degree (69%), and were employed (87%). All of the subjects were PG's according to both SOGS (score 5+) and DSM-IV (score 5+). The mean scores were 14.0 for SOGS and 8.0 for DSM-IV. 49% of the subjects reported being smokers. The drop-out rate was 51% at the end of the study. The main findings of the study are shown in Figures 1 and 2. The primary outcome measure, PG-YBOCS, showed large positive changes in compulsive gambling and in the urge to gamble during the study period. According to linear random effects modeling, the decrease in PG-YBOCS scores compared to baseline was highly significant ($p \leq 0.01$).

The PG-YBOCS scores had decreased markedly already at study week 4; this decrease continued throughout the rest of the study period but at a slower rate (see Figures 1 and 2). At baseline, 87% of the subjects had moderate to severe obsessive-compulsive symptoms towards gambling (PG-YBOCS 16+) whereas at the end of the study only 16% of the patients suffered from such severe symptoms. The slope describing change from baseline to week 8 was significant (coefficient = -0.99 , $se = 0.21$, $p < 0.001$). The slope estimated thereafter however was non-significantly different from zero (coefficient = 0.16 , $se = 0.17$, $p = 0.19$), underlining a stabilization of the score at the second half of the study period. In figures 1 and 2 the observed outcome variables are represented graphically.

According to the EQ-5D measure of health outcome and the physical examination, the overall health condition of the subjects was good, but over half (59%) of them reported suffering from depression and

FIGURE 1

INDIVIDUAL OBSERVED SUM SCORES FOR QUALITY OF HEALTH (EQ-5D), HARMFUL USE OF ALCOHOL (AUDIT), DEPRESSION (BDI) AND OBSESSIVE-COMPULSIVE SYMPTOMS (PG-YBOCS) DURING THE STUDY PERIOD



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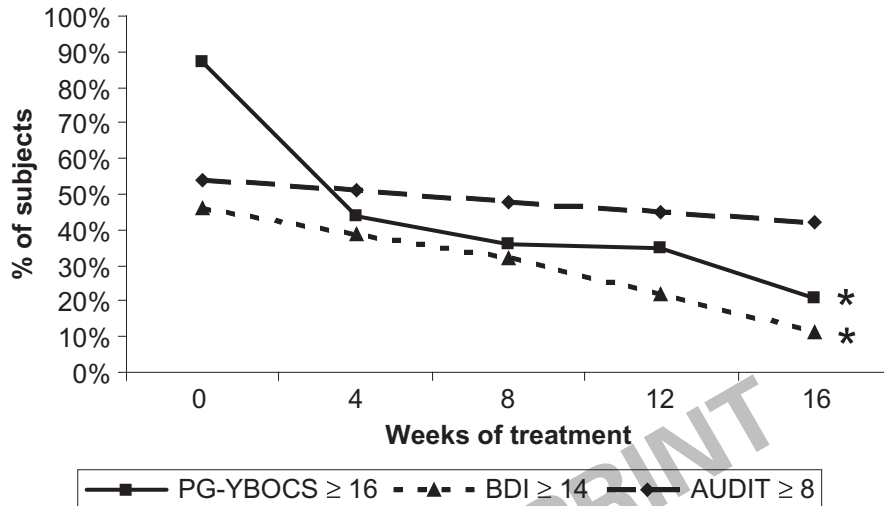
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anxiety. At baseline, the EQ-5D sum score was 0.83 (Fig. 1) and by the end of the study it had significantly improved to 0.93. Random effects model estimated a positive slope for the score from baseline to week 16, indicating that this decline was also significant (coefficient = 0.11, se = 0.02, $p < 0.001$).

Highly significant improvement was also seen in depressive symptoms of the patients as measured with BDI ($p < 0.01$). The proportion of subjects with BDI scores of 14 or more (Fig. 2) decreased from 46% to 28% during the study period. According to the random effects model the decline was significant throughout the study period (weeks 0–8: coefficient = -0.64 , se = 0.17, $p < 0.01$, weeks 8–16: coefficient = -0.46 , se = 0.22, $p < 0.05$).

FIGURE 2

PERCENTAGE OF RESPONDENTS AT EACH TIME POINT HAVING OBSESSIVE-COMPULSIVE (PG-YBOCS) OR DEPRESSIVE (BDI) SYMPTOMS OR HARMFUL USE OF ALCOHOL (AUDIT). * = $p < 0.01$ WHEN COMPARED TO BASELINE



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Only a small non-significant change was seen in AUDIT scores during the study period (coefficient = -0.09 , $se = 0.15$, $p = 0.27$). At baseline, 54% of the subjects scored at least 8 in AUDIT and were considered as hazardous or harmful drinkers. At the end of the treatment, the AUDIT scores decreased slightly and 42% of the subjects were classified as hazardous or harmful drinkers at the end of the study.

At the end of the study period, we also asked the subjects to report their own estimation on how the treatment had affected their gambling behavior. 80% ($n = 15$) of the respondents reported that their gambling reduced markedly during the study period.

DISCUSSION

Both non-pharmacological psychosocial treatment or interventions and pharmacological treatment options have been shown to be more effective than no treatment/placebo in terms of changes from immediate pretreatment baselines to post-treatment outcomes.^{4,17} However, it still remains unclear whether the non-pharmacological treatment options should be used alone or in conjunction with pharmacological treatment options. As PG is associated with many devastating effects such as financial, social and mental health problems, it is necessary to

develop methods for the prevention and treatment of PG and to learn to recognize those who are at increased risk to become PG's.

This pilot study (no control group) shows positive changes during the 16 weeks study period: the quality of life reported by the subjects was increased, and their depressive symptoms measured by BDI were decreased. Our primary efficacy measure, the obsessive-compulsive gambling symptoms as measured with PG-YBOCS, decreased markedly. Our results herein suggest that even a very "light" (one visit with study doctor) and motivational brief intervention based treatment together with targeted naltrexone) can improve the quality of life and reduce the pathological gambling. However, the small sample size and lack of placebo controlled peer group limit the interpretation of our results. This study cannot determine which aspects of the treatment—the brief intervention, the targeted naltrexone, or both—were responsible for the improvement. We also cannot evaluate the possible benefits of encouraging the subjects to practice healthy alternative behaviors when they are not gambling. The drop-out rate was also relatively high, being 51% at the end of the study. Despite these limitations the results are promising, and thus we are going to test targeted naltrexone treatment in a larger placebo-controlled clinical trial. ❖

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