A Randomised, Double-Blind, Placebo-Controlled Trial of As-Needed Naltrexone in the Treatment of Pathological Gambling

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Key Words

Randomized controlled trial · Pathological gambling · Naltrexone · Psychosocial support · *OPRM1*

Abstract

Background/Aims: Effective treatment strategies are needed for the treatment of pathological gambling (PG). The efficacy of as-needed naltrexone was assessed in a single-centre, randomised, double-blind, placebo-controlled trial.

Methods: The participants (n = 101) received either as-needed placebo or naltrexone (50 mg) and psychosocial support for 20 weeks. The primary outcome measure was the severity of PG assessed by the Yale-Brown Obsessive Compulsive Scale adapted for PG (PG-YBOCS). Secondary gambling-related outcome measures included thoughts/urges and behaviour subscales of PG-YBOCS as well as the highest daily expenditure and gambling frequency. In addition, RAND-36 scales of emotional well-being and social functioning were used as outcomes. The results were analysed using the intention-to-treat principle and linear random effects modelling. **Results:** No significant treatment group differences were found. In an exploratory analysis, emotional well-being increased in a subgroup of participants with AA genotype of opioid receptor, mu 1 (*OPRM1*) A118G polymorphism (p = 0.02). **Conclusion:** Overall, the as-needed naltrexone may

not provide substantial additional benefit for PG patients receiving psychosocial support. Replication by larger scale studies is warranted to further evaluate naltrexone administration schedules for the treatment of PG and the role of *OPRM1*.

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Introduction

Pathological gambling (PG) is a persistent and recurrent maladaptive gambling behaviour [1] with a lifetime prevalence of 1% in Finland [2]. Currently, as no US Food and Drug Administration-approved pharmacotherapy is in existence, psychosocial approaches are the first choice of treatment [3]. Psychosocial approaches may be complemented with pharmacotherapy, as combination therapies may be more effective than monotherapies [4].

Opioid antagonists naltrexone and nalmefene have shown some evidence of effectiveness in the treatment of PG [5–12]. Despite their benefits, problems with adherence to daily use of naltrexone medication have limited their usability [5, 9]. One solution could be as-needed ad-

S.B. and L.K. contributed equally to this work.

ministration, that is, taking the pharmacotherapy before gambling or when craving to gamble. As-needed naltrexone has been shown to be effective in the treatment of alcohol dependence and problem drinking [13–15]. Moreover, in our earlier non-controlled pilot study, as-needed naltrexone combined with a brief intervention decreased participants' gambling behaviour and depressive symptoms; as well as increased the subjective quality of life [16, 17].

In addition to the emerging data of the effectiveness of as-needed naltrexone, there is emerging data of naltrexone's pharmacological effects being modified by *A118G* (Asn40Asp, rs1799971) polymorphism of opioid receptor, μ 1 (*OPRM1*) gene [18]. μ -Opioid receptors are the main pharmacological target for naltrexone, and meta-analysis suggests that the *G* allele lowers relapse rates of heavy drinking in response to naltrexone treatment [19]. So far, the moderating role of *OPRM1* polymorphism has not been studied in PG treatment.

Based on these promising findings, this study was designed to compare the efficacy of as-needed naltrexone to placebo together with adjunctive psychosocial support in the treatment of PG. In addition, the role of *OPRM1 A118G* polymorphism in moderating the treatment response was studied. We hypothesised that as-needed naltrexone would reduce gambling symptoms.

Materials and Methods

Trial Recruitment

Screening 236 persons recruited through advertisements in widely distributed free newspapers and announcements in gambling-related websites yielded 101 eligible participants (online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000435876). The main inclusion criterion at pre-screening over telephone was a score of 5 or over in the South Oaks Gambling Screen-Revised (SOGS-R) [20]. The inclusion criteria were age 18 or over, ability to speak Finnish, meeting the criteria for PG by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [1] and a score of five or over in SOGS-R. Exclusion criteria were severe depression (Finnish Depression Scale (DEPS) [21] score ≥ 25), bipolar disorder (indication of mania/hypomania with Mood Disorder Questionnaire (MDQ) [22]), suicide risk (assessed by a medical doctor), self-reported medical conditions (e.g. acute hepatitis, severe liver or kidney dysfunction, substance abuse or pregnancy), simultaneous participation in other PG-related trials, lack of reliable contact information, being a prisoner, mental retardation or use of opioid antagonists or agonists. Excluded individuals were directed to online self-help websites.

This trial was conducted between May 2011 and May 2013 in a single-centre setting at the Problem Gambling Clinic of Helsinki Metropolitan area in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice, and was started only

after Ethics Committee approval (permission EudraCT number: 2010-021123-26; sponsor's protocol code number: 03062010; Ethics Committee number: 193/13/03/00/2010). All the participants gave written informed consent.

Pharmacotherapy and Psychosocial Support

Participants ($n = 101$) were randomized in 1:1 ratio according to a computer-generated randomisation list to a double-blind, placebo-controlled 20-week treatment with as-needed, self-administered pharmacotherapy (50 mg naltrexone or indistinguishable placebo capsules received free of charge from AOP Orphan) with no titration period. Participants and staff were all blind to the treatment assignment. Two sets of sealed envelopes containing study medication details for each patient were to be broken only in case of an emergency.

Participants were instructed to take one capsule, up to once daily, always in an as-needed manner when planning to gamble or when experiencing a strong urge to gamble (preferably 30–60 min before gambling for proper absorption of the pharmacotherapy). Participants were provided 30 capsules every 4 weeks if needed. Medication compliance was evaluated by the pills taken based on participants' self-report marked in their gambling/medication diary. The diary was checked at each trial visit. Safety assessment at each visit included follow-up of adverse events, vital signs and mood states.

The trial altogether included eight visits (online suppl. table 1). In addition to pharmacotherapy, all participants received psychosocial support to enhance medication and treatment compliance. Psychosocial support was described within a framework of the BRENDA model [23]. Specific elements targeted for changing gambling behaviour (i.e. psycho-education, motivation for change, recognition of high-risk situations and coping skill enhancements) were offered by a psychologist on 3 visits. Both abstinence and reduction of gambling were accepted goals. Smoking and concomitant medication, except opioid antagonists or agonists, were allowed during the trial.

Assessments

SOGS-R, DSM-IV criteria for PG, DEPS, MDQ, and Alcohol Use Disorders Identification Test (AUDIT) [24] were assessed at screening. Gambling activity (expenditure, frequency and type of gambling) 3 weeks prior to trial was assessed by interview using the Timeline-Follow-Back (TLFB) method [25]. During the trial, gambling activity was assessed by review of the gambling/medication diary filled by the participants and at each visit by further interview with the participants.

In addition, participants were asked about their smoking (yes/no), height, weight, onset age of active gambling (≥ 3 times/week) and onset age of gambling problem (thought/decided to seek help or significant other asked to reduce gambling or to seek help). Body mass index (BMI), early onset gambling problem (≤ 25 years of age) and lag time, that is, the transition from active gambling to problem gambling, were computed from the above questions. Hazardous alcohol consumption was computed from AUDIT (score ≥ 8 for males and ≥ 7 for females).

The predefined primary outcome measure was the total score of the Yale-Brown Obsessive Compulsive Scale adapted for PG (PG-YBOCS) [26], measuring the past 1-month severity of PG. Secondary outcome measures included changes in PG-YBOCS thoughts/urges and behaviour subscales as well as the RAND 36-

Item Health Survey 1.0 [27] scales of emotional well-being and social functioning. In addition, gambling activity outcomes were computed from TLFB interview and gambling/medication diary. They included participants' highest daily expenditure in a week and gambling frequency as the percentage of days in a week in which gambling occurred.

OPRM1 A118G Genotyping

Saliva samples were collected using Oragene DNA Self-Collection Kit OG-500 (DNAgenotek) according to the manufacturer's instructions. Standard methods were used to extract DNA from the samples and sequence the *OPRM1 A118G* polymorphism at the Institute for Molecular Medicine Finland (FIMM), Technology Centre and University of Helsinki. The genotypes were analysed on Applied Bio-systems Variant Reporter software (version 1.0). Ten samples failed sequencing with the first primer set (forward primer: CAGCCAGGACTGGTTTCTGT and reverse primer: TGACCAGGAAGTTTCCGAAG) and were re-sequenced with a second set (forward primer: TACTCCTTGGATCGCTTTGC and reverse primer: GATGGAGTAGAGGGCCATGA). In total, 97% of the samples were successfully sequenced for *A118G* polymorphism. In addition, 6% of the samples were re-sequenced with the second set of primers to confirm that sequencing had no error. For genetic case-control association analysis, 506 previously genotyped (98 females) participants [28] free of mood, anxiety and substance use disorders according to DSM-IV were used as controls.

Statistical Analyses

Statistical analyses were based on the intention-to-treat principle. Treatment and genotype differences at the baseline were tested using χ^2 test and Fisher's exact test for categorical variables and t test for continuous variables. Linear random effects modelling, which accounts for repeated measures over time, was used to study the treatment effect [29]. The method was selected since it is effective in accommodating missing data, assuming missingness at random. The fixed effects of the model contained the main effects of the treatment group and follow-up time as a continuous variable, and their interaction. Models were controlled for the baseline value of the outcome, gender and genotype. Different genotypes were analysed separately. In genetic analysis, the dominant model of inheritance was assumed.

In addition, possible associations between sample characteristics and dropouts were examined using logistic regression. The logistic regression model controlling for age and gender was used for the case-control association analysis of *OPRM1 A118G*. Logarithmic transformation was performed for the highest daily expenditure and square root transformation for the gambling frequency for normality. Analyses were performed using R software (version 3.0.2) [30] and IBM SPSS Statistics software version 22.0 (IBM Corp., Armonk, N.Y., USA).

Results

Subject Characteristics

The participants' baseline demographics and clinical characteristics are reported in table 1. The participants (68% males) were on average 46 years (range from 20 to

73 years). Males were on average 16 years younger ($t = -5.8$, $p < 0.001$). Smoking (52%) and hazardous alcohol consumption (46%) were common. No significant differences between the treatment groups or genotypes at baseline were observed except for education between the treatment groups ($\chi = 6.2$, $p = 0.05$) and females having AG/GG genotype more often ($\chi = 5.8$, $p = 0.02$). Furthermore, the *OPRM1 A118G* genotype frequencies (table 2) of PG participants were similar to healthy controls (odds ratio (OR) 1.1, 95% confidence interval (CI) 0.7–1.6, $p = 0.8$).

Over 40% of the participants (56% males vs. 6.9% females, $\chi^2 = 20.1$, $p < 0.001$) had an early onset (≤ 25 years) gambling problem. On average, the participants started active gambling at the age of 29 and developed a gambling problem at the age of 34. For half of the participants, the transition took 2 years or even less. Slot machines (78%) and weekly lotteries (44%) were the most popular games gambled. Prior to the trial, the participants gambled on average 2–3 times per week and the average highest daily expenditure in a week was 380 €.

Treatment Adherence

Of the 101 participants, 69 (68%) completed the 20-week treatment (i.e. did not dropout). The dropout rate (online suppl. fig. 1 for the reasons) was highest at the beginning (19% from baseline to week 4, 11% from week 5 to week 12, and 6% from week 13 to week 20). Dropout analysis shows that completers did not differ significantly from dropouts with respect to the treatment group (OR 1.5, 95% CI 0.64–3.5, $p = 0.4$). However, smoking (OR 4.5, 95% CI 1.5–14.1, $p = 0.009$), lower BMI (OR 0.85, 95% CI 0.73–0.99, $p = 0.04$) and younger age (OR 0.96, 95% CI 0.93–1.00, $p = 0.05$) was associated with dropout.

Medication intake (yes/no) was reported in the gambling/medication diaries on average for 67% of the days. In the beginning, as-needed medication was taken about 3 times per week and in the end, about twice per week by the participants in the placebo group and once per week by the participants in the naltrexone group. Participants in the placebo group used the medication more often than participants in the naltrexone group (33.0% of the days reported vs. 30.1%, $\chi^2 = 9.0$, $p = 0.003$). Participants in the naltrexone group reported adverse events twice as often as the ones in the placebo group (38 vs. 20%, $\chi^2 = 4.2$, $p = 0.04$; table 3). The reported adverse events were relatively similar between the groups ($\chi^2 = 4.0$, $p = 0.4$). Two participants in the naltrexone group dropped out due to medication-related adverse events (online suppl. fig. 1).

Table 1. Baseline clinical characteristics and demographics of the participants

	Whole sample	Placebo		Naltrexone		AG/GG		Medication		Genotype	
		All	AA	All	AA	All	AA	t	p	t	p
Number of subjects, n	101	51	34	50	26	22					
<i>Clinical characteristics</i>											
DSM-IV for PG	7.2±1.5	7.3±1.5	7.1±1.5	7.2±1.5	7.1±1.5	7.4±1.4		t = 0.31	p = 0.8	t = -1.3	p = 0.2
AUDIT score	7.6±6.4	8.7±7.0	8.9±6.5	6.6±5.5	6.2±5.4	7.1±6.0		t = 1.66	p = 0.1	t = 0.17	p = 0.9
DEPS score	6.6±5.4	6.9±5.3	6.4±4.8	6.4±5.5	6.0±5.6	7.2±5.6		t = 0.47	p = 0.6	t = -1.32	p = 0.2
BMI, kg/m ²	26.9±4.6	27.3±4.8	27.5±5.0	26.6±4.3	26.7±4.8	26.4±3.8		t = 0.80	p = 0.4	t = 0.63	p = 0.5
<i>PG-YBOCS</i>											
Severity of PG	24.6±5.5	25.4±4.9	25.2±5.2	23.8±6.0	25.7±5.5	22.0±6.0		t = 1.50	p = 0.1	t = 1.69	p = 0.1
Thoughts/urges	12.8±2.8	13.2±2.4	13.1±2.7	12.3±3.00	13.1±2.9	11.6±2.9		t = 1.69	p = 0.1	t = 1.16	p = 0.2
Behaviour	11.8±3.3	12.2±3.2	12.2±3.3	11.5±3.5	12.6±3.3	10.4±3.4		t = 1.08	p = 0.3	t = 1.81	p = 0.07
Highest daily expenditure, €	380±545	372±513	397±602	388±581	467±685	278±443		t = -0.14	p = 0.9	t = 1.32	p = 0.2
Gambling frequency	37.9±20.6	39.3±22.4	41.0±23.3	36.5±18.7	35.7±21.2	37.0±16.0		t = 0.67	p = 0.5	t = 0.50	p = 0.6
RAND-36 emotional well-being	63.8±17.1	63.7±16.7	63.5±16.4	64.0±17.8	62.2±21.4	65.6±12.6		t = -0.092	p = 0.9	t = -0.62	p = 0.5
RAND-36 social functioning	74.6±20.6	71.8±20.6	67.6±21.6	77.5±20.4	76.4±20.1	78.4±21.2		t = -1.40	p = 0.2	t = -1.70	p = 0.09
Smoker	50 (52.1)	27 (56.3)	17 (53.1)	23 (47.9)	14 (56.0)	9 (42.9)		$\chi^2 = 0.67$	p = 0.4	$\chi^2 = 0.17$	p = 0.7
Hazardous alcohol consumption*	46 (45.5)	25 (49.0)	17 (50.0)	21 (42.0)	11 (42.3)	9 (40.9)		$\chi^2 = 0.50$	p = 0.5	$\chi^2 = 0.20$	p = 0.7
Early onset gambling problem**	39 (41.1)	22 (45.8)	18 (56.3)	17 (36.2)	8 (33.3)	9 (42.9)		$\chi^2 = 0.92$	p = 0.3	$\chi^2 = 0.96$	p = 0.3
<i>Demographics</i>											
Age, years	45.9±15.2	44.5±15.3	42.1±15.4	47.4±15.1	48.4±15.4	45.7±14.6		t = -0.96	p = 0.3	t = -0.80	p = 0.4
Female gender	32 (31.7)	15 (29.4)	5 (14.7)	17 (34.0)	8 (30.8)	8 (36.4)		$\chi^2 = 0.25$	p = 0.6	$\chi^2 = 5.8$	p = 0.02
<i>Education</i>											
Primary school	34 (33.7)	21 (41.2)		13 (26.0)							
Vocational school	46 (45.5)	17 (33.3)		29 (58.0)							
University/college degree	21 (20.8)	13 (25.5)		8 (16.0)				$\chi^2 = 0.23$	p = 0.9		
<i>Living arrangements</i>											
Alone	46 (46.5)	24 (47.1)		22 (45.8)							
With partner/children	46 (46.5)	24 (47.1)		22 (45.8)							
Other	7 (7.1)	3 (5.9)		4 (8.3)				$\chi^2 = 0.92$	p = 0.8		
<i>Marital status</i>											
Single	29 (28.7)	14 (27.5)		15 (30.0)							
Married/cohabitating	43 (42.6)	21 (41.2)		22 (44.0)							
Separated	24 (23.8)	14 (27.5)		10 (20.0)							
Widow	5 (5.0)	2 (3.9)		3 (6.0)							
<i>Employment status</i>											
Employed	60 (60.0)	29 (56.9)		31 (63.3)				$\chi^2 = 2.1$	p = 0.6		
Unemployed	9 (9.0)	6 (11.8)		3 (6.1)							
Pensioner	27 (27.0)	13 (25.5)		14 (28.6)							
Student	4 (4.0)	3 (5.9)		1 (2.0)							

Values are means ± SD for continuous variables and n (%) for binomial/categorical variables.

* Hazardous alcohol consumption: AUDIT score ≥8 for males and ≥7 for females.

** Early onset gambling problem: onset before or at the age of 25 years.

Table 2. Genotype and allele counts and frequencies and Hardy-Weinberg Equilibrium p values

	Genotypes, n (%)			Alleles, n (%)		p
	AA	AG	GG	A	G	
Naltrexone	26 (54.2)	20 (41.7)	2 (4.2)	72 (75.0)	24 (25.0)	0.7
Placebo	34 (68.0)	13 (26.0)	3 (6.0)	81 (81.0)	19 (19.0)	0.3
Whole PG sample	60 (61.2)	33 (33.7)	5 (5.1)	153 (78.1)	43 (21.9)	0.8
Controls [28]	320 (63.2)	157 (31.0)	29 (5.7)	797 (78.8)	215 (21.2)	0.1

Table 3. Adverse events reported

	Naltrexone, n (%)	Placebo, n (%)
Adverse events*	19 (38.0)	10 (19.6)
Diarrhoea/nausea	13	5
Headache/somatic pain	11	5
Restlessness/irritability	6	2
Insomnia	4	1
Others	2	4
No adverse events	31 (62.0)	41 (80.4)

* Each participant could report more than one adverse event.

However, dropouts due to medication-related adverse events did not differ significantly between the treatment groups ($\chi^2 = 1.8$, $p = 0.2$).

Treatment Response

Severity of gambling (PG-YBOCS, $b = -4.4$, $SE = 0.32$, $p < 0.001$), thoughts/urges (PG-YBOCS, $b = -2.8$, $SE = 0.17$, $p < 0.001$), behaviour (PG-YBOCS, $b = -2.7$, $SE = 0.16$, $p < 0.001$), gambling frequency ($b = -0.3$, $SE = 0.09$, $p = 0.001$) and highest daily expenditure ($b = -0.47$, $SE = 0.07$, $p < 0.001$) decreased and emotional well-being ($b = 2.2$, $SE = 0.64$, $p = 0.001$) increased significantly overall with no significant difference between the treatment groups (table 4). Social functioning did not improve with time ($b = 0.53$, $SE = 0.9$, $p = 0.6$) nor was there a difference between the treatment groups (table 4). In the exploratory analysis, emotional well-being increased among the subgroup of participants with AA genotype ($b = 3.6$, $SE = 1.5$, $p = 0.02$; table 5).

Discussion

This is the first study to compare the effects of as-needed naltrexone with placebo in the treatment of PG and the possible role of *OPRM1 A118G* polymorphism in moder-

ating the treatment response. We found no evidence in the effectiveness of as-needed naltrexone with adjunctive psychosocial support overall. In the exploratory analysis, within a subgroup of subjects with AA genotype of *OPRM1 A118G* polymorphism, naltrexone improved participants' emotional well-being.

In the whole study population, all except one outcome improved significantly; however, no treatment group differences in response to as-needed naltrexone were observed. One explanation could be limited sample size, although the size is similar to the previous PG treatment studies [11]. Another explanation could be the lack of placebo lead-in period to exclude placebo responders. However, a study with such a period found no significant group differences when treating concurrent alcohol use disorder and PG with daily naltrexone/placebo combined with cognitive behavioural therapy [31]. On the other hand, in some previous studies, daily naltrexone has been superior to placebo in PG treatment [5, 8] and as-needed naltrexone combined with brief skills training has been superior to placebo in the treatment of alcohol dependency and problem drinking [13–15]. However, a recent meta-analysis does not support the observed efficacy of opioid antagonists in PG treatment due to the efficacy being significantly associated with nonadherence to the intention-to-treat principle and earlier year of publication [11]. Additionally, the aim of the psychosocial support offered may influence the effectiveness of pharmacotherapy as in alcohol dependence treatment targeted naltrexone combined with supportive therapy aimed at abstinence was not effective, whereas with cognitive behavioural therapy aimed at coping with a slip to prevent proceeding to binge drinking it was effective [13]. We accepted both abstinence and reduction of gambling as treatment goals. In our study, the psychosocial support provided to all participants or therapist effect [32–34] may have masked the effect of quite infrequently taken medication. Psychosocial support including BRENDA components [23] was chosen to include many types of

Table 4. Outcome measures during the trial in placebo and naltrexone groups and results of the linear random effects models

	Placebo				Naltrexone				Time*		Time-treatment**		Cohen's d***
	-1 week	4 weeks	12 weeks	20 weeks	-1 week	4 weeks	12 weeks	20 weeks	b (SE)	p	b (SE)	p	
Number of subjects	51	45	38	37	50	37	35	32					
PG- YBOCS	25.4	16.2	12.6	13.1	23.8	14.1	10.7	10.3	-4.4±0.32	0	-0.42±0.63	0.5	0.35
	4.9	6.6	8.6	8.3	6.0	7.2	8.5	7.6					
	51	40	37	35	50	35	33	32					
PG- YBOCS: thoughts/urges	13.2	7.3	4.9	5.0	12.3	5.5	4.2	3.5	-2.8±0.17	0	-0.10±0.34	0.8	0.41
	2.5	4.1	4.7	4.9	3.0	4.4	4.5	4.0					
	51	44	38	36	50	36	35	32					
PG- YBOCS: behaviour	12.2	6.3	4.4	4.1	11.5	4.7	3.3	3.0	-2.7±0.16	0	-0.13±0.33	0.7	0.31
	3.2	4.3	4.5	4.3	3.5	4.5	4.1	3.7					
	51	40	37	34	50	35	33	30					
Highest daily expenditure, €****	372	304	359	312	388	174	220	137	-0.47±0.07	0	-0.20±0.14	0.1	0.33
	513	610	1,044	791	581	263	438	266					
	51	45	43	36	50	44	36	35					
Gambling frequency****	39.3	48.3	38.6	34.8	36.5	37.8	36.6	32.3	-0.30±0.09	0.001	-0.010±0.18	0.9	0.03
	22.4	34.2	32.8	33.9	18.7	33.1	33.7	32.7					
	51	46	44	37	50	44	37	36					
RAND-36-emotional well-being	63.7	59.9	65.3	66.6	64.0	62.7	71.5	74.0	2.2±0.64	0.001	2.1±1.2	0.1	-0.46
	16.7	17.9	19.5	16.8	17.8	19.5	18.4	14.5					
	51	45	38	37	50	37	35	32					
RAND-36-social functioning	71.8	66.9	65.5	71.6	77.5	72.0	73.2	84.4	0.53±0.90	0.6	1.7±1.8	0.3	-0.59

Values are means, ±SD, n.

* Linear random effects model 'outcome~time'.

** Linear random effects model 'outcome~time*treatment*treatment' adjusted for baseline (-1 week) value of the outcome, gender and genotype.

*** Effect size for week 20 between naltrexone and placebo groups.

**** Averaged from the weeks between the visits.

Table 5. Outcome measures during the trial in the genotype subgroups for placebo and naltrexone groups and time-treatment interaction results of the linear random effects models

	Placebo		Naltrexone				Time-treatment*		Cohen's d**
	-1 week	4 weeks	12 weeks	20 weeks	-1 week	4 weeks	12 weeks	20 weeks	
<i>AA genotype</i>									
Number of subjects, n	34	29	23	22	26	20	19	17	
PG-YBOCS	25.2 5.3 34	16.4 6.5 27	12.1 9.3 22	14.0 8.8 21	25.7 5.5 26	12.9 8.1 19	10.1 7.6 18	8.9 6.2 17	0.06 0.66
PG-YBOCS: thoughts/urges	13.1 2.7 34	7.3 4.3 29	4.3 4.8 23	4.7 5.3 21	13.1 2.9 26	5.0 4.5 19	4.1 3.8 19	3.2 3.4 17	0.67
PG-YBOCS: behaviour	12.2 3.3 34	6.1 4.3 27	3.8 4.7 22	3.8 4.4 20	12.6 3.3 26	4.5 4.5 19	3.2 4.0 18	2.5 2.8 16	0.83
Highest daily expenditure, €***	397 602 34	349 700 29	325 943 27	243 615 21	467 685 26	190 319 24	140 185 19	87 187 18	0.2 0.27
Gambling frequency***	41.0 23.3 34	51.2 35.7 30	40.9 35.2 28	38.8 38.1 22	35.8 21.2 26	33.8 32.7 24	36.0 34.4 20	29.0 31.9 19	-0.11
RAND-36-emotional well-being	63.5 16.4 34	58.2 17.5 29	62.8 19.9 23	63.1 15.9 22	62.2 21.4 26	62.8 21.6 20	73.9 20.1 19	75.8 13.7 17	0.02 -0.85
RAND-36-social functioning	67.7 21.6 34	65.5 25.2 29	62.0 26.8 23	65.3 28.1 22	76.4 20.1 26	67.5 27.6 20	75.0 20.4 19	87.5 13.3 17	0.1 -1
<i>AG/GG genotypes</i>									
Number of subjects, n	16	15	14	14	22	15	14	13	
PG-YBOCS	25.8 4.3 16	16.2 7.1 12	12.6 7.4 14	12.2 7.7 13	22 6.0 22	15.8 6.1 15	11.9 10.0 13	12.1 8.9 13	0.2 0.01
PG-YBOCS: thoughts/urges	13.6 2.0 16	7.4 3.6 14	5.8 4.1 14	5.8 4.1 14	11.6 2.9 22	5.7 4.5 15	4.4 5.4 14	3.6 4.6 13	1 0.11
PG-YBOCS: behaviour	12.1 3.1 16	6.5 4.4 12	5.3 4.1 14	4.7 4.1 13	10.4 3.4 22	5.1 4.7 15	3.3 4.4 13	3.6 4.5 12	0.8 -0.21
Highest daily expenditure, €***	314 272 16	224 420 15	444 1,264 15	437 1,035 14	278 443 22	165 186 18	345 636 15	210 344 15	0.3 0.24

Table 5. (continued)

	Placebo		Naltrexone					Time-treatment*		Cohen's d**
	-1 week	4 weeks	12 weeks	20 weeks	-1 week	4 weeks	12 weeks	20 weeks	b (SE)	p
Gambling frequency***	36.3 21.1 16	43.5 32.4 15	35.8 29.2 15	30.0 27.5 14	37.0 16.0 22	42.3 34.2 18	36.0 32.4 15	35.4 33.3 15	0.030±0.27	0.9
RAND-36-emotional well-being	64.5 18.2 16	61.9 18.9 15	68.0 19.1 14	70.4 17.1 14	65.6 12.6 22	60.2 17.2 15	68.6 16.5 14	70.5 15.8 13	-0.17±2.1	0.9
RAND-36-social functioning	78.9 15.6 16	67.5 19.4 15	70.5 20.6 14	79.5 16.0 14	78.4 21.2 22	76.7 18.8 15	72.3 22.6 14	79.8 22.6 13	-1.0±2.9	0.7
										0.9
										-0.017

Values are means, ±SD, n.

* Linear random effects model 'outcome~time*treatment*time:treatment' adjusted for baseline (-1 week) value of the outcome and gender.

** Effect size for week 20 between naltrexone and placebo groups.

*** Averaged from the weeks between the visits.

health care providers and to keep the intervention minimal; the elements targeted specially for gambling behaviour were offered only 3 times. Nevertheless, the psychosocial support was highly appreciated by participants based on participants' qualitative evaluation of the treatment (not reported here).

The *OPRM1* A118G allele and genotype frequencies of the PG participants were similar to those reported earlier in the Finnish population [28]. Even though no evidence of *OPRM1* A118G polymorphism's association with PG diagnosis compared to healthy controls was observed, it cannot be excluded that the lack of association in our data could be due to the low power of our sample to detect small effects. In the exploratory analysis of the moderating effect of *OPRM1* gene on naltrexone treatment response, a significant increase in emotional well-being was observed among a subgroup of participants with the AA genotype. In line with our data, AA genotype has previously been linked to beneficial treatment response in the treatment of alcoholism [35]. However, several studies report that *OPRM1* A118G does not modify the treatment response [36–39] or that AG/GG genotype is linked to beneficial treatment response to naltrexone [40–42]. Moreover, a meta-analysis of 6 studies found that G allele carriers treated with naltrexone had lower relapse rates [19]. However, the study observed no effect on abstinence rates. Our finding that naltrexone treatment provides some benefit in AA homozygous individuals should be interpreted with caution due to the pharmacogenetic analysis being underpowered.

The adverse event profile of as-needed naltrexone was similar to previous data [43, 44]. Adverse events were more common in the naltrexone group with nausea being the most commonly reported adverse event. As naltrexone was taken as-needed, about 30% of the days, nausea may have continued due to participants not getting used to it and naltrexone not building up in the system. The 32% dropout rate was similar to previous PG treatment studies reporting dropout rates from 14 to 50% [45]. Smokers dropped out three times more often. This is in line with previous findings: the urge to gamble is an antecedent for relapse [46] and smokers have earlier been reported to have higher gambling urge, lower ability to control their gambling [47] and increased gambling problem severity [47–49].

This study has strengths such as fairly diverse assessments and recruitment through which our sample was community derived. Nevertheless, this study has certain limitations to be acknowledged. Due to ethical reasons, the study lacked treatment groups with no psychosocial

support and no treatment control group. Comorbid conditions were not assessed. Attending another therapy, support group or Internet self-help program was not recorded. Sample size was limited and the participants were not randomized based on genotype. Due to dropout and exclusion criteria used, the results may not be generalizable to the larger population of pathological gamblers.

In conclusion, overall as-needed naltrexone taken quite infrequently and combined with psychosocial support was not superior to placebo. The role of *OPRM1 A118G* polymorphism remains inconclusive even though our exploratory analysis indicated that *AA* genotype may moderate the treatment response to naltrexone. Replication by larger-scale studies is warranted to further evaluate naltrexone administration schedules for the treatment of PG and the role of *OPRM1*. In addition, further research is warranted to explore other patient characteristics possibly moderating the effect of pharmacotherapy and the effect of psychosocial support. Such characteristics could be used to match a patient to the most effective treatment.

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