Treatment of Gambling Disorder- A Systematic Review of Current Evidence

OCTAVIAN VASILIU*, DANIEL VASILE**
* University Military Central Emergency Hospital "Dr. Carol Davila" Bucharest
** University of Medicine and Pharmacy "Dr.Carol Davila"
Mircea Vulcanescu Str., no.88, Bucharest
ROMANIA
octavvasiliu@yahoo.com

Abstract: Gambling disorder is a difficult to treat, persistent and recurrent problematic gambling behavior, associated with a significant degree of impairment or distress. Several reviews of available pharmacological and/or psychotherapeutic approaches have been conducted, with very few clinical useful conclusions. We conducted a systematic review of the literature regarding the efficacy and tolerability of treatments for gambling disorder, but our option was to include only randomized, high-quality trials, with a sound methodological design. This research is based on the systematic search of medical databases (Pubmed, Medscape, Cochrane, CINAHL, EMBASE, PsychINFO) for informations regarding the efficacy and tolerability of treatment methods for gambling disorder. Keywords used and search paradigms were "psychotherapy", "psychotropic", "antidepressant", "antipsychotics", "mood-stabilizers", individual non-proprietary names of the most widely used psychotropics, and "gambling disorder", "pathological gambling", "behavioural addiction". The period of study detection was established between 2000 and 2017, due to the lack of clear definition of the gambling disorder until the beginning of this century. Based on high quality data, few recommendations could be formulated. Paroxetine, followed by naltrexone, topiramate, motivational interview and CBT appear to be the most supported treatments for gambling disorders. However, most of the analyzed treatments were associated with negative results, as well. Therefore, more trials need to be conducted with solid methodology and long duration, in order to support clear-cut treatment recommendations.

Key-Words: gambling disorder, pathological gambling, behavioral addiction, psychotherapy, antidepressants, antipsychotics, mood-stabilizers, treatment recommendations

1 Introduction

Gambling disorder is a persistent and recurrent problematic gambling behavior, associated with a significant degree of impairment or distress, and its prevalence in general population is estimated to be 1.2-7.1% [1,2]. The impairment induced by this disorder could be manifold, from the most obvious financial losses, to more complex relational and professional aspects.

Gambling disorder is a condition that could have severe complications, like major depression, or even death through suicide [3].

This behavioral addiction is included in the most recent edition of the American Psychiatric Association classification of mental disorders, DSM-5, in the category of "substance-related and addictive disorders", for the first time [2]. This reflects the importance gained by the behavioral addictions in the epidemiological and clinical evaluations, and also a re-framing of the impulse control disorders.

Gambling disorder, as well as other behavioral addictions, are difficult to treat, although a large armamentarium of drugs and psychotherapies have been mobilized for controlling this group of disorders' manifestations. The need for delineating more specific pathophysiologic and psychogenetic factors in behavioral addiction is obvious, and explains at least partially why clear-cut therapeutic recommendations are still lacking.

A recent review of 30 studies focused on treatment, conducted between 2007 and 2016, detected that cognitive-behavioral therapy (CBT) has the largest evidence base when compared to any other type of treatment, but definitive conclusions related to its benefits are difficult to formulate [4].

Opioid receptor antagonists, selective serotonin reuptake inhibitors, bupropion, lithium, and atypical antipsychotics have been associated with various degree of success in the treatment of gambling disorders, although limitations regarding the methodology used in many trials focused on this

topic make difficult to interpret the results [1]. Available treatments have been prescribed based mainly on the supposed pathophysiology of drug related disorders, with serotonin, dopamine and opioid neurotransmission being the most supported involved mechanisms. New data support the implication of noradrenergic, glutamatergic and other pathways, and treatments like N-acetylcystein was associated with some positive data [5].

A preclinical model of gambling disorder tested the efficacy of cannabinoid ligands in the modeling of addictive behavior on an Iowa gambling task on rats [6]. The results are encouraging, because stimulation of cannabinoid receptors affected gambling choice behaviors differentially in some subgroups of subjects [6].

Gambling disorder presents 50-60% heritability in several studies, which suggest a thoroughly investigation of the genetic components could be beneficial in discovering vulnerability factors [7].

Neuroimagistic data support abnormalities, both structural and functional, of networks involved in reward processing and top-down control [7].

2 Objective

A new review of the available data regarding the efficacy and tolerability of the available data on the gambling disorder treatment is considered opportune, with more restrictive inclusion and exclusion criteria, in order to eliminate low-quality data.

3 Methods

This research is based on the systematic search of medical databases (Pubmed, Medscape, Cochrane, CINAHL, EMBASE, PsychINFO) for informations regarding the efficacy and tolerability of treatment methods for gambling disorder.

Keywords used and search paradigms were “psychotherapy”, “psychotropic”, “antidepressant”, “antipsychotics”, “mood-stabilizers”, individual non-proprietary names of the most widely used psychotropics, plus “gambling disorder”, “pathological gambling”, “behavioural addiction”.

The period of study detection was established between 2000 and 2017, due to the lack of clear definition of the gambling disorder until the beginning of this century.

Population age limits were established at 18 and 65 years. Diagnoses were limited to gambling disorders, but studies with comorbid disorders were allowed if statistical analysis allowed for a differentiation between groups.

Selection of the trials was restricted to randomized clinical trials, but single as well as double blind designs were allowed. No meta-analysis or systematic literature review was allowed, in order to avoid over-inclusion of some specified trials.

The main variable(s) monitored by the study should have value for determining the efficacy and/or tolerability of the specified therapeutic intervention, in order to select the respective trial in this analysis.

All the inclusion/exclusion criteria for this analysis are specified in Table 1.

Table 1. Inclusion and exclusion criteria

Operational criteria	**Inclusion**	**Exclusion**
Population	Age between 18 and 65 Diagnosis of gambling disorder/ pathological gambling No severe organic comorbidity that could negatively impact the patient’s evolution under treatment	<18 years and >65 years old Psychiatric comorbidities without the possibility to separate statistically variables related to efficacy and/or tolerability of the therapeutic intervention
Intervention	Any psychotherapy, pharmacotherapy or combined intervention	Unspecified intervention
Environment	Hospital-based or outpatient regimen	Unspecified environment
Variables	Efficacy and/or tolerability of a specified treatment	
Studies design	Randomized clinical trials, single blind or double blind	Unspecified design Meta-analyses,

		systematic literature reviews Pilot studies Protocols for studies, with no actual data
Language	English, French, German	

4 Results

Data obtained from the analysis are synthesized in Table 2. Based on these data, recommendations have been formulated in Table 2.

From the initial 202 results, a number of 17 clinical trials were selected according to the inclusion/exclusion criteria. A large number of trials were excluded due to their open-label design, and yet another large number of trials were only pilot studies. Unfortunately, most of the psychotherapy focused trials didn't respect the selected criteria for this systematic analysis.

Table 2. Results of the systematic review

Authors & Study design	**Variables**	**Results**
de Britto AM et al. [8] 2-center, randomized, double-blind clinical trial Topiramate/placebo combined with a brief cognitive intervention 12-week N=30	Gambling craving, behavior, cognitions; impulsivity; depression, social adjustment	Topiramate> Placebo in reducing gambling craving (p=0.017), time and money spent (p=0.007) gambling (p=0.047), cognitive distorsions related to gambling (p=0.003), social adjustment (p=0.040)
Kovanen L et al. [9] Randomized, double-blind, placebo-controlled trial N=101 Naltrexone vs. placebo (as-needed) plus psychosocial support 20 weeks	Problem gambling severity (Yale-Brown Obsessive Compulsive Scale adapted for pathological gambling-PG-YBOCS) Secondary variables-thoughts/urges and behavior subscales of PG-YBOCS; highest daily expenditure and gambling frequency	No significant differences between groups were found. Emotional well-being increased in a subgroup of participants with AA genotype of opioid receptor (p=0.02) in an exploratory analysis
Grant JE et al. [10] N=28 Ecopipam (50-100 mg/day as needed) 6 weeks, 1 week follow-up	PG-YBOCS	Reductions of total PG-YBOCS scores were significant (p>0.001), and PG-YBOCS subscales (Thought-urge and Behavior, p>0.001)
Berlin HA et al. [11] Double-blind, placebo-controlled, parallel-group trial N=42 Topiramate vs. placebo 14-week	PG-YBOCS Barratt-Impulsive-ness Scale (BIS)	No significant effect of topiramate on the primary or secondary outcomes. BIS total score and Motor and Non-Planning subscales scores - topiramate outperformed placebo at p<0.1
Grant JE et al. [12] Randomized, placebo-controlled trial	PG-YBOCS, each subscale of PG-YBOCS	No differences between

N=233 Nalmefene 20 mg, nalmefene 40 mg, placebo		groups reached the level of significance. Post-hoc analysis demonstrated that nalmefene 40 mg/day reduced significantly more PG-YBOCS
Carlbring P et al. [13] Randomized controlled trial, motivational interview (MI) vs. group CBT vs. wait-list N=150 9 weeks, with follow-up at 6 and 12 months	NORC-DSM-IV (NODS), Beck Depression Inventory-2 (BDI-2), Beck Anxiety Inventory (BAI)	Treatment superior over wait-list in the primary outcome measure. No difference between MI and CBT, but both treatments reduced most of the outcomes up to 12-month
Toneatto T et al. [14] Randomized, double-blind, placebo-controlled trial N=52 11 weeks Naltrexone plus cognitive-behavioral counselling. Alcohol use disorder+ pathological gambling	Alcohol frequency and quantity Gambling frequency and expenditures/ day	No significant group differences on alcohol or gambling variable at post-treatment or at 1-year follow-up. However, a strong time effect was found suggesting the treatment was overall effective
Grant JE et al. [15] Randomized, double-blind, placebo-controlled N=77 18-week Naltrexone 50 mg/d vs. naltrexone 100 mg/d vs. Naltrexone 150 mg/d vs. placebo	PG-YBOCS, Urge and behavior PG-YBOCS subscales, Gambling Symptom Assessment Scale (G-SAS), Clinical Global Impressions-Severity of Illness Scale (CGI-S), measures of depression, anxiety and psychosocial functioning	Data didn't differ significantly between various doses of naltrexone. PG-YBOCS total scores and subscales scores had significantly greater reduction than placebo. Overall gambling severity, and functioning had higher improvements with naltrexone
McElroy SL et al. [16] Single-center, randomized, placebo-controlled, flexible dose (2.5-15 mg/day) or placebo 12-week N=21	PG-YBOCS CGI-S	Olanzapine has a similar rate of total PG-YBOCS score reduction, CGI-S and other secondary variables. 3 patients treated with olanzapine discontinued due to adverse events (pneumonia, sedation, and hypomania)
Black DW et al. [17] Randomized, double-blind, placebo-controlled trial Flexible-dose bupropion	PG-YBOCS, G-SAS, CGI-S, Global Assessment Scale (GAF), Timeline Follow Back,	High non-completion rate (43.6%) Bupropion was well tolerated

12-week N=39	measures for ADHD and overall disability	High placebo response rate
Grant JE et al. [18] Randomized, dose-ranging, double-blind, placebo-controlled trail Nalmefene 25 mg/d vs. nalmefene 50 mg/d vs. placebo N=15 centers, 207 subjects 16 weeks	PG-YBOCS	Both doses of nalmefene were superior to placebo. 59.2% of the 25 mg/d nalmefene treated subjects were “much improved” or “very much improved” vs. 34% in the placebo group. Adverse vents- nausea, dizziness, insomnia, lower incidence in lower dose group, higher dose were associated with intolerable side effects
Dannon PN et al. [19] Randomized, rater-blind, topiramate vs. fluvoxamine 12 weeks N=31	YBOCS, South Oaks Gambling Screen, Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS), CGI-Improvement (CGI-I)	CGI-I score was significantly better for topiramate group at 12-week vs. baseline. CGI-I in fluvoxamine treated group improved at week 12, but the difference was not significant. Remissions: 9 out of 12 topiramate treated patients, and 6 out of 8 fluvoxamine completers.
Grant JE et al. [20] Double-blind, randomized, placebo-controlled trial 16 weeks N=5 academic centers, 76 outpatients Paroxetine flexible dose 10-60 mg/day vs. placebo	CGI, PG-YBOCS, G-SAS	High rates of symptom improvement were observed after 16 weeks in both groups. Paroxetine was superior to placebo on CGI.
Pallanti S et al. [21] Randomized, single blind, 14 weeks Lithium vs. valproate N=42	PG-YBOCS	No significant improvement between groups. 60.9% of the lithium treated patients and 68.4% of the valproate treated subjects were responders, based on the CGI-I scores
Kim SW et al. [22] Randomized, placebo-controleld trial 9 weeks Paroxetine max. 60mg/d vs. placebo N=49	G-SAS, CGI	G-SAS better results in paroxetine treated patients vs. placebo at weeks 6 to 8. CGI improvement was greater in paroxetine vs. placebo

Kim SW et al. [23] Randomized, placebo-controleld Naltrexone (25-250 mg/d) vs. placebo N=83	CGI, G-SAS	75% of naltrexone treated subjects were much or very much improved vs. 24% placebo. Elevated hepatic enzymes occurred in 4 naltrexone treated subjects who took analgesics concomitantly , nausea common during the first week of naltrexone treatment
Hollander E et al. [24] Randomized, double-blind cross-over design 16 weeks (8 weeks fluvoxamine and 8 weeks placebo) N=50	PG-YBOCS, CGI	Fluvoxamine improved significantly overall gambling severity on both scales. Fluvoxamine induced only mild adverse events

A significant number of the selected trials were negative [9], [11], [12], [14], [16], [17]. Therefore, recommendations are based on a rather limited number of trials (n=11).

Recommendations are formulated according to the GRADE suggested criteria [25].

Table 3. Recommendations based on evidence

Medication used **Source data**	**Strength**	**Observations**
Lithium and valproate Positive results [21]	C	No placebo arm in the cited study
Paroxetine Positive results [20,22]	A	
Fluvoxamine Positive results [24] Negative results [19]	C	
Naltrexone Positive results [215,23] Negative results [9,14]	B	
Nalmefene Positive results [18] Negative results [12]	C	
Topiramate Positive results [8,19] Negative results [11]	B	
Ecopipam Positive results [10]	C	Small scale study, not replicated results
Motivational interview and CBT Positive results [13]	B	Non-superiority study
Olanzapine Negative results [16]	D	
Bupropion Negative results [17]	D	

Even recommendations of the greatest level (A and B) need further replication in larger scale trials, so precaution should be maintained when approaching gambling disorder patients.

Regarding the tolerability of treatments, bupropion [17] and nalmefene at low doses [18] were associated with low incidence of adverse events. Naltrexone induced increase of transaminases and other transient somatic symptoms in the first week of treatment [23].

5 Conclusions

Contrary to other reviews and systematic reviews, this analysis included only randomized, single blind or double blind trials focused on gambling disorders. Based on high quality data, few recommendations could be formulated. Paroxetine, followed by naltrexone, topiramate, motivational interview and CBT appear to be the most supported treatments for gambling disorders.

However, most of the analyzed treatments were associated with negative results, as well. Therefore, more trials need to be conducted with

solid methodology and long duration, in order to support clear-cut treatment recommendations.

References:

[1] Choi SW, Shin YC, Kim DJ et al. Treatment modalities for patients with gambling disorder. *Ann Gen Psychiatry* 16, 2017, 23.

[2] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 5th Ed*. Arlington, VA, American Psychiatric Publishing, 2013.

[3] Hodgins DC, Stea JN, Grant JE. Gambling disorders. *Lancet* 378, 2011, 1874-1884.

[4] King DL, Delfabbro PH, Wu AMS et al. Treatment of Internet gaming disorder: An international systematic review and CONSORT evaluation. *Clin Psychol Rev* 54, 2017, 123-133.

[5] Hloch K, Mladenka P, Dosedel M et al. The current clinical knowledge on the treatment of gambling disorder: A summary. *Synapse* 2017 Apr 18. Doi: 10.1002/syn.21976.

[6] Gueye AB, Trigo JM, Vemuri KV et al. Effects of various cannabinoid ligands on choice behaviour in a rat model of gambling. *Behav Pharmacol* 27(2-3 Spec Issue), 2016, 258-69.

[7] Grant JE, Odlaug BL, Chamberlain SR. Neural and psychological underpinnings of gambling disorder: A review. *Prog Neuropsychopharmacol Biol Psychiatry* 65, 2016, 188-193.

[8] de Britto AM, de Almeida Pinto MG, Bronstein G et al. Topiramate combined with cognitive restructuring for the treatment of gambling disorder: A two-center, randomized, double-blind clinical trial. *J Gambl* 33(1), 2017, 249-263.

[9] Kovanen L, Basnet S, Castren S et al. A randomised, double-blind, placebo-controlled trial of as-needed naltrexone in the treatment of pathological gambling. *Eur Addict Res* 22(2), 2016, 70-9.

[10] Grant JE, Odlaug BL, Black DW et al. A single-blind study of "as-needed" ecopipam for gambling disorder. *Ann Clin Psychiatry* 26(3), 2014, 179-86.

[11] Berlin HA, Braun A, Simeon D et al. A double-blind, placebo-controlled trial of topiramate for pathological gambling. *World J Biol Psychiatry* 14(2), 2013, 121-8.

[12] Grant JE, Odlaug Bl, Potenza MN et al. Nalmefene in the treatment of pathological gambling: multicentre, double-blind, placebo-controlled study. *Br J Psychiatry* 197(4), 2010, 330-1.

[13] Carlbring P, Jonsson J, Josephson H, Forsberg L. Motivational interviewing versus cognitive behavioural group therapy in the treatment of problem and pathological gambling: a randomized controlled trial. *Cogn Behav Ther* 39(2), 2010, 92-103.

[14] Toneatto T, Brands B, Selby P. A randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of concurrent alcohol use disorder and pathological gambling. *Am J Addict* 18(3), 2009, 219-25.

[15] Grant JE, Kim SW, Hartman BK. A double-blind, placebo-controlled study of the opiate antagonist naltrexone in the treatment of pathological gambling urges. *J Clin Psychiatry* 69(5), 2008, 783-9.

[16] McElroy SL, Nelson EB, Welge JA et al. Olanzapine in the treatment of pathological gambling: a negative randomized placebo-controlled trial. *J Clin Psychiatry* 69(3), 2008, 433-40.

[17] Black DW, Arndt S, Coryell WH et al. Bupropion in the treatment of pathological gambling: a randomized, double-blind, placebo-controlled, flexible-dose study. *J Clin Psychopharmacol* 27(2), 2007, 143-50.

[18] Grant JE, Potenza MN, Hollander E et al. Multicenter investigation of the opioid antagonist nalmefene in the treatment of pathological gambling. *Am J Psychiatry* 163(2), 2006, 303-12.

[19] Dannon PN, Lowengrub K, Gonopolski Y et al. Topiramate versus fluvoxamine in the treatment of pathological gambling: a randomized, blind-rater comparison study. *Clin Neuropharmacol* 28(1), 2005, 6-10.

[20] Grant JE, Kim SW, Potenza MN et al. Paroxetine treatment of pathological gambling: a multicentre randomized controlled trial. *Int Clin Psychopharmacol* 18(4), 2003, 243-9.

[21] Pallanti S, Quercioli L, Sood E, Hollander E. Lithium and valproate treatment of pathological gambling: a randomized single-blind study. *J Clin Psychiatry* 63(7), 2002, 559-64.

[22] Kim SW, Grant JE, Adson DE et al. A double-blind placebo-controlled study of the efficacy and safety of paroxetine in the treatment of pathological gambling. *J Clin Psychiatry* 63(6), 2002, 501-7.

[23] Kim SW, Grant JE, Adson DE, Shin YC. Double-blind naltrexone and placebo comparison study in the treatment of

pathological gambling. *Biol Psychiatry* 49(11), 2001, 914-21.
[24] Hollander E, DeCarla CM, Finkell JN et al. A randomized double-blind fluvoxamine/placebo crossover trial in pathological gambling. *Biol Psychiatry* 47(9), 2000, 813-7.
[25] GRADE Recommendations. Accessed at www.gradeworkinggroup.org in 02/04/2017, 12:35.