Treatment of Gambling Disorder- A Systematic Review of Current Evidence

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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 pathophysiology 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>
<thead>
<tr>
<th>Operational criteria</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Age between 18 and 65 Diagnosis of gambling disorder/ pathological gambling</td>
<td>&lt;18 years and &gt;65 years old Psychiatric comorbidities without the possibility to separate statistically variables related to efficacy and/or tolerability of the therapeutic intervention</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Any psychotherapy, pharmacotherapy or combined intervention</td>
<td>Unspecified intervention</td>
</tr>
<tr>
<td><strong>Environment</strong></td>
<td>Hospital-based or outpatient regimen</td>
<td>Unspecified environment</td>
</tr>
<tr>
<td><strong>Variables</strong></td>
<td>Efficacy and/or tolerability of a specified treatment</td>
<td></td>
</tr>
<tr>
<td><strong>Studies design</strong></td>
<td>Randomized clinical trials, single blind or double blind</td>
<td>Unspecified design Meta-analyses,</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Authors &amp; Study design</th>
<th>Variables</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Britto AM et al. [8]</td>
<td>Gambling craving, behavior, cognitions; impulsivity; depression, social adjustment</td>
<td>Topiramate &gt; Placebo in reducing gambling craving (p=0.017), time and money spent (p=0.007) gambling (p=0.047), cognitive distortions related to gambling (p=0.003), social adjustment (p=0.040)</td>
</tr>
<tr>
<td>Kovanen L et al. [9]</td>
<td>Problem gambling severity (Yale-Brown)</td>
<td>No significant differences between</td>
</tr>
<tr>
<td>Berlin HA et al. [11]</td>
<td>PG-YBOCS</td>
<td>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&lt;0.1</td>
</tr>
<tr>
<td>Grant JE et al. [12]</td>
<td>PG-YBOCS, each subscale of PG-YBOCS</td>
<td>No differences between</td>
</tr>
</tbody>
</table>

N=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.
N=233  
Nalmefene 20 mg, nalmefene 40 mg, placebo  

| 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]  
PG-YBOCS,  
Data didn’t |  

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  

| 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 | 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  
Different 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  
N=21  
12-week  
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 |  

**References:**  
Carlbring P et al. [13]  
Toneatto T et al. [14]  
Grant JE et al. [15]  
McElroy SL et al. [16]  
Black DW et al. [17]
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant JE et al. [18]</td>
<td>Randomized, dose-ranging, double-blind, placebo-controlled trial</td>
<td>Nalmefene 25 mg/d vs. nalmefene 50 mg/d vs. placebo</td>
<td>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 events: nausea, dizziness, insomnia, lower incidence in lower dose group, higher dose were associated with intolerable side effects.</td>
</tr>
<tr>
<td>Dannon PN et al. [19]</td>
<td>Randomized, rater-blind, topiramate vs. fluvoxamine</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Pallanti S et al. [21]</td>
<td>Randomized, single blind, 14 weeks</td>
<td>Lithium vs. valproate</td>
<td>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.</td>
</tr>
<tr>
<td>Kim SW et al. [22]</td>
<td>Randomized, placebo-controled trial</td>
<td>Paroxetine max. 60mg/d vs. placebo</td>
<td>G-SAS better results in paroxetine treated patients vs. placebo at weeks 6 to 8. CGI improvement was greater in paroxetine vs. placebo.</td>
</tr>
</tbody>
</table>
Kim SW et al. [23]
Randomized, placebo-controlled
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

Table 3. Recommendations based on evidence

<table>
<thead>
<tr>
<th>Medication used</th>
<th>Source data</th>
<th>Strength</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium and valproate</td>
<td>Positive results [21]</td>
<td>C</td>
<td>No placebo arm in the cited study</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Positive results [20,22]</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Positive results [21,23] Negative results [9,14]</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Nalmefene</td>
<td>Positive results [18] Negative results [12]</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Ecopipam</td>
<td>Positive results [10]</td>
<td>C</td>
<td>Small scale study, not replicated results</td>
</tr>
<tr>
<td>Motivational interview and CBT</td>
<td>Positive results [13]</td>
<td>B</td>
<td>Non-superiority study</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Negative results [16]</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>Negative results [17]</td>
<td>D</td>
<td></td>
</tr>
</tbody>
</table>

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].

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:


