# Pharmacological Interventions in Gambling Disorder

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## 8.1 Introduction

Gambling disorder (GD) is associated with a wide range of negative consequences such as familial, occupational, legal, and financial difficulties as well as suicidality and lower quality of life [1–3]. Despite the significant personal and social impact, the number of clinical trials in GD is relatively small.

With respect to the management of GD, the most established therapeutic approaches are either psychotherapy (particularly cognitive behavioral therapy) or pharmacological interventions. Although psychotherapeutic treatments have shown significant benefits [4, 5], there are some difficulties in providing psychological treatment on a large scale given the insufficient number of trained therapists [5]. Consequently, pharmacological interventions are an important tool in the therapeutic arsenal.

Pharmacotherapy in GD has some important aims. First, psychotropic drugs are important to effectively treat co-occurring psychiatric disorders, which are highly prevalent in GD [3]. Alcohol-use disorder, substance-use disorder, major depression, and anxiety disorders are particularly common in subjects with GD. Second, some medications appear to reduce urges to gamble and gambling behavior independent of any underlying co-occurring psychiatric disorder. Therefore, there are medications that appear to target the pathophysiology of GD. In this chapter, we will review the evidence regarding the different pharmacotherapies that have been investigated in GD.

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## 8.2 Classification and Clinical Approaches

GD, previously called pathological gambling, has been theoretically associated with different categories of mental disorders. Understanding the diverse approaches to the categorization of GD provides important insight into the different strategies used in clinical trials.

GD was originally thought to belong to the obsessive-compulsive disorder spectrum. This parallel was established due to the repetitive thoughts and behaviors associated with gambling in disordered gamblers. There was also a theory that GD was a bipolar spectrum disorder, i.e., the inappropriate gambling behavior would be a consequence of underlying hypomanic/cyclothymic states. The assumptions that GD was an obsessive-compulsive spectrum disorder incentivized trials focused on selective serotonin reuptake inhibitors—SSRIs [6]. Similarly, the affective theory of GD led to clinical studies with mood stabilizers and antipsychotics.

Phenomenological, genetic, epidemiological, and neurobiological research over the ensuing years has suggested that GD actually has much more in common with addictions, especially alcohol-use disorders [7–10]. This understanding of GD as a type of behavioral addiction has led to a stronger interest in medications that directly or indirectly might modulate the reward system and/or the prefrontal cortex to improve inhibition. Based on this conceptualization of GD, trials using opioid antagonists (naltrexone, nalmefene) or glutamate modulators (N-acetylcysteine, memantine, topiramate) have been conducted.

Although the number of clinical trials for GD in the last decade has increased, the available evidence available is still limited. There is no drug approved by the Food and Drug Administration (FDA) and no established treatment guidelines. Since there are still significant rates of relapse and chronicity in GD, the need for more and larger clinical trials is evident. Despite these limitations, clinical trials have provided important insights with respect to pharmacological interventions in GD.

## 8.3 The Reward System

The reward system comprises complex and interconnected neurocircuits affiliated with pleasure, reward-seeking, and motivation. A basic understanding of its structures and neurotransmitters gives important insights regarding pharmacological interventions in GD. The reward system consists of evolutionary old circuits located deep in the brain. Natural behaviors such as food and sex classically activate the reward system, and this stimulation is essential to the repetition of these vital behaviors. Other behaviors such as gambling were found to stimulate the reward system as well. In other words, gambling "hijacks" a neurocircuitry naturally associated with reward and repetition of behaviors. This is a major process in the development of disordered gambling.

Two major structures of the reward system are the ventral tegmental area and the nucleus accumbens. They use dopamine as primary neurotransmitter. The strength by which substances or behaviors stimulate the reward system (thought to be largely

via dopamine release) is roughly correlated with the addictive potential. In this context, dopaminergic agonists such as the drug pramipexole have been linked with the development of impulsive/addictive behaviors (such as disordered gambling) as a side effect.

It is important to note that the dopamine release is under control of secondary pathways that use diverse neurotransmitters. One of the major modulators of the reward system is the opioid system, i.e., endogenous opioids indirectly control the release of dopamine in the reward system. Hence, by modulation of dopamine activity, opioid drugs may modulate pleasure, excitement, and craving [11]. Thus, several clinical trials have investigated opioid antagonists such as naltrexone and nalmefene for GD.

Part of the complexity of the reward system comes from its connections with other brain regions such as the hippocampus (associated with memory) and the prefrontal cortex (associated with planning and decision-making). Glutamatergic neurocircuits seem to modulate the interaction between the prefrontal cortex and the nucleus accumbens, a main component of the reward system [12]. It is postulated that glutamate is implicated with the regulation of motivational responses and reward-seeking behaviors [12]. Consequently, medications that affect the glutamatergic neurotransmission may also benefit disordered gamblers.

## 8.4 Opioid Antagonists

Endogenous opioids indirectly modulate dopamine release in the reward system. Consequently, several trials investigated the efficacy of opioid antagonists in GD (main trials displayed in Table 8.1). Opioid antagonists are probably the class of medication with the strongest evidence for GD.

**Table 8.1** Summary of clinical trials conducted with opioid antagonists for gambling disorder

| Study | Drug | Sample | Study design | Duration | Result |
|---|---|---|---|---|---|
| Kim and Grant [13] | Naltrexone | $n = 17$ | Open-label flexible dose trial | 6 weeks | Positive |
| Kim et al. [14] | Naltrexone | $n = 83$ | Double-blind, placebo-controlled | 12 weeks | Positive |
| Grant et al. [15] | Nalmefene | $n = 207$ | Double-blind, placebo-controlled | 16 weeks | Positive |
| Grant et al. [16] | Naltrexone | $n = 73$ | Double-blind, placebo-controlled | 18 weeks | Positive |
| Toneatto et al. [17] | Naltrexone | $n = 52$ | Double-blind, placebo-controlled | 11 weeks | Negative |
| Grant et al. [18] | Nalmefene | $n = 233$ | Double-blind, placebo-controlled | 16 weeks | Positive |
| Kovanen et al. [19] | Naltrexone | $n = 101$ | Double-blind, placebo-controlled as needed design + psychological support | 20 weeks | Negative |

Naltrexone and nalmefene have been the opioid antagonists investigated. Naltrexone is available orally and intramuscularly (long-acting formulation). Nalmefene presents less hepatotoxicity and has a longer half-life than naltrexone. Nalmefene is available in oral and intravenous preparations, but only the intravenous form is available in the United States.

The results of opioid antagonists in the treatment of GD are encouraging. The clinical trials also suggest that the majority of the responders tend to show improvement within 4 weeks of treatment [13]. Although individual responses vary, some additional research suggests that they may be preferentially effective in gambling disordered individuals with urges to gamble, comorbid alcohol-use disorder, or a family history of alcohol-use disorders [16, 18].

Regarding the side effect profile, the most common adverse reaction is nausea [13, 19]. Regular checking of liver enzymes is suggested. Opioid antagonists are contraindicated in opioid-use disorders as they may precipitate a withdrawal syndrome.

## 8.5 Glutamatergic Drugs

As seen in the section reward system (see above), glutamate has been implicated in neurocircuits important for the regulation of motivational responses and reward-seeking behaviors [12]. There have been trials assessing the efficacy of glutamatergic drugs in GD. The main glutamatergic agents investigated are N-acetylcysteine (NAC), memantine, topiramate, and amantadine. The mechanism of action of these drugs is complex and includes modulation of different neurotransmitters, i.e., they do not have an exclusive action on glutamate receptions.

*NAC*

NAC has been used for decades in the treatment of paracetamol intoxication and respiratory conditions. Due to its modulation of glutamatergic neurotransmission, NAC has been increasingly investigated for the treatment of a range of addictive behaviors [20]. NAC has shown efficacy in some clinical trials on cocaine-use disorders and cannabis-use disorders.

One clinical trial assessed the efficacy of NAC in GD, and the reduction in gambling symptoms was promising [21]. Additionally, the fact that NAC has been used for a long time and tends to be well tolerated (benign side effect profile) should encourage further investigations in GD. With respect to the dose used, research in addictions has tended to use doses higher than in other clinical indications. Studies have used doses ranging from 1.2 g/day to 3.6 g/day. The positive trial in GD used 1.8 g/day.

*Memantine*

Memantine is an antagonist of N-methyl-D-aspartate NMDA glutamate receptors. This medication has shown pro-cognitive effects in disorders such as Alzheimer's disease. It was also effective in treating alcohol-use disorder [22].

This medication is promising since it may modulate not only urges to gamble but also produce addition to cognitive enhancement via modulation of the prefrontal cortex. Regarding the cognitive effects of memantine, it is possible that this medication promotes cognitive flexibility and, therefore, improves cognitive distortions associated with continuous gambling despite negative consequences. An open-label trial showed that memantine was well tolerated and associated with improvement in measures of gambling behavior and neuropsychology [18]. However, this is, from the best of our knowledge, the only study investigating this medication in GD.

*Topiramate*

Topiramate has shown promise in the management of impulsive and addictive behaviors such as binge eating and alcohol-use disorder [23, 24]. The two double-blind, placebo-controlled trials conducted in GD with this medication demonstrated mixed results. Berlin et al. [25] found that topiramate was not superior to placebo, while de Brito et al. [26] had positive results for topiramate combined with cognitive restructuring.

*Amantadine*

Amantadine is a psychotropic drug classically used for Parkinson's disease. It has glutamatergic and NMDA-blocking activities and increases dopaminergic neurotransmission. One small double-blind, placebo-controlled clinical trial demonstrated that amantadine was effective for the treatment of GD in Parkinson's disease [27]. The dose used was 200 mg/day.

## 8.6 Antidepressants

*SSRIs*

SSRIs are probably the most investigated class of drugs in GD. There have been several clinical trials examining SSRIs including fluoxetine, fluvoxamine, paroxetine, citalopram, and escitalopram. They have shown mixed results and a tendency to have high rates of placebo effect. Due to the inconsistent results and the high comorbidity of GD and depression, there is some question whether the positive trials with SSRIs were largely due to alleviating depressive or anxiety symptoms rather than targeting GD symptoms specifically. There is evidence that SSRIs might be appropriate for gamblers with co-occurring anxiety disorder [28]. Open-label studies with citalopram and fluoxetine have shown positive results in non-depressed subjects [29, 30]; however, the lack of double-blind placebo-controlled trial significantly weakens the evidence. In light of this discussion, SSRIs may be particularly appropriate for GD comorbid with depression or anxiety disorders.

*Bupropion*

Bupropion is a dual antidepressant with noradrenergic and dopaminergic effects, and the medication has been used for impulsive/addictive disorders. Bupropion is indicated for smoking cessation and has demonstrated reduction in urges and symptoms of nicotine withdrawn [31]. It also has some efficiency in attention deficit hyperactivity disorder (ADHD)—[32]. Nonetheless, bupropion demonstrated mixed results in GD. A preliminary open-label clinical study showed efficacy [33], but a later double-blind, placebo-controlled trial was negative [34]. Consequently, there is no solid evidence that bupropion is efficient in GD.

## 8.7 Mood Stabilizers

There were some studies assessing the efficiency of mood stabilizers in GD. These clinical trials were mainly performed with subjects with bipolar disorder or bipolar spectrum disorder. The use of mood stabilizers is particularly interesting for the comorbidity GD and bipolar disorder.

*Lithium and Valproate*

A single-blind trial observed that lithium and valproate were associated with statistical improvement in gambling behavior [35]. A later double-blind placebo-controlled study showed that lithium was superior to placebo in subjects with a bipolar spectrum disorder and co-occurring GD [36].

*Carbamazepine*

The evidence for carbamazepine in GD is weak. There is only a small ($n = 8$) open-label trial with positive results [37].

## 8.8 Atypical Antipsychotics

The idea that antipsychotics could be effective in GD was based on the following: (1) GD appears to have clinical similarities to bipolar disorder and obsessive compulsive disorder, conditions in which antipsychotics have shown some efficacy; and (2) lithium, a mood stabilizer, has demonstrated effectiveness compared to placebo in subjects with bipolar spectrum disorders and GD.

*Olanzapine*

Olanzapine is the only antipsychotic medication formally investigated for the treatment of GD. Additionally to the dopamine antagonist action, this drug has some effect on neurocircuits rich in dopamine and serotonin, two neurotransmitters that

have been implicated in the pathophysiology of GD. In spite of that, two double-blind, placebo-controlled clinical trials found that olanzapine did not differ from placebo in the treatment of GD [38, 39].

## 8.9 Other Drugs

*Modafinil*

Modafinil is a stimulant drug that increases dopaminergic and adrenergic tone in the central nervous system. It is classically used in patients with attention deficit hyperactivity disorder (ADHD) and has some evidence for the comorbidity of ADHD and cocaine-use disorder [40]. In a clinical trial with GD, modafinil reduced gambling behavior in highly impulsive gamblers but worsened gambling behavior in subjects with low impulsivity [41].

## 8.10 Future Directions

GD is a clinically heterogeneous disorder, and different subtypes of disordered gamblers have been identified [42, 43]. As a result of this, it is important to understand the effects of medications on different gambling domains and, therefore, which medications are more appropriated for specific subgroups of disordered gamblers. For example, there is evidence that opioid antagonists are particularly efficient for subjects with personal and/or family history of alcohol-use disorder/substance-use disorder. Similar insights are needed in order to develop customized pharmacological treatments. There is a need for larger clinical trials that give the opportunity of analysis of subtypes.

Another crucial point is to better elucidate how pharmacotherapy and psychotherapy interact. There are a few clinical trials where medications were used concomitantly with psychotherapeutic approaches [26, 44]. It is therefore possible that pharmacotherapy may have synergistic effects with psychotherapy.

As in other fields in psychiatry, the majority of clinical trials have examined only short-term outcomes. Hence, it is important to assess midterm and long-term effects of medication.

Finally, in many pharmacotherapy trials, there has been little information about optimal dose or duration of treatment needed for GD.

## 8.11 Conclusions

- Despite the significant personal and social impact, the number of pharmacotherapy clinical trials in GD is relatively small.
- Due to the high rates of co-occurring psychiatric disorders in individuals with GD, especially alcohol-use disorders, substance-use disorders, mood disorders,

and anxiety disorders, pharmacotherapy needs to address the potentially complex interaction of GD and these other disorders.

- Some evidence suggest that pharmacological interventions may have a synergistic effect on psychotherapeutic approaches. Psychotherapeutic treatments (especially cognitive behavioral therapy) have demonstrated efficacy in GD. Which medications may be most effective when used in combination with psychotherapy however remains unknown.
- Despite some promising results, pharmacological interventions for GD are currently used off-label, i.e., no drug is formally approved by the Food and Drug Administration. Therefore, it is necessary to inform patients about the nature of the treatment and discuss in detail risks and benefits.
- More double-blind, placebo-controlled trials are needed. There is a need for larger studies that might help develop customized pharmacological interventions.

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