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Pharmacological Treatments for Gambling Disorder: A Current Review of Literature

Kumar Oynama Bozukluğunda Farmakolojik Tedaviler: Güncel Literatürün Gözden Geçirilmesi

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Abstract

This narrative review aims to examine pharmacological treatment modalities for gambling disorder (GD) by analyzing recent literature and identifying significant trends in the field. A thorough examination of relevant literature, focusing primarily on recent studies and reviews, in order to identify significant pharmacological treatment approaches and current trends. Results: The review identifies several pharmacological approaches for GD, including opioid antagonists, serotonergic agents, dopaminergic modulators, glutamatergic agents, and mood stabilizers. Recent studies suggest that opioid antagonists such as naltrexone and nalmefene show promise in reducing gambling urges and behaviors. Additionally, serotonergic agents like selective serotonin reuptake inhibitors (SSRIs) have demonstrated efficacy in alleviating the impulsivity and compulsivity associated with GD. Dopaminergic and glutamatergic agents, while showing some potential, require further investigation for their role in GD treatment. Mood stabilizers, particularly lithium, appear to be beneficial, especially in individuals with co-occurring bipolar affective disorder. Pharmacological interventions play a crucial role in the management of GD, with opioid antagonists and SSRIs emerging as promising options. However, further research is needed to elucidate the optimal pharmacotherapeutic approach and develop more targeted treatments for GD. Integration of pharmacotherapy with psychotherapeutic interventions may enhance treatment outcomes for individuals with GD.

Keywords: Gambling disorder, addictive behaviors, glutamatergic agents, mood stabilizers

Öz

Bu derlemede, güncel literatür gözden geçirilerek ve bu alandaki önemli eğilimler belirlenerek kumar oynama bozukluğu (KOB) için farmakolojik tedavi yöntemlerinin araştırılması amaçlanmıştır. Öncelikle güncel ve kanıt düzeyi yüksek çalışmalara ve derlemelere odaklanılarak ilgili literatür kapsamlı bir şekilde incelenmiştir. İncelemede; KOB tedavisinde opioid antagonistleri, serotonerjik ajanlar, dopaminerjik modülatörler, glutamaterjik ajanlar ve duygudurum düzenleyicileri de içeren çeşitli farmakolojik yaklaşımlar belirlenmiştir. Son araştırmalarda, naltrekson ve nalmefen gibi opioid antagonistlerinin kumar oynama isteği ve davranışlarını azaltmada umut verici olduğu gösterilmiştir. Ek olarak, seçici serotonin geri alım inhibitörleri (SSGİ'ler) gibi serotonerjik ajanların KOB ile ilişkili impulsivite ve kompülsiviteyi hafifletmede etkin olduğu belirtilmiştir. Dopaminerjik ve glutamaterjik ajanların KOB tedavisindeki rolü net olarak gösterilememiştir. Duygudurum düzenleyicilerin, özellikle de lityumun, bipolar affektif bozukluğun eşlik ettiği bireylerde faydalı olduğu görülmüştür. KOB tedavisinde farmakolojik müdahaleler önemli bir rol oynamakta olup opioid antagonistleri ve SSGİ'ler umut verici seçenekler olarak ortaya çıkmaktadır. Bununla birlikte, optimal farmakoterapötik yaklaşımı aydınlatmak ve KOB için daha hedefe yönelik tedaviler geliştirmek için ileri çalışmalara ihtiyaç duyulmaktadır. Farmakoterapinin psikoterapötik müdahalelerle entegrasyonu KOB'a sahip bireyler için tedavi sonuçlarını iyileştirebilir.

Anahtar kelimeler: Kumar oynama bozukluğu, davranışsal bağımlılıklar, glutamaterjik ajanlar, duygudurum düzenleyiciler

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Introduction

Gambling disorder (GD) is a psychiatric condition characterized by persistent, dysfunctional, and repetitive involvement in gambling behavior that results in significant psychological and social consequences. An essential aspect of GD is the inability to maintain control over one's gambling activities and the persistence of engaging in gambling despite being aware of the negative consequences it brings (1). The negative impacts of GD include higher rates of suicide attempts, unemployment, difficulties in marriage and family relationships, legal issues, and engagement in criminal activities (2).

Within the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, GD was moved from its previous classification as “pathological gambling” in the impulse control disorders and placed under the substance-related and addictive disorders” category, making it the only behavioral disorder in this category (1,3). The decision was made because of the parallels between the clinical, epidemiological, genetic, and neurobiological profiles of GD and substance use disorders (4,5). Brain imaging studies suggest that GD and substance use disorders share similar characteristics, particularly in terms of how the brain responds to rewards and punishments, reacts to stimuli, displays impulsivity, and makes decisions (6).

Epidemiological research indicates that GD has prevalence rates ranging from 0.5% to 2.5% (7). There is a widespread belief that over the past thirty years, the increased accessibility of gambling, particularly through online platforms, has resulted in higher levels of engagement and negative consequences (8). While it is accurate that the prevalence of online gambling has surged in recent years, in part, because it is now more readily available and accessible, recent statistics indicate that the prevalence of GD has remained relatively consistent over the past four decades (8,9). Higher prevalence rates are reported in specific populations, such as individuals with substance use disorders (4.3%), psychotic disorders (6.4-17%), or undergoing inpatient treatment for psychiatric disorders (6.9-9%) (10-13). Common co-morbidities are substance use disorders, mood and anxiety disorders, impulse-control disorders, and neurological conditions such as Parkinson's disease (12,13). Females diagnosed with GD exhibit a higher likelihood of having concurrent mood and anxiety disorders compared to males (9).

Various treatment modalities are available for GD, including limiting access to gambling, decreasing demand, participating in self-help groups, utilizing diverse therapeutic approaches (such as cognitive behavioral therapies, motivational interviews, psychoeducation, etc.), and using pharmacological interventions (14). Despite encouraging research into pharmacological treatment options for GD, it should be noted that no guidelines, treatment algorithms, or approved medications have yet been established (15).

Pathophysiology

Pharmacological treatments rely on current understanding of the pathophysiology of GD, focusing on the involved brain regions, underlying mechanisms, neurotransmitters, and pathways. The subsequent sections will examine the potential mechanisms implicated in the ethiopathogenesis of GD. Table 1 provides a concise overview of the mechanisms that will be discussed under the corresponding headings.

Brain Regions

Functional neuroimaging studies have revealed that GD is associated with dysregulation in the corticostriatal-limbic circuitry (16). Key regions implicated include the ventromedial prefrontal cortex (vmPFC) and the ventral striatum (VS), both crucial for reward processing and decision-making (17). Individuals with GD often exhibit blunted activation in these areas during tasks related to cognitive control, reward anticipation, and decision-making (17,18). Blunted vmPFC and VS activation have been observed during various tasks. Studies using the Stroop task show reduced activation in these regions, indicating impaired cognitive control mechanisms in individuals with GD (17,19). Tasks simulating gambling situations reveal diminished vmPFC and VS activation, highlighting deficiencies in reward processing and decision-making processes (17,20). The monetary incentive delay task indicates blunted anticipatory responses to monetary gains and losses,

aligning GD with other addictive disorders such as alcohol-use disorder and tobacco-use disorder, which show similar patterns of VS activation (17,18,21). These neural patterns suggest that GD might be conceptualized as a disorder of reward processing (5). Alternatively, dysfunction in the corticostriatal and limbic circuitry and related regions may contribute to key features of GD, such as abnormalities in craving, decision-making, delay discounting, and cognitive control (16-18).

Neurotransmitters

The neurochemical landscape of GD involves several neurotransmitter systems, including dopaminergic, serotonergic, noradrenergic, and opioidergic systems, each contributing to various aspects of the disorder (9,22).

Dopamine

Dopamine plays a pivotal role in reward and reinforcement, with evidence suggesting both hyper- and hypodopaminergic states in GD (18). Dopamine agonists used to treat Parkinson's disease can induce GD, implying that prodopaminergic states promote gambling behaviors (9). Recent imaging studies have begun to investigate dopamine function in GD using radioligands and positron-emission tomography (23-25). Positron emission tomography (PET) studies using radioligands such as raclopride (D2/D3 receptor binding) have shown that individuals with GD have increased dopamine sensitivity in the VS during gambling tasks (23). In PET studies, the use of propyl-hexahydro-naphtho-oxazin, a D3 receptor-preferring radioligand, suggests that the dopamine D3 receptor in the substantia nigra is significantly involved, with greater binding correlating to higher problem-gambling severity and impulsiveness (24). These findings suggest that dopamine function may be related to specific aspects of GD, indicating that GD is a heterogeneous condition.

Serotonin and Noroepinephrine

Serotonergic dysregulation is implicated in impulsivity and mood regulation. PET studies with serotonergic radioligands highlight the involvement of the serotonin 1B receptor system, which is also implicated in other addictions like alcohol and cocaine use disorders (16,22). It has been observed that individuals with GD exhibit low levels of 5-hydroxy-indole-acetic acid, the primary metabolite of serotonin in the cerebrospinal fluid, as well as decreased density of the platelet serotonin transporter (26,27). The noradrenergic system is linked to arousal and stress responses. Alpha-adrenergic mechanisms, particularly those related to stress responsiveness, are relevant to the compulsive engagement seen in GD (16,18).

Opioids

The opioidergic system, which includes various opioid receptors and their endogenous ligands (endorphins, enkephalins, and dynorphins), also plays a crucial role in modulating reward, reinforcement, and craving. This system is deeply involved in the neurobiology of addiction, including behavioral addictions such as GD. The mechanisms through which the opioidergic system contributes to GD are multifaceted and involve both direct and indirect pathways influencing reward processing, motivation, and stress response (9,16,22).

Opioids modulate dopaminergic pathways by enhancing dopamine release in the nucleus accumbens, and ventral pallidum. This is achieved through the inhibition of GABAergic input into dopamine neurons in the ventral tegmental area. Elevated dopamine levels in these regions are associated with pleasure and impulsive behavior (9,16,22). Opioid receptors, especially mu receptors, are present in the majority of the structures linked to the mesolimbic and mesocortical pathways, which are integral to the brain’s reward system. These receptors are implicated in the majority of addiction-related pathways (22). Among the opioid receptors, kappa receptors are also prevalent in the mesolimbic and mesocortical pathways and are thought to play an important role in addiction. Kappa receptor activation contributes to the development of negative reinforcement in various addictions (26).

Glutamate

Glutamatergic pathways are associated with compulsive behaviors in GD (16,18,22). This system's role in synaptic plasticity and cognitive function underscores its importance in GD pathophysiology (18). Glutamate

has a role in the processes of learning and memory and stimulates N-methyl-D-aspartate (NMDA) receptors in certain areas of the brain (28). Engaging in repetitive actions and receiving rewards leads to an elevation in glutamate levels (29). Glutamic acid levels in the cerebrospinal fluid, which attaches to NMDA receptors, were found to be higher in individuals with GD compared to those in the control group, according to research (30). GD is affected by the dopaminergic and glutamatergic systems in the brain, with dopamine playing a role in rewarding, reinforcing, and addictive behaviors, as previously mentioned (31). However, glutamate may also have a role in persistent changes in the corticostriatal circuitry, which is responsible for the long-term susceptibility to relapse (32).

Table 1. Summary of the mechanisms involved in gambling disorder pathophysiology

Aspect	Description
Brain Regions	Corticostriatal-Limbic Circuitry: Involvement in cognitive control and emotional regulation. Impaired cognitive control mechanisms evident in reduced activation during the Stroop task. vmPFC: Critical for reward processing and decision-making. VS: Key in reward anticipation and processing. Dorsal Executive Systems: Involved in cognitive control and decision-making during affective processing. Deficiencies in decision-making processes highlighted during gambling simulations. Altered functional connectivity between ventral affective and dorsal executive systems during affective processing. Increased connectivity similar to findings in substance use disorders.
Neural Activation Patterns	Blunted activation in vmPFC and VS during tasks related to cognitive control, reward anticipation, and decision-making. Stroop Task: Reduced activation in vmPFC and VS, indicating impaired cognitive control. Gambling Simulation Tasks: Diminished activation in vmPFC and VS, highlighting deficiencies in reward processing and decision-making. Monetary Incentive Delay Task: Blunted anticipatory responses to monetary gains and losses, similar to other addictive disorders.
Neurotransmitters	Dopamine: Central in reward and reinforcement. Both hyper- and hypodopaminergic states are implicated. Dopamine agonists can induce gambling behaviors. Increased dopamine sensitivity in the VS. Drugs altering dopamine address dopaminergic dysregulation and D3 receptor involvement in gambling severity and impulsiveness. Serotonin: Involved in impulsivity and mood regulation. Serotonin 1B receptor system is crucial. Noradrenaline: Linked to arousal and stress responses. Alpha-adrenergic mechanisms are relevant to compulsive engagement. Glutamate: Associated with compulsive behaviors and synaptic plasticity. Opioids: Modulate reward, reinforcement, and craving through various opioid receptors (mu, delta, kappa). Opioid antagonists block opioid receptors, reducing the reward response and craving (e.g., naltrexone).

vmPFC: Ventromedial prefrontal cortex; VS: Ventral striatum.

Recent studies indicate that individuals with GD exhibit altered functional connectivity between the ventral affective and dorsal executive systems during affective processing. This increased connectivity mirrors findings in substance use disorders, such as cocaine dependence, where enhanced connectivity is seen during cognitive control tasks (16,17,22,33). The context in which gambling behaviors occur also significantly influences neural activations. Situational cues closely related to gambling can elicit increased activation of the VS and other reward-related brain regions. Furthermore, peer influence, especially among

adolescents, can enhance risk-taking behaviors, highlighting the need for context-specific studies to understand these dynamics fully (16).

Intermediate phenotypes and transdiagnostic considerations should also be taken into account when discussing GD pathophysiology (16). Impulsivity is a widely studied intermediate phenotype in GD, linked to various psychiatric conditions. Impulsivity in GD factors into multiple domains, such as choice and motor forms, and has been associated with treatment outcomes. Compulsivity, although historically less studied, also plays a crucial role, particularly as gambling behaviors become more habitual (16,34). Other intermediate phenotypes, such as emotional regulation and stress responsiveness, are increasingly recognized for their relevance (35). Negative mood states and stress can promote gambling behaviors, particularly in individuals who gamble to escape negative affective states (35,36). These findings suggest that GD shares common pathways with other impulse control disorders, mood disorders and addictive disorders.

These similarities and co-occurrences influence the use of drug treatments. From a neuropharmacological perspective, the drugs under study for the treatment of GD have pharmacological effects on the neurotransmitter pathways associated with the opioid, serotonergic, dopaminergic, or glutamatergic systems that are involved in the mentioned brain regions. This overview evaluates the mechanisms of these systems and the pharmacological agents that target them. Table 2 provides a summary of the medications that have been studied, along with the dosages and durations of treatment.

Pharmacological Treatment Modalities

Opioid Receptor Antagonists

The opioidergic system plays a crucial role in various behavioral addictions, including GD, and shopping addiction (22). Gambling, similar to substance use, stimulates the release of dopamine in the brain, resulting in a sense of euphoria and satisfaction (9,16,18,22). Notably, the administration of dopamine agonists or partial agonists for conditions such as Parkinson's disease has been observed to impair impulse control, leading to gambling behaviors (9). The antagonism of the opioid system can variably impact dopamine levels depending on the ratio of opioid receptors involved. Opioid antagonists are believed to diminish the urge to gamble and cravings by reducing the transmission of dopamine neurotransmitters in the nucleus accumbens (9,26). Despite this understanding, the intricate role of opioid pathways in GD remains complex and not fully elucidated (9).

Several studies show that agents that block the opioid system can decrease gambling behavior (37). Nevertheless, it is crucial to note that there is currently no officially approved medication for the treatment of GD. Naltrexone and nalmefene, opioid antagonists, show potential in treating GD (38). Meta-analyses have demonstrated that opioid antagonists are significantly more effective than placebo, exhibiting moderate to high efficacy (39). Two randomized, double-blind, placebo-controlled studies found significant improvement with naltrexone (50- 150mg/day) compared to the placebo over 12- and 18-week periods (40,41). Two studies on nalmefene showed positive results, with 25 mg and 50 mg nalmefene showing more improvement in problem-gambling severity than placebo, and 40 mg nalmefene showing significant improvement over 16 weeks compared to the placebo (42,43). A comprehensive meta-analysis confirmed that opioid antagonists exhibited a modest yet statistically significant advantage when compared to placebo (15). Opioid antagonists naltrexone and nalmefene are considered the most clinically validated pharmacological treatments for behavioral addictions, including GD. Their effectiveness underscores the importance of the opioidergic system in the pathophysiology of GD and suggests a promising avenue for therapeutic intervention (44,45).

Serotonergic Drugs

Research suggests that the serotonergic system and serotonin reuptake inhibitors that work through this

system are useful for treating GD (35). Non-selective serotonin reuptake inhibitors and selective serotonin reuptake inhibitors (SSRIs) have been found to be useful in treating GD, particularly in alleviating impulsivity and compulsivity-related behaviors (38). Fluvoxamine and paroxetine were found to be beneficial in treating GD in studies that used a double-blind, placebo-controlled design and excluded individuals with co-morbid psychiatric conditions (46-48). Fluvoxamine was administered at daily doses ranging from 100 to 250 mg, while paroxetine was given at daily doses ranging from 10 to 60 mg over the course of 16 weeks. Both fluvoxamine and paroxetine have demonstrated efficacy in improving the Clinical Global Impression Scale; however, fluvoxamine was more effective than paroxetine (35,46-48). Research studies including escitalopram (10-30 mg/day, over the course of 10 weeks) and citalopram (20-60 mg/day over the course of 12 weeks) have demonstrated their efficacy in diminishing the frequency of gambling, decreasing monetary expenditure, and alleviating cravings (38,49-51). Research also highlights the importance of administering antidepressant drugs at higher doses than those typically used for depressive disorders.

Nevertheless, only five randomized, double-blind, placebo-controlled studies have been conducted with SSRIs (two with paroxetine, two with fluvoxamine, and one with sertraline). Only two SSRIs, specifically paroxetine and fluvoxamine, have demonstrated a significant superiority over placebo (9).

It is noteworthy that several important findings emerged from antidepressant studies. First, antidepressants, especially those that affect serotonergic systems, such as serotonergic reuptake inhibitors and possibly 5-HT1/5-HT2 receptor antagonists, may be effective in reducing the symptoms of GD. Second, as in the treatment of obsessive-compulsive disorder, the doses of antidepressants required to treat GD symptoms generally appear to be higher than those required to treat depressive disorders. Third, in studies in which participants have no or minimal symptoms of depression or anxiety, antidepressants stand out as effective agents in lowering gambling symptoms. Findings indicate that these medications target the serotonergic systems, which are involved in the regulation of impaired impulse control. A positive response to antidepressants typically results in a reduction in gambling-related thoughts, a decrease in gambling activity, and an improvement in social and occupational functioning. Patients undergoing antidepressant treatment reported reduced preoccupation with gambling and diminished concern about gambling thoughts (31,35).

Dopaminergic Drugs

Dopamine, implicated in substance use disorders, has been suggested to play a similar role in GD. However, medications targeting dopamine function have not shown significant clinical effects in GD (52). A well-documented association exists between dopamine and GD in Parkinson's disease. Dopamine agonists and levodopa dosing have been associated with GD and excessive or problematic behaviors in Parkinson's disease (53). Studies show varying proportions of patients developing impulse-control disorders with different agonists. There is a correlation between drug selectivity for D3 receptors and the occurrence of impulse control disorders. Pramipexole, with its high D3 selectivity, shows the highest occurrence of these disorders (54).

Moreover, increasing data supports the idea that third-generation antipsychotics (TGA) are associated with impulse-control disorders. It is thought that this could be primarily due to their partial agonist activity at dopamine receptors. A meta-analysis suggests that the TGA aripiprazole, cariprazine, and brexpiprazole can be associated with an increased risk of GD (55). Currently, it is hypothesized that aripiprazole may induce impulse control issues by creating a hyperdopaminergic environment in the mesolimbic pathway, also known as the reward pathway. This is primarily due to its strong impact on dopamine D3 receptors (56).

On the other hand, an atypical antipsychotic olanzapine was researched for the treatment of GD and two double-blind, placebo-controlled trials (5-15 mg/day for a period of 7-12 weeks) found no significant difference (57,58). Another study indicates that haloperidol, a D2-like dopamine receptor antagonist, may promote gambling-related thoughts and behaviors in GD (59).

Nonetheless, amphetamine, a dopaminergic drug, is also linked to an increase in gambling behavior and related thoughts (60). Other drugs with dopaminergic effects, such as bupropion (75-375 mg/day for 12

weeks), have been shown not to be superior in terms of efficacy when compared to placebo for the treatment of GD (61).

Despite the conflicting findings, prefrontal dopamine might be used as a therapy for GD. A pilot study found that tolcapone (300 mg/day for 8 weeks), a catechol-o-methyl-transferase (COMT) inhibitor, can improve GD symptoms, particularly in individuals with certain COMT polymorphisms (62). Additionally, a preliminary study indicates that D4 dopamine receptors may have a role in gambling habits, and further investigation is required to comprehend the interplay between genes and the environment (31). The D1 dopaminergic system, which is associated with addictions such as cocaine dependency, also needs further investigation. All in all, current research on the involvement of dopaminergic systems in GD is still in its nascent phase, and the systems that control dopamine activity should be accounted for when developing treatments.

Glutamatergic Drugs

Glutamate, a neurotransmitter with excitatory roles in the brain, is associated with both motivation and substance use disorders. Manipulating glutamatergic neurotransmission shows promise as a treatment approach for substance use disorders, behavioral addictions, mood disorders, and co-morbid conditions. Ligands that act on this system play a crucial role in neurobiology (63).

N-Acetylcysteine (NAC) has demonstrated initial effectiveness in the treatment of substance use disorders, possibly by inducing a decrease in the release of glutamate at the synaptic level (64,65). In a pilot study, NAC (600-1800 mg/day over a period of 8 weeks) showed efficacy in diminishing both impulses and actual engagement in gambling activities (66). A more recent randomized-controlled trial (RCT) has demonstrated that adding NAC (1200-3000 mg/day over a period of 12 weeks) to behavioral treatment is effective in treating GD in individuals with co-occurring nicotine dependence. The study found that NAC provided substantial extra advantages compared to a placebo over the final 3-month follow-up period (67).

Topiramate, a glutamatergic antagonist, decreases impulsive behavior and obsessive tendencies in conditions such as alcohol use disorder, cocaine use disorder, bulimia nervosa, and binge eating disorder (68,69). It has been discovered to be efficacious in treating subgroups of individuals with GD who have elevated levels of impulsivity (200±20 mg/day over the period of 14 weeks) (68,69). Research indicates that topiramate has promising potential for treating the co-occurrence of GD and bipolar affective disorder (70).

Acamprosate, a taurine derivative and GABA agonist, promotes a balance between excitatory and inhibitory neurotransmitters. It has been approved for alcohol use disorder treatment, but its effectiveness in GD treatment has been inconsistent (71,72).

Amantadine, an antiglutamatergic drug, has been tested for treating gambling and compulsive behaviors in Parkinson's disease patients. It was found to be safe and effective in 17 patients, reducing gambling urges and behaviors (200 mg/day over the course of 17 weeks) (73). A case study suggests that modulating glutamatergic and dopaminergic systems may reduce gambling in GD, potentially reversing addictive behaviors (74).

Memantine, is a noncompetitive NMDA receptor antagonist with neuroprotective properties. A study was conducted using memantine in an open-label trial, where participants were given a daily dose of 10-30 mg for a period of 10 weeks. The results of the study revealed notable enhancements in the duration of gambling, reduced impulsive and compulsive behavior, and improved cognitive flexibility (63).

In conclusion, the involvement of the glutamatergic system in GD is both complex and promising. Further research is needed to fully understand the role of glutamate and its modulation in the treatment of GD.

Mood Stabilizers

There is a suggestion that addictive disorders and bipolar affective disorder have comparable predispositions that might impact their progression and management (75). Despite this, it is not clearly understood whether this complex and overlapping relationship between GD and mood disorders is causal (76). Both disorders

share similar affective symptoms such as arousal and restlessness, depressive symptoms, anxiety, and compulsive behaviors (77). The shared features of bipolar disorder and GD, together with their propensity to co-occur, underscore the presence of a comparable pathological framework that might inform treatment choices.

Table 2. Summary of reviewed medications and posology

	Dosage	Duration	Additional notes
Antidepressants			Consider particularly with co-occurring anxiety and mood disorders. It is recommended to administer antidepressant drugs at higher doses.
Paroxetine	20-60 mg/day	8-16 weeks	
Escitalopram	10-30 mg/day	10 weeks	
Bupropion	75-375 mg/day	12 weeks	
Fluvoxamine	100-250 mg/day	16 weeks	
Sertraline	50-150 mg/day	24 weeks	
Citalopram	20-60 mg/day	12 weeks	
Opioid antagonists			Superior to placebo in clinical trials, particularly helpful for people with a family drinking history and significant gambling cravings at the start of treatment.
Nalmefene	20-50 mg/day	16 weeks	
Naltrexone	50-150 mg/day	12-18 weeks	
Antipsychotics			
Olanzapine	5-15 mg/day	7-12 weeks	Preliminary efficacy for ICD, No significant difference for GD
Aripiprazole and other TGA			Associated with increased risk for GD
Mood stabilizers			Consider with co-occurring BSD
Topiramate	200±20 mg/day	12-14 weeks	
Carbamazepine	Maximum 800 mg/day Mean 675 mg/day	10 weeks	
Lithium	Serum level 0.6-1.2 mEq/L	10-14 weeks	
Valproic acid	Serum level 50-100 mcg/mL	14 weeks	
Glutamatergic agents			Superior to placebo in preliminary research
Acamprosate	1998 mg/day	8 weeks	
N-Acetylcysteine	1200-3000 mg/day	8-12 weeks	
Amantadine	200 mg/day	17 weeks	Consider when Co-morbid PD
Memantine	10-30 mg/day	10 weeks	Decreased time spent gambling, decreased impulsive and compulsive behavior, increased cognitive flexibility

GD: Gambling disorder; ICD: Impulse control disorders; BSD: Bipolar spectrum disorders; PD: Parkinson's disease.

Studies show that lithium treatment (10-week period, titrated with a schedule, constant blood levels between 0.6-1.2 mEq/L during the last 4 weeks) in individuals with co-occurring GD and bipolar disorder improves mood symptoms and substance use, reduces gambling urges and behavior, and lowers affective instability (78,79). Among the anticonvulsants valproic acid and carbamazepine, initial data suggest their efficacy in bipolar disorder with co-morbid substance use disorders. However, there is scarce evidence for its utility in the treatment of GD. A study compared valproate and lithium in the treatment of individuals with GD without bipolar disorder, and both groups showed significant improvement (14-week period, aimed blood levels for valproate between 50-100 mcg/mL and for lithium 0.6-1.2 mEq/L) (80). Another anticonvulsant, carbamazepine (10-week period, maximum dose of 800 mg/day) was tested in a prospective study, and a significant improvement was observed (81).

To summarize, given the substantial clinical data, it is advisable to use mood stabilizers, particularly lithium, in the treatment of GD and concurrent bipolar disorder. Further randomized controlled trials are necessary to fully comprehend the efficacy of mood stabilizers in treating GD or GD with comorbid bipolar disorder. When individuals apply for treatment for GD, it would be advisable to assess for accompanying affective symptoms.

Conclusion

GD is a diagnosis that is continuously reassessed. It is classified as an impulse control disorder, a behavioral addiction that is similar to substance-related disorders, or even a disorder within the obsessive-compulsive spectrum. The neurobiology of this pathology involves dysfunctions in various neurotransmitter systems, including dopaminergic, serotonergic, noradrenergic, opioidergic, glutamatergic, and GABAergic systems. These dysfunctions affect several brain regions, such as the amygdala, striatum, prefrontal cortex, and other areas. The primary categories of pharmacological agents investigated for the management of GD include antidepressants, mood stabilizers, and opioid receptor antagonists. Furthermore, ongoing research is being conducted on the use of psychostimulants like modafinil, glutamatergic agents such as amantadine and NAC, and GABA-ergic modulators like disulfiram and baclofen for the pharmacological treatment of GD.

At present, there is no authorized pharmacological treatment for the management of GD. Nevertheless, certain medications have been noted to be exceedingly efficacious and widely approved. It is important to remember that these drugs can be utilized in clinical settings, and incorporating additional therapeutic methods into treatments will enhance the effectiveness of recovery.

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