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Substance Use Disorders (RD Weiss and HS Connery, Section Editors)

Treatment of Gambling Disorders

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Opinion statement

Preclinical and clinical research implicate several neurotransmitter systems in the pathophysiology of gambling disorder (GD). In particular, neurobiological research suggests alterations in serotonergic, dopaminergic, glutamatergic and opioidergic functioning. The relative efficacy of medications targeting these systems remains a topic of ongoing research, and there is currently no Food and Drug Administration (FDA) approved medication with an indication for GD. Considering co-occurring disorders may be particularly important when devising a treatment plan for GD: extant data suggest that the opioid antagonist naltrexone may by the most effective form of current pharmacotherapy for GD, particularly for individuals with a co-occurring substance-use disorder (SUD) or with a family history of alcoholism. In contrast, lithium or other mood stabilizers may be most effective for GD for patients presenting with a co-occurring bipolar spectrum disorder (BSD). Further, serotonin reuptake inhibitors (SRIs) may be efficacious in reducing GD symptoms for individuals also presenting with a (non-BSD) mood or anxiety disorder. Finally, elevated rates of GD (and other impulse control disorders; ICDs) have been noted among individuals with Parkinson's disease (PD), and clinicians should assess for vulnerability to GD when considering treatment options for PD.

Reducing levodopa or dopamine agonist (DA) dosages may partially reduce GD symptoms among patients with co-occurring PD. For GD patients not willing to consider drug treatment, n-acetyl cysteine or behavioral therapies may be effective. Ongoing research into the effectiveness of combined behavioral and pharmacotherapies is being conducted; thus combined treatments should also be considered.

Introduction

The recently released fifth edition of the Diagnostic and Statistical Manual (DSM-5) [1] includes gambling disorder (GD) in the category of Addictions and Related Disorders. This classification differs from that used in earlier versions of the DSM, which listed the condition of pathological gambling (PG) under Disorders of Impulse Control (DSM-III) [2] or Impulse Control Disorders (ICDs) Not Elsewhere Classified (DSM-IV) [3]. This shift in classification reflects the clinical and neurobiological similarities between GD and substance-related addictions. In addition to the change in classification, the diagnostic criteria for GD in the DSM-5 differ from those for PG in the DSM-IV in two key aspects. Firstly, the criterion of 'commission of gambling-related illegal acts' has been removed (*reviewed in* [4–6]). Secondly, the number of criteria needed for a diagnosis of GD has been lowered to four criteria (whereas five criteria were required for a diagnosis of PG in DSM-IV [4–6]). While these changes remain somewhat controversial [6], retrospective analyses suggest that the revised diagnostic criteria will have relatively little impact on prevalence estimates and may improve the accuracy of diagnoses [7]. Thus, in order to be consistent with the new DSM-5, we will use the term 'gambling disorder' or 'GD' (as opposed to 'pathological gambling') throughout the remainder of this paper.

Although no Food and Drug Administration (FDA) approved treatment has an indication for GD, a number of controlled trials have assessed the efficacy and tolerability of different pharmacotherapies. Given the similarities between GD and other addictive disorders, many trials have focused on FDA-approved treatments for substance-use disorders (e.g., opioid antagonists). Overall, findings thus far suggest that the efficacies of different pharmacotherapies may depend on individual differences such as the presence of co-occurring disorders and familial history of alcohol use. Based on these findings, Bullock and Potenza have published a 'Proposed Pharmacotherapy Algorithm' for GD [8••].

While findings from clinical trials thus far suggest some efficacy for specific pharmacological treatments, conflicting reports also exist. Such conflicting data may be partially due to the high rates of placebo responses reported among individuals with GD or difficulties inherent when interpreting findings from studies without appropriate control conditions (e.g., case reports). In the remainder of this review, we will, therefore, focus on findings from controlled trials, although novel findings of interest from open-label trials will also be discussed. For example, early studies suggest efficacy of glutamatergic agents for GD (and other addictions) [9•], and these preliminary findings warrant further investigation in larger samples. Finally, given the necessarily 'off-label' nature of all pharmacotherapies for GD, it is important to note that the following treatment recommendations should be carefully considered by clinicians and discussed in detail with patients.

Treatment

Diet and lifestyle

- There are no specific approved diet- or lifestyle-related treatment interventions for GD.
- Individual differences including gender [10], race/ethnicity [11], types of gambling [12] and the presence of other co-occurring dis-

orders [13] appear to contribute to the clinical presentation of GD and may influence treatment responses; e.g., [14; Class I].

- Epidemiological data suggest increased prevalence of multiple disorders or conditions (below), and these should be taken into account when considering treatment options.

  – Alcohol-, tobacco- and other substance-use disorders [15]
  – Mood disorders [15]
  – Parkinson's disease [16]
  – Impulse control disorders (ICDs) [17]
  – Obesity [18]

Pharmacologic treatment

- Controlled trials of multiple pharmacotherapies have been conducted; however, there is currently no FDA-approved pharmacotherapy with an indication for GD.
- While precise outcome measures vary across studies, the primary aim of pharmacotherapy is generally the reduction of GD-related symptoms.
- As there is no FDA-approved treatment; 'standard dosage' information (below) is based on the dosage tested in individual clinical trials.
- For each type of medication, 'general' side effects are first given (e.g., those listed in the Physician's Desk Reference; PDR), followed by side effects specifically reported in treatment trials for GD.

Selective serotonin reuptake inhibitors (SSRIs)

Evidence from multiple lines of research suggests alterations in serotonergic functioning among individuals with GD (e.g., [19]); however, findings from clinical trials thus far suggest limited efficacy of selective serotonin reuptake inhibitors (SSRIs) for the treatment of GD (for a review see [8••]). To date, four different SSRIs have been studied: fluvoxamine [20; Class III; 21; Class I; 22; Class I; 23; Class II], sertraline [24]; Class I], escitalopram [25; Class II; 26]; Class II] and paroxetine [27; Class I; 28; Class I]. Findings from most of these studies have been mixed or negative, and large placebo responses and high drop-out rates have been reported across studies [24]. However, some evidence suggests that SSRIs might be effective for the treatment of GD among individuals with a co-occurring mood or anxiety disorder, with the exception of co-occurring bipolar disorder (for which SSRI medications are not advised) [25; Class II; *reviewed in* 8••].

Fluvoxamine

Standard dosage	Initial dose of 100 mg/day, increase to 200 mg/day after 14 days [22; Class I].
Contraindications	Concomitant monoamine oxidase (MAO) inhibitor, thioridazine, pimozide, alosetron, or tizanidine use [29].

Main drug interactions	May interact with alcohol, diazepam, lithium, tryptophan, mexiletine, theophylline, benzodiazepines, metoprolol, propranolol, warfarin, clozapine, methadone, tacrine, amitriptyline, clomipramine, imipramine, carbamazepine [29].
Main side effects	*General:* anorexia, somnolence, insomnia, agitation, nervousness, dyspepsia, sexual dysfunction, sweating, tremor, dry mouth, rhinitis, nausea, vomiting [29]; *Gambling disorder:* insomnia, dizziness, headache, nausea, weight loss, diarrhea [22; Class I].
Special points	May increase risk for suicidality and depression [30]; off-label for the treatment of GD.
Cost	$264.14 for 100 × 100 mg (Apotex) [30]; Approximately $158 for 30 days at 200 mg/day.

Sertraline

Standard dosage	Initial dose of 50 mg/day, can increase to 100 mg/day after 28 days, and up to 150 mg/day after 56 days as needed [24; Class I].
Contraindications	Concomitant MAO inhibitor, pimozide or disulfiram use [29].
Main drug interactions	May interact with other serotonergic agents, warfarin, alcohol, diazepam, tolbutamide and other drugs influencing the central nervous system (CNS) [29].
Main side effects	*General:* anorexia, agitation, insomnia, fatigue, somnolence, dizziness, tremor, headache, dry mouth, sweating, nausea, dyspepsia, diarrhea, constipation, ejaculation failure [29]; *Gambling disorder:* insomnia, dizziness, headache, dyspepsia, diarrhea [24; Class I].
Special points	May increase risk for suicidality and depression; [30]; off-label for the treatment of GD.
Cost	$85.40 for 30 × 100 mg (Actavis) [30]; Approximately $128 for 30 days at 150 mg/day.

Escitalopram

Standard dosage	Initial dose of 5 mg/day, increase to 10 mg/day after 7 days, then to 20 mg/day after an additional 7 days [25; Class II]; initial dose of 10 mg/day, increase to 20 mg/day after 14 days, then increase to 30 mg/day after an additional 14 days if needed [26; Class II].
Contraindications	Concomitant use of MAO inhibitors or pimozide [29].
Main drug interactions	May interact with other serotonergic agents, desipramine, warfarin, sumatriptan, cimetidine, alcohol, carbamazepine, metoprolol, and other drugs influencing the CNS [29].
Main side effects	*General:* insomnia, somnolence, fatigue, decreased appetite, headache, sexual dysfunction, sweating, diarrhea, constipation, dry mouth, neck/shoulder pain [29]; *Gambling disorder:* mania, fatigue, nausea, sexual dysfunction, sweating [25; Class II]; headaches, anorgasmia [26; Class II].
Special points	May increase risk for suicidality and depression [29]; may be most efficacious among individuals with co-occurring GD and anxiety disorders [25; Class II]; off-label for the treatment of GD.
Cost	$85.40 for 30 × 100 mg (Actavis) [30]; Approximately $128 for 30 days at 30 mg/day.

Paroxetine

Standard dosage	Initial dose of 10 mg/day, increase by 10 mg/day in weekly increments up to a maximum of 60 mg/day [27; Class I].
Contraindications	Concomitant MAO inhibitor, thioridazine or pimozide use [29].
Main drug interactions	May interact with other serotonergic agents, antipsychotics, dopamine antagonists, alcohol, anticoagulants, phenobarbital, phenytoin, fosamprenavir, desipramine, risperidone, atomoxetine, tamoxifen, metoprolol, theophylline, lithium, phenytoin [29].
Main side effects	*General:* suicidality, insomnia, somnolence, dizziness, headache, sexual dysfunction, asthenia, dry mouth, constipation, diarrhea, sweating, tremor, decreased appetite [29]; *Gambling disorder:* headache, nausea, dry mouth [27; Class I].
Special points	May increase risk for suicidality and depression [30]; off-label for the treatment of GD.
Cost	$86.25 for 40 mg/day × 30 (Caraco) [30]; Approximately $129 for 30 days at 60 mg/day.

Mood stabilizers

Initial studies suggest some efficacy of the mood stabilizers lithium and valproate in treating GD (e.g., [31; Class I]), and mood stabilizer treatment is recommended for the treatment of GD among individuals with a co-occurring bipolar spectrum disorder (BSD) [*reviewed in* 8••]. Controlled trials of topiramate, an anticonvulsant with mood-stabilizing effects, have also been conducted for the treatment of GD, and are reviewed under the 'Glutamatergic pharmacotherapies' section below.

Lithium

	Findings from a 10-week, randomized, double-blind, placebo-controlled study suggest that lithium may be an effective treatment for GD among individuals with a co-occurring BSD [31; Class I]. One small study also suggests efficacy for lithium treatment of GD among individuals without a co-occurring BSD; however, this study was not placebo-controlled [32; Class II].
Standard dosage	300 mg initially, increase to 600 mg after four days, increase to 900 mg after additional 4 days [29; Class I].
Contraindications	Cardiovascular or renal disease, dehydration, Na+ depletion [29].
Main drug interactions	May interact with SSRIs, neuromuscular blockers, calcium channel blockers, diuretics, ACE inhibitors [29].
Main side effects	*General:* hyperthyroidism, tremor, polyuria, mild thirst, general discomfort, diarrhea, drowsiness, muscular weakness, lack of coordination, ataxia [29]; *Gambling disorder:* sedation, dry mouth, nausea, diarrhea, polyuria [31; Class I].
Special points	Monitor renal and thyroid functioning; monitor for possible lithium toxicity [30]; off-label for the treatment of GD.
Cost	$17.91 for 300 mg/day × 100 (Apotex) [30]; Approximately $16 for 30 days at 900 mg/day.

Valproate

	Preliminary data suggest that valproate may be effective in treating GD [32; Class II]; however, further studies including a placebo group are needed to confirm this.
Standard dosage	600 mg/day for 5 days, titrate up to 1500 mg/day [32; Class II].
Contraindications	Hepatic disease/dysfunction, urea cycle disorders [29].
Main drug interactions	May interact with drugs influencing the expression of hepatic enzymes; may interact with aspirin, carbapenem antibiotics, lamotragine, protein-bound drugs (e.g., warfarin), clonazepam, CNS depressants (e.g., alcohol) [29].
Main side effects	*General:* hepatoxicity, pancreatitis, headache, somnolence, chest pain, paresthesia [29]; *Gambling disorder:* not specified [32; Class II].
Special points	Off-label for the treatment of GD.
Cost	$190.03 for 500 mg/day × 10 (Abbott) [30]; Approximately $1,710 for 1500 mg/day for 30 days.

Dopaminergic pharmacotherapies

As with serotonin, substantial preclinical and clinical research implicates dopaminergic neurotransmission in the biology of GD (e.g., [33]); however, controlled trials of dopaminergic pharmacotherapies suggest limited clinical utility of these medications [34; Class I].

Bupropion

	The only placebo-controlled trial of bupropion—a dopamine and norepinephrine transporter inhibitor and nicotinic acetylcholine receptor (nAChRs) antagonist [35]—found no benefit over placebo [34; Class I].
Standard dosage	Initial dose of 75 mg/day, increase in weekly increments of 150 mg to a maximum of 375 mg/day [34; Class I].
Contraindications	Seizure disorder, past/present anorexia or bulimia, concomitant use of a MAO inhibitor, sudden discontinuation of sedatives or alcohol, bipolar depression [29].
Main drug interactions	May interact with alcohol, levodopa, amantadine and SSRIs [29].
Main side effects	*General:* anxiety, insomnia, dry mouth, weight loss, dizziness, some neuropsychiatric symptoms have been reported (e.g., hallucinations, delusions, psychosis) [29]; *Gambling disorder:* nervousness, headache, dry mouth, stomach discomfort [34; Class I].
Special points	Associated with mixed/manic episodes among individuals at increased risk for BSD [30]; off-label for the treatment of GD.
Cost	$59.99 for 75 mg/day × 30 (Bryant Ranch) [30]; Approximately $300 for 30 days at 375 mg/day.

Olanzapine

	There have been two double-blind, placebo-controlled trials of the atypical antipsychotic olanzapine—a dopamine and serotonin antagonist with high affinity for D_2 and 5-HT_{2A} receptors [36]—for the treatment of GD; however, no benefit over placebo was found in either study [37; Class I; 38; Class II].

Standard dosage	2.5 mg/day, increase by 2.5 mg/day in weekly increments up to a maximum of 15 mg/day [37; Class I].
Contraindications	None [29].
Main drug interactions	May interact with diazepam, alcohol, levodopa, dopamine agonists, SSRIs, anticholinergics, lorazepam, hepatoxic drugs, CNS–acting drugs [29].
Main side effects	*General:* Weight gain, hypotension, personality disorder, insomnia, somnolence, dizziness, abdominal pain, cognitive/motor impairment [29]; *Gambling disorder:* Depression, nervousness, thinking abnormality, somnolence, increased appetite/food intake, weight gain, dry mouth, headache, paresthesias, joint stiffness, edema, gastrointestinal virus [37; Class I].
Special points	Increased risk of death among elderly patients with dementia-related psychosis [30]; off-label for the treatment of GD.
Cost	$702.00 for 15 mg/day for 30 days (Lilly) [30].

Opioidergic pharmacotherapies

There have been several double-blind, placebo-controlled trials of the opioid antagonists naltrexone and nalmefene which suggest clinical efficacy over placebo [39; Class I; 40; Class I; 41 Class I]. Thus, opioidergic agents may be the most effective form of current pharmacotherapy for GD (*reviewed in* [14]). However, not all individuals with GD respond to opioid antagonist treatment; e.g., data suggest that both naltrexone and nalmefene may be most effective in treating GD among individuals who are family history-positive for alcoholism [42•; Class I].

Naltrexone

There have been two double-blind, placebo-controlled studies of naltrexone treatment which suggest significant clinical efficacy over placebo in treating GD [39; Class I; 40; Class I].

Standard dosage	Different dosages have been investigated; data suggest that relatively low-dose (i.e., 50 mg/day) treatment may be as effective as higher doses (i.e., 150 mg/day) [40; Class I].
Contraindications	Liver failure, current opioid use, dependence or withdrawal, hepatitis, current use of opioid analgesics [29].
Main drug interactions	Alters effects of other opioid medications [29].
Main side effects	*General:* depression, anorexia, insomnia, somnolence, appetite disorder, dizziness, diarrhea, syncope, hepatic enzyme abnormalities, nasopharyngitis, toothache [29]; *Gambling disorder:* nausea [40; Class I; 39, Class I], dry mouth [40; Class I; 39, Class I], vivid dreams [40; Class I], headache, diarrhea, constipation, dizziness, insomnia [39; Class I].
Special points	May increase risk for suicidality and depression; monitor alcohol intake [30]; off-label for the treatment of GD.
Cost	$404.00 for 50 mg/day × 100 [30]; Approximately $121 for 30 days at 50 mg/day.

Nalmefene

Two placebo-controlled trials suggest efficacy of nalmefene for the treatment of GD [41 Class I; 42•; Class I].

Standard dosage	Dosages ranging between 20 mg/day to 40 mg/day show efficacy in reducing GD [42•; Class I]; higher doses (50 or 100 mg/day) may be poorly tolerated [41; Class I].
Contraindications	Hypersensitivity to nalmefene [43].
Main drug interactions	May interact with flumazenil [43].
Main side effects	*General:* nausea, vomiting, tachycardia, hypertension, postoperative pain, fever, dizziness, headache, chills, hypotension, vasodilation [43]; *Gambling disorder:* insomnia, somnolence, dizziness, decreased appetite, nausea, vomiting, constipation, urinary infrequency, sweating, dry mouth [41; Class I].
Special points	Off-label for the treatment of GD.
Cost	Not available in oral formulation in the United States.

Glutamatergic pharmacotherapies

An imbalance in glutamate homeostasis—the relative ratio of synaptic versus nonsynaptic glutamate—may inhibit successful prefrontal cortical control over limbic regions such as the nucleus accumbens, resulting in increased reward-seeking behaviors [44, 45]. Thus, recent controlled trials have explored the efficacy of glutamatergic agents in treating GD and other addictive disorders. Preliminary data suggest some efficacy in reducing impulsivity symptoms and improving cognitive flexibility [46•; Class III; 47; Class I].

Amantadine

A double-blind, placebo-controlled, crossover trial of amantadine—an antiglutamatergic ligand with N-methyl-d-aspartate (NMDA) antagonist action and with indirect prodopaminergic properties [48]—has been shown to abolish or significantly abate GD symptoms among individuals with Parkinson's disease (PD) [47; Class I]. However, five of the 17 patients enrolled in this trial discontinued due to medication-associated adverse effects. Cross-sectional data suggest increased rates of ICDs among individuals with PD who are taking amantadine; thus, further research is needed to assess the efficacy of amantadine in the treatment of GD [48].

Standard dosage	100 mg/day initial dose, increased to 200 mg/day after 2 days [47; Class I].
Contraindications	None [29].
Main drug interactions	May interact with neuroleptics and CNS medications; concomitant anticholinergic drug use may increase anticholinergic-like side effects [29].
Main side effects	*General:* anxiety, depression, suicidality, anorexia, insomnia, hallucinations, confusion, dizziness, nausea, dry mouth, constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension, headache [29]; *Gambling disorder:* confusion, insomnia, visual hallucinations, orthostatic hypotension [47; Class I].
Special points	May increase rates of ICDs among individuals with PD [48]; may worsen tremors in PD patients with thioridazine; may exacerbate existing mental health problems [30]; off-label for the treatment of GD.
Cost	$17.65 for 100 mg/day × 20 (Nucare) [30]; Approximately $53 for 30 days at 200 mg/day.

Memantine

	Memantine—an NMDA receptor antagonist with antiglutamatergic action, frequently used to treat cognitive decline associated with Alzheimer's disease [9•, 49]—may be effective in improving cognitive flexibility via its modulation of glutamate within the prefrontal cortex [9•]. In the only published trial, short-term, open-label memantine treatment was found to improve cognitive flexibility and decrease GD symptoms [9•; Class III].
Standard dosage	Initial dosage of 10 mg/day and increase dose by 10 mg/day in 14-day increments up to maximum of 30 mg/day [9•; Class III].
Contraindications	None, but caution advised for patients with renal or hepatic problems [29].
Main drug interactions	May interact with other NMDA antagonists, urinary alkalinizers, or drugs with renal elimination mechanisms [29].
Main side effects	*General:* hallucination, somnolence, confusion, dizziness, headache, pain, diarrhea, vomiting [30]; *Gambling disorder:* dizziness, headache, lethargy, deceased libido, nausea [9•; Class III].
Special points	Off-label for the treatment of GD.
Cost	$132 for 10 mg/day × 30 (Nucare) [30]; Approximately $396 for 30 days at 30 mg/day.

N-Acetyl cysteine

	N-acetyl cysteine (NAC)—an amino acid that increases glutathione production and extracellular glutamate via the promotion of cysteine-glutamate exchange—has been found to reduce GD symptoms in one open-label trial with a double-blind discontinuation period [50; Class II]. It has also been found in a randomized, double-blind, placebo-controlled trial to reduce nicotine dependence and longer-term GD treatment outcome in individuals with co-occurring nicotine dependence and GD who were receiving imaginal desensitization therapy for GD [51; Class I].
Standard dosage	Initial dose of 600 mg/day, increased to 1,200 mg/day after 14-days, increased again after an additional 14-days for an ending dosage of 1,800 mg/day [50; Class II].
Contraindications	None; however, may antagonize asthma symptoms [29].
Main drug interactions	None [29].
Main side effects	*General:* drowsiness, gastrointestinal symptoms, bronchoconstriction, chest tightness, fever, rhinorrhea, clamminess, stomatitis [30]; *Gambling disorder:* flatulence [50; Class II].
Special points	Off-label for the treatment of GD.
Cost	$76.67 for 25,000 mg (Spectrum Pharmacy) [30]; Approximately $166 for 30 days at 1,800 mg/day.

Topiramate

	Topiramate—an anticonvulsant medication with antiglutamatergic, pro γ-aminobutyric acid (GABA) and α-amine-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist properties [46•]—has not been found to reduce GD symptoms [46• Class I; 52 Class I], although some data suggest that it may reduce impulsivity [46•; Class I].
Standard dosage	Initial dose of 25 mg/day, increase to 50 mg/day after 1 week, then increase by 50 mg/day every 7 days up to 300 mg/day [46•; Class I].

Contraindications	Pregnancy, glaucoma, hyperthyroidism, concomitant MAO inhibitor treatment, hypersensitivity to sympathomimetic amines [53].
Main drug interactions	May increase effects of CNS depressants including alcohol; concomitant use of oral contraceptives may cause spotting; concomitant use of non-potassium sparing diuretics may increase hypokalemia (advise: measurement of potassium prior and subsequent to treatment) [53].
Main side effects	*General:* Paresthesia, dizziness, dysgeusia, insomnia, constipation, dry mouth [30]; *Gambling disorder:* fatigue, headache, nausea, shoulder pain [46•; Class I].
Special points	Off-label for the treatment of GD.
Cost	$489.10 for 200 mg/day × 60 (Aurobindo) [30]; Approximately $367 for 30 days at 300 mg/day.

Interventional procedures

Psychological therapies

- Psychological/behavioral therapies for GD are generally aimed at the reduction of GD-related symptoms, and a range of different treatment approaches have been studied (for a review, see [54]).
- Recent meta-analytic data suggest that both cognitive behavioral therapy (CBT) and motivational interviewing (MI) may be effective in treating GD symptoms, although further research into the long-term effectiveness of these treatments is needed [55••; Class I].

Cognitive behavioral therapies

Standard procedure	Individual or group therapy sessions targeting specific cognitive processes relating to gambling behaviors.
Contraindications	None.
Complications	None.
Special points	Two recent meta-analyses found that CBT was effective in reducing both GD symptom severity and in reducing the amount of money lost to gambling [55••; Class I; 56; Class I].

Motivational interviewing (MI)

Standard procedure	Relatively brief therapeutic intervention (i.e., between one and four sessions) aimed at increasing patient's motivation to change [57; Class I].
Contraindications	None.
Complications	None.
Special points	Meta-analytic data suggest that MI may be effective in reducing the amount of money lost to gambling [55••; Class I].

Gamblers Anonymous

Standard procedure	12-step, group-based therapy adapted from Alcoholics Anonymous.
Contraindications	None.
Complications	None.
Special points	Meta-analytic data and evidence from a recent controlled trial suggest that MI therapy and CBT are superior to referral to Gamblers Anonymous for the treatment of GD symptoms [57; Class I; 58; Class I].

Surgery

Subthalamic nucleus deep brain stimulation (STN DBS) for patients with co-occurring Parkinson's disease

- Elevated co-occurrence rates of GD have been reported among individuals with Parkinson's disease (PD).
- Deep brain stimulation (DBS) is a commonly used surgical intervention for the treatment of advanced PD, involving the implantation of electrodes within the subthalamic nucleus (STN) in order to provide neurostimulation [59; Class I].
- The primary aim of this surgical intervention is the reduction of levodopa-related motor symptoms [60; Class I].
- Recent data suggests that STN DBS may decrease GD symptoms among individuals with PD; however, cases of GD subsequent to STN BDS have also been reported (*reviewed in* [61]).
- Other treatment options, such as the reduction of levodopa or dopamine replacement therapies, should be considered (*reviewed in* [60]).

Emerging therapies

- Ongoing research is being conducted into the efficacy of different pharmacotherapeutic agents, as well as into the effectiveness of combined behavioral and pharmacotherapy for the treatment of GD.

Combined behavioral and pharmacotherapy

A recent randomized controlled trial compared the effectiveness of combined escitalopram (20 mg/day) and CBT versus CBT alone for the treatment of GD, and found no evidence for improved outcomes among those receiving both escitalopram and CBT in comparison to those receiving CBT only [62; Class II]. Additionally, as noted above, combined NAC and imaginal desensitization therapy has been found to reduce nicotine dependence and improve longer-term GD treatment outcome [51; Class I]. Further research into combined behavioral and pharmacotherapy with respect to different medication types (e.g., opioid antagonists) is needed.

Tolcapone

A recently completed open-label trial explored the efficacy of tolcapone—a catechol-O-methyltransferase (COMT) inhibitor—for the treatment of GD found reductions in GD severity, depression, anxiety and disability and improvement in quality of life [63]. Placebo-controlled study is warranted to examine the efficacy and tolerability of tolcapone in the treatment of GD [63; Class III].

Ecopipam

An open-label trial into the efficacy of ecopipam—a dopamine D1/5 antagonist—for the treatment of GD has been conducted, although results for this study have not yet been published [64].

Pediatric considerations

- Prevalence estimates suggest increased rates of GD among adolescents [65–67].
- There have been no studies investigating the efficacy of pharmacotherapies for the treatment of GD amongst adolescents [68].
- Given the lack of data relating to pharmacotherapies, behavioral interventions may be considered an optimal first approach; however, controlled trials in adolescence are needed to determine most effective therapy [66].

Compliance with Ethics Guidelines

Conflict of Interest

Sarah Yip declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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