Published in final edited form as:
Curr Psychopharmacol. 2013 ; 2(3): 204–211. doi:10.2174/2211556011302999008.

Update on the Pharmacological Treatment of Pathological Gambling

Scott A. Bullock[1] and **Marc N. Potenza**[1,2]

[1]Department of Psychiatry, Yale University School of Medicine, 1 Church Street 7th floor, New Haven, CT, 06510, USA

[2]Departments of Psychiatry and Child Study Center, Yale University School of Medicine, Connecticut Mental Health Center, 34 Park Street, New Haven, CT, 06519, USA

Abstract

This is an update to a previously published article discussing the neuropsychopharmacology of pathological gambling (PG) (1). In the prior manuscript, we described how cortico-limbic circuitry and neurotransmitter systems (norepinephrine, serotonin, dopamine, opioids, glutamate, and gamma-aminobutyric acid (GABA)) have been implicated in PG. These systems represent potential targets for psychopharmacological treatments for PG, with opioid antagonists arguably showing the most consistent benefit in RCTs. In the past year and half since this publication was prepared, there has been one additional randomized clinical trial (RCT) published along with a single case study. Our original manuscript did not describe in detail findings from case studies or open-label studies so in addition to the new RCT data and a new case report involving naltrexone, here we describe case and open-label findings. A PubMed search was conducted using terms such as “pathological gambling treatment”, “clinical trials and gambling”, and “gambling psychopharmacology.” Using these search terms, numerous results were obtained, necessitating further search modifiers. For example, using just “pathological gambling treatment” results in over 1600 hits. In order to focus in on the search modalities, we searched within the initial results for specific phrases such as “psychopharmacology, clinical trial, medication, serotonergic, dopaminergic, etc.” in addition to searching for specific medications. Results not directly related to the treatment of pathological gambling were not included. The study of pathological gambling is relatively new. As such, our search did not exclude any studies due to age of material, but with a few exceptions, the majority of the studies discussed were published later than 2000. This resulted

Corresponding author at: Connecticut Mental Health Center, Room S-104, 34 Park Street, New Haven, CT 06519, USA. Tel.: +1 203 974 7356; fax: +1 203 974 7366. marc.potenza@yale.edu (M.N. Potenza).

Conflicts of Interest: The authors report that they have no financial conflicts of interest with respect to the content of this manuscript. Dr. Potenza has received financial support or compensation for the following: Dr. Potenza has consulted for and advised Boehringer Ingelheim, Lundbeck and Ironwood; has consulted for and has financial interests in Somaxon; has received research support from the National Institutes of Health, Veteran's Administration, Mohegan Sun Casino, the National Center for Responsible Gaming and its affiliated Institute for Research on Gambling Disorders, and Forest Laboratories, Ortho-McNeil, Oy-Control/Biotie, Glaxo-SmithKline, and Psyadon pharmaceuticals; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse control disorders or other health topics; has consulted for law offices and the federal public defender's office in issues related to impulse control disorders; provides clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the National Institutes of Health and other agencies; has guest-edited journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts. Mr. Bullock reports no biomedical financial interests or other conflicts of interest.

in 24 case studies and/or RCTs not previously included in our original review article. These findings in conjunction with our prior publication provide a comprehensive overview of controlled investigations and exploratory reports of pharmacotherapies for PG.

Keywords

Neuropsychopharmacology; Pathological Gambling; Psychopharmacology; Treatment

Background

With the publication of the DSM-5, changes to the classification and diagnostic criteria for PG have been introduced. The name of the diagnosis ("Pathological Gambling" in DSM-IV) has been changed to "Gambling Disorder" (GD). While PG was classified under "Impulse-Control Disorders Not Elsewhere Classified", it is now grouped with substance-use disorders in the "Substance Related and Addictive Disorders" section. In addition, the criterion relating to the commission of illegal acts to support gambling was removed from the diagnostic requirements, with the rationale that this criterion was mainly endorsed only by those with the most severe form of the disorder. This criterion was usually endorsed along with multiple other criteria, and the removal of the criterion did not substantially alter prevalence estimates (2). With this change, the number of inclusionary criteria needed to meet a diagnosis of GD was reduced from five of ten to four of nine. However, the threshold for making a diagnosis of a substance-use disorder was reduced to acknowledgment of 2 of 11 inclusionary criteria. Thus, it would seem more difficult to meet the criteria for GD than a substance-use disorder. These differing thresholds hold significant implications for policy, prevention and treatment and may reduce the perceived impact of gambling problems. Nonetheless, given these changes, it is likely that future RCTs will target individuals with GD rather than PG, introducing complications into the literature when comparing results from studies performed at different times. While these changes may not be substantial for comparing and contrasting data across temporal epochs given the relatively minor changes, they warrant consideration. For a review of the gambling-related changes in DSM-5 and the rationale for the changes, see Petry et al. (3).

In our previous publication entitled, "Neuropsychopharmacology of Pathological Gambling" (1), we discussed the neurological underpinnings of pathological gambling with a focus on RCTs. We did not review the case studies or open-label studies as these are considered less methodologically stringent. However, they do provide an important insight into how treatment modalities might work in individual cases and offer information that might form the foundation for future RCTs. They can also show how individual cases respond to treatment outside a laboratory/controlled setting. Given the low incidence of patients seeking treatment for pathological gambling, case studies and open-label studies can provide further information for practicing clinicians. Case studies and open-label studies cannot be reviewed in the same light as RCTs, and as such, they were not included in our originally published article. Their review here is to augment our earlier work and bolster the argument that further research is needed in this area.

Serotoninergic

Clomipramine

Clomipramine is a tricyclic antidepressant (TCA) that works by increasing in the brain the activity of serotonin and norepinephrine, two neurotransmitters implicated in PG. Clomipramine is often prescribed for treating Obsessive-Compulsive Disorder (OCD). Aspects of PG (compulsive behavior followed by a reward that strengthens that behavior) have been compared to OCD (4), although some data suggest that OCD and PG may not overlap substantially (5, 6).

Hollander et al., in a letter to the editor, reported on a case study of a double-blind, placebo-controlled treatment with clomipramine (7). They describe a 31-year-old woman with PG who despite different treatment attempts had not been able to stop gambling. She was started in a placebo trial for 10 weeks, followed by 10 weeks of active medication. During the placebo phase, her gambling continued and she showed little improvement by the end of the first phase. She was started in phase II at 25 mg/day of active medication and increased by 25 mg every three days to 150 mg/day. Due to irritability at that dose, the dose was reduced to 125 mg/day which was tolerated. By the end of the phase, her clinician-rated global improvement score was “very much improved” and her gambling had stopped by week three of phase II. Her gambling ceased (except for one brief relapse at week 17) for an additional 28 weeks of open-label treatment.

Clomipramine and Modafinil

Modafinil is a dopamine agonist, increasing cortical concentrations of dopamine. As has been reported in subjects taking L-Dopa or dopamine agonists, Tarrant et al. reported on a case study where a previously non-problem gambler began to experience problem gambling upon taking modafinil (8). The patient, a 39-year-old male presenting for narcolepsy, was placed on modafinil 300 mg daily in two doses. He was responding well at first, but a tolerance appeared to develop. The patient reported hesitancy to the possibility of a dose increase due to increasing problems with his gambling. Modafinil was withheld for a two-month trial during which the patient's somnolence returned but his gambling having decreased considerably. Modafinil was restarted to treat the somnolence with a subsequent return of problem gambling behaviors. The patient was switched to clomipramine and ceased modafinil with his gambling behavior ceasing completely at his eighteen-month follow-up. As individual differences (e.g., relating to impulsivity) may relate to responses to dopaminergic medications (9), future research is needed to understand the potential for modafinil to possibly exacerbate problematic gambling behaviors.

Escitalopram

Escitalopram is a selective serotonin reuptake inhibitor (SSRI) and may be used to treat depression, anxiety disorders and OCD. As dysfunction of the serotonin system in the brain has been linked to PG (10), studying serotonergic medications in the treatment of PG is indicated.

In a recent comparison study, Rosenburg et al., conducted a 4-year follow up study of PG treatment with patients assigned to one of four medication regimens – escitalopram, naltrexone, bupropion, or topiramate (11). Enrolled patients were randomly assigned to open-label treatment for two years with an additional 2-year follow-up post medication cessation. Patients were treated with escitalopram at 20-30 mg/day, naltrexone 50-100 mg/day, topiramate 100-300 mg/day, or bupropion 300-450 mg/day. Outcome measures included the Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS), Global Assessment of Functioning (GAF), and Visual Analog Scale (VAS) which were administered at intake, 1 month, 6 months, 24 months, and 48 months. Seventy-eight patients were enrolled with 44 patients completing the initial two-year treatment period. These 44 patients were followed for an additional two years with just one more patient dropping out. Drop-out rates between the topiramate, bupropion, and escitalopram groups did not differ significantly. However, all three arms differed significantly from the naltrexone group (4 out of 21 dropped in naltrexone, 10 of 20 in each of the bupropion and escitalopram groups, and 10 out of 17 in the topiramate group). Mean values on all measures improved across all the medication arms, with naltrexone showing statistically significant lower HDRS/HARS scores and statistically significant higher VAS scores compared to the other three medications. The lack of a placebo group, and the relatively small sample sizes represented main limitations. The naltrexone findings suggest that this as compared to other medications may be particularly well-tolerated in the longer term treatment of PG.

Nefazodone

Nefazodone is synthetically derived phenylpiperazine antidepressant. It differs from SSRIs and TCAs, but its actions influence serotonergic systems; as such, its possible efficacy in treating PG was examined by Pallanti et al.

Only one clinical trial has been conducted using nefazodone. Nefazodone has a primarily antagonistic activity on serotonin 5-HT2 receptors. Pallanti et al. conducted an 8-week open-label trial of nefazodone for treating PG (12). The primary outcome measures were the Yale Brown Obsessive Compulsive Scale adapted for Pathological Gambling (PG-YBOCS) and the Pathological Gambling Clinical Global Impression (PG-CGI). Fourteen subjects were enrolled in the study, with two dropping out before finishing all study visits. Nefazodone was started at 50 mg/day and titrated up to 500 mg/day depending on efficacy and tolerability, but with all patients having a minimum dose of 100 mg/day. Adverse effects included dry mouth and moderate sedation, but otherwise the medication appeared well tolerated with no patients dropping out due to adverse effects. Nine of the 12 subjects who completed the trial met the *a priori* criteria to be considered responders. These criteria included scoring a 1 or 2 on the PG-CGI and having significant improvement in PG-YBOCS scores (there was a 37% reduction from baseline). In addition, there was significant improvement noted on self-report measures of how much time was spent gambling, number of times gambled, and how much money lost to gambling over the course of the study.

Dopaminergic

Bupropion

Bupropion, a drug with documented efficacy in the treatment of depression and nicotine dependence, belongs to an aminoketone class of drugs and is related to phenylethylamines. Its primary actions are to inhibit the reuptake of dopamine and norepinephrine. As dopamine has been linked to PG (13), medications affecting this neurotransmitter have been investigated in treating PG.

In the first study exploring the efficacy and tolerability of bupropion in PG patients, ten subjects were enrolled in the open-label study (14). Subjects had a 3-week titration phase followed by a 5-week maintenance phase; all subjects were tapered off the drug unless they wished to continue on the medication. The initial dose was 100 mg/day and could be increased by up to 100 mg/week before the 5-week maintenance phase. All subjects were given baseline assessments including the PG-YBOCS, Attention Deficit Hyperactivity Disorder (ADHD) checklist, Mini International Neuropsychiatric Interview (MINI), and HDRS. The primary outcome was measured by improvement on the PG-YBOCS, CGI, and Sheehan Disability Scale (SDS). Scores on the PG-YBOCS decreased significantly and seven subjects achieved a score of 1 (very much improved) or 2 (much improved) on the CGI. The limitations of this study are the sample size, length of treatment, lack of randomization (open-label), and lack of placebo control.

A subsequent case study was reported by Padala et al. (15). Their case involved a 61-year-old male with a 40-year history of PG. He had unsuccessfully sought treatment through behavioral therapies in the past. Though obtaining abstinence during his treatments, he would relapse within a month or two following his release. After completing a 30-day outpatient treatment program, the patient was started on sustained-release (SR) bupropion 100 mg twice daily dosing. He maintained abstinence for eight months, and only after his medications ran out, did he begin to feel the urge to gamble return. He was started back on the medication and experienced a decrease in his cravings. As this was a case study only, the results may not generalize. As a placebo-controlled for bupropion in the treatment of PG was negative, the clinical utility of the medication in treating PG may be limited. However, as the case study involved the maintenance of abstinence (rather than the achievement of abstinence in the RCT), a role for bupropion in PG warrants continued investigation.

Disulfiram

Disulfiram may alter the relative balance of dopamine and norepinephrine in the central nervous system through its effects on dopamine beta-hydroxylase (16). There have been no published RCTs examining the efficacy and tolerability of disulfiram in PG as of this date. Disulfiram has shown efficacy in treating alcohol dependence (AD) and cocaine dependence (17, 18). Due to similarities between these substance addictions and behavioral addictions such as PG, Mutschler et al. hypothesized that disulfiram may prove effective in treating PG (19). The authors then presented a case report of a subject with AD and co-morbid PG (20). This patient developed AD about 25 years prior to this report, and around the same time also developed PG. Though he intermittently sought treatment for AD for 25 years, he did not

seek treatment specifically for PG. After an inpatient treatment for AD, he remained abstinent for alcohol for 6-7 months, but continued to gamble. In 2008, he presented to the authors' clinic for AD treatment. He was treated inpatient for 5 weeks and then continued outpatient treatment for another 12 months. Treatment included disulfiram (500 mg, 3 days a week) and psychotherapy. Although being treated specifically for AD, the patient was able to maintain abstinence from alcohol and gambling for a period of 12 months. The patient had not been treated with supervised disulfiram previously. In all his previous detoxifications, his gambling was not affected, so the authors proposed that the disulfiram may have targeted not only his AD, but also his PG. Limitations include the single-subject case study. However, as many individuals with PG may have co-morbid AD, future studies of disulfiram in this population warrant consideration.

Additional case studies report on disulfiram in treating PG. Müller et al. presented two case studies of patients being treated for PG with disulfiram (21). The first patient was a 44-year-old male with no previous psychiatric treatment history and no co-occurring disorders. He was started on outpatient cognitive behavioral therapy and offered pharmacological treatment in conjunction. He did not want to be treated with SSRIs so he chose to take disulfiram. He was started on 200 mg/day. After one week of therapy, his PG-YBOCS score lowered from 17 to 13. He also reported adverse effects of sedation and an increase in hours slept per day. Seventeen days into his treatment he relapsed and discontinued the medication himself for a one-week period, after which he began to take the medication again. He continued with the medication but kept experiencing sedation. A reduction to 100 mg/day did not alleviate the sedation so the patient chose to discontinue the medication. His last follow-up showed a complete remission of the sedative effects, and at that time his PG-YBOCS was at 8.

The second patient was a 56-year-old male. He had received previous psychiatric treatment for depressive episodes at ages 33 and 51. In addition, he was able to achieve abstinence from his gambling, during his last depressive episode, for one year. He had additional periods of abstinence from counseling visits of up to four weeks, but due to continuous relapses, he presented for additional treatment options. His therapy initially involved cognitive behavioral therapy and due to his lack of responses to previous treatments with citalopram and venlafaxine he was offered disulfiram. His initial PG-YBOCS score was 22.The patient tolerated the medication well in the beginning, but there was no significant impact on his gambling. After just a short period of being on the medication (23 days), the patient developed psychotic symptoms necessitating admission to an inpatient unit. Disulfiram was discontinued and his symptoms remitted almost completely within three days. Three weeks after discharge from the unit, he had relapsed and his PG-YBOCS score was 25.

In both case reports, the dose of disulfiram was much smaller than with other treatment studies involving cocaine or alcohol. However, due to the side effects both patients exhibited, higher doses were not an option. As the only studies to date are case studies, a larger clinical trial is needed to better determine the efficacy and tolerability of disulfiram in treating PG, particularly in individuals with co-occurring AD.

Glutamatergic

Memantine

Memantine is a noncompetitive antagonist of N-methyl D-aspartate (NMDA) glutamate receptors. It is thought to reduce glutamate excitability and has been used primarily in treating cognitive decline in patients with Alzheimer's disease. It has shown efficacy in treating alcoholism, and thus may have efficacy in treating PG.

In the only study to date to examine the efficacy and tolerability of memantine in treating PG, Grant et al. conducted a 10-week open-label treatment study (22). Twenty-nine subjects were enrolled with a starting dose of 10 mg/day and then increased to 20 mg/day by two weeks and up to 30 mg/day after four weeks unless results and/or side effects were noticed earlier. The primary outcome measure was the PG-YBOCS, with secondary measures including the G-SAS and CGI. Twenty subjects completed the entire study (this higher than normal retention rate was noted by the authors). PG-YBOCS scores showed an average of 59.17% reduction from baseline. Eighteen subjects met the criteria of >35% reduction in PG-YBOCS and a CGI score of 1 or 2, and thus were considered “responders.” The mean effective dose at study end was 23.4±8.1 mg/day. In addition to improvement on gambling measures, the authors noted an increase in cognitive flexibility. Side effects were minimal and included headaches, dizziness, and lethargy, all of which were of mild to moderate intensity and resolved without additional effects. Limitations of this study include the open-label nature of the study, that weekly visits with a clinician may have introduced bias, the small sample size, and the short duration of the trial.

Topiramate

In a case study out of Brazil, Nicolato et al. describe a 57-year-old woman with a history of bipolar disorder II and PG (23). She was hypomanic at initial visit and started on lithium up to 900 mg/day. Her affective state improved but there was no concurrent improvement in her gambling behavior. As such, topiramate was added and titrated up to 200 mg/day with marked improvement in her gambling behavior. After 2 months of combined treatment, her gambling behavior remitted. Long-term follow-up showed continued abstinence.

Acamprosate

In the only report of acamprosate in the treatment of PG, Raj described a case study of a 50-year-old woman with a long history of depression who presented to his clinic in May 2008 for treatment of depressive symptoms (24). She was determined to have AD and PG, although the patient had not been seeking treatment for either condition. She was started on venlafaxine for depression given a prior response to the medication. She was not seen again until September 2009. She presented for a follow-up visit just prior to entering an alcohol treatment program, stating she could no longer control her drinking or gambling. At this time, she was only looking for treatment for her AD. She was started on 666 mg/day acamprosate and continued on venlafaxine for her depressive symptoms. By January of 2010, the patient was reporting partial remission of her AD, but full remission of her PG. At one point her acamprosate ran out and she returned to her gambling behavior, but upon resuming acamprosate she again stopped gambling entirely.

Amantadine

In a case study published in November 2012, Pettorruso et al., reported on a 47-year-old male with a 25-year history of PG (25). Unlike previous studies, this was the first to examine amantadine in patients without comorbid Parkinson's disease (PD). In addition to PG, the patient also endorsed AD, nicotine dependence, opioid dependence, and cocaine abuse. At intake, the patient was also experiencing a major depressive episode. The patient was admitted to a treatment program where he was treated for his depression, alcohol withdrawal and sleep disturbances while attending group sessions to manage his PG. One month into treatment, he was improved on all disorders with the exception of his gambling. He was then placed in a psychiatric ward where he was treated with open-label amantadine titrated from 50 mg/day for week one, 50 mg/bid for week two, and then 100 mg and 50 mg in divided daily dosage for the remainder of his treatment period. He was also currently receiving pregabalin 225 mg/day and trazodone 50 mg/day for his alcohol withdrawal symptoms. He was discharged from the unit to outpatient therapy after two weeks, continuing on his amantadine regimen and showed improvement of 43-64% in G-SAS scores with noted reductions in his gambling urges.

Salts (Lithium) and Other Mood Stabilizers

Lithium

In this first study of lithium in treating PG, Moskowitz et al. conducted an open-label study of three individuals with PG and comorbid bipolar disorder who were treated with lithium (26). All three patients responded to the treatment, but it was many years later until the first RCT was conducted to evaluate lithium in the treatment of PG.

In a case study reported by Dell'Osso and Hollander in 2005, a 30-year-old woman presented to their program with severe PG and cyclothymia (27). She reported gambling to help relieve her depressed mood. Her gambling, though controlled at first, quickly intensified. She was started on 300 mg/day lithium, and was titrated up to 1200 mg/day over the 10-week study without reporting any adverse effects. Her condition improved significantly as determined by her scores on the PG-YBOCS and CGI at study end as compared to baseline (the authors did not note either scores in their published article). By the last week of the trial, the patient reported no gambling. The improvement in her gambling coincided with improvement in her affective stability.

Carbamazepine

Black et al. conducted an open-label treatment study of extended release carbamazepine in the treatment of PG (28). Eight subjects were enrolled in the 12-week study and had at least one visit after baseline (one dropped out after the first week, one after five weeks and one after eight weeks). Five subjects completed the study. All subjects had a two-week observation period prior to starting the medication. Dosage was started at 200 mg twice daily for seven days and then titrated up to 800 mg/day divided into two doses. The final dosage was determined by subject's response to medication and any adverse effects. The primary outcome measure was the PG-YBOCS. Secondary measures included the Clinical Global Impression Improvement and Severity (CGI I & S), Gambling Severity Assessment

Scale (GSAS), and SDS. By the final two weeks of the study, five subjects were abstinent from gambling. In addition, there was significant improvement across all measures, including an average weekly decrease on the PG-YBOCS of 1.44 points. The average PG-YBOCS at baseline was 22.5 and at the final visit it was down to 8. There were several adverse effects among seven of the eight subjects, with somnolence being the most common. Limitations include the small sample size, lack of placebo control, exclusion of individuals with co-occurring disorders, and short length of trial.

In a case study using carbamazepine, Haller and Hinterhuber described the positive results they obtained when treating a single patient who failed to respond to conventional treatment (behavior therapy, psychoanalysis, GA) (29). The patient was started on 600 mg/day of carbamazepine and achieved abstinence within two weeks, maintaining that abstinence over the 30-month period of treatment.

Serotonin/Dopamine Antagonists (Antipsychotic Drugs)

Multiple cases in which PG is being treated with atypical antipsychotic drugs involve patients with Parkinson's disease (PD), some of whom developed PG after being started on dopamine replacement therapy for PD. As this is a unique subset of individuals with PG, findings with treatments used in this population may not extend to the general population. Consistent with this notion, there have been several RCTs of PG subjects without PD who have been treated with antipsychotics, and these trials have been negative (30-32).

In one case of treating PG reportedly emerging following dopamine agonist treatment of PD, Seedat et al., describe a 59-year-old woman with no history of PG seeking treatment for her gambling behavior a couple years after beginning dopamine agonist treatment for her PD (33, 34). She was treated with 1mg daily risperidone in addition to her PD medications. This addition worsened her PD, but this was improved with adjuvant low dose levodopa/carbidopa treatment. Her gambling behavior ceased altogether four weeks after the addition of risperidone. While just a single case study, and unique to PD patients who develop PG, it does highlight the role of the dopaminergic system in PG and other ICDs.

The next case report involves a 42-year-old male who was admitted to inpatient treatment for gambling problems and jealous delusions six months after beginning 3.5 mg/day of pergolide for PD (35). He was started on 100 mg/day of quetiapine and this was increased to 700 mg/day within four weeks. After 10 weeks, his PG behavior remitted and his delusional behavior was also significantly improved. There was no adverse impact on his PD. This was the first reported case of quetiapine in the treatment of PG.

Rotondo et al. reported on three case studies of PD patients who developed PG (36). In all three cases, SSRIs were initially prescribed to target gambling behaviors with no apparent success. They switched from SSRIs to clozapine and in two of three cases, problem-gambling symptoms remitted. All three cases had past histories of major depression and alcohol abuse, although all were in remission for several years.

Though not treated with antipsychotics, two additional case reports of PD patients who developed PG on dopamine agonists are reported by Kurlan (37). They are reviewed here as

they presented with PG only after being treated for their PD symptoms. The first report involves a 48-year-old male who developed PG over several years. The prescriber tried to discontinue one of his daily PD medications (pramipexole) without effect, prescribed modafinil to treat sedation (again without effect), and finally tried citalopram, which helped with his depression, but did not alleviate his gambling. The patient began attending GA sessions and reported a significant reduction and finally abstinence in his gambling behavior. In the second case, a 53-year-old woman developed PG after being treated for her PD. Discontinuation of her PD medications had no effect on her gambling. The authors did not report on additional treatment options.

Opioid Antagonists

Naltrexone

Naltrexone is an opioid receptor antagonist used primarily to treat alcohol and opioid dependence. Adverse effects include headaches, nausea, diarrhea, constipation, dry mouth, insomnia, and dizziness. The first case study exploring naltrexone in the treatment of PG was described by Crockford and el-Guebaly in 1998 (38). The report described a case study of a 49-year-old male with AD and PG. He was given 50 mg/day naltrexone for a four-week period. By the end of the first 48 hours, he had a cessation in his craving for alcohol and gambling. No relapses were noted during the four-week period he was on naltrexone.

The next case study was described by Kim in 1998 (39). In this case, a 55-year-old male with severe PG and compulsive shopping presented. He was started on 50 mg/day naltrexone for two weeks with no improvement. His dose was increased to 100 mg/day and by his second visit, he had improved significantly and maintained abstinence during the subsequent nine months.

Kim and Grant next conducted an open-label trial of naltrexone to test its efficacy and tolerability for further testing (40). Seventeen patients were enrolled into 6-week, open-label, flexible-dose trial of naltrexone for treating PG. Primary outcome measures were the CGI-PT (patient rated), CGI-MD (clinician rated), and G-SAS. Dosing started at 25 mg/day for two days, followed by 50 mg/day for the rest of the first week. After the first week, the dosage was titrated up by 50 mg/week until improvement was noted, significant adverse effects emerged, or the maximum dose of 250 mg/day was reached. Fourteen patients completed the study, and all 17 were included in the intent-to-treat analysis. The average dose at the end of the study was 157 mg/day. Adverse effects included nausea, diarrhea, drowsiness, and insomnia. Significant improvement on all measures was noted across all subjects, with the therapeutic effects emerging between one to four weeks. Limitations include the open-label nature of the study, short duration of the trials, small sample size, and dosage above 50 mg/day which is associated with a greater frequency of adverse effects including hepatotoxicity.

Recently, an individual with PG reported increased anxiety, vivid dreams, a feeling of doom, and racing thoughts after two doses of 25 mg oral naltrexone. This physically healthy, middle-aged male with DSM-IV PG was enrolled in a double blind, placebo-controlled clinical trial of naltrexone treatment concomitant with treatment as usual (TAU) through a

problem-gambling treatment program. The patient reported gambling an average of about $2,000 per week on slot machines at a casino for 14 years, losing in the past year around $95,000 and over his lifetime about $400,000. He met eight of ten inclusionary criteria for PG and reported gambling to escape from stressors in his life. The patient had a history of self-reported anxiety over his gambling behavior and how it affected his life, though it failed to reach threshold for a diagnosis of anxiety disorder. The patient also reported intermittent suicidal thoughts and trouble sleeping due to his gambling-related problems. The patient had no history of alcohol or substance dependence/abuse. On the second day of taking naltrexone/placebo at 25 mg/day, the patient reported awakening at around 3:00 am with racing thoughts, vivid dreams, and increased anxiety. He reported going for a walk, which he reported did not help much, although eventually he was able to go back to sleep. The patient discontinued the medication, reported improvement and denied any effects after the following day. The blind for this patient was broken and it was determined he was on active naltrexone at 25 mg/day. The patient continued with the TAU component of treatment. No similar episodes of racing thoughts and anxiety were reported. These findings complement those of a panic attack related to naltrexone dosing in a woman with anorexia nervosa and also resonate with observations of manic features following naltrexone treatment during heroin detoxification (41, 42).

Conclusions and Future Directions

The data reported here complement those reviewed recently describing pharmacological treatments for PG (1). The pharmacological treatment algorithm proposed in that article still appears relevant. In this algorithm, clinicians can determine which treatment course may best serve their clients by answering yes or no questions largely related to co-occurring psychiatric conditions, leading to the most appropriate treatment option. Specifically, if patients are less willing to take a pharmacological drug but are more willing to take an over-the-counter health supplement or neutraceutical, then n-acetyl cysteine might be considered. If the patient is willing to take a medication, the best available data support the use of an opioid antagonist like naltrexone, particularly in individuals with a familial history of alcoholism or strong gambling urges at treatment onset. However, if the patient has a cycling mood disorder, then a mood-stabilizing agent like lithium appears indicated. On the other hand, some data support the use of a serotonin reuptake inhibitor like escitalopram for co-occurring anxiety disorders and PG, although this approach (and others in the algorithm) warrants additional investigation.

In addition, lines of future study (e.g., testing the efficacy of combined pharmacological and behavioral treatments) appear important. As recent studies have begun to examine individual differences in biological and behavioral features that may relate importantly to treatment outcome, the goal of more precisely matching treatments with specific people seeking treatment remains an important and perhaps more attainable prospect. Research into the molecular genetics of PG has mainly focused on familial links and alleles implicated in dopaminergic and serotonergic dysfunctions (43). No genetic variants have been definitively linked to PG. However, treatment outcome in response to some medications showing efficacy in the treatment of PG have been linked in the treatment of other disorders with genetic variations (e.g., naltrexone treatment in alcohol dependence being linked to variation

in the gene coding for the mu-opioid receptor)(44). Thus, the extent to which such polymorphisms might relate to treatment outcome to naltrexone treatment in PG warrants consideration. Future studies may also consider identifying genetic variants for traits (such as impulsiveness, compulsiveness, or sensation-seeking) that are associated with PG as these may provide important information to target specific medications to specific subsets of people with PG. Several of the trials reviewed here noted comorbidities such as SUDs, an important consideration when determining a treatment course. As noted in our original article, some clinical trials for PG were based on findings in SUDs and, as such, these treatments, especially when combined with behavioral therapy, may be helpful for people with co-morbid PG and SUDs.

Acknowledgments

This research was supported by NIH grants R01 DA019039, P20 DA027844, RC1 DA028279, and by a grant from the National Center for Responsible Gaming and its Institute for Research on Gambling Disorders. The views presented here do not necessarily reflect those of the funding agencies, and the work was generated solely by the contributing authors.

References

1. Bullock SA, Potenza MN. Pathological Gambling: Neuropsychopharmacology and Treatment. Current Psychopharmacol. 2012; 1:67–85.
2. Zimmerman M, Chelminski I, Young D. A psychometric evaluation of the DSM-IV pathological gambling diagnostic criteria. J Gambl Stud. 2006; 22(3):329–37. [PubMed: 17009124]
3. Petry NM, Blanco C, Auriacombe M, Borges G, Bucholz K, Crowley TJ, et al. An Overview of and Rationale for Changes Proposed for Pathological Gambling in DSM-5. J Gambl Stud. 2013
4. Choi JS, Shin YC, Jung WH, Jang JH, Kang DH, Choi CH, et al. Altered brain activity during reward anticipation in pathological gambling and obsessive-compulsive disorder. PLoS One. 2012; 7(9):e45938. [PubMed: 23029329]
5. El-Guebaly N, Mudry T, Zohar J, Tavares H, Potenza MN. Compulsive features in behavioural addictions: the case of pathological gambling. Addiction. 2011
6. Hur JW, Shin N, Kim SN, Jang JH, Choi JS, Shin YC, et al. Do pathological gambling and obsessive-compulsive disorder overlap? a neurocognitive perspective. CNS Spectr. 2012; 17(4): 207–13. [PubMed: 22794118]
7. Hollander E, Frenkel M, Decaria C, Trungold S, Stein DJ. Treatment of pathological gambling with clomipramine. Am J Psychiatry. 1992; 149(5):710–1. [PubMed: 1575267]
8. Tarrant N, Cavanna AE, Rickards H. Pathological gambling associated with modafinil. J Neuropsychiatry Clin Neurosci. 2010; 22(1):123 E27–8. [PubMed: 20160236]
9. Zack M, Poulos CX. Effects of the atypical stimulant modafinil on a brief gambling episode in pathological gamblers with high vs. low impulsivity. J Psychopharmacol. 2009; 23(6):660–71. [PubMed: 18583430]
10. Campbell-Meiklejohn DK, Wakeley J, Herbert V, Cook J, Scollo P, Kar Ray M, et al. Serotonin and dopamine play complementary roles in gambling to recover losses. Neuropsychopharmacol. 2011; 36:402–10.
11. Rosenberg O, Dinur LK, Dannon PN. Four-year follow-up study of pharmacological treatment in pathological gamblers. Clin Neuropharmacol. 2013; 36(2):42–5. [PubMed: 23503545]
12. Pallanti S, Baldini Rossi N, Sood E, Hollander E. Nefazodone treatment of pathological gambling: a prospective open-label controlled trial. J Clin Psychiatry. 2002; 63(11):1034–9. [PubMed: 12444818]
13. Pine A, Shiner T, Seymour B, Dolan RJ. Dopamine, time, and impulsivity in humans. J Neurosci. 2010; 30(26):8888–96. [PubMed: 20592211]

14. Black D. An open-label trial of bupropion in the treatment of pathological gambling. J Clin Psychopharmacol. 2004; 24:108–10. [PubMed: 14709965]
15. Padala PR, Madaan V, Sattar SP. Bupropion therapy for pathological gambling. Ann Pharmacother. 2007; 41(3):529. [PubMed: 17341539]
16. Weinshenker D, Schroeder JP. There and back again: a tale of norepinephrine and drug addiction. Neuropsychopharmacology. 2007; 32(7):1433–51. [PubMed: 17164822]
17. Carroll K, Fenton LR, Ball SA, Nich C, Frankforter TL, Shi J, Rounsaville BJ. Efficacy of disulfiram and cognitive-behavioral therapy in cocaine-dependent outpatients. Arch Gen Psychiatry. 2004; 61:264–72. [PubMed: 14993114]
18. De Sousa A, De Sousa A. A one-year pragmatic trial of naltrexone vs disulfiram in the treatment of alcohol dependence. Alcohol Alcohol. 2004; 39(6):528–31. [PubMed: 15525790]
19. Mutschler J, Buhler M, Grosshans M, Diehl A, Mann K, Kiefer F. Disulfiram, an option for the treatment of pathological gambling? Alcohol Alcohol. 2010; 45(2):214–6. [PubMed: 20083479]
20. Mutschler J, Buhler M, Diehl A, Mann K, Kiefer F. Disulfiram, an old drug with new potential in the treatment of pathological gambling? Med Hypotheses. 2010; 74(1):209–10. [PubMed: 19660874]
21. Muller CA, Banas R, Heinz A, Hein J. Treatment of pathological gambling with disulfiram: a report of 2 cases. Pharmacopsychiatry. 2011; 44(2):81–3. [PubMed: 21328196]
22. Grant JE, Chamberlain SR, Odlaug BL, Potenza MN, Kim SW. Memantine shows promise in reducing gambling severity and cognitive inflexibility in pathological gambling: a pilot study. Psychopharmacology (Berl). 2010; 212(4):603–12. [PubMed: 20721537]
23. Nicolato R, Romano-Silva MA, Correa H, Salgado JV, Teixeira AL. Lithium and topiramate association in the treatment of comorbid pathological gambling and bipolar disorder. Aust N Z J Psychiatry. 2007; 41(7):628. [PubMed: 17558627]
24. Raj YP. Gambling on acamprosate: a case report. J Clin Psychiatry. 2010; 71(9):1245–6. [PubMed: 20923626]
25. Pettorruso M, Martinotti G, Di Nicola M, Onofrj M, Di Giannantonio M, Conte G, et al. Amantadine in the treatment of pathological gambling: a case report. Front Psychiatry. 2012; 3:102. [PubMed: 23205015]
26. Moskowitz JA. Lithium and lady luck; use of lithium carbonate in compulsive gambling. N Y State J Med. 1980; 80(5):785–8. [PubMed: 6930557]
27. Dell'Osso B, Hollander E. The impact of comorbidity on the management of pathological gambling. CNS Spectr. 2005; 10(8):619–21. [PubMed: 16041292]
28. Black DW, Shaw MC, Allen J. Extended release carbamazepine in the treatment of pathological gambling: an open-label study. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32(5):1191–4. [PubMed: 18436362]
29. Haller R, Hinterhuber H. Treatment of pathological gambling with carbamazepine. Pharmacopsychiatry. 1994; 27(3):129. [PubMed: 8078954]
30. McElroy S, Nelson EB, Welge JA, Kaehler L, Keck PE. Olanzapine in the Treatment of Pathological Gambling : A Negative Randomized Placebo-Controlled Trial. J Clin Psychiatry. 2008; 69:443–0.
31. Fong T, Kalechstein A, Bernhard B, Rosenthal R, Rugle L. A double-blind, placebo-controlled trial of olanzapine for the treatment of video poker pathological gamblers. Pharmacol, Biochem, Behav. 2008; 89:298–303. [PubMed: 18261787]
32. Pallanti S, Quercioli L, Sood E, Hollander E. Lithium and valproate treatment of pathological gambling: a randomized single-blind study. J Clin Psychiatry. 2002; 63(7):559–64. [PubMed: 12143910]
33. Seedat S, Kesler S, Niehaus DJ, Stein DJ. Pathological gambling behaviour: emergence secondary to treatment of Parkinson's disease with dopaminergic agents. Depress Anxiety. 2000; 11(4):185–6. [PubMed: 10945141]
34. Stein DJ, Grant JE. Betting on dopamine. CNS Spectr. 2005; 10(4):268–70. [PubMed: 15788954]
35. Sevincok L, Akoglu A, Akyol A. Quetiapine in a case with Parkinson disease and pathological gambling. J Clin Psychopharmacol. 2007; 27(1):107–8. [PubMed: 17224732]

36. Rotondo A, Bosco D, Plastino M, Consoli A, Bosco F. Clozapine for medication-related pathological gambling in Parkinson disease. Mov Disord. 2010; 25(12):1994–5. [PubMed: 20669252]
37. Kurlan R. Disabling repetitive behaviors in Parkinson's disease. Mov Disord. 2004; 19(4):433–7. [PubMed: 15077241]
38. Crockford DN, el-Guebaly N. Naltrexone in the treatment of pathological gambling and alcohol dependence. Can J Psychiatry. 1998; 43(1):86. [PubMed: 9494755]
39. Kim SW. Opioid antagonists in the treatment of impulse-control disorders. J Clin Psychiatry. 1998; 59(4):159–64. [PubMed: 9590665]
40. Kim SW, Grant JE. An open naltrexone treatment study in pathological gambling disorder. Int Clin Psychopharmacol. 2001; 16(5):285–9. [PubMed: 11552772]
41. Sullivan MA, Nunes EV. New-onset mania and psychosis following heroin detoxification and naltrexone maintenance. Am J Addict. 2005; 14(5):486–7. [PubMed: 16257886]
42. Luby ED, Marrazzi MA. A panic attack precipitated by opiate blockade--a case study. J Clin Psychopharmacol. 1987; 7(5):361–2. [PubMed: 3680614]
43. Gyollai A, Griffiths MD, Barta C, Vereczkei A, Urban R, Kun B, et al. The Genetics of Problem and Pathological Gambling: A Systematic Review. Curr Pharm Des. 2013
44. Oslin DW, Berrettini W, Kranzler HR, Pettinate H, Gelernter J, Volpicelli JR, et al. A functional polymorphism of the mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. Neuropsychophamacology. 2003; 28:1546–52.