CASE REPORT

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The use of naltrexone in pathological and problem gambling: A UK case series

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Background and aims: To investigate the potential indications and adverse effects of using the opioid antagonist naltrexone to treat problem gamblers. *Case presentation:* The files of the 1,192 patients who were referred to the National Problem Gambling Clinic between January 2015 and June 2016 were audited. Seventeen patients were considered appropriate for treatment with naltrexone, having attended and failed to respond to psychological therapies at the clinic. Fourteen patients were placed on a regimen of 50 mg/day naltrexone. *Discussion:* Of the 14 patients who were treated with naltrexone, there were 10 for whom sufficient follow-up existed to analyze the treatment efficacy and side effects of naltrexone. Patients showed significant decreases in their craving to gamble and the majority (60%) were able to abstain completely from gambling in the treatment period, with a further 20% reducing their gambling to almost nothing. The reported side effects from the naltrexone included: loss of appetite, gastrointestinal pain, headaches, sedation, dizziness, and vivid dreams. Two patients with concurrent alcohol-use disorder relapsed during the treatment. One patient relapsed after the treatment period. *Conclusions:* The study showed significant outcomes in reducing gambling cravings for the sample set. Given the design of the study as a case series, there was no control group, and a number of patients were on other psychotropic medications. We recommend care when prescribing to those suffering from concurrent alcohol-use disorder.

Keywords: naltrexone, gambling disorder, UK

BACKGROUND

Pathological and problem gambling (PG) is a psychiatric disorder characterized by persistent and recurrent gambling behavior leading to clinically significant impairment or distress (American Psychiatric Association, 2013). Sufferers tend to become increasingly involved in terms of time and financial commitment, continuing to gamble regardless of the impact on their personal, social, and financial well-being (Hodgins, Stea, & Grant, 2011). There is a lack of remission in PG, despite psychological intervention. PG is known to have a negative impact on physical and mental health, occupation, financial matters, and interpersonal relationships (Grant & Kim, 2001). There is a significant relationship between PG and comorbid psychiatric disorders, where they are likely to have a mutually reinforcing effect on the sufferer. Attempted or completed suicide is not uncommon (Ledgerwood & Petry, 2004).

The UK Gambling Commission (2017) reported that, as of December 2016, 48% of people had participated in gambling in the past 4 weeks, an increase from 43% in December 2015. The commission reported that 0.7% of respondents identified as problem gamblers, amounting to there being around 300,000 problem gamblers in the UK at any one time. Those in the 18- to 24-year-old-age group are least likely to gamble, with 33% reporting having participated in the past 4 weeks, versus 54% for the highest participant group (45–54 years old people). However, these young gamblers are almost twice as likely to be a problem gambler, with 1.1% estimated to be so. Framing National Health Service (NHS) treatment policy is particularly important, provided the risks of this vulnerable group and the ease of accessing gambling online. It is one of the aims of this study to help in guiding such policy.

Naltrexone is a US Food and Drug Administration (FDA)- and National Institute for Health and Care Excellence (NICE)-approved treatment for alcohol and opiate dependence (Center for Substance Abuse Treatment, 2009). In preclinical data, naltrexone is advocated to help treat addictions more diversely by blocking binding of endogenous opioids. The suggested role of gambling in the stimulation of the endogenous opioid system forms the clinical basis for using opioid antagonists in the treatment of PG (Grant, Odlaug, & Schreiber, 2014). Indeed, this is the basis of its use in behavioral addictions more broadly

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(Grant, Schreiber, & Odlaug, 2013). In a randomized controlled trial on kleptomania, it was found that subjects randomized to receive naltrexone reported significant reductions in urges in stealing and stealing behavior (Grant, Kim, & Odlaug, 2009). A case series looking at compulsive buying found that high-dose naltrexone led to partial or complete remission of urges to shop (Grant, 2003). A systematic review of the use of naltrexone in diverse behavioral addictions showed consistent efficacy of the drug (Aboujaoude & Salame, 2016).

The body of literature on the pharmacological treatment of PG is supportive of the use of opioid antagonists as a treatment of "last resort" once psychological interventions have failed. Grant et al. (2014) reviewed 18 randomized control trials across five drug classes in the treatment of PG. Antidepressants, mood stabilizers, and atypical antipsychotics have shown mixed results, and there is no evidence to recommend their use as a treatment protocol in PG. The literature demonstrates a higher treatment efficacy with opioid antagonists (Grant, Kim, & Odlaug, 2007). The earliest clinical indication for using naltrexone in PG came from a single case report of a pathological gambler with a 13-year history of alcohol dependence. Significant reductions in scores measuring compulsive drinking and compulsive gambling were observed (Crockford & el-Guebaly, 1998). We reviewed the evidence from three randomized control trials that specifically looked at the efficacy of daily naltrexone in PG (Kim & Grant 2001; Kim, Grant, Adson, & Shin, 2001; Grant, Kim, & Hartman, 2008), finding significant reductions in gambling outcomes in all three. We also reviewed two "as needed" (pro re nata) studies (Lahti, Halme, Pankakoski, Sinclair, & Alho, 2010; Kovanen et al., 2016), finding more mixed results. For completeness, we reviewed studies of another opioid antagonist, nalmefene. Grant et al. (2006) showed significant reductions in gambling urges; however, a later trial suggested that only those patients on high doses reported reductions in the primary outcome measure (Grant, Odlaug, Potenza, Hollander, & Kim, 2010). It was on this basis that it was decided to treat our patients with a daily dose of naltrexone.

To date, there has been no research performed in the UK on the use of naltrexone in PG. There have been no NICE guidelines for the treatment of PG; thus, as elsewhere, UK clinicians have been referring to the Monash guidelines. According to GambleAware, only 2.7% of those affected by PG are in treatment at any one time, compared with 6% of problem drinkers and 50% of Class A drug misusers. Given the psychosocial and medical impact of PG, we believe that parity of esteem in its treatment with other mental health issues is required, including in pharmacological intervention. As such, we saw value in a case series discussion for patients who had been pharmacologically treated with naltrexone in the UK. Our findings add credibility to the international evidence base on the pharmacological treatment of PG, which is still limited.

The pharmacokinetic safety of naltrexone indicates that it is a well-tolerated drug, with transient and self-limiting side effects (Foss et al., 1997). Naltrexone is known to cause overdose symptoms, if used simultaneously as opioids. The British National Formulary notes that naltrexone is contraindicated in patients suffering from hepatic or renal impairment (Joint Formulary Committee, 2015). These are important areas of clinical monitoring.

CASE PRESENTATION

The case series was performed through a retrospective audit of the case files of the 1,192 patients who attended the National Problem Gambling Clinic in the 18-month period between January 2016 and June 2017. Five hundred and sixteen of these patients entered treatment, of which 17 were screened as appropriate for treatment with naltrexone.

Naltrexone was indicated for severely affected patients, as measured by the Problem Gambling Severity Index (PGSI). These patients had already undergone psychological therapy for PG at the National Problem Gambling Clinic (NPGC) with limited success. The severity of their craving to gamble was measured again at the naltrexone assessment using the Gambling Craving Scale (GCS). It was confirmed at this stage that the patient was committed to either abstain from or dramatically reduce their gambling behavior. Only patients with normal liver and renal function tests and who would be able to avoid abuse of alcohol throughout the treatment period were considered. Patients with an existing recreational or prescription use of opiates were also excluded, due to the risk of overdose. Out of the 17 patients, 14 had commenced treatment.

The treatment commencement dates for the patients in the sample set fell between January 2016 and April 2017. Patients were prescribed an initial dose of 25 mg per day for 3 days, and then 50 mg per day as the usual maintenance dose. Details of other support services, such as Gamblers Anonymous, as well as information on the potential side effects of naltrexone were provided to the patients. Any patient-reported side effects or unintended treatment outcomes of the naltrexone were recorded.

Patients were called for follow-up after 6 weeks, where a further GCS was answered as well as a reflective questionnaire on the patient's experience of treatment. If the treatment suited the patient, a further prescription of the maintenance dose was offered for 8 weeks, after which prescribing was handed-over to the patient's general practitioner.

Of the 14 cases, there were 10 for whom sufficient follow-up existed to enable a meaningful analysis of the efficacy of their treatment. These patients are summarized in Table 1. The information considered adequate was the presence of a complete psychosocial and forensic history, information on comorbidities and other addictions, gambling history, history of past treatment modalities, a correctly completed GCS for both prior to and 6 weeks following commencement of treatment with naltrexone, and the reflective questionnaire. There were a further two cases for whom answers to the reflective questionnaire were available. We comment on the responses to this questionnaire at the end of the discussion.

Of the 10 patients, 8 were male and 2 were female. The ages of the patients ranged from 29 to 56 years, with a median age of 44 years. These patients had gambling careers spanning from 3 to 40 years, with a median career length of 21 years. The patients reported estimated total losses (ETLs) of between £5,000 and £1,700,000, with the majority having

Table 1. Summary of pathological and problem patients treated with naltrexone for whom there existed a full complement of follow-up materials

	Age, Sex	Referral route	Gambling career (years)	ETL	PGSI (/27)	Medical comorbidities	Psychiatric comorbidities	Other addictive pathologies	Reported medications	Social history	Forensic history	Treatment goal	Pre-treatment GCS (/30)	Post-treatment GCS (/30)	Naltrexone side effects	Reported gambling activity
1	43, M	GP	17	£1,700,000	27	Hypercholesterolerria Angina Recurrent urinary tract Lipomas	Schizophrenia	History of cocaine abuse	Risperidone 4 mg Citalopram 20 mg Atorvastatin 20 mg	Divorced, lives alone, three children (no contact), unemployed, reported domestic violence, and poor relationship with family	Six custodial sentences related to gambling, longest 6 years	Abstinence	30	9	None	Gambled a small ticket on two occasions in the first 3 weeks Abstained from the fourth week of treatment
2	56, F	Psychiatrist	3	£5,000	19	Raised alanine transaminase and night seizures	Bipolar affective disorder	None reported	Aripiprazole 20 mg	Lives with daughter (30), physically abused by mother, and raped by brother at 13	None reported	Reduction	28	6	Loss of appetite	One episode of PG in 7 weeks. Now does the Euromillions once a week – £9, which was her treatment goal
3	29, M	Past patient	5	£100,000	21	None reported	None reported	None reported	None reported	Weekly binge drinking and cocaine use	Stealing to fund gambling	Reduction	7	4	Stomach pains	None
4	45, M	Self-referral	25	None reported	23	None reported	None reported	Alcohol and cocaine	None reported	Use of MDMA, family history of gambling, brother PG, and facial disfigurement	None reported	Abstinence	27	3	Evening tiredness	None during treatment period. Report of relapse afterward
5	47, F	Past patient	30	£10,000	22	Osteoarthritis, hypertension, and Crohn's disease	Depression and obsessive and compulsive traits	None reported	Sertraline 150 mg	Spent time in care as child, father PG and alcoholic, unemployed, with adult children	None reported	Abstinence	30	7	Rapid pulse first few days	None
6	37, M	From inpatient unit	25	£1,000,000	14	None reported	Obsessive compulsive traits	None reported	None reported	No significant family history, having young children	Under investigation for missing stock at work	Abstinence	28	5	Stomach pains, dizziness, nausea, and headaches for the first few days	None

(Continued)

Table 1. (Continued)

	Age, Sex	Referral route	Gambling career (years)	ETL	PGSI (/27)	Medical comorbidities	Psychiatric comorbidities	Other addictive pathologies	Reported medications	Social history	Forensic history	Treatment goal	Pre-treatment GCS (/30)	Post-treatment GCS (/30)	Naltrexone side effects	Reported gambling activity
7	54, M	Self-referral	40	£300,000	12	Hypertension	Attention-deficit hyperactivity disorder	Pomography, shopping, and eating	Citalopram 30 mg	Divorced, taxi driving creates temptation, having two young children	None reported	Abstinence	27	13	Nausea for the first few days	None
8	31, M	Self-referral	15	£60,000	27	None reported	Anxiety and depression	None reported	None reported	Heavy social drinking housed by social services, three children by two mothers, and umemployed	None reported	Abstinence	7	0	None	None
9	47, M	Self-referral	30	£500,000	23	None reported	Depression	Alcohol	Citalopram 20 mg	Two brothers with drug addictions, single and living alone, beaten by father as child	Significant forensic history	Abstinence	27	17	Stomach cramps, vivid deams, headaches	Relapse – had a relapse of his alcoholism and failed to take the naltrexone
10	34, M	GP	14	None reported	12	None reported	Depression	Alcohol, heroin, tramadol, and codeine		Single, in care as a child, previously homelessness, and unemployed	None reported	Abstinence	25	3	Reduced appetitie, and feeling "spaced out"	Relapse – intrusive side effects and could not forsake heavy drinking Advised to stop taking the naltrexone as a result

Note. ETL: estimated total loss; PGSI: Problem Gambling Severity Index; GP: general practitioner.

significant personal indebtedness as a consequence of their losses. The average ETL was £459,375. All of the patients had already completed, or attempted to complete a previous gambling-specific treatment modality. These modalities included self-exclusion, GamCare counselling, Gamblers Anonymous, and Gordon Moody. All patients had attended a previous NPGC psychotherapy or cognitive behavioral therapy program. The responses to the PGSI before the commencement of naltrexone ranged from 12/27 to 27/27, with a median score of 21.5. For eight patients, the treatment goal was abstinence and for two it was reduction.

Eight of the 10 patients reported diagnosis of an axis I psychiatric disorder, including schizophrenia, bipolar affective disorder, attention deficit hyperactivity disorder (ADHD), depressive disorder, or a concurrent addictive pathology. Six patients were taking another psychotropic medication, which included antidepressants and antipsychotics. Four patients reported a chronic medical comorbidity. All 10 patients had significant social history including family breakdown, previous emotional or sexual abuse by a close friend or family member, family history of an axis I disorder, unemployment, time spent in care as a child, and homelessness. Four of the patients had a history of illegal activity in order to fund their gambling.

The reported side effects of the naltrexone were loss of appetite, gastrointestinal pain, sedative symptoms or feeling "spaced out," headaches, nausea, dizziness, and vivid dreams. The majority of side effects resolved within the first week. Unintended treatment outcomes included reduced anger, reduced impulsiveness, improvement in mood, improved concentration, less compulsion to overexercise, less interest in overeating, and increased calmness.

As demonstrated in Table 1, all 10 patients experienced a reduction in cravings to gamble as tested by the pre- and post-commencement GCS. Responses to the pre-commencement GCS ranged from 7/30 to 30/30, with a median score of 27, making the median patient at "very high risk" of gambling. Responses to the 6-week follow-up GCS ranged from 0/30 to 17/30, with a median score of 5.5, representing a "low risk" of gambling. Of the 10 patients, 6 were able to abstain completely for the whole treatment period. Of the four who did not abstain, gambling behavior was much reduced in two cases. Two patients relapsed. One had a relapse of alcoholism and failed to continue taking the naltrexone. One was experiencing intrusive side effects, decided they could not forsake heavy drinking and was advised to stop taking the naltrexone as a result. One patient was reported to have relapsed after being discharged at the end of the treatment period.

The reflective questionnaire of the 12 naltrexone-consumed patients provided further color on the treatment response:

- 11 said they had gambled less since started consuming naltrexone.
- 10 said they had experienced less gambling-related thoughts and urges.
- 8 said they had experienced side effects.
- 10 said it had not been difficult to stick to the treatment. Of those answering "yes," one had found it hard to abstain from opiate-based painkillers and one found it hard to avoid alcohol-binges as well as struggling with the side effects.
- When asked whether there had been any overall impact on their day-to-day life, four cited a positive effect, one a mixed effect, one specified that they had experienced an effect but did not specify any details, and six reported no impact.
- All 12 said they would recommend naltrexone to someone else facing gambling difficulties.

Ethics

The study procedures were carried out in accordance with the Declaration of Helsinki. All subjects were informed about the study and provided informed consent.

DISCUSSION

The patient set was small and heterogeneous in terms of presenting comorbidities, concurrent medication, and psychosocial history, yet we observed marked improvement in craving-to-gamble in all cases. In the context of the literature to date, we view that our results with this sample of patients from the NPGC give support of the use of naltrexone as an adjunct treatment in PG.

We were not able to control for the presence of comorbidities and other psychotropic medications. We were not able to comment on the effect of dosage, given that each patient was given the same treatment regimen. However, the review of Grant et al. (2008) suggested that 50 mg/day was as efficacious in treating PG as higher doses, which was the basis of the decision to use 50 mg/day in the study. We were not able to provide any evidence of the effect of naltrexone on gambling urges and behavior following cessation of treatment, although a 12-month follow-up study showed that the majority (60%) of patients did not relapse within 6 months of stopping naltrexone (Dannon, Lowengrub, Musin, Gonopolsky, & Kotler, 2007). There is a scope for a randomized control trial over a longer period of time to ascertain long-term treatment outcomes and the tolerability of the treatment medically and psychologically, especially once cessation has occurred.

To date, although evidence suggests that naltrexone has the most potential as a pharmacological treatment for PG, there has been no formal comparison study of its efficacy vis-à-vis other opioid antagonists in PG, notably nalmefene. A comparative study of naltrexone and nalmefene was conducted by Drobes, Anton, Thomas, and Voronin (2003), testing their respective effects on alcohol consumption, showing that the efficacy was similar to each medication. The results suggested that the side effect burden was lesser in the case of naltrexone. Once opioid antagonists are established as a treatment modality for PG, a comparative study between the two drugs for specific efficacy in PG would be worthwhile.

We found that alcohol consumption seemed to increase the treatment resistance of a patient's PG, based upon the relapses of the heavy drinkers in the sample set. Baron and Dickerson (1999) found that alcohol consumption significantly increases impairment in control of gambling

behavior. Further work to investigate this relationship would be useful in order to inform treatment protocol for PG suffers who also drink heavily.

We believe that NICE guidelines are now required to address a pathology that affects almost half a million people in the UK, but that has not been given parity of esteem with other mental health disorders by the NHS. The introduction of naltrexone as a "last resort" treatment for those who have been resistant to psychological therapies seems logical, given its approval by both the FDA and NICE for other addictive pathologies and the benefits it has shown for PG in the evidence, to date, further supported by our work at the NPGC.

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