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CASE REPORT

Disulfiram, an Option for the Treatment of Pathological Gambling?

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Abstract — Aim: Pathological gambling and comorbid alcohol dependence often occur in combination. Disulfiram is one of the proven drugs for alcohol dependence. In addition to its inhibiting acetaldehyde dehydrogenase, disulfiram inhibits dopamine β-hydroxylase and may thereby increase dopamine and decrease norepinephrine cerebral concentrations. Because there may be common neurochemical substrates and neuronal circuits for pathological gambling and addiction, we wished to explore the effect of disulfiram in gambling. **Method:** We describe the outcome of a patient with alcohol dependence and pathological gambling treated with disulfiram D. **Results:** During treatment with disulfiram, the patient reported that his desire to gamble disappeared entirely. Follow-up indicated that he has not gambled for >12 months. **Conclusions:** Although uncontrolled case observations should be interpreted with caution, disulfiram deserves further investigation in pathological gambling.

INTRODUCTION

Pathological gambling (PG) is a public health problem characterized by recurrent and pathological patterns of gambling. PG is associated with a range of social and psychological problems like high rates of bankruptcy, divorce, suicide and reduced quality of life. Although the lifetime prevalence rate of pathological gambling in the German population is 0.2–0.4%, it often remains unrecognized and, therefore, untreated (Wölfling *et al.*, 2009). Comorbidity of DSM-IV pathological gambling and other psychiatric disorders are very common. In particular, high comorbidity rates have been reported between PG and drug dependence. Rates vary from 34 to 80% for substance use disorders (excluding tobacco) (Hall *et al.*, 2000; McCormick *et al.*, 1984). The occurrence of PG in alcohol-dependent patients is at least three times higher than in the general population (Hall *et al.*, 2000). In cocaine-dependent patients, lifetime comorbidity rates have been reported that are even five times higher as in the general population (Hall *et al.*, 2000). These observations suggest that common pathophysiological factors might underlie PG and drug addiction. However, this hypothesis is not proven yet.

PG is currently classified as an 'impulse control disorder (ICD) not elsewhere categorized' in the DSM, although the current diagnostic criteria indeed share many features with those for drug dependence, including (i) continued engagement in a behaviour despite adverse consequences, (ii) diminished self-control over engagement in the behaviour, (iii) compulsive engagement in the behaviour and (iv) an appetitive urge or craving state prior to engaging in the behaviour as well as tolerance and withdrawal (Potenza, 2006, 2008). Similarities between PG and drug dependence include not only phenomenological criteria but also epidemiological, clinical, genetic and neurobiological characteristics (Goudriaan *et al.*, 2004; Potenza, 2006, 2008). Therefore, PG might best be characterized as a non-substance-related or behavioural addiction with a compulsive urge for a non-drug reward (Tamminga and Nestler, 2006).

Recent evidence indicates that similar mechanisms are involved in PG and drug addiction. Neuroimaging data suggest that in PG and drug addiction, the same brain areas are involved. Reduced activity in the ventral striatum and the ventromedial and ventrolateral prefrontal cortex has been reported in PG, which is also a hallmark of drug addiction (Reuter *et al.*, 2005). A neuroendocrinological study in casino gamblers found that gambling elevated dopamine levels in problem gamblers more than in healthy controls (Meyer *et al.*, 2004). The mesocorticolimbic dopaminergic system has been found to be implicated in rewarding and reinforcing behaviours. It has been suggested that PG might be related to a deficiency of the mesocorticolimbic dopaminergic reward system, as has been shown for drug addiction.

Another hallmark of drug addiction that also holds for pathological gambling is the inability to inhibit inappropriate responses. Accumulating evidence points towards an important role of brain dopamine and noradrenergic systems in impulsive behaviour. The inferior frontal gyrus is critically involved in response inhibition and might be particularly impacted by the brain's noradrenergic system.

Other preclinical studies suggest that engaging in casino gambling elevates activity of the hypothalamic–pituitary axis in problem and non-problem gamblers, as indicated by increased plasma levels of norepinephrine, cortisol and increased heart rate. Roy and colleagues found higher levels of norepinephrine or its metabolites in urine, blood or cerebrospinal fluid samples in pathologic gamblers (Roy *et al.*, 1988).

The similarities between PG and drug addiction suggest that patients with pathological gambling may also benefit from medication used for the treatment of drug addiction. Pharmacotherapy research and validated treatment options for PG are limited.. At the present time, there is no medication for treatment of PG that is approved by the Food and Drug Administration. Controlled clinical trials provide some evidence for beneficial effects of opiate antagonists (naltrexone and nalmefene) (Grant *et al.*, 2006; Kim *et al.*, 2001), *N*-acetyl-cysteine (Grant *et al.*, 2007), lithium (Hollander *et al.*,

2005) and selective serotonin reuptake inhibitors, which have been shown to reduce craving for gambling. Additionally, cognitive behavioural therapy has been shown to be an effective treatment for some patients with PG. However, all these therapies have only limited success.

Disulfiram is well known as a treatment for alcohol dependence (e.g. de Sousa and de Sousa 2004, 2005; Suh *et al.*, 2006; Laaksonen *et al.*, 2009). Disulfiram also helps in the treatment of cocaine addiction (Carroll *et al.*, 2004; Gossop and Carroll, 2006), possibly by reducing cocaine craving by increasing neurotransmitter levels of dopamine and decreasing the norepinephrine levels by blocking the activity of the enzyme dopamine beta hydroxylase (DBH) involved in the metabolism of brain monoamines (Weinshenker and Schroeder, 2007; Mutschler *et al.*, 2009a, 2009b). As similar neurochemical disturbances have been reported in PG, disulfiram might not only be effective in the treatment of cocaine addiction but also in the treatment of PG (Mutschler *et al.*, 2009a, 2009b).

We present a case in which a patient with PG and comorbid alcohol dependence was treated with disulfiram. We suggest that disulfiram has the potential to reduce craving and pathological gambling behaviour in PG.

CASE REPORT

Mr K. is a 48-year-old married male working as a part-time nurse. His alcohol dependence developed 25 years ago. He also started problematic gambling at slot machines at around the same time. He met all of the criteria for PG according to DSM-IV and ICD-10 for ~20 years. The patient has no criminal history, but has run up about 10,000 euros in debts due to PG. Mr K is a smoker and nicotine-addicted but has never taken any illegal drugs.

He was treated for alcohol dependence for the first time ~10 years ago. He has undergone 28 inpatient detoxifications. In 2000, he had long-term residential treatment for alcohol dependence. Afterwards, he participated in a self-help group on a regular basis but did not receive specific treatment for PG. He remained completely abstinent from alcohol for 6–7 months. However, he continued to gamble during those alcohol-abstinent months.

After the first contact with our team in 2008, he was treated for 5 weeks in our inpatient department, which specializes in addiction medicine. The treatment included behavioural therapy as well as relapse prevention medication with disulfiram (dosage 500 mg/3 days per week). The patient tolerated the medication without any side effects (apart from short-term, moderate fatigue at the beginning of the treatment).

After discharge from our inpatient treatment, we continued treating the patient over a period of 12 months in our outpatient programme for chronic alcohol patients. The disulfiram medication was supervised by a physician three times per week, establishing a therapeutic ritual with high frequency of short-term individual contacts. During this therapeutic ritual, the therapist praised the patient for taking disulfiram and for maintaining abstinence, thereby providing continuous reinforcement of an alcohol-free lifestyle. Additionally, alternative coping skills were developed and breathalyzer tests to monitor abstinence from alcohol were conducted. Throughout this treatment, the patient reported that not only craving for alcohol had disappeared but that he surprisingly had no urge to gamble anymore.

In conclusion, we found that, since initiating the supervised treatment with disulfiram, the patient has been abstinent from alcohol and gambling for >12 months.

DISCUSSION

This case report suggests that disulfiram might provide treatment in PG. Disulfiram helps in the treatment of alcoholism, cocaine addiction, human cancers and fungal infections (Brewer, 1990; Suh *et al.*, 2006; Cvek and Dvorak, 2008). For more than half a century, disulfiram has been successfully used for alcohol aversion therapy (Brewer, 1993). Disulfiram's pharmacokinetics have been extensively studied; it also has a good safety record (Suh *et al.*, 2006). It is a well-known vicious circle that substance use may lead to more gambling and more gambling may lead to substance use. Personality traits like impulsivity and reward sensitivity may contribute to excessive engagement in both behaviours.

In the presented case, the patient has abstained from alcohol consumption for >12 months now and, notably, he has not gambled either since treatment with disulfiram started. One possible explanation might be that the patient was abstinent from alcohol. However, it can be argued that the patient was treated for alcohol dependence several times, but PG was never markedly affected. Furthermore, despite numerous previous detoxifications, the patient had never been treated with supervised disulfiram before.

Psychological aspects of the supervised disulfiram therapy and the high placebo response rate seen in treatment studies of pathological gambling may have contributed to the good clinical outcome, and this is a methodological limitation of this case report.

However, we propose that a possible neurobiological contributant might be that disulfiram directly modulates reward sensitivity and craving for gambling by increasing the level of the brain chemical dopamine and decreasing the norepinephrine levels through blocking the activity of the DBH, which metabolizes brain monoamines (Mutschler *et al.*, 2009a, 2009b). Most strikingly, these two neurotransmitter systems are thought to be altered in PG (Reuter *et al.*, 2005; Roy *et al.*, 1988).

The disappearance of the patient's desire to gamble during treatment with disulfiram points towards the potential of disulfiram in reward modulation in PG, similar to that described in the treatment of cocaine dependence (Mutschler *et al.*, 2009a, 2009b). Our preliminary clinical data support the hypothesis that disulfiram affects the desire to gamble, thereby promoting gambling abstinence. The possible involvement of DBH was mentioned above.

Previous studies in drug-dependent patients and patients with PG have shown that a combination of pharmacological treatment in combination with psychosocial treatment methods, group therapies or contingency management therapies is more effective than either treatment alone (Oakley-Browne *et al.*, 2000; Pallesen *et al.*, 2007). More studies investigating the potential of combined treatment approaches using disulfiram and cognitive behavioural therapies are necessary.

In summary, this report suggests that disulfiram might be a promising pharmacological agent in the treatment of PG.

Future studies should assess the efficacy of disulfiram in reducing relapse rates in larger samples of pathological gamblers without comorbid alcohol dependence, with research to understand the underlying neuronal mechanisms.

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