

CHAPTER 11

PATHOLOGICAL GAMBLING: NEUROBIOLOGY AND PHARMACOLOGICAL TREATMENT

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Pathological gambling, a highly disabling condition at the severe end of the spectrum of gambling behaviours, is a progressive and chronic disorder. An estimated 2-3% of the general population suffers from this disorder (American Psychiatric Association, 1994), with potentially huge adverse impacts on the individuals, their families and society as a whole. Over the past four decades, pathological gambling has gained wide research interest, and understanding of its epidemiological findings and phenomenology has developed momentum.

The research on pathological gambling varied according to how researchers conceptualised it. Earlier studies explored pathological gambling as an obsessive-compulsive spectrum disorder, but more recently it has been investigated as an impulse-control disorder and addictive disorder respectively.

Although pathological gambling is classified as an impulse-control disorder under the DSM-IV classification system, with presumably impulsivity as its central feature, phenomenologically it shares similar characteristics with an addiction disorder. Conceptualising it as an addictive disorder, pathological gambling denotes a moderate to severe dependence. As such, its treatment has been largely modelled on the treatment of alcohol dependence. Evaluations of the treatment of pathological gambling have been relatively few and limited, mostly done on limited samples and of variable quality.

Oakley-Browne and colleagues (Oakley-Browne et al, 2003) conducted a systematic review of the pathological gambling interventions and found only four randomised control trials of psychological treatments. The results indicated a paucity of evidence for effective treatment. Indeed,

various psychological techniques have been employed in the treatment of pathological gambling and they usually constitute traditional approaches for alcohol dependence. These techniques include group therapy (interactive and self-help), motivational enhancement techniques and cognitive behavioural therapy with relapse prevention strategies. Less commonly, imaginal desensitisation treatment and aversion therapies were described. Overall, treatment is individualised according to the developmental stages of the gambling behaviour, the severity and complexity of adverse consequences, and the treatment settings (Russon et al, 1984). Currently it would appear that an eclectic approach, rather than any specific one, is being widely adopted in the community treatment of pathological gambling in New Zealand.

In the field of substance addiction there have been progressive advances in pharmacological treatment of alcohol, nicotine and opioid dependence. In particular, the effective use of anti-craving agents such as Naltrexone in reducing relapse rates in alcohol dependent persons (O'Malley et al, 1992; Volpicelli et al, 1992; Volpicelli et al, 1995) has generated much interest in its use for behavioural addiction disorders, including pathological gambling. Today, the neurobiology of pathological gambling is better understood than previously (Davis, Charney et al, 2002). In this chapter, we describe some of these known neurobiological mechanisms with the goal of discussing the pharmacological treatment of pathological gambling.

Neurobiology of pathological gambling

In the past three decades, there has been increased understanding of the neurological mechanisms underlying various addictive behaviours, particularly in respect of the arousal mechanism, reinforcement and reward-circuitry involving reinforcing or compulsive behaviours, impulsivity and craving. Many of these findings are derived from research on chemically addictive substances. The transition from normal to addictive behaviour appears to involve reward circuits in the orbito-frontal-cortex, nucleus accumbens and other structures in the limbic region of the brain (Volkow & Fowler, 2000; Hammer, 2002).

Neurotransmitters that mediate these neuronal pathways have also been studied in detail. The main neurotransmitter systems in the central nervous systems implicated in the pathophysiology of pathological gambling include the following:

1. Norepinephrine – which may be involved in the arousal, sensation-seeking and excitement processes of gambling. The norepinephrine system changes under gambling conditions with elevated norepinephrine and its metabolites, which are maintained even after the gambling has stopped (DeCaria et al, 1998; Roy et al, 1988; Roy et al, 1989).
2. Serotonergic – which may be involved in impulse control, behavioural initiation and cessation, and mood regulation. Pharmacological studies with the selective serotonin re-uptake inhibitors (SSRIs) and meta-chlorophenylpiperazine (m-CPP), genetic studies with regard to genes involved in modulating serotonergic function and investigations of the cerebral spinal fluid for its metabolites, suggest underlying serotonergic dysfunction in individuals who are pathological gamblers (DeCaria et al, 1998; Roy et al, 1988; Kennett & Curzon, 1988).
3. Dopaminergic – which may contribute to the reward and reinforcement of addictive stimuli. Studies involving neuro-imaging and measurement of both the central and peripheral Dopamine levels during gambling suggest changes relating to the motivational processes, mediation and reinforcement roles similar to other addictive substances (DeCaria et al, 1998; Bergh et al, 1997; Koob, 1992).
4. Opioidergic – an endogenous opioid which may mediate levels of pleasure and craving for the gambling activity. The mu-opioid receptor is involved in the dopaminergic reward and reinforcement pathways and preliminary efficacy from mu-opioid receptor antagonist Naltrexone in the treatment of pathological gambling suggest possible opioidergic involvement (Crockford & el-Guebaly, 1998a; Kim, 1998). It is believed that the antagonism appears to inhibit the actions of endogenous opioids on the mesolimbic pathway, which would otherwise produce a rise in dopamine in the accumbens nuclei.

Other neurotransmitter systems that have been studied, but which have not been found to have any significant roles for pathological gamblers, include the monoamine oxidase activity, gamma acetyl-butyrac acid (GABA), neuropeptide, neurotensin, somatostatin and growth hormone releasing hormone (Davis et al, 2002).

Pharmacological treatment of pathological gambling

Overview

With the progressive increase in knowledge regarding neuropharmacological mechanisms, it is not surprising that attention has been drawn to the search for and development of medications suitable for the treatment of pathological gambling. Gambling exists as a spectrum phenomenon along a continuum of behaviours. At one end of the spectrum people may gamble recreationally or infrequently and develop no psychosocial problems at all. With progressive engagement in gambling, they begin to experience problems with increased dyscontrol and distress, and eventually the emergence of a pathological gambling disorder.

Pharmacotherapy of pathological gambling has to be understood in this context. By and large, in the mildly problematic group of problem gamblers with no major co-morbid psychiatric disorders, psychological techniques may help them overcome their gambling problem. As the clinical presentation becomes increasingly complex, psychopharmacological treatment is likely to feature more prominently. At the severe end of the spectrum, a combination of specialised psycho-therapeutic techniques, together with psychotropic medications, often become necessary and may yield better results, although these interventions need further exploration, including outcome research. As in the treatment of severe alcohol dependence, pharmacotherapy is best utilised as an adjunctive treatment at the present time, along with psycho-therapeutic and rehabilitative efforts. Multi-modality treatment will in turn require expertise from a multi-disciplinary workforce.

Indications

Pharmacotherapy of pathological gambling is not new, although it is still at an early stage of development and largely follows the established treatment of alcohol or chemical dependence disorders. Over the years medications have been used to treat people with gambling problems in a number of contexts. First, more than 50% of pathological gamblers suffer from co-morbid psychiatric conditions such as depressive illnesses, anxiety disorders and alcohol use disorders (Blaszczynski & McConaghy, 1989; Crockford & el-Guebaly, 1998b; Linden et al, 1986), which can be treated. In a sample of 39 treatment-seeking pathological gamblers in Christchurch, the lifetime prevalence of co-morbid psychiatric disorders recorded was more than 80% (Lim & Sellman, 2003). Currently

medications are used to treat these co-morbid conditions. Second, the use of medications has been aimed at improving an individual's dyscontrol, obsessionality and compulsivity associated with gambling. Third and more recently, medications have been used to reduce the craving or urge to gamble.

Medications

There have been a range of clinical trials involving a variety of medications, including mood stabilisers such as Lithium (Moskowitz, 1980) and Carbamazepine (Haller & Hinterhuber, 1994), serotonin re-uptake inhibitors (SRIs) such as Clomipramine (Hollander et al, 1992), selective serotonin re-uptake inhibitors (SSRIs) and the opioid-receptor antagonists.

(A) Mood stabilisers

The reports on the use of Lithium and Carbamazepine (Haller & Hinterhuber, 1994; Hollander et al, 1992), which are both mood stabilisers, have involved relatively small sample sizes of patients with co-morbid cyclical moods. Within this limitation, the results have been equivocal and the underlying mechanisms of the mood stabilisers unclear. It is generally accepted that neither medication has a direct effect on pathological gambling.

(B) Serotonin Re-uptake Inhibitors (SRIs)

The initial trials of Clomipramine showed possible positive effects (Hollander et al, 1992). More recent methodologically controlled research also demonstrated an improvement in the gambling behaviour with the administration of Clomipramine (DeCaria et al, 1996). However, interest in Clomipramine probably waned with the advent of the newer SSRIs.

(C) Selective Serotonin Re-uptake Inhibitors (SSRIs)

The SSRIs form the largest category of psychotropic medications trialled for pathological gambling, and they include Fluvoxamine (Hollander et al, 2000), Fluoxetine (De La Gandara et al, 1999), and Citalopram (Zimmerman et al, 2002). In unpublished research, Paroxetine was trialled in a double-blind, placebo-controlled trial, with improvement in the Clinical Global Index, a measure of clinical response, amongst the gamblers. Pharmacological trials with Fluvoxamine have been reported in small sample-sized, randomized double-blind cross-over design studies involving 15 subjects, and the results suggested possible benefit and good tolerability (Hollander et al, 2000). Overall, the results from SSRI trials

were mixed and limited by small sample sizes and unsatisfactory outcome measurements. It would be fair to conclude that SSRIs had some evidence of success in patients with co-morbid depression and that the clinical improvement observed was due to the improvement of the co-morbid psychiatric conditions. They were effective as an adjunctive treatment to other interventions rather than as 'first line' agents for the treatment of pathological gambling.

The direct action of SSRIs in regulating both dyscontrol and the gambling behaviour remains controversial and insufficiently studied at this stage. Similarly, the use of SSRIs augmented with opioids antagonist (to be described in the next section) to bring about an enhanced pharmacological effect may offer possible positive responses. However, these augmentation strategies have not been systematically studied.

(D) Opioid-Receptor Antagonists

Naltrexone, an opioid-receptor antagonist, is a significant breakthrough in the pharmaco-therapeutic treatment development in alcohol addiction, following two important studies in 1992 by Volpicelli and colleagues (Volpicelli et al, 1992) and O'Malley and colleagues (O'Malley et al, 1992). Subsequent studies confirmed Naltrexone to be both efficacious and safe. The USA Food and Drug Administration moved quickly to approve its use, so Naltrexone became widely used in American clinical practice for the treatment of alcohol dependence, with a standard dose of 50mg per day (Berg et al, 1996). It had been reported to reduce alcohol intake, improve abstinence and reduce the risk of relapse in alcohol-dependent or misusing individuals. Neuro-biologically, Naltrexone is postulated to act by blocking the endogenous opioid system thought to mediate the alcohol-induced 'high' (King et al, 1997), although this has not been definitively established in empirical studies (McCaul et al, 2000).

The use of Naltrexone has been extended to the treatment of other addiction conditions, including pathological gambling. Kim reported three cases of impulse-control disorders (pathological gambling with compulsive shopping and kleptomania) that he managed with Naltrexone (Kim, 1998). He argued that the major problem underlying the impulse control disorder was urge, which was usually the first symptom and the primary driving force behind a motor or behaviour programme designed to relieve the underlying tension and/or to generate pleasure temporarily. Hence Naltrexone might bring about quicker and more complete symptom relief as it reduced urge symptoms. Up to 100mg per day of Naltrexone for

nine months was prescribed for a 55 year-old man with pathological gambling and compulsive shopping behaviours, and he achieved almost full remission of the gambling problem.

In a later study, Kim and colleagues (Kim et al, 2001) conducted a double-blind placebo-controlled trial of Naltrexone in pathological gambling. In this study, the Naltrexone dosages were adjusted upwards from 25mg per day, according to patient acceptability, until up to 250mg per day was achieved, resulting in a mean Naltrexone dose of 188mg and a positive therapeutic effect. Findings of other studies involving the use of Naltrexone at higher doses in other conditions (Knopman & Harman, 1986; Wildt et al, 1993) suggest that the use of doses higher than 50mg should be seriously explored in addiction disorders, and perhaps particularly in behavioural addictions such as pathological gambling.

So far, the results of clinical drug trials with Naltrexone suggest that it is generally a safe drug with a favourable side-effect profile. Only seven subjects treated with Naltrexone in the two original studies (n=167) withdrew because of side-effects (O'Malley et al, 1992; Volpicelli et al, 1992). The most common adverse effects reported with Naltrexone (50mg/day) were nausea and vomiting, with headaches, anxiety, low energy, depression, skin rashes and decreased alertness occurring less commonly and these side-effects typically resolving spontaneously after the first few doses (Berg et al, 1996). In Kim's study, the participants consumed up to 250mg per day of Naltrexone, and elevated liver enzymes occurred in only 8% of patients, who were all taking concurrent analgesic medications (Kim et al, 2001).

The use of Naltrexone has been reported in a patient with co-morbid alcohol dependence and pathological gambling with resultant improvement (Crockford & el-Guebaly, 1998a). This patient had co-morbid depression, treated with Fluoxetine, and in addition received maximal psycho-social support, including an AA (Alcoholics Anonymous) programme and financial reparations. The use of Naltrexone led to a dramatic cessation of cravings, with concurrent significant reduction in his scores on the Obsessive Compulsive Drinking Scale (OCDS) and a version of this scale modified for gambling, which was maintained over four weeks with no evidence of relapse. Placebo effect aside, this suggests a possible role for this drug in the case of pathological gamblers with significant cravings, who benefit from the addition of an opioid antagonist to their treatment regimen.

While the use of Naltrexone to treat problem gambling has received research attention, the trials so far have been mainly small-scale, open-labelled ones. Further larger scale, placebo-controlled studies are warranted to further establish its usefulness. At the National Addiction Centre, Aotearoa New Zealand, one such trial is under way.

In summary, generally, pharmacological agents were used for their neurological mechanisms thought to contribute to the development of pathological gambling. Unfortunately, some of the medication research was unsatisfactorily co-ordinated and fraught with methodological difficulties, including small sample sizes and non-standardised outcome measures.

Issues with pharmacological treatment of problem gambling in New Zealand

Currently the clinical management of problem gambling is almost entirely carried out by counselling agencies in the community, funded largely from the gambling industry. These counselling services usually employ eclectic psychological approaches with links to the Gambling Anonymous and GamAnon networks. Limited residential programme options are available, although some gambling clients are treated under the cover of alcohol and drug dependence problems. Hence their specific therapeutic needs may be overlooked. A small number of therapists in private practice may provide private consultation for people with gambling problems.

There is a gap in overall service provision, since clients who need psychiatric assessment and treatment of their psychiatric co-morbidity may not access the service fast enough. Also, services that provide multi-disciplinary and multi-modality treatment team input similar to those provided by the community alcohol and drug services are almost non-existent for the more severe pathological gamblers. There is a need to strengthen the link, first within the mental health service to provide expertise in the treatment of this addictive disorder, and second between the gambling agencies and the mental health service. A single department overseeing the overall co-ordination and delivery of the treatment services for pathological gambling would be advantageous.

Overall, the current service arrangement limits the use of psychotropic medications for the treatment of pathological gambling and its associated co-morbidities. In addition, Naltrexone remains unfunded by PHARMAC, the agency of the New Zealand government that approves the use of

medicines by the national health system. This means that individuals who may benefit from Naltrexone first will have to obtain assessment by suitably qualified doctors/psychiatrists with expertise and knowledge regarding the pharmacological treatment of pathological gambling, and second will have to privately fund the medication administration. Both of these may be difficult for many pathological gamblers who typically already have financial constraints. The current system could be improved through the development of the workforce at two levels. First, the medical workforce should be up-skilled to assess the need for and to prescribe Naltrexone. Second, a non-medical workforce should be providing specialised psychotherapeutic intervention and case management as part of the ongoing treatment plan. Additionally, appropriate funding should be considered for a subgroup of people who might benefit from anti-craving medication such as Naltrexone.

Conclusion

As research increases understanding of the bio-neuro-chemical mechanisms underlying pathological gambling, the pharmacotherapy of pathological gamblers will gain increasing prominence in future, especially for those who have severe problems and those with psychiatric comorbidities. In line with treatment developments in the field of substance use disorders, it is likely that medications will be employed as an important alternative intervention to help people with pathological gambling behaviour deal with their craving, impulse control and other co-morbid psychiatric conditions. This would be of special relevance for persons at the severe end of the gambling spectrum. While there is a need to increase therapeutic options and treatment settings in the community, there should also be a conscious effort to co-ordinate the treatment services for pathological gambling with the relevant research and mental health services, in order to enhance treatment effectiveness for those seeking help.