Problem gambling is the condition of being unable to resist or control impulses to gamble, which can lead to severe personal or social consequences. Pathological gambling is a clinically significant mental disorder and describes people with problem gambling that meet the respective diagnostic criteria for this disorder. People with pathological gambling disorder will continue their gambling behaviour even in the face of damaging consequences to themselves and their families, such as large gambling losses, committing crimes to get money to gamble, or losing a job, relationship, or educational or career opportunity due to gambling. Pathological gambling usually begins in early adolescence in men and between the ages of 20 and 40 in women, and is highly comorbid with other mental health and substance use disorders. So far, several distinct treatment approaches for pathological gambling disorders have been favourably evaluated, such as cognitive behavioural therapy and brief treatment models as well as pharmacological interventions (Hodgins et al., 2011).

Over the past three decades pathological gambling has received increased attention from clinicians and researchers, as gambling opportunities have expanded around the world. Public exposure to gambling, which may increase the risk of developing pathological gambling, continues to increase in the form of lotteries, casinos, electronic and internet gambling. Pathological gambling is relatively common across the world, with prevalence rates ranging from 0.2% to up to 5% of adults in high risk groups (Hodgins et al., 2011).

In recent years, significant progress has been made in elucidating the neurobiological underpinnings of gambling, the relationship to pathological gambling and addiction with important implications for future pharmacological interventions.

How we are tricked by our brain: The role of expecting wins and losses in the brain of problem gamblers

Having the right expectations is necessary to make advantageous choices in real life. For instance, the expectation that everything will go wrong may lead an individual to not initiating anything and doing nothing. Overestimating chances, on the other hand, may lead an individual to plunge precipitately into actions, with disappointing results. For future events, expectations on the outcomes rule behaviour, and the choices made. Addiction is characterised by making disadvantageous decisions over and over again, so someone with problem gambling will keep gambling, while losing large amounts of money. Therefore, it is an intriguing question whether expectations in the brain of those with addictions are different from persons without addictions.
Neural mechanisms of pathological gambling

Researchers at the Amsterdam Institute for Addiction Research have investigated what happens in the brain of pathological gamblers and in those without addictions using functional magnetic resonance imaging (fMRI) scans (van Holst et al., 2012a). Brain activity was investigated when individuals with gambling problems and persons without gambling problems expected monetary wins or losses during a gambling game. A new finding in people with gambling problems was a higher activation in the reward areas of the brain, when expecting potential wins, in comparison to persons without gambling problems.

This is an intriguing finding, since diminished responsivity to the outcome of wins is generally found in those with gambling problems and in persons with substance dependence. These last findings are usually interpreted as diminished reward sensitivity, which makes people with an addiction prone to search for the high rewards that drugs render. The higher reactivity in the reward areas when expecting potential wins can explain the attraction of gambling, and the exclusive addictive mechanism for problem gamblers: When the brain of problem gamblers was activated more during the expectation phase of gambling (before the outcome of the game), this was associated with a higher level of intense, urgent or abnormal desire (craving) to take up gambling activities. When the brain responds to a higher degree to potential rewards, it may trigger increased propensity to gamble.

These findings provide interesting perspectives for future treatments for pathological gambling that are targeted at its neural mechanisms: When thinking of neuromodulation, the possibility of stimulating the cognitive-control system by implementing high-frequency repeated Transcranial Magnetic Stimulation (high-frequency rTMS), and thus diminishing the responsivity of the reward system, may provide a new way of normalising the abnormal neural mechanisms as present in pathological gambling as an add-on treatment combined with cognitive behavioural therapy. Currently, the possibility of rTMS to change the reward-responsivity in alcohol dependent patients is tested.

Real-time fMRI neurofeedback is another possibility to treat the abnormal reward system in pathological gamblers. Likewise, the development of behavioural and/or pharmacological treatments targeted at changing the reward mechanisms of pathological gambling, are relevant.

Pathological gamblers are characterised by abnormally increased reward expectancy, which may render them overoptimistic with regard to gambling outcomes (van Holst et al., 2012a).

Pharmacological treatment of pathological gambling

As yet, no medication has received regulatory approval in any jurisdiction as a treatment for pathological gambling disorders.

Pharmacological treatments are more effective than no treatment (placebo), yielding an overall effect size of 0.78 according to a meta-analysis of 16 randomised trials including 597 patients (Pallesen et al., 2007). In recent years, significant progress in pharmacotherapy has been generated through neurobiological research and clinical trials, and new medications for pathological gambling have been investigated:

• Opioid receptor antagonists, which are commonly used as anti-craving medication for alcohol and drug addictions, should be considered a first-line medication for pathological gambling, particularly for individuals with family histories of alcoholism and for those with strong urges to gamble. Its effects are due to their ability to modulate dopamine neurotransmission in the reward areas of the brain. Two double-blind, placebo-controlled studies of naltrexone and two double-blind, placebo-controlled trials of nalmefene suggest the efficacy of opioid antagonists in reducing
the intensity of urges to gamble, gambling thoughts and gambling behaviour (Hodgins et al., 2011). In patients who responded to opioid antagonists, particularly among those with a positive family history of alcohol dependence, a significant reduction in gambling urges was demonstrated (Grant et al., 2008).

- **Glutamatergic medications** have shown early promise in the treatment of pathological gambling and await further examination, since improving glutamate neurotransmission in the brain is associated with reducing the reward-seeking behaviour in addictions. N-acetyl cysteine, an amino acid and glutamate-modulating agent, has been studied in the treatment of pathological gambling and showed positive effects on urges and gambling behaviour (Grant et al., 2008).

- **Lithium**, a commonly used mood stabiliser, has demonstrated benefit for pathological gamblers with co-occurring bipolar spectrum disorders.

- **Serotonin reuptake inhibitors (SSRIs)**, the most commonly prescribed antidepressants, may help treat pathological gambling, particularly in individuals with co-occurring anxiety disorders.

Although medications appear beneficial for the treatment of pathological gambling, future research needs to address some unanswered questions. Several different classes of medication have shown efficacy in treating pathological gambling in individual studies, but no comparison studies of medications have been performed in a randomised, placebo-controlled design. Furthermore, there are limited data concerning the effectiveness of pharmacotherapy for gamblers with co-occurring psychiatric conditions.

In addition, no study has examined whether certain individuals with pathological gambling would benefit differentially from specific pharmacotherapies. A predictor analysis performed on 284 gamblers who received an opioid antagonist found that a **positive family history of alcoholism** (p=0.006) predicted robust response to the medication, and that among individuals receiving higher doses of **opiate antagonists**, intensity of gambling urges was associated with a positive response (p=0.036) (Grant et al., 2008). For the future, understanding clinical variables related to treatment outcome should help generate treatment algorithms for pathological gambling.

### Conclusion

Like alcohol or drug addiction, pathological gambling is a chronic mental disorder that tends to get worse without treatment.

Neurobiological study findings show that pathological gambling is more than just an impulse control disorder, since it is characterised by brain activation patterns of reward-seeking addictive behaviours and seems to fit well with recent models of addiction.

Intervention at the earliest signs of pathological gambling is essential to prevent severe personal and social consequences of the illness.

Highly topical findings provide interesting perspectives for future treatments that are targeted at the neural mechanisms of pathological gambling, such as high-frequency repeated Transcranial Magnetic Stimulation (rTMS), real-time functional Magnetic Resonance Imaging (fMRI) neurofeedback, as well as behavioural and/or pharmacological treatments.

Pathological gambling disorders can be successfully treated with medications that decrease the urges to take up gambling. The public health significance of pathological gambling warrants more sophisticated research into its pharmacological treatment.
References


Correspondence:

Professor Jon E. Grant, J.D., M.D.
The University of Chicago
Department of Psychiatry & Behavioral Neuroscience
5841 S. Maryland Ave., MC 3077
Chicago, IL 60637
E-mail: jongrant@uchicago.edu

Dr. Anna E. Goudriaan, Ph.D.
Arkin Mental Health Care
&
Amsterdam Institute for Addiction Research
Department of Psychiatry, Academic Medical Center
University of Amsterdam, The Netherlands
Permanent E-mail: agoudriaan@gmail.com
AMC E-mail: A.E.Goudriaan@amc.uva.nl