

OPIOID RECEPTOR ANTAGONISTS IN THE TREATMENT OF PATHOLOGICAL GAMBLING

To the Editor:

Pathological gambling is a chronic and disabling brain disorder showing neurobiological mechanisms similar to those involved in the drug addiction and classified as an addictive disorder.¹ Numerous pharmacological treatments have been experimented with in order to reduce the recurrent maladaptive gambling behavior, however, to date no drug has been approved for this disorder.² In the last two decades there has been an increased interest in the use of opioid receptor antagonists for the treatment of addictive gambling behavior in pathological gamblers.²

In the first double-blind naltrexone versus placebo study performed by Kim et al., authors showed that after 11 weeks, naltrexone, a mu, delta and kappa-opioid receptor antagonist, was effective in reducing gambling urges, gambling behavior, subjective experience of pleasure and gambling thoughts.³ In 2005, Dannon et al. showed that naltrexone and sustained-release bupropion were both effective in reducing the frequency of gambling behavior and the amount of money spent on gambling.⁴ In 2007, a naturalistic long-term follow-up outcome study performed by Dannon et al. showed that patients who had responded to a 6-month treatment with naltrexone maintained full-response during a 6-month medication-free follow-up phase.⁵

In 2008, a 18 week, double-blind, placebo controlled study performed by Grant et al. displayed that naltrexone was significantly more effective than placebo in reducing gambling urges and gambling behavior.⁶ In 2010, Lahti et al. showed that naltrexone decreased the Pathological Gambling Yale Brown Obsessive Compulsive Scale score, depressive symptoms and increased quality of life in patients involved in their open label study.⁷

In 2012, Bosco et al. demonstrated that naltrexone was effective in reducing gambling behavior in three cases of patient affected by Parkinson's disease and treated with dopamine agonists.⁸ On the other hand, naltrexone was not effective in reducing gambling urges and gambling behavior when used as an as-needed medicine in the double-blind, placebo-controlled trial performed by Kovanen et

al. in 2016.⁹ In 2006 and 2010, two double-blind, placebo-controlled trials evaluated the effect of nalmefene, a mu and delta-opioid receptor antagonist and a partial kappa-opioid receptor agonist, in pathological gamblers.^{10,11} In particular, in the 16-week study performed by Grant et al. in 2006, nalmefene was effective in reducing the severity of pathological gambling already at low dose (25 mg per day).¹⁰

In the second study, nalmefene at 20 or 40 mg per day failed to show statistically significant differences from placebo in reducing the Pathological Gambling Yale Brown Obsessive Compulsive Scale score using an intention to treat analyses.¹¹ However, in a post hoc analyses in which authors only evaluated patients who received a full titration of the nalmefene for at least one week showed that 40 mg per day produced a significant reduction of the Pathological Gambling Yale Brown Obsessive Compulsive Scale score.¹¹ In recent years, the interest in the opioid system as a potential target for medications effective in the treatment of pathological gambling is significantly increased. Preclinical evidences have shown that opioid receptors are widely distributed in the mesolimbic system and that they can modulate the dopamine transmission in brain circuits involved in the regulation of hedonic aspects of reward processing.^{12,13}

In healthy volunteers treated with naltrexone, a fMRI study showed an attenuated reward-related response in the ventral striatum, and an enhanced loss-related activity in the medial prefrontal cortex on a wheel of fortune task.¹⁴ A study of Porchet et al. performed in 2013 in which authors compared a single dose of naltrexone and haloperidol in male gamblers showed that naltrexone group displayed a greater physiological response to wins, and marginally higher confidence ratings on winning streaks when patients completed both a slot machine and a roulette task.¹⁵

These studies confirm that the block at opioid receptors is involved in the modulation of cognition during gambling-like tasks as well as in the modulation of hedonic responses for both money wins and money losses. In conclusion, although not conclusive, preliminary studies have shown that opioid antagonists may be effective in pathological gamblers reducing severity of gambling, gambling urges,

gambling behavior and craving. However, some adverse effects such as: depressive symptoms (controversial) and liver toxicity should be considered before starting the treatment.^{16,17} In this regard, nalmefene may be a first choice in gamblers affected by mood disorders and/or liver diseases. Further studies are needed to confirm the efficacy of these medications in pathological gamblers, however, physicians may select subtypes of gamblers in which opioid receptor antagonists can be effective in the treatment of this severe addiction.

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ERRATUM

It has come to our attention that in the article, Cattaneo S, Ingelmo P, Scudeller L, et al.: Sex differences in the daily rhythmicity of morphine consumption after major abdominal surgery. 2017; 13(2): 85-94, the author Massimo Allegri, MD was incorrectly listed as Allegri Massimo, MD. We regret the error.