Mu-opioid antagonism in the treatment of cannabis use disorder

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A 55-year-old man presented to our outpatient department for severe cannabis use disorder (CUD): he had been using 10 joints of cannabis resin per day for 25 years. He reported a withdrawal syndrome with dysphoria, anxiety and insomnia. He was highly motivated to quit cannabis.

The man’s medical history was remarkable for a recently diagnosed diffuse coronary artery disease not amenable to revascularization and a remitted opioid use disorder (OUD), with buprenorphine treatment discontinued 3 years previously.

We started the patient on weekly motivational enhancement therapy. His withdrawal symptoms decreased gradually with hydroxyzine 25 mg/d. Two months later, the patient had not yet achieved complete abstinence; he was using 5 joints per day. He expressed strong feelings of despair and resignation.

We initiated naltrexone 25 mg/d. The patient reported a quick disappearance of craving, reaching complete abstinence in a few days. However, he reported nausea and a marked apathy that persisted beyond lowering his dosage to 12.5 mg/d. Treatment discontinuation led to cannabis craving rebound (2 joints per day) after 2 weeks. As the available 50 mg naltrexone tablets did not allow for a precise dosage lower than 12.5 mg, we prescribed a pharmaceutical preparation of naltrexone 6 mg. The patient was then able to achieve a rapid, complete and maintained abstinence of cannabis without any substantial adverse effects.

Cannabis is one of the most widely used substances in the world. The lifetime probability of users developing moderate to severe CUD is about 9%.1 Cannabis use and CUD have doubled in prevalence in a decade, and demand for cannabis-related health care services is steadily rising.2 There is no approved pharmacological treatment of CUD.3 Effective therapeutic approaches rely on cognitive behavioural therapy and motivational enhancement therapy.4 Treating CUD is particularly challenging when evolution is chronic and severe, when access to the therapies is limited, when self-motivation is reduced by marked or prolonged cannabis exposure, and when a comorbid psychiatric disorder is untreated.

Naltrexone is an antagonist of mu-opioid receptors. Preclinical studies found bidirectional interaction between endocannabinoids and the endogenous opioid peptides.5 In turn, opioid antagonists can modulate the effects of cannabinoids.6 In humans, this antagonism was observed with administration of a single 12 mg dose of naltrexone in individuals with chronic use of cannabis, but not in nonsmokers.7 However, a single 50 mg dose was reported to increase tetrahydrocannabinol (THC) reinforcing effects in heavy smokers,8 and a single 25 mg dose did not prevent the psychological effects of intravenous THC administration in nonusers.9 Recently, naltrexone maintenance treatment (50 mg/d for 16 d) was reported to decrease cannabis use and its subjective effects in daily smokers.10 Naltrexone is approved for maintenance of alcohol abstinence and relapse prevention after opioid detoxification. In patients with alcohol use disorder (AUD), many studies reported that the efficacy of naltrexone was enhanced in the presence of the following clinical characteristics: a familial history of AUD, antisocial traits, or presence of the sweet-liking phenotype.11,12 Additionally, it can be hypothesized that in individuals with remitted OUD, hypersensitivity to mu-opioid receptors is involved in the dramatic therapeutic effect of low doses of naltrexone on nonopioid substance addiction. Nausea could explain the dramatic improvement only during initiation of naltrexone. However, in our patient’s case, a very low dosage of naltrexone was effective without nausea occurrence.

Attaining complete remission of CUD could be challenging for patients and caregivers. Targeting the mu-opioidergic pathway may help to personalize pharmacotherapy of severe CUD with the right efficacy/safety balance. Finally, many pharmacological treatments are being considered for CUD, with some promising results warranting the need for more work in this area.13,14

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References


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