Title: Mμ-opioid antagonism in the treatment of cannabis use disorder

Authors: **Oussama KEBIR, MD-PhD [1,2], Xavier LAQUEILLE, MD [1], Fayçal MOUAFFAK, MD-PhD [3]**

[1] Service d'Addictologie « Moreau de Tours », Centre hospitalier Sainte Anne, GHU Paris Psychiatrie & Neurosciences, Paris, France.

[2] Laboratoire « physiopathologie des maladies psychiatriques », Institut de Psychiatrie et Neurosciences de Paris, INSERM U1266, Paris, France.

[3] Unité de Psychiatrie de Liaison, d'Urgence et de Recherche, Pôle 93G04, EPS Ville Evrard, Saint Denis, France.

Words count: 602

Tables : 0

Figures : 0

Cannabis is one of the most widely used substances in the world. The lifetime probability of developing moderate to severe cannabis use disorder (CUD) in users is approximately 9% [1]. Cannabis use and CUD had 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 yet rely on cognitive-behavioral and motivational enhancement therapies [4].

We report the case of a 55 years old man, who presented to our out-patient department for a severe CUD (ten 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.

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 three years ago.

We implemented a motivational enhancement therapy weekly. Withdrawal symptoms decreased gradually under hydroxyzine 25 mg per day. Two months later, the patient failed to achieve complete abstinence (to five joints per day). He expressed strong feelings of despair and resignation.

We initiated naltrexone (NTX) at 25 mg per day. The patient reported a quick disappearing of craving, reaching complete abstinence in a few days. However, He complained of nausea and a marked apathy that persisted beyond NTX dosage lowering to 12.5 mg daily. Treatment discontinuation led to cannabis craving rebound (two joints per day), in two weeks. As an available dosage form of NTX (tablets containing 50 mg) did not allow a precise dosage lower than 12.5 mg, we prescribed a pharmaceutical preparation of 6 mg of NTX. A rapid, complete and maintained abstinence of cannabis without any significant side effect was obtained.

CUD is a particularly challenging condition in addictive medicine when: i) evolution is chronic and severe, ii) accessibility to the therapies is limited, iii) self-motivation is reduced by marked or prolonged cannabis exposure, and iv) a comorbid psychiatric disorder is untreated.

NTX is an antagonist of mμ-opioid receptors. Preclinical studies showed bi-directional interaction between endocannabinoids and the endogenous opioid peptides [5]. In turn, opioid antagonists can modulate cannabinoids effects (Justinova ref). In humans, this antagonism is observed under NTX (single dose of 12 mg) administered to individuals with chronic use of cannabis but not in non-smokers [6]. However, a single dose of NTX (50 mg) was reported to increase tetrahydrocannabinol (THC) reinforcing effects in heavy smokers [7] and a single dose of 25 mg did not

prevent the psychological effects of an intravenous THC administration in non-users [8]. Recently, NTX maintenance treatment (50 mg per day for 16 days) was reported to decrease cannabis use and its subjective effects in daily smokers [9].

NTX is approved for alcohol abstinence maintenance and relapse prevention after opioid detoxification. In alcohol use disorder (AUD), many studies underline that NTX efficacy is enhanced in the presence of some clinical characteristics: a familial history of AUD, antisocial traits or sweet liking [10,11]. Additionally, it could be hypothesized that in individuals with remitted OUD, hypersensitivity of mμ receptors is involved in the dramatic therapeutic effect of low doses of NTX on non-opioid substance addiction. Nausea could explain the dramatic improvement only during NTX initiation. However, in our case, a very low dosage of NTX was efficient without nausea occurrence.

Attaining complete remission of CUD could be a difficult challenge for patients and caregivers. Targeting the potentially involved mμ-opioidergic pathway informed by specific clinical variables can help to personalize pharmacotherapy of severe CUD with the right efficacy/safety balance. Finally, it is also important to mention that many pharmacological treatments are being considered for CUD with some promising results warranting the need for more work in this area [12-13].

REFERENCES

1. Lopez-Quintero C, Pérez de los Cobos J, Hasin DS, et al. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend* 2011;115(1-2):120-30.

2. United Nations Office on D, Crime: World Drug Report 2015. Vienna, Austria: United Nations Office on Drugs and Crime (UNODC);2015.

3. Nielsen S, Gowing L, Sabioni P, et al. Pharmacotherapies for cannabis dependence. *Cochrane Database Syst Rev* 2019;1:CD008940.

4. Sabioni P, Le Foll B. Psychosocial and pharmacological interventions for the treatment of cannabis use disorder. *F1000Res* 2018;7:173.

5. Manzanares J, Corchero J, Romero J, et al. Pharmacological and biochemical interactions between opioids and cannabinoids. *Trends Pharmacol Sci* 1999;20(7):287-94.

6. Haney M. Opioid antagonism of cannabinoid effects: differences between marijuana smokers and nonmarijuana smokers. *Neuropsychopharmacology* 2007;32(6):1391-403.

7. Haney M, Bisaga A, Foltin RW. Interaction between naltrexone and oral THC in heavy marijuana smokers. *Psychopharmacology (Berl)* 2003;166(1):77-85.

8. Ranganathan M, Carbuto M, Braley G, et al. Naltrexone does not attenuate the effects of intravenous Δ9-tetrahydrocannabinol in healthy humans. *Int J Neuropsychopharmacol* 2012;15(9):1251-64.

9. Haney M, Ramesh D, Glass A, et al. Naltrexone Maintenance Decreases Cannabis Self-Administration and Subjective Effects in Daily Cannabis Smokers. *Neuropsychopharmacology* 2015;40(11):2489-98.

10. Rohsenow DJ, Miranda R Jr, McGeary JE, et al. Family history and antisocial traits moderate naltrexone's effects on heavy drinking in alcoholics. *Exp Clin Psychopharmacol* 2007;15(3):272-81.

11. Garbutt JC, Kampov-Polevoy AB, Kalka-Juhl LS, et al. Association of the Sweet-Liking Phenotype and Craving for Alcohol With the Response to Naltrexone Treatment in Alcohol

Dependence: A Randomized Clinical Trial. *JAMA Psychiatry* 2016;73(10):1056-63.

Nielsen S, Sabioni P, Gowing L, Le Foll B. Pharmacotherapies for Cannabis Use Disorders: Clinical Challenges and Promising Therapeutic Agents. Handb Exp Pharmacol. 2019 Aug 3. doi: 10.1007/164_2019_258. [Epub ahead of print]

Brezing CA, Levin FR. The Current State of Pharmacological Treatments for Cannabis Use Disorder and Withdrawal. Neuropsychopharmacology. 2018 Jan;43(1):173-194.