

### **Cannabinoids in Opioid Addiction Treatment: Pharmacological Mechanisms**

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#### **Abstract**

Opioid addiction, a chronic relapsing disorder, continues to impose great health and economic burden on our society. America's opioid crisis has become an epidemic due in part to the lack of effective treatments for the negative physical and emotional states suffered by the individuals during withdrawal from chronic opioid use. These symptoms might be major contributing factors to relapse. Recently, cannabis and cannabinoids have emerged as a potential therapeutic strategy in the treatment of opioid addiction. This review differs from many other reports in the field by focusing on the possible mechanisms underlying the effects of cannabinoids on the negative physical and emotional states induced by opioid withdrawal. We start by briefly outlining the current opioid crisis and how both opioids and cannabinoids affect the mammalian central nervous system (CNS). Next, we present findings that illustrate how cannabinoids may be used to enhance opioid analgesia and to mitigate opioid withdrawal syndromes. Finally, we summarize these findings and propose directions for future research.

#### **Keywords**

Cannabis; Cannabinoids; Opioids; Addiction; Mechanisms

#### **Introduction**

Since morphine was first extracted in 1803 [1], opioids have grown to be the standard of care around the world for the

treatment of pain [2]. Although opioid consumption has always posed the risk of addiction, opioid use disorders and opioid overdoses have rapidly increased since the late 1990s [3]. Today, prescription opioid dependency affects over 2.1 million Americans, and over 130 people in the United States die from opioid overdoses every day [4]. In 2017, these trends prompted the Department of Health and Human Services to declare the opioid overdose crisis an epidemic.

As the opioid epidemic continues to reach new heights in North America, the need to find viable alternatives to opioid treatment becomes increasingly urgent. Given its antinociceptive properties and lower potential for overdose, Cannabis has received increasing attention as both a substitute for opioid-based pain treatment and also as a treatment strategy for opioid addiction [6]. Preclinical studies with cannabinoids have mitigated morphine withdrawal symptoms in animals, including jumping, weight loss, head shakes and paw tremors [7-9]. Furthermore, states that had legalized medicinal marijuana saw a 24.8% lower mean annual opioid overdose rate compared to states that had not [10], and the number of opioid abuse and dependence-related hospitalizations decreased by 23% without changes in the number of marijuana-related admissions [11]. These reports suggest that cannabinoids might be used by some opioid addicts to reduce the risk of overdose

The clinical aspects of cannabinoids and opioid interactions have been recently reviewed by Scavone et al. [7]. His narrative review will examine the signaling pathways common to both cannabinoids' effects and several opioid withdrawal symptoms including hyperalgesia, anxiety, and depression. From the perspective of these shared pathways, this review aims to evaluate some of the mechanisms that may contribute to cannabinoids' potential therapeutic effects on opioid addiction and withdrawal.

#### **Opioid signaling**

Although opioids can bind to several types of receptors ( $\kappa$ ,  $\delta$ ,  $\mu$ , nociceptin/orphanin FQ), [12] their analgesic [13] and rewarding [14] effects are primarily mediated by  $\mu$  opioid receptors (MORs), a class of G protein-coupled receptors (GPCR) found in the CNS. MORs is present throughout the mammalian CNS but are concentrated in areas such as the ventral tegmental area (VTA), striatum, locus coeruleus, and spinal dorsal horn [15]. Activation of MORs by opiate ligands in the mesolimbic reward system produces a highly addictive euphoria [14], whereas activation in the brainstem is responsible for respiratory depression associated with opioid overdose.

### **Cannabinoid signaling**

Historically, the use of cannabis dates to before 500 B.C. in central Asia, where *Cannabis sativa*, the plant that produces cannabis, was used in herbal medicine and spiritual practices. Today, marijuana is one of the most abused recreational drugs around the world, with a plurality of Western nations and US states liberalizing or legalizing cannabis use in various forms. The psychoactive ingredients within cannabis bind to endogenous cannabinoid GPCR (CB1 and CB2) receptors. CB1 receptors (CB1R) are the most abundant GPCR in the CNS and are highly expressed in regions involved in reward, addiction, and cognition, including the amygdala, cingulate cortex, prefrontal cortex (PFC), ventral pallidum, caudate putamen, nucleus accumbens, VTA, and lateral hypothalamus. The psychomimetic and rewarding effects of cannabis are generally attributed to the activation of CB1R in these areas. CB1R activation by exogenous compounds, such as  $\Delta^9$ -THC, has been linked to cognitive dysfunction, dysregulated stress responses, psychosis, mania, and amotivated.

### **Conclusion**

Opioid addiction and relapse are complex biological and psychological processes that are partially fueled by the negative physical and emotional states that precipitate upon opiate withdrawal. Accumulating evidence suggests that

cannabinoids have significant effects on a variety of negative physical and emotional states characteristic of opioid withdrawal through their shared use of various mechanisms. However, despite advancements in the understanding of cannabinoid pharmacology, the role of cannabinoids in mitigating symptoms of opioid withdrawal remains elusive. Because the current topography of the debate predominantly centers on  $\Delta^9$ -THC, WIN55, 212-2, endocannabinoids, CBD, morphine, and heroin, there is a paucity of studies on the other 50+ cannabinoids found in the marijuana plant.

### **References**

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