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Review Article

Potential Cannabis Antagonists for Marijuana Intoxication

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Abstract

Cannabis use is on the rise leading to the need to address the medical, psychosocial, and economic effects of cannabis intoxication. While effective agents have not yet been implemented for the treatment of acute marijuana intoxication, a number of compounds continue to hold promise for treatment of cannabinoid intoxication. Potential therapeutic agents are reviewed with advantages and side effects. Three agents appear to merit further inquiry; most notably Cannabidiol with some evidence of antipsychotic activity and in addition Virodhamine and Tetrahydrocannabivarin with a similar mixed receptor profile. Given the results of this research, continued development of agents acting on cannabinoid receptors with and without peripheral selectivity may lead to an effective treatment for acute cannabinoid intoxication. Much work still remains to develop strategies that will interrupt and reverse the effects of acute marijuana intoxication.

ABBREVIATIONS

CBD: Cannabidiol; CBG: Cannabigerol; THCV: Tetrahydrocannabivarin; THC: Tetrahydrocannabinol

INTRODUCTION

According to the World Health Organization (WHO), 147 million people, or 2.5% of the world population, consume cannabis (marijuana) compared with 0.2% consuming opiates, making it the world's most widely cultivated, trafficked, and abused illicit substance [1]. Marijuana consumption in the United States has significantly increased within the past few decades to over 22 million frequent users, as cannabis is now legal in 9 states recreationally and 31 states for medical purposes [2].

The symptoms of acute cannabis (marijuana) intoxication vary according to age. In adolescents and adults, physiological symptoms include dry mouth, increased appetite, tachycardia, increased blood pressure, conjunctival injection, ataxia, slurred speech [3,4]. Neuropsychiatric symptoms include changes in mood, perception, thought content, cognition, and psychomotor performance [3-5]. For example, ingestion leads to feeling "high"- pleasurable feeling and a decrease in anxiety, alertness, depression, and tension. However, first-time marijuana users may experience anxiety, dysphoria, and panic. Sensation that colors are brighter, and music is more vivid, and time is faster than clock time [4]. Grandiosity and mystical thinking, increased self-consciousness, and paranoia may also occur [6]. Marijuana use also impairs attention, concentration, and short-term memory and interferes with the ability to operate heavy machinery and motor vehicles [7].

Therapeutic uses of cannabis include chronic pain, loss of appetite, spasticity, and chemotherapy-associated nausea and vomiting [8]. Recreational cannabis use is on the rise with more states approving its use and it is viewed as no different from recreational use of alcohol or tobacco [9]. Risky cannabis use is suspected when quantity, frequency, and/or duration of use are increased and detrimental effects on health start to appear with cannabis use disorder usually manifesting with additional interference with social and occupational functioning [10].

With such an ease and abundance to exposure, more research studies are revealing marijuana's effect on public health [11-14]. For instance, from 2005 to 2015 in Colorado, marijuana-related visits to the emergency department (ED) increased almost threefold from 2009 to 2015 [15]. Moreover, an association between psychiatric admissions and marijuana usage was found [16]. The medical risks of acute marijuana intoxication are mainly cardiovascular in nature. Tetrahydrocannabinol (THC) is the main psychoactive chemical in marijuana of which concentrations vary. In recent years, the concentration of THC has gone up significantly, creating more serious reactions [17]. THC increases the sympathetic tone, thereby increasing blood pressure and heart rate [18]. Marijuana also increases the risk of myocardial infarction [19,20] and acute cardiovascular fatalities [21]. Complications associated with inhalation include acute asthmatic exacerbations [22] and pneumothorax [23]. Patients with psychiatric disorders (e.g. schizophrenia and bipolar disorder) are at high risk for developing psychosis [24,25]. Approximately half of patients with cannabis-induced psychosis will later be diagnosed with a primary psychotic disorder [26,27]. Synthetic cannabis products with higher receptor affinity and

THC concentrations affect receptors in a much more dramatic, negative, and enduring way with higher risk of serious illness or death. Numerous case studies have reported deaths related to synthetic cannabis intoxication. Compared to only one compound reported in 2008, 169 different synthetic cannabinoids were reported to the European Monitoring Centre for Drugs and Drug Addiction as of December 2016 [28].

Therefore, the common economic and medical complications of cannabis intoxication are increasing the need for pharmacological interventions that reverse marijuana effects in a timely manner and prompting the search for some safe form of antagonist or symptom-reducer.

POTENTIAL CANNABIS ANTAGONISTS

There are two well characterized cannabinoid receptors CB1 and CB2. CB1 receptors are concentrated in the central nervous system, and are also found in the peripheral nerves, uterus, testis, and bones. CB2 receptors are mostly found in the periphery, often associated with immune cells, and are detected in the CNS in conditions of inflammation [29]. Since, cannabis antagonists have weight loss as a frequent side effect, many of them have been developed for obesity or metabolic syndrome as a main indication. The CB1 receptors stimulate appetite, and blocking these receptors leads to a decreased appetite [30]. Driven largely by the search for an effective treatment for metabolic syndrome, most cannabinoid research has focused on decreased consumption and satiety research. However, these same compounds are of interest in the search for treatment for acute cannabinoid intoxication. A number of compounds have been identified and their effects characterized as depicted in Table 1.

CANNABIS ANTAGONISTS DERIVED FROM HUMAN STUDIES

Beta-caryophyllene (in Black pepper or Peppercorns)

A natural terpene isolated from the essential oil of many spices and herbs like black pepper, cinnamon, basil, rosemary, and cloves, Beta (β)-caryophyllene is also found in cannabis and binds to the same receptors targeted by THC [31,32]. β-caryophyllene selectively binds to the CB2 receptor and acts as a CB2 agonist. At 5 mg/kg the compound strongly reduces the carrageen an-induced inflammatory response in wild-type mice. Binding to the CB2 receptor activates the mitogen-activated kinases Erk1/2 and p38 in primary human monocytes and, at the same time, inhibits lipopolysaccharide (LPS)-stimulated TNF-α and IL1β protein expression. This leads to an anti-inflammatory effect; however, the underlying molecular mechanism remains unknown [32]. Activation of CB2 receptors is typically devoid of psychoactive side effects associated with CB1 receptor activation. Caryophyllene has potential to modulate inflammatory cytokines and other pathophysiological processes via the endocannabinoid system. Therefore, the pharmacokinetics of β-caryophyllene in humans and its potential impact on cannabis intoxication should be addressed in future studies.

Cannabidiol (CBD)

CBD is a cannabinoid found in cannabis and acts as an antagonist and modulator of THC at the CB1 and CB2 receptors [33] with potential to reduce the effects of marijuana intoxication. In healthy volunteers, at dose of 1 mg/kg CBD acts as an anxiolytic and reduces psychotic symptoms induced by THC [33]. A study conducted by Bosi et al., 2003 showed that CBD inhibits THC-induced psychotic episodes as well as the psychotic symptoms induced by subanesthetic doses of ketamine. Side effects of BD include decreased appetite, sleepiness, weakness, and diarrhea [34]. The use of CBD in the clinical practice is still in the experimental phase and requires further investigation.

Rimonabant

Rimonabant, or SR-141716, blocks dopamine release and "rewarding" sensation of THC. The drug also decreases narcotic-seeking behavior, lending possibility to treatment of dependence [35]. Research studies on humans showed its effectiveness in reversing the effects of cannabis-induced tachycardia [36]. Rimonabant is a CB1 receptor antagonist given two hours before the use of marijuana and exerted effect at different doses (40mg and 90mg). The drug has not been shown to have a rapid onset, but its long-term effects on treating drug dependence have proven effective thus far [37]. It has been removed in the EU and rejected by the FDA due to alarming mood changes including suicidal ideation [38].

Surinabant

Surinabant or SR-147778, has been found to reverse effects of cannabis by blocking CB1 receptors in humans [39]. Depending on route of administration the chemical was found to reverse different cannabis effects. Oral doses of 20-60mg of surinabant displaced cannabinoid elements from binding to the receptors, but when given by injection, the compound was seen to reverse effects such as hypothermia [40]. The most common side effects are headache, nausea, insomnia, anxiety, nasopharyngitis, and diarrhea. Surinabant was discontinued by the manufacturer due to severe psychiatric side effects such as depression, anxiety, and suicidal ideation seen with similar acting agent rimonabant [41].

Taranabant

Taranabant is a CB1 inverse agonist and was investigated as an obesity treatment [42]. Double-blind randomized placebo-controlled study of taranabant showed significant weight loss compared to placebo with a small portion of dose-dependent adverse effects such as hyperhidrosis, pruritus, flushing anxiety, and depression headache and nausea [43]. Gastrointestinal and psychiatric symptoms were observed when doses are increased beyond 10mg and included high frequency of insomnia, drowsiness, dizziness, mood changes, nervousness and anxiety [44]. Phase III trials were discontinued in 2008 as a result.

Rosonabant

Rosonabant is a CB1 receptor antagonist and inverse agonist that was originally indicated for treatment of obesity [45]. It was discontinued after the severe side effect of rimonabant, a similarly acting compound, became apparent.

Drinabant

Drinabant is a selective CB1 receptor antagonist investigated for its appetite suppression effects [46]. Further human studies were cancelled due to notable side effects in human subjects of anxiety, depression, suicidal ideation associated with the similar acting drug rimonabant [41].

Table 1: Potential Cannabis Antagonists.

COMPOUND	RECEPTOR	MECHANISM	Main Effects
AM-251	CB1	Antagonist	Animal studies showed reversal of cannabis effects
AM-6545	CB1	Antagonist	Treatment of obesity
Beta Caryophyllene	CB2	Agonist	Anti-Inflammatory
Brizantine Ab	CB1	Antibody Binding Antagonism	Nicotine dependence, anxiolytic, antidepressant
Cannabidiol (CBD)	CB1/CB2	Antagonist and Inverse Agonist	Anxiolytic, antipsychotic
Cannabigerol (CBG)	CB1/CB2	Antagonist	Reducing inflammation in inflammatory colitis
Dietressa Ab	CB1	Antibody Binding Antagonism	Least weight gain
Drinabant	CB1	Antagonist	Anxiety, depression, suicidal ideation
Falcarinol	CB1	Inverse Agonist	Pro inflammatory
Hemopressin	CB1	Inverse Agonist	Decreased food intake
Ibipinabant	CB1	Selective Inverse Antagonist	Decreased Feeding, myotoxicity
LY-320-135	CB1	Antagonist / Inverse Agonist	No animal studies
MK-9470	CB1	Inverse Agonist	PET CB1 Tracer
NESS-0327	CB1	Selective Inverse Antagonist	Weight loss, no associated anxiety
O-2050	CB1	Antagonist	Decreased food consumption, water intake, locomotor activity, preference for high fat diets
Otenabant	CB1	Antagonist	Weight loss, insomnia, irritability, dizziness, headache, nasopharyngitis and pruritus
PF-514273	CB1	Antagonist	Weight loss, alcohol use disorder, discontinued
PIPISB	CB1	Inverse Agonist	No animal studies
Pregnenolone	CB1	Antagonist	Reduced hyperlocomotion in THC exposed rodents
Rimonabant	CB1	Antagonist	Worsening mood and suicidal ideation
Rosonabant	CB1	Antagonist / Inverse Agonist	Discontinued
Surinabant	CB1	Antagonist	Depression, anxiety, suicidal ideation
Taranabant	CB1	Inverse Agonist	Insomnia, drowsiness, dizziness, mood changes, nervousness, anxiety
Tetrahydrocannabivarin (THCV)	CB1/CB2	Neutral CB1 antagonist / CB2 partial agonist	Appetite Suppressant, Enhanced reward pathway
TM-38837	CB1	Inverse Agonist Antagonist	Clinical Trials only
VCHSR	CB1	Antagonist	No animal studies
Virodhamine	CB1/CB2	Partial agonist CB1 receptor / Full CB2 agonist	Relaxes pulmonary artery, promise for intoxication (endogenous)

TM-38837

TM-38837is an inverse agonist/antagonist of the CB1 receptor developed for treatment of obesity and metabolic disorder. It was designed to avoid CNS penetration in order to circumvent the side effects seen with centrally acting rimonabant [47]. TM-38837 is a promising anti-obesity compound that is theorized to have similar efficacy to rimonabant without the notable central side effects. The drug is currently undergoing clinical trials.

CANNABIS ANTAGONISTS DERIVED FROM PRECLINICAL STUDIES

The following compounds were only tested in preclinical studies with no human studies to date. Although they have theoretical potential, their application in reversing cannabis intoxication has not been yet tested.

AM-251

The AM-251 compound is a CB1 receptor antagonist structurally similar to Rimonabant, with confirmed their affinity to CB1 receptor in the brain [48]. A recent study on mice, CNS-related cannabis effects including sedation were reversed by AM-251 [49].

AM-6545

AM-6545 is a peripheral selective silent CB1 receptor antagonist with a 300-fold selectivity over CB2 receptors developed for treatment of obesity and as an alternative to rimonabant [50,51]. Some advantages of AM-6545 over rimonabant is a lack of notable neuropsychiatric side effects as well as nausea due to the compound's low CNS penetration [50].

Cannabigerol (CBG)

Cannabigerol (CBG) is a naturally occurring compound in cannabis [52] and acts as a CB1 and CB2 antagonist [53-55]. In a meta-analysis that encompassed 51 pre-clinical studies found that CBG had the largest effect size in reducing inflammation in inflammatory colitis [56]. Brierley et al., found that CBG lacked

the typical side effects of sedation, impaired balance, analgesia and hypomotility associated with other CB1 antagonists [57].

Falcarinol

Falcarinol is a natural compound occurring in a variety of plants including carrots, parsley, celery and ginseng [58,59]. It was shown to have CB1 receptor inverse agonist effects similar to rimonabant [59]. The most notable side effects on human tissue is its inducement of pro-allergic chemokines including IL-8 and histamine induced edema reactions in the skin [59].

Hemopressin

Hemopressin is an alpha hemoglobin fragment and acts as a CB1 receptor inverse agonist that inhibits appetite and induces anti-nociception [60,61]. Animal studies showed that it significantly reduced food intake without the typical side effects of hypothermia, catalepsy and hypoactivity normally associated with centrally acting CB1 receptor ligands [62,63].

Ibipinabant

Ibipinabant is a potent and highly selective CB1 antagonist [64] that was found to significantly decrease feeding in animal models [65]. One study noted a significant side effect of myotoxicity in beagle dogs [66]. It is currently not used outside laboratory research.

NESS-0327

NESS-0327 is a synthesized potent CB1 selective antagonist with selectivity of more than 60,000x for CB1 versus CB2 [67]. Unlike Rimonabant, NESS-0327 does not suppress constitutive CB1R activity in the ventral tegmental area and lacks the negative mood effects of Rimonabant as a result [68]. In a comparison trial where NESS-0327 was compared to Rimonabant in rats, the two compounds were equally effective at inducing weight loss with no side effects of anxiety with NESS-0327 [68].

O-2050

O-2050 is an antagonist of the CB1 receptor and does not exhibit inverse agonism at higher doses like other cannabinoid antagonists [69]. Animal model studies showed that O-2050 decreased food consumption, water intake and locomotor activity [70], and decreased preference for high fat diets [71].

Otenabant

Otenabant is a potent selective CB1 receptor antagonist developed to treat obesity [72,73]. During phase III clinical trials 10mg and 20mg doses of otenabant resulted in superior weight loss over placebo at 12-months [74]. Side effects observed in phase III of otenabant trial included insomnia, irritability, dizziness, headache, nasopharyngitis and pruritus and trials for this drug have been suspended due to adverse psychiatric effects similar to Rimonabant [75].

PF-514273

PF-514273 is a CB1 receptor antagonist that is extremely selective with a 10,000-fold selectivity of CB1 over CB2 receptor [76]. It was originally designed as a treatment for obesity and had shown promise in alcohol use disorders but was discontinued in phase I trials for unknown reasons [77].

Pregnenolone

Pregnenolone is a potent endogenous signal-specific inhibitor of CB1 receptor and blocks THC-induced activation of extracellular-regulated kinases and reduction of mitochondrial activity [78,79]. Pregnenolone blocks acute "positive" psychotic-like effects of cannabinoids in rodents. A recent study cautioned that increased pregnenolone in the brain may induce a hypodopaminergic state, and lead to worsening substance addictions [80].

Tetrahydrocannabivarin (THCV)

THCV is a homologue of THC differing only by a propyl side chain. It acts as a neutral CB1 receptor antagonist and CB2 partial agonist [81]. THCV has also been studied as an alternative appetite suppressant to rimonabant. Unlike rimonabant, THCV did not reduce the reward pathway in the CNS, the likely source of depression induced by rimonabant. THCV actually enhanced the reward pathway, which could possibly help reduce food intake and derive greater satisfaction from smaller amounts of food [82].

Virodhamine

Virodhamine is an endocannabinoid formed from arachidonic acid and ethanolamine joined by an ester and acts as a partial agonist of the CB1 receptor and full agonist of the CB2 receptor [83]. It was found to relax pulmonary arterial vasculature in addition to possible appetite suppressant qualities and demonstrates potential in reversing cannabinoid intoxication [84].

CANNABINOID RECEPTOR ANTIBODIES

Brizantine

Brizantine is a CB1 receptor antibody developed and used in Russia where it is indicated for use in nicotine dependence [85]. Brizantine shows strong evidence of efficacy in animal models for nicotine dependence, anxiety and depression. The anxiolytic and antidepressant effects of Brizantine were tested in rodents during a 2015 study showing signs of improvement [86].

Dietressa

Dietressa is drug containing ultra-low doses of antibodies designed in Russia that targets the CB1 receptor [85,87]. Dietressa caused the least amount of weight gain in mice being fed a standard high fat ration [88]. Discontinuation of the drug did not cause withdrawal symptoms [87].

CANNABIS ANTAGONISTS WITH NO PRECLINICAL OR CLINICAL STUDIES

LY-320,135 is a selective antagonist of CB1 receptors with a binding affinity of 70-fold for CB1 over CB2 receptors [89]. At high doses it can act as a CB1 inverse agonist [90]. No preclinical animal or clinical human studies were conducted yet for this compound.

MK-9470 is a synthetic cannabinoid that acts as a high affinity inverse agonist on the CB1R receptor [91]. This compound was developed as a CB1R PET radiotracer and is frequently used in mapping CB1 receptor distributions [91].

PIPlSB is a synthetically created highly selective inverse agonist of CB1 that crosses the blood brain barrier and has the ability to be radiolabeled and is used in research for mapping CB1 receptor distribution [92,93]. This compound has not been indicated or studied for any therapeutic purpose in the literature.

VCHSR is a selective antagonist of the CB1 receptor and a modified form of rimonabant with the hydrogen bonding of the C3 substituent region removed, thus preventing the inverse agonist effect at high doses [94,95]. It acts as a neutral antagonist by occupying the receptor while not exhibiting any physiologic action [94,95]. This compound is only used for research purposes and had not been indicated for clinical use.

DISCUSSION

Marijuana cultivation and consumption is expanding, and marijuana restrictions are easing in the United States and other Western countries [96]. With increased legalization and use across demographic lines [97], clinical presentations of acute marijuana intoxication are on the rise [98]. Unintentional pediatric intoxication has increased with legalization [98]. The risks of acute marijuana intoxication are primarily related to cardiac and psychiatric effects on homeostasis. Synthetic cannabinoids, with a higher concentration of THC and higher affinity for cannabinoid receptors, could cause more severe acute intoxication with an increased duration of effects. Marijuana intoxication is related to CB1 agonism which include sedation, increased appetite, tachycardia, conjunctival injection, memory impairment, decreased goal directed activity, feelings of euphoria and paranoia. CB1 antagonism includes effects that are typically opposite of those produced by the drug, such as insomnia, anxiety, anorexia, irritability, depression, and tremor. A safe and effective cannabinoid antagonist may be the treatment of choice for acute intoxication. Cannabinoid antagonists may be divided into categories based on receptor selection, binding affinity, peripherally selective versus non-selective, endogenous, antibodies, and fragments.

The first generation of medications were CB1 antagonists and inverse agonists without peripheral selectivity and were developed for the treatment of metabolic syndrome includes Rimonabant, Surinabant, Taranabant, Rosonabant, and Drinabant. Most exert their effects through full antagonism, except Taranabant and Rosonabant, which act as inverse agonists. Unfortunately, due to CNS side effects of depression, anxiety, and suicidal ideation, most clinical trials of these drugs have been discontinued despite evidence that some show promise for weight loss. Few would argue that the most serious side effect to emerge with non-selective CB1 receptor antagonists is suicidal ideation linked to anxiety and depression. Given that marijuana intoxication has long been linked to feelings of euphoria and apathy, antagonists yielding the opposite effects should not come as too great a surprise. One recent study notes a decline in the suicide rate in men aged 20-39 coincided with the legalization of recreational marijuana in Colorado [99].

The second generation of medications are under development and they are Peripherally Selective (PS) CB1 antagonists and inverse agonists. These medications are similar to the first round of CB1 antagonists, which did show promise for weight loss, but produced the alarming psychiatric symptoms described above. The PS lines of CB1 antagonists are bound to a molecule that is unlikely to cross the blood brain barrier and cause undesirable side effects. While this may be advantageous for the search for a weight loss medication, the peripherally selective medications may not address the problematic psychiatric side effects of cannabinoid intoxication. The medications to watch are TM-38837, AM-251, and AM-6545. Leading the pipeline to market in this group, TM-38837 is currently in clinical trials [47].

Public awareness and education regarding the harmful effects of cannabis have been, in many respects, eclipsed by the potential benefits of medical uses of marijuana and CBD. The latter, legitimate benefits may include alleviation of chronic pain, antiemetic properties and anticonvulsant activity. Furthermore, CBD was shown to alleviate psychotic symptoms in a placebo-controlled study of schizophrenic patients [100]. These potential medical benefits of marijuana have increased the stature of this substance and have contributed to increased legalization and social acceptance of recreational marijuana, even more apparent in the growing number of states choosing to make it legal. These factors may be expected to cause an exponential rise in the numbers of patients requiring medical attention for cannabis intoxication and dependence, and the anticipated medical demands stemming from cannabis use are expected to draw the attention of the pharmaceutical industry and medical researchers. The occurrence of cases of childhood cannabis intoxication in Colorado, for example, following legalization of this substance, has spurred a flurry of early studies in the search for an effective and safe cannabis antagonist.

The staggering rise in marijuana usage around the world provides the medical community with a meaningful reason to pursue further exploration and research on this development. As cannabis has become the world's mostly widely abused substance, it becomes of paramount importance to investigate how this drug may affect the health and well-being of the population at large. A dramatic increase in emergency room visits related to cannabis intoxication and concerns regarding the economic impact of cannabis use heighten the urgency of expediting the search for medical protocols addressing the adverse sequelae of marijuana intoxication. As marijuana is often described and even marketed as a harmless and natural substance, many do not consider the various dangers and risks associated with cannabis consumption. Recent advances in research have shed light on the correlation between mental illness, psychiatric symptoms, medical complications, reduced productivity and marijuana usage. It is important to highlight that an alarming increase in the concentration of THC in marijuana has been detected, adding to the concerns of this potent agent.

With research in this arena in its infancy, certain potential treatments offer theoretical benefits but unacceptable side effects. For example, Rimonabant, a CB1 receptor antagonist, offers the promise of blocking dopamine release and rewarding sensations of THC. However, clinical studies of this agent and other agents with a similar mechanism of action, such as Surinabant, Drinabant, Otenabant, and Rosonabant, were suspended or discontinued because of untoward psychiatric side effects. Researchers have focused their search for therapeutic targets

upon naturally occurring substances, such as black pepper, which contains beta (β)-caryophyllene (a CB2 agonist), Cannabigerol (a CB1 and CB2 antagonist), and Falcarinol (with effects similar to Rimonabant). Pregnenolone, a steroid hormone precursor, and Cannabidiol (CBD), a component of cannabis, may offer promise in addressing psychotic symptoms of cannabis intoxication, but further study is required. Two substances with vasoactive properties, Hemopressin (a CB1 receptor inverse agonist which may lower blood pressure) and Virodhamine (a CB1 receptor antagonist and CB2 receptor agonist, which relaxes pulmonary arterial vessels) may also be worthy of further investigation. In addition to a variety of other agents, including those with CB1 antagonist activity, CB1 receptor antibodies may also offer a novel therapeutic strategy for the management of cannabis intoxication and dependence. As research in this area progresses, agents with agonist or antagonist activity or other receptor sites, immunologic strategies targeting CNS receptors, and other potential strategies will require intensive research activity so that clinically effective treatments can be made available in the near-term foreseeable future. Three treatments appear to merit further inquiry; most notably CBD with some evidence of antipsychotic activity and in addition Virodhamine and THVC with a similar mixed receptor profile. Given the results of this research, continued development of agents acting on cannabinoid receptors with and without peripheral selectivity may lead to an effective treatment for acute cannabinoid intoxication.

CONCLUSION

With cannabis use on the rise, one may expect increased demands upon the medical community to address the medical, psychosocial, and economic effects of cannabis intoxication. With worldwide cannabis use more than tenfold greater than opiate use, a major public healthcare crisis has emerged and will likely worsen if appropriate measures are not taken. Although certain preliminary therapeutic agents are presently being scrutinized, much work remains to develop strategies that will interrupt and reverse the effects of acute cannabis intoxication. While effective agents have not yet been implemented for the treatment of acute cannabinoid intoxication, a number of compounds continue to hold promise for treatment of cannabinoid intoxication. The outcome of drug development in this arena is still evolving and public education will be of the utmost importance in order to reduce the adverse impact of this rapidly evolving healthcare challenge.

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