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Research Article

INVESTIGATION OF THE NEGATIVE EFFECTS OF THE SYNTHETIC CANNABINOID JWH-018: A LITERATURE REVIEW

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A B S T R A C T

Despite legal regulations restricting their use, synthetic cannabinoids (SCs) (e.g., JWH-018, K2)can be easily found on the Internet. Today, less than one percent of the general community uses SCs, which is rather a low rate. However, this rate is higher among students and some niche groups subject to drug testing. A meta-analysis of 323 records from the database search has shown that using JWH-018 may lead to more negative and severer effects than using cannabis.

To these records, we added 41 studies obtained as a result of manually looking through references. After eliminating duplicates and screening titles, we took into consideration a total of 136 full texts. Then, we excluded 30 studies. Eventually, the study included a total of 106 papers, letters, and conference abstracts, which represented data for more than 4,000 cases and at least 26 deaths. Cardiovascular events (ischemic stroke, emboli, and myocardial infarction), acute renal damage, generalized tonic-clonic seizures, psychiatric presentations (including first episode psychosis, paranoia, suicidal ideation, and hyperemesis) are among the significant consequences. On the other hand, the majority of the cases were not severe: young male individuals with tachyarrhythmia (≈ 37-77%), agitation (≈ 16-41%), and nausea (≈ 13-94%), who received only supportive therapy during less than eight-hour hospital stay.

Tachyarrhythmia, restlessness, and uneasiness of the stomach are the most prevalent effects, which are usually treated with supportive care, including the use of antiemetics, benzodiazepines, and intravenous fluids; so they do not often require overnight hospitalization. Severerproblems such as death, seizure, stroke, rhabdomyolysis, myocardialinfarction, hyperemesis, psychosis, or acute kidney injury are less prevalent.

INTRODUCTION

JWH-018 was among the first compounds discovered to be a psychoactive component in SC medicines. The largest SC groups are the JWH series, which was created by JW Huffman. When compared to THC, JWH-018 has 4 times the affinity for CB1 receptors and 10 times the affinity for CB2 receptors (Pertwee, 2008). The effects of JWH-018 last less for about 1-2 hours (Winstock & Barrat, 2013) and peak sooner. Mental disorders such as schizophrenia, psychotic–states, and affective disorders are some of the most well-known psychological side effects (Hall *et al*., 2009).

Pharmacodynamics

Compared to the binding affinities of THC at the CB1 and the CB2 receptor (Compton *et al*., 1999); JWH-018 has a relatively high binding affinity (expressed as IC50 (occupation of 50% of the receptors) towards CB1 (cannabinoid receptor type 1) and CB2 (cannabinoid receptor type 2) (Aung *et al*., 2000). Common effects of CB1 agonists (e.g., dry mouth, immune suppression, sedation, tachyarrhythmia, ataxia, cognitive dysfunction, postural hypotension, and psychotropic effects) are also seen in JWH-018 (Auwarter *et al*., 2009). The occurrence of potential pharmacologically active JWH-018 metabolites is the noticeable difference with THC. While several JWH-018 metabolites maintain high CB1 receptor binding affinity towards cannabinoid receptors (11-OH-THC: Ki at the CB1 receptor) (Brents *et al*., 2012), only one of the major THC-metabolites is known to be psychoactive and to maintain binding affinity (Compton *et al*., 1993). The glucuronidated JWH-018 N-(5- OH-pentyl) metabolite, as a neutral antagonist, maintains binding affinity towards the CB1 receptor and activity. Currently, we have no data regarding whether this metabolite of JWH-018 is able toact as an antagonist of the pharmacological results of JWH-018 *in vivo.* Moreover, there is no information on whether enough

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concentrations appear at the site of action. Metabolites of JWH-018, like the retention of CB1 receptor affinity, also bind with a high level of affinity at the CB2 receptor. JWH-018 absorption may modify immunological function, which could result in immune suppression because CB2 receptors are mainly expressed in multiple immune cell types. Nakajima *et al*. (2013) studied the effect of JWH-018 on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation and carcinogenesis in mice. The authors reported a higher anti-inflammatory activity of JWH-018 than indomethacin (Nakajima *et al*., 2013). Besides, in the skin carcinogenesis model, JWH-018 suppressed tumor promotion by TPA. Atwood *et al*., in their study on neuropharmacology and effects on the central nervous system, examined the impact of JWH-018 on glutamatergic neurotransmission in cultured autaptic hippocampal neurons and the activation of ERK1/2 mitogen-activated protein kinase (MAPK), as well as the internalization of CB1 receptors (Atwood *et al*., 2010). In a concentration and CB1 receptor-dependent manner (IC50: 14.9 nM), excitatory postsynaptic currents were suppressed by JWH-018, which also led to an increase in MAPK phosphorylation and brought on rapid and robust internalization of the receptor. Hence, the usual effects after JWH-018 uptake are highly probable because of CB1 receptor activation.

Rominger *et al*. (2013) published a case report describing the short-term changes in the availability of dopamine D2/3 receptors in a patient before and after acute detoxification from a 'herbal mixture.' The authors stated that severe health problems, where significant changes in the dopaminergic system have to be considered, may arise from using synthetic cannabinoids (Rominger *et al*., 2013).

Sadly, the herbal mixture taken in this case was not examined, therefore no conclusions about which synthetic cannabinoid was used can be reached. The effects on the cardiovascular, respiratory, gastrointestinal, liver, kidneys, and genitourinary systems have not been studied. Yet, one of the most common clinical symptoms of synthetic cannabis intoxication is a considerable rise in heart rate.

Behavioral studies in animals

Poklis *et al*. (2012) utilized a tetrad test to investigate the behavioral effects of inhaling smoke from 200 mg of a herbal combination comprising 3.6 percent JWH-018, 5.7 percent JWH-073, and less than 0.1 percent JWH-398 in mice (response in all four groups indicate CB1 activity).The drop in the body temperature of the mice was more pronounced after inhaling 200 mg marijuana (3.5 % THC) than after smoking it. For more than 20 minutes, the animals remained in a cataleptic state. In a similar study, tetrad testing was performed on mice that were subjected to the smoke from 10, 20, or 50 mg of a 5.4% JWH-018 containing an herbal mixture (Wiebelhaus *et al*., 2012). Hypomotility, antinociception, catalepsy, and hypothermia were noted in the mice. Rimonabant (CB1 receptor antagonist) inhibited the behavioral effects, which supports the idea that CB1 receptor activation mediates the effects. Furthermore, ptosis and hyper reflexive responses were also observed in the mice. It was found that 50 mg of the herbal mixture and 200 mg of marijuana (14.8 mg THC) led to similar outcomes. Both of the studies identified JWH018 in the brain tissue of the mice.

The injection of JWH-018 led to hypomotility, antinociception, catalepsy, and hypothermiain mice in the study by Wiley *et al*. (1998).Drug discrimination research carried out in THC-trained rats concluded that JWH-018 was eight times more powerful than THC. Jarbe *et al*. (2011) found that the existence of rimonabant caused a 4.4- fold parallel shift to the right of the JWH-018 dose-response curve, which indicates antagonism and mediation through CB1 receptors. THC-trained rhesus macaques were also used in drug discrimination research (Ginsburg *et al*., 2012). JWH-018, which was 3.4-fold powerful than THC, increased the response on the THC-lever in a dose-dependent manner in the tested macaques. Yet, the duration of action of THC was substantially longer than that of JWH-018 (4 h vs. 2 h). Ginsburg *et al*. also used rimonabant-trained rhesus macaques in their drug discrimination research. They found that the response rate was reduced by JWH-018 in a dose-dependent manner. Their finding suggests the mediation of the THC-like effects through CB1 receptors. Indeed, this finding is consistent with those reported by drug discrimination studies carried out with rats. In consequence, the above data reported from drug discrimination research suggest that pharmacologically active JWH-018 may lead to effects that are like those experienced with marijuana use. Also, according to Ginsburg *et al*. (2012), the shorter duration of action could give rise to more frequent use, which may, in turn, increase misuse and dependence liability.

Uchiyama *et al*. (2012) investigated JWH-018's effects on electroencephalogram (EEG) power spectra and locomotor activity in mouse models. The authors determined that JWH-018 led to an increase in the EEG power up to 3.9 fold and a decrease in the EEG activity but THC led to a decrease in the EEG power. Thus, compared to THC, JWH-018 had a different effect on the EEG (Uchiyama *et al*., 2012). Moreover, JWH-018 reduced locomotor activity more strongly and for a longer time. The trials revealed that JWH-018 altered the EEG power spectra and inhibited the locomotor activity of rats more remarkably and for a longer time than THC. This suggests a powerful pharmacological action in the central nervous system.

In a repeated dose study (0.1 to 10 mg/kg) by Vardakou *et al*. (2010), rats were reported to be in a severe lethargic, unresponsive catatonic state. Moreover, one rat died and there was a decrease in the breathing frequency at 10 mg/kg. However, the study does not contain any data on the exact methodology used (Vardakou *et al*., 2010).

Macri *et al*. (2013) investigated the behavioral reactions to acute and sub-chronic administration of JWH-018 in adult mice. General locomotion and body temperature were reduced by the IP injection of JWH-018. These effects have been reported to be similar to the effects brought about by classical cannabinoids. In addition, the administration of JWH-018 led to a decrease in pain sensitivity. The researchers found that when prenatal corticosterone was administered to the mice, some of the effects did not arise (mimicking precocious stress). This, according to the authors, points to the differences in the individual responses to psychotropic drugs.

The NIDA (National Institute on Drug Abuse) also carried out pharmacological studies on JWH-018. They found that JWH-018 and THC had similar discriminative stimulus effects

because these effects were fully substituted in rats by JWH-018 (Leonhart, 2012).

Effects in humans

Besides user reviews on the Internet, the literature contains two self-experiments describing experienced effects. Auwärter *et al*., after smoking 300 mg of a "herbal mixture" including the C8 homolog of CP47,497 and JWH-018, reported reddish conjunctivae, huge increases in pulse rates, xerostomia, and changes in mood and perception (Auarter *et al*., 2009). In the study by Teske *et al*. (2010), sickness, drowsiness, and xerostomia were reported by two volunteers who smoked about 50 µg/kg dose of JWH-018. Moreover, the authors noted hot flashes, thought disturbances, and burning eyes in the volunteers. Maximum JWH-018 serum concentrations in these two volunteers were roughly 10 ng/ml (Teske *et al*., 2010).

Interactions with other substances and medicines

Brents *et al*., who researched the interaction between JWH-018 and JWH-073, reported the synergistic effects of these two compounds in THC-like discriminative stimulus effects, analgesia (ratio JWH-018: JWH-073 of 2:3), and displacement of [3H] CP55,940 from CB1 receptors. On the other hand, the authors observed only additive interaction for analgesia when they tested a JWH-018: JWH-073 ratio of 1:1 and for the inhibition of the adenylyl cyclase activity (Brents *et al*., 2011). Additionally, antagonistic interaction for hypothermia and sub-additive inhibition of food-maintained responses in mice were obtained as a result of a mixture of JWH-018 and JWH07 (substitute for negative effects such as disorientation in space, numbness, and delirium). The findings given above indicate that JWH018 and JWH-073 might bind at separate sites of the CB1 receptors. Also, intracellular effectors other than adenylyl cyclase might mediate the synergistic effects. Also, Chimalakonda *et al*. (2013) used sulfaphenazole (selective CYP2C9 inhibitor) and αnaphthoflavone (selective CYP1A2 inhibitor) to research the inhibition of oxidation of JWH-018 in human liver microsomes.

Toxicity of JWH-018

Koller *et al*. (2013) employed human cell lines (hepatoma line [HepG2]; mammary line [MCF-7]; buccal epithelial cells [TR146]) and primary cell lines to evaluate JWH-018's cytotoxic, genotoxic, immunomodulatory, and hormonal activities. Although about 10-fold anti-estrogenic features were seen for JWH-018 than for THC, no considerable acute toxicity or estrogenic activity was observed for JWH-018. In MCF-7 and TR146 cells, JWH-018 showed cytotoxicity at 100 µM, which was the highest concentration level tested. On the other hand, the highest concentration level where THC showed cytotoxicity was 75 µM, where THC damaged the mitochondria and suppressed cell proliferation. In the test, JWH-018 did not lead to any changes in the immune function. The amounts contributing to toxicity were two to three orders of magnitude greater than the serum levels normally found in people (maximum concentration: 32.2 nM).However, epithelial cells in the upper aerodigestive tract may be exposed to concentrations at higher levels, as a result of which cell injury may occur. Previous studies have also researched the toxicity of JWH-018 in primary neuronal cells of the forebrain and found that cytotoxicity was induced in a concentration-dependent manner. JWH-018 (30 µM) cytotoxicity was inhibited through the use of preincubation with a CB1 selective antagonist (AM-251). This points to a major role that CB1 receptors play in the induction of cytotoxicity in this cell line. Moreover, via apoptosis, the JWH-018 cytotoxicity progressed, and it was mediated by caspases, which, in turn, revealed a strong neurotoxic consequence, as the authors stated.

However, given the tested concentrations in the above study of 10 µM and 30 µM JWH-018, inferences about cytotoxicity *in vivo* must be made with caution, as serum concentration levels reported in the literature or obtained from analysis of clinical or forensic samples were not greater than 32.2 nM (11 ng/ml), which is 300-fold lesser than the concentrations used by Tomiyama *et al*. However, owing to JWH-018's lipophilicity, it cannot be ruled out that larger concentrations may arise in deeper (fat-rich) compartments after prolonged misuse and accumulation or in epithelial cells of the aerodigestive tract. Other than these trials, no study has provided any information on the toxicity of JWH-018, and no information has been disclosed on potential teratogenic effects. Yet, it should be kept in mind that in the developing central nervous system, the endocannabinoid system is present from insemination onwards. Also, THC, as well as the cannabimimetic WIN-55,212-2, cause anencephaly and neurobehavioural deficiencies in the offspring by interfering with the endocannabinoid system (Psychoyos& Vinod, 2013).

It is unclear whether JWH-018 goes across the placental barrier. However, given its physicochemical attributes, it is likely to enter fetal tissue through the placenta.

Adverse reactions in humans

Non-fatal Cases

In the literature, it has been reported that the consumption of synthetic cannabinoids causes adverse effects such as acute psychosis, hallucination, tachyarrhythmia, hypertension, agitation, the minor elevation of blood glucose, vomiting, hypokalemia, chest pain, myoclonia, seizures, extreme anxiety-causing panic attacks (Hermanns-Clausen *et al*., 2013).

Human cases of JWH-018 intoxications reported in the literature: After 30 minutes of intake of an ethanolic JWH-018 mixture, a 48-year-old male in good health suffered a generalized seizure and supraventricular tachyarrhythmia. In the patient's urine, JWH-018 metabolites were analytically confirmed, with approximately 74 ng/ml JWH-018 pentanoic acid concentration (Lapoint *et al*., 2011).

In a study by Young *et al*. (2012), a boy who was 17 years old developed chest pain, tachyarrhythmia, and subsequently bradycardia after 10 minutes of inhaling a herbal mixture comprising JWH-018 and JWH-073 and one hour after consuming 100 mg of caffeine.

Meijer *et al*. (2014) described the adverse effects of JWH-018 consumption in three more cases. Case 1: Seizures, acidosis, tachyarrhythmia, and unresponsiveness were seen in a male who was 25 years old after smoking a 'herbal mixture.' Also, JWH-018 metabolites were confirmed in his urine. Case 2: JWH-018 and JWH-073 metabolites were found in the urine of a 21-year-old male, who was found unconscious (Glasgow Coma Score of 7) with hypertension and heated dry skin. However, the analysis of the metabolites failed to reveal whether JWH-018 alone or combined with JWH-073 was smoked. Case 3: Similar to case 2, paranoia and delusions

were seen in a 19-year-old male after one hour of smoking a herbal mixture. JWH-018 and JWH-073 metabolites were detected in the case's urine sample.

Hermanns-Clausen *et al*. mention seven acute intoxication cases with JWH-018 uptake that were confirmed analytically (Forrester *et al*., 2011). Symptoms observed in these seven cases were as follows: tachyarrhythmia (n=4), mydriasis (n=3), conjunctival hyperemia (n=3), restlessness (n =3), altered perception (n=2), shivering (n=2), dry mouth (n=2), hypertension (n=2), somnolence (n=1), hypokalemia (n=1), nausea/vomiting (n=1), anaesthesia (n=1), vertigo (n=1), and thoracic pain (n=1). However, the extent to which JWH-018 caused or exacerbated symptoms could not be determined as other synthetic cannabinoids were detected in the biological samples of four cases. In the serum sample of a 19-year-old male obtained two hours after the last consumption, 0.39 ng/ml JWH-018 along with JWH-122 (230 ng/ml) and JWH-210 (7.8 ng/ml) were detected. The case developed unresponsiveness and continued vomiting and later lost consciousness without adequate respiration. Mechanical ventilation was performed for three hours (Hermanns-Clausen *et al*., 2013).

Fatal cases

The literature has reports of three cases with JWH-018 found in blood samples obtained after death. A 36-year-old German male collapsed and suffered from seizures after smoking 'herbal mixtures.' Despite attempts to resuscitate the man, he lost his life after being admitted to the hospital. Synthetic cannabinoids JWH-122, AM-2201, MAM-2201, and UR-144 were present in the residue of the joint smoked. JWH-018 was found in the man's femoral blood sample (0.1 ng/ml), gastric content (~9.0 µg absolute), hair sample (~ 0.05 ng/mg), and adipose tissue (~ 30 ng/g).The extent to which JWH-018 contributed to the man's demise could not be assessed due to the presence of various substances in the femoral blood.

Another case is that of a 26-year-old Swedish male, who died of methoxetamine intoxication. In the case's femoral blood sample, three synthetic cannabinoids (femoral blood: AM-2201 (0.3 ng/g), AM-694 (0.09 ng/g), and JWH-018 0.05 ng/g) were present, which may have contributed to the man's death (Wikstrom *et al*., 2013).

One last case describes a 19-year-old student who died four days after collapsing on a basketball court. The cause of death was determined by the coroner as drug toxicity and organ failure due to the intake of JWH-018 revealed in the toxicological analysis (Castaneto *et al*., 2014)

METHOD

The Pubmed, PsycInfo, Medline, Google Scholar, and Embase databases were searched for reports during the literature review.The strategy was briefly (emergency department or hospital or Poison Control Centers or substance-related disorders or Drug Overdose) and (JWH-018). Due to the recently evolving state of the literature, the references of retrieved papers were also backward searched so that early sources (e.g., conference presentations) could be identified.

Inclusion criteria

JWH-018 was the target substance. Rather than self-reported data, it was required that professional medical staff recorded adverse effects. One exclusion to this criteria was the reports written by experts (e.g., nurses, pharmacists, or scientists) in poisons information centers. Both analytically confirmed and self-reported use of SCs, as well as presentations about JWH-018, were included.

RESULTS

The database search yielded a total of 323 reports. To these records, we added 41 studies obtained as a result of manually looking through references. After eliminating duplicates and screening titles, we took into consideration a total of 136 full texts. Subsequently, we excluded 30 papers. Eventually, the study included a total of 106 papers, letters, and conference abstracts, which represented data for more than 4,000 cases.
Case series (defined as > 10 cases) and case studies (three of the cases, whilst, in the fourth, liver and kidney failure was noted) (Behonick *et al*., 2014). SC abuse (JWH-018) was assigned as the direct cause of deaths (Streich *et al*., 2014). In other cases, the use seems to have indirectly led to lethal outcomes (Hill *et al*., 2013).

Fatalities described in other USA case studies may be included in the two studies conducted by Shanks *et al*. (Behonick *et al*., 2014). Hence, a cautious prediction of the number of reported synthetic cannabinoid deaths is 22 (maximum 27) in the USA, three in Europe, and one in Japan.

In the literature, cardiovascular tachyarrhythmia has been reported as the most common clinical effect. According to the reports by poison centers, cardiovascular tachyarrhythmia is accompanied by hypertension in one-third to three-quarters of presentations (Nacca *et al*., 2013). Chest pain has also been reported in some cases. 34-36 Besides, more severe effects such as peri mesencephalic subarachnoid hemorrhage (Kamat *et al*., 2012), middle cerebral artery occlusion (Leung *et al*., 2014), and three cases of myocardial infarction in adolescent males (Mir *et al*., 2011) have been reported in some cases. A cardiac arrest has also been reported in a 56-year-old man with a history of quadruple bypass heart surgery (Ibrahim *et al*., 2014).

Acute kidney injury (AKI)

Data obtained from poison centers indicate that inquiries about kidney issues constitute less than one percent of all JWH-018 calls. However, multiple reports have mentioned AKI in acute SC toxicity cases. Over a nine-month period, 16 AKI cases were identified by the Centers for Disease Control (CDC). The cases usually included gastrointestinal symptoms (e.g., nausea, vomiting) and flank pain accompanied by elevated peak serum creatinine (range 3.3-21.0 mg/dl).

Also, high levels of white blood cells, proteinuria, and hematuria were evidenced. Acute interstitial nephritis (two cases), acute tubular injury (five cases), or both (one case) were found in eight cases as a result of kidney biopsies. (CDC, 2012) Four young healthy men with acute kidney injuries were reported in Alabama (Bhanushali *et al*., 2013). Also, nine patients, five of whom had entered into the records of the CDC, were reported in Oregon. All of the cases in Alabama and Oregon had to stay in the hospital for up to eight days. (Buser *et al*., 2014)

Generalized tonic-clonic (GTC) seizures

In the review by Hoyte *et al*. (2010), GTC seizures were mentioned in 52 (3.8%) SC reports published by poison centers. Moreover, two of the cases had prolonged seizures known as status epilepticus (SC). On the other hand, a case

series of SC presentations to emergency departments published by the CDC reported GTC seizures in 14% of the cases (CDC, 2012). Also, a review of the reports by pediatric poison centers determined seizures in 15% of the cases (Plumb *et al*., 2012). In the literature related to case reports, seizures, including the ones with confirmed SC exposure (e.g. JWH-122, -210, - 018: PB-22: AM-2233, BB-22, PB-22, 5F-PB-22,), are also important (Gugelmann *et al*., 2014).

Gastrointestinal

Gastrointestinal symptoms are usually apparent features of SC cases. Cannabinoid hyperemesis subsequent to JWH-018 abuse has been reported in two studies (Ukaigwe *et al*., 2014). Like the hyperemesis syndromes associated with cannabis consumption, a cycle of nausea, vomiting, and abdominal pain eased by hot showers is described in both case reports. In patients receiving psychiatric treatment, JWH-018 abuse has been reported to worsen symptoms (Every-Palmer, 2010), instigate substance-induced psychotic disorder (with no known history of the substance-induced psychotic disorder) (Macri *et al*., 2013), and accelerate the reiteration of cannabis-induced psychosis (Muller *et al*., 2010). Anxiety, panic attacks (Hermanns-clausen *et al*., 2013), paranoia, and hallucinations have also been reported in JWH-018 cases (Bebarta *et al*., 2012).

DISCUSSION

In the general population, the use of synthetic cannabinoids (SC) is not common (AIH &Walfare, 2013). Yet, using JWH-018 seems to be associated with a higher risk of needing medical treatment than using cannabis. Our systematic analysis of adverse outcomes revealed that the majority of them were mild, only necessitating symptomatic or supportive therapy, and lasted only for a short time. Nonetheless, JWH-018 use has been, either directly or indirectly, linked to a number of deaths along with some other major effects such as the sudden onset of psychotic episodes (despite no family history of psychosis) (Hurst *et al*., 2011).

In this analysis, media reports or unpublished research was not included, although doing so would possibly bring to light more cases, but with probably unreliable medical data. The potential overlap between data from poison centers and hospitals barred us from identifying the precise number of cases. We were even unable to conclusively determine the number of deaths linked with JWH-018 abuse.

There were only 22 fatalities that took place in the United States through the end of 2014, according to our review of published cases. Currently, JWH-018 cases may be underreported since JWH-018 abuse is not assessed in all presentations (especially for psychiatric issues or palpitations).

Therefore, the size of health problems arising from JWH-018 consumption is much bigger than that which has been recorded thus far. The majority of the data was based on self-reported JWH-018 intake, as there is no simple screening method for clinicians at the moment. Some of the material about the negative effects of JWH-018 comes from poison control centers. Wood *et al*. discussed the strengths and weaknesses of poison center data on novel psychoactive drugs. In short, new and unfamiliar exposures may be detected in poison centers; however, familiarity with the drugs involved may reduce the detection rates.

Cannabis use has an effect on the circulatory system, raising the risk of heart attack (Poklis *et al*., 2012). Cannabis has also been linked to ischemic stroke, particularly multifocal intracranial stenosis in young individuals (Psychoyos& Vinod, 2013). Among potential mechanisms are cardiac ischemia due to elevated heart rate, orthostatic hypotension, hypoxia due to elevated carboxyhemoglobin levels, particularly when coupled with tobacco smoking, and catecholamine mediated pro-arrhythmic outcomes (Aryana & Williams, 2007). Considering their greater efficacy at CB1 receptors, it is probably not surprising that similar negative consequences have arisen following JWH-018 use. It is yet unclear whether these chemicals have any direct impacts on other receptors. Because JWH-018 has been present and utilized in the general public for a relatively short time, its long-term results are currently not known. A meta-analysis has revealed that those who have had AKI have a nearly nine-fold increased risk of acquiring the chronic renal disease and a three-fold increased risk of end-stage renal disease, compared to those without a history of AKI (Coca *et al*., 2013). As a result, even low-prevalence disorders with a short duration, such as AKI, are likely to lead to substantial health expenses once acute symptoms have been resolved. The onset or worsening of psychiatric diseases, including psychosis, are other outcomes with long-term possible health results. These are very severe and burdensome disorders that have significant socioeconomic and health consequences for patients, their families, and the healthcare system.

Clinical Implications

Intoxication with JWH-018 seems to represent a new and unique medical phenomenon. Consumption of JWH-018 is likely to cause more clinical effects than that of marijuana. Besides, there appear to be significant variations in the nature of the complaints that patients present with. Investigations related to the size of the problem are complicated due to the amount of JWH-018 available and the rate at which they change (EMCD, 2015). According to Trecki *et al*. (2015), the frequency of clusters and the seriousness of adverse events associated with JWH-018 seem to escalate. The latter encompasses seizures (which can cause rhabdomyolysis and hyperthermia if prolonged), myocardial ischemia, acute kidney injuries, and infarction in demographic groups where this would be most unlikely. Mild intoxications usually only necessitate supportive care but not hospitalization. Cases involving seizures, serious restlessness or psychological disorders, arrhythmias, and severe chest pain should all be hospitalized for further assessment. Management is complicated by the absence of an antidote for JWH-018, similar to that for opioid overdose, as well as by the unforeseeable effects and lack of a toxidrome to discern SCs from other recreational drugs. (Trecki *et al*., 2015)

Low blood sugar, CNS infection, thyroid hyperactivity, head injuries, and psychological disorders are among the disorders that must be ruled out in the differential diagnosis (Robert, 2015). To control agitation, using benzodiazepines is usually sufficient but haloperidol use has also been suggested (Robert, 2015). Undifferentiated agitation should be handled with caution. Failure of benzodiazepines should precipitate the use of airway management in the patient. Securing the airway, avoiding rhabdomyolysis, and screening for cardiac or cerebral ischemia are the key priorities, in addition to intravenous fluids for dehydration (Robert, 2015).

CONCLUSIONS

Data published by poison control centers and drug monitoring systems in Europe, the United Kingdom, the United States, and Australia indicate more frequent use of JWH-018. Doctors should be cautious about serious cardiovascular, cerebrovascular, neurological, mental, and renal consequences that occur in a small percentage of cases. Methods for detecting, identifying, and confirming SCs lag the appearance of these drugs. Moreover, most of the cases rely on patients' self-reports, which might be imprecise or misleading. Better access to modern laboratories will help us identify JWH-018 as having a higher potential for severe toxicity. Tachyarrhythmia, restlessness, and uneasiness of the stomach are the most prevalent effects, which are usually treated with supportive care.

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