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STRUGGLE WITH BONZAI: A REVIEW ON SYNTHETIC CANNABINOID ABUSE

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ABSTRACT

Cannabis has been a widely favored recreational drug throughout history. It has also been used as medicine, due to its analgesic and anti-inflammatory effects. Following the discovery of its main ingredient, Δ9-tetrahydrocannabinol (THC), studies focused on synthesizing new cannabinoids to be used in medicine. However, possessing the highly demanded qualities of a recreational drug, synthetic cannabinoids are nowadays being marketed as safe, natural and legal alternatives of cannabis around the world. Turkey is one of the countries in which these synthetic cannabinoids are readily available and the rate of abuse continues to increase. This review focuses on these misperceptions, examining the acute and long-term effects of synthetic cannabis abuse in addition to the medical and forensic advancements necessary to prevent this growing trend of cannabinoid abuse.

Key Words: cannabinoid, JWH-018, cannabinoid receptor agonists, synthetic cannabinoid, tetrahydrocannabinol

INTRODUCTION

Cannabis sativa, or marijuana, as named in Western societies, or hashish, a more widely used name in Eastern cultures, is a plant which both dates far back in history and is still as popular and widely used as it has been thousands of years ago as a recreational drug (1). Earliest use of cannabis by humans has been discovered in Taiwan, in an ancient village discovered by archeologists and dates back over 10,000 years into the Stone Age (2). Since then, it has continued to attract attention due to its recreational effects and the possibility of a medical use along with its potential to be abused. However, it was not until 1964 that Mechoulam and Gaoni (3) configured the chemical structure of the plant. It was understood that although multiple chemical structures were available in the plant, Δ9-tetrahydrocannabinol (THC) was the actual psychoactive component causing the high demand for cannabis. Indeed, this quality of THC has been shown to decrease brain-stimulation reward thresholds (1), explaining the pleasurable nature of cannabis and repeating substance-seeking behavior seen afterwards.
Besides its abuse, cannabis has also been used for medical purposes throughout the history, some of its most frequently preferred effects being analgesia and anti-inflammation (4). Although cannabis itself has no definitively accepted medical value, its synthetic derivatives are benefited from in certain medical conditions (5). Dronabinol, levonantradol, (whose use has later been discontinued) and nabilone are such derivatives of THC and are used in conditions such as neuropathic syndromes, chemotherapy-induced nausea and spasticity in multiple sclerosis, generally after all other possible medications have been tried and exhausted (5, 6). Despite being used in a controlled manner as a medication, those compounds have revealed psychotomimetic side effects similar to those of cannabis, such as loss of control and anxiety (6). Researches for eliminating the undesirable side effects while preserving the analgesic and anti-inflammatory nature of cannabis, led to a breakthrough in synthesis of synthetic cannabinoids, starting with John W. Huffman, professor of emeritus at Clemson University, USA. Beginning in 1980s, his main focus was on synthesizing new cannabinoids which would have properties similar to those of THC. Huffman named and numbered the compounds he synthesized after his initials, such as JWH-018 and JWH-205 (7, 8). What is now, for almost a decade, known as synthetic cannabinoids or "legal highs" has arised from Huffman's work outside legal research facilities, which Huffman

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calls "hijacking of basic research". He states that this is neither the first nor the last time that a substance developed legitimately through scientific discovery has been abused (7).

Emergence of synthetic cannabinoids as recreational substances

Synthetic cannabinoids used outside of scientific research presented themselves first in Germany in 2004 as recreational drugs (9). Sold as herbal incenses, they are advertised to be the legal, nontoxic and natural alternatives to cannabis (5, 10, 11). Marketed under brand names such as Spice and K2 (K2 being named after the second-highest mountain on Earth), exotically and colorfully decorated packages contain a "not for human consumption" label but are consumed for their cannabimimetic affects. (see Image 1.) Due to the rapid increase in synthetic cannabinoid abuse, sufficient data in terms of its pharmacological and toxicological aspects has not yet been gathered (5). However, as the number of medical cases affected by synthetic cannabinoids increases, so does the concern regarding public health. Researches involving adolescents show that despite a dramatic decrease in alcohol and tobacco use, there is a high demand for synthetic cannabinoids (12). A number of reasons could explain this phenomenon. First reason why synthetic cannabinoids are widely used is that they are advertised to be natural herbal blends, legally produced and served to public. Patient interviews reveal that those who prefer synthetic cannabinoids over classic cannabis seek to experience the desired effects of cannabis but do not wish legal consequences to follow (13). In 2013, the largest survey ever conducted on synthetic cannabinoid users revealed that when given a chance, users prefer classic cannabis over synthetic cannabinoids, stating that classic cannabis was more enjoyable in terms of experienced pleasure, that their cognitive functions were more efficient after classic cannabis uptake and synthetic cannabinoids caused unpleasant hangovers compared to classic cannabis (14). Such substances are known to be readily obtained via internet, gas stations, so called "headshops" mostly in Europe or even on the street in some countries.

Another reason for being popular is that synthetic cannabinoids are advertised to be and perceived as natural herbs. The actual production method, although not very clear, is hypothesized as the synthesis of cannabinoids, dissolution of the synthesized substance in solvent and the mixing procedure which consists of spraying different kinds of dry plant leaves with the mixture. After the solvent evaporates, what remains behind is the leaves loaded with synthetic cannabinoid (15). One other significant aspect is the fact that because there is no definitive evidence as to which chemical compounds are found in synthetic cannabinoid mixtures, there is no drug screening developed to detect such substances of abuse in body fluids. It is hypothesized that some compounds might have different psychostimulating effects or are added to the blend just to make it more challenging to identify which specific type of synthetic cannabinoid is the main ingredient in a given package (11). These circumstances further add to the perception that synthetic cannabinoids are safe for regular use (5, 6, 13). Yet, this is not the case. Undeclared substances in these blends, possibly many times stronger than cannabis (16), lead synthetic cannabinoids to present a growing public health problem in the ways that they affect human body with not only its psychotic effects but also by causing psychosis and impaired cognitive function (6, 17, 18-28), addiction, cytotoxicity of forebrain (29), cannabinoid hyperemesis syndrome (30), withdrawal syndrome (31), kidney injuries (13), cardiac arrests (32) and even deaths (due to disruption of physiologic processes or suicide committed in a synthetic cannabinoid-induced state) (5). Medical professionals are not fully equipped to handle acute and long term outcomes of synthetic cannabinoid abuse due to two main reasons: i) Effects of synthetic cannabinoids on humans have never been studied in a controlled scientific research. Even though series of cases have been published, there is no assertive data as to what changes occur in human physiology at a certain amount of synthetic cannabinoids intake. ii) THC content varies in different mixtures, thus the studies to examine the dose-response relationship are to be further complicated (6). Due to the preparation technique described above, synthetic cannabinoids are likely to be unevenly distributed in marketed herbal incenses, resulting in unpredictable effects and an increased risk of overdosing (5).

Mechanism of action, desired effects leading to abuse and long-term results

Two types of cannabinoid receptors have been

defined up to date, named cannabinoid-1 (CB1) and cannabinoid-2 (CB2) receptors. CB1 receptors are abundant on presynaptic terminals in central nervous system and function via retrograde signaling, whereas CB2 receptors are primarily available in tissues involved in immune activities, such as lymphocytes and bone marrow (1, 5, 15). Analgesic and anti-inflammatory properties of cannabis result from the dispersal of CB1 and CB2 receptors in human body, respectively. Defined as the target of THC, these receptors are actually a significant part of the endocannabinoid system, which is crucial in homeostasis. Endocannabinoids are defined as endogenous ligands which activate CB1 and CB2 receptors in order to regulate physiological processes such as cognitive functions, immunity and pain modulation (33). Seeing as these receptors play a crucial role in homeostasis, it is not unusual that cannabis and its derivatives cause a variety of systemic effects, be it desired or unfavorable (5).

Primary way of cannabinoid intake, be it classic cannabis or synthetic cannabinoids, is inhalation but ingestion is also not rare (9). Smoking enables the substances to be absorbed quickly through lungs, which is a matter of seconds. Because cannabinoids are highly lipophilic, they are readily absorbed by fat tissues and more importantly, neural tissues (34).

Following THC exposure, which acts as a partial agonist especially on CB1 receptors, GABAergic neurons are suppressed, resulting in the cessation of inhibitory mechanisms on dopaminergic neurons (1, 5, 15). The desired effects of cannabinoids occur following these alterations in metabolism, such as euphoria and altered perception. Yet, the unwanted side effects such as anxiety, hallucinations, delusions, cognitive impairment and somatic effects such as tachycardia, nausea-vomiting, cardiac arrhythmias and kidney injuries also follow through these mechanisms. These complications are much more likely to occur in the presence of synthetic cannabinoids, which are full agonists of CB1 and CB2 receptors and have been proven to be hundreds of times potent compared to THC (15). Because the chemical composition varies, so does these effects and their durations, making it more problematic for health professionals to handle acute intoxications (9).

There has never been the chance to conduct controlled studies examining the effects of cannabinoids on humans, as stated above. But Compton et al. (35) have studied the effects of CB1 receptor agonists on laboratory animals and defined the phenomenon which is now named as the cannabinoid tetrad. The study revealed that the organism responded to the CB1 agonist intake with hypothermia, analgesia, catalepsy and locomotor suppression. These results obtained with cannabis became more drastic as the experiment was performed with JWH-018 and JWH-073, two substances most frequently detected in synthetic herbal blends.

These findings bring scientists to this question: In what way do synthetic cannabinoids differ from classic cannabis so that they end up resulting in more severe side effects? In addition to the higher affinity they have towards CB1 receptors (15), it is speculated that synthetic cannabinoids may also be acting on non-cannabinoid receptors. Furthermore, classic cannabis contains substances named "terpenoids", which help increase the desired effects of THC while reducing the unpleasant side effects. However, no such regulating substance have been come across in synthetic blends, which thus cause more dramatic results than classic cannabis (5).

It would seem paradoxical for a substance used for its euphoric effects to result in toxicity and long-term manifestations which might be irreversible, but regarding synthetic cannabinoid abuse, this is the case. Ibrahim et al. (32) describes a case of cardiac arrest in a patient who has been a long time user of cannabis but has recently started using the blends named K2. It is reported that the arrest occurred within an hour of substance use. The direct relationship between the abused substance and cardiac problems is derived from the fact that there was evidence of myocardial necrosis (elevated troponin T and CKMB levels), though no coronary occlusion which might have caused the necrosis could be found. Furthermore, as the patient stopped abusing synthetic cannabinoids, no recurring cardiac problems took place. In addition to cardiac manifestations, series of cases suffering from nephrotoxicity as a result of synthetic cannabinoid abuse have been reported, presenting themselves with nausea, abdominal/flank pain and dangerously elevated creatinine levels along with no other possible pathology to explain the renal injury (9, 13). Tomiyama and Funada (29) have shown the cytotoxic effect of synthetic cannabinoids in brain tissue cultures is mediated through CB1 receptors and that this effect occurs via apoptosis. Although there has been no study to examine the cytotoxicity of synthetic cannabinoids on other tissues, this mechanism might be the fact underlying organ pathologies following synthetic cannabinoid abuse.

Considering that the main target of cannabinoids is the nervous system, it can be anticipated that the most severe long-term results of cannabinoid abu-

se arise from neurologic and psychiatric dysfunctions. Along with the acute effects such as hallucinations and disorientation, long-term effects of cannabinoids have also raised concern among healthcare professionals. Acute effects of cannabinoids are presumed to be modified by genetic factors and personality traits, therefore it is observed that only a fraction of cannabinoid abusers undergo psychotic disorders. Nevertheless, evidence also suggests that early and heavy exposure to cannabis can result in an elevated risk for developing psychotic outcomes, the most critical one being schizophrenia (6). Schizophrenia is known to be one of the most serious psychotic disorders. Although still a hypothesis, the fluctuating dopamine levels are considered significant in schizophrenia (36), which might possibly relate to the CB1-dopamine activity explained above.

Studies indicate that the risk of developing psychotic symptoms is related to the age of onset of cannabis abuse, a family history of psychotic disorders, a history of childhood abuse and genetic structure. The age of exposure seems to be the most important factor because adolescence is the time interval in which nervous system is highly susceptible to damage from outside. On the other hand, the fact that a greater number of cases developing psychotic symptoms are aged 25 or younger brings up the question whether cannabinoids actually aggravate a pre-existing prodromal phase of a certain psychotic pathology. Arseneault et al. point out that such an early onset is risky because it both increases the risk of developing schizophrenia and the probability that the cannabinoid abuse will be long-lasting grows stronger (25). Gaffuri et al. (26) approach the situation from the view that because the CB1 receptors and their activity modulated by endocannabinoids are invaluable to neural development which starts in utero and continues to 20s, an interference of psychoactive stimulants such as THC to this development might interrupt this process.

The results of cannabinoid abuse on cognitive function has been examined in various studies. Tramèr et al. state that cannabinoid administration to patients with chemotherapy-induced nausea and vomiting caused an increase in their risk of developing depression and paranoia. (19) Andréasson et al. examined more than 45,000 males aged 18-20 during a time interval of 15 years in terms of cannabinoid abuse and hospitalization for psychotic disorders. The result stated that the risk of developing schizophrenia increases significantly even in those who have used cannabis only once in their lifetime, proving that cannabis abuse is an independent risk factor for schizophrenia. (20) Compton and Broussard found that the risk of developing acute psychosis increases significantly in those who consume classic herbal cannabis on a daily basis compared to non-daily consumers. (18). A birth cohort involving 1265 children in New Zealand (21) showed that those who use cannabis daily have a 2.3 to 3.3fold increased risk of psychosis compared to non-abusers. Solowij et al. (22) showed that the memory impairment continues in heavy cannabis users even after the acute toxic phase. Fontes and Balla (23) studied cognitive performance in chronic cannabis users in groups whose cannabis abuse started before and after the age 15. The result is that although both groups showed dysfunction, those who started younger than 15 have greater cognitive impairment. One of the most striking studies in this area has been conducted by Meier and Caspi (24), revealing that chronic cannabis abuse is significantly related to a decline in IQ, which cannot be entirely reversed even after the cannabis abuse has been terminated.

Patient and family history have also been proven to be significant. In a study involving more than 2 million patients, Arendt et al. (27) showed that having a family history of schizophrenia translates into a significant increase in the risk of developing cannabis-induced psychosis. Another study revealed that sexual or physical abuse in childhood increases the cannabis-induced psychosis risk (28).

Cannabinoid Hyperemesis Syndrome is certainly an intriguing phenomenon caused by chronic cannabis consumption. First described by Allen et al. (37) in 2004 in a series of cases, it is defined as persistent abdominal pain, nausea and vomiting among chronic cannabis users, where chronic stands for cannabis use at least once every week. An urge to take hot showers/baths several times a day also accompanies. It is hypothesized that because CB1 receptors in the brain are very close to hypothalamus, chronic stimulation of these receptors may cause irregulations in hypothalamic thermoregulation. Therefore, the urge to take hot showers may be the way the body tries to oppose this change in thermal regulation (38). It would seem contradictory that cannabis and its derivatives, despite being used as anti-emetic agents in cases such as chemotherapy-induced nausea, can cause emesis itself. Although the pathophysiology has not been illuminated, it is hypothesized that the stimulation of CB1 receptors can cause peristaltic movements to cease, resulting in emesis. Because there are no definitive drug screening tests for synthetic cannabinoids, it may very well be a challenge to diagnose Cannabinoid Hyperemesis Syndrome, presuming the patient

is not honest about substance abuse. All categories of antiemetics can be administered as treatment. Volume depletion is a significant situation to take precautions for and when untreated, may cause prerenal failure. Opioid analgesics against persistent abdominal pain should be carefully administered, as it might potentiate the side effects of cannabinoids already available in the tissues (30).

Synthetic Cannabinoid Withdrawal Syndrome, described by Haney in 2005 (39), is the solid proof that cannabinoids, be it classic cannabis or synthetic cannabinoids, have the capacity to be significantly addictive. A less common outcome of chronic cannabis abuse, the symptoms range from irritability to anxiety, loss of appetite and an urge for cannabis intake (31, 39). Despite the fact that cannabis and its synthetic derivatives possess all the aspects of an addictive substance including a withdrawal syndrome, they are still advertised to be non-addictive recreational drugs.

Last issue to discuss regarding synthetic cannabinoids should be what treatment should be administered if cannabinoid toxicity is suspected. It is recommended to run a complete blood count and metabolic panel, and cardiac enzymes if chest pain is among the complaints of the patient. Lorazepam is recommended for agitation and seizures. If there is an ongoing seizure causing muscle spasms, blood levels of CPK and myoglobin should also be determined to be cautious against a possible rhabdomyolysis. As with opioids, antipsychotics should be used cautiously, as it may lower seizure threshold of the patient, further complicating the situation (12, 40).

Synthetic cannabinoid abuse in Turkey: a growing epidemic

As the so called synthetic cannabinoid industry extends around the world, the number of synthetic cannabinoid abusers also increases. Turkey, in that respect, is no exception. Turkey is a country where narcotic plants such as opium can be cultivated and the use of such recreational substances dates back to 10th century. It is known that the country is exposed to an intense drug trafficking, in which synthetic cannabinoids are transported from Europe to Asia while opiates follow the opposite route. (41) Press shows great interest in cases where adolescents found overdosed on streets, people intoxicated by cannabinoids or how easily these products can be obtained.
Official records show that these products were captured the first time in 2010 with the most frequent ingredient being JWH-018. The names on the packages were and still are different from Spice and K2, which are more widely used in Europe. "Bonzai Aromatic Potpourri", "Bonzai Plant Growth Regulator", "Jamaican Gold", "Heaven", "Yukatan Fire", "Smoke XXX", "Aromatic Incense" are few of the market names of these products. (see Image 2.) Tracking the internet, it is evident that these synthetic cannabinoids are accessible to young population of every age. Several websites excite and encourage people into buying these herbal blends, which are, similar to the rest of the world, often referred as herbal incenses not for human use. However, the data obtained from Istanbul Narcotic Department of the Council of Forensic Medicine, Turkey, reveals that this is not the case. Herbal compounds other than classical cannabis, captured and analyzed between August 2010 and March 2012, revealed that 98, 3 % of the blends contained synthetic cannabinoids (16). Even though most of these familiar synthetic cannabinoids such as JWH-018 are illegal in Turkey, there is no regulation against their derivatives to be synthesized and abused.

CONCLUSION

Synthetic cannabinoids are not safe, legal alternatives of cannabis, inferred from the studies mentioned above, regarding enhanced toxicity. They can be a significantly addictive and lead to irreversible results on human health, or even death. It should be manifested by the authorities that just because these products are advertised to be safe does not necessarily mean that they are. Those with a family history for schizophrenia or those who have experienced a psychosis before should be further informed regarding the nature of these substances.
The actual problem synthetic cannabinoids pose on health professionals is that they do not have the in-

formation of where and how the production of these blends take place, how much of a given synthetic compound is available on a given brand name or the dose-response relationship of cannabinoids in human body. Observing the cases, it is inferred that the blends are a mixture of ingredients instead of pure cannabinoid, which is risky because these ingredients can, and sometimes do, potentiate each other's effects, deteriorating the acute toxic state. The fact that there is no established drug screening test both obstruct the synthetic cannabinoid diagnosis of atypical cases and contribute to the popularity of the substances as non-detectable drugs. Legal status of cannabinoids also varies widely throughout the world, further adding to the perception that these substances are safe.

In conclusion, it would be too optimistic, to believe that banning these substances would bring their abuse to an end. Instead, development of new analysis methods to detect these substances are necessary, along with the need for increased public awareness. Only then it would be possible to obviate this ever-growing health risk.

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