Synthetic and Non-synthetic Cannabinoid Drugs and Their Adverse Effects-A Review From Public Health Prospective

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There is a growing use of novel psychoactive substances containing synthetic cannabinoids. Synthetic cannabinoid products have effects similar to those of natural cannabis, yet, these drugs are more potent and dangerous, and have been associated with dangerous adverse effects. Here, we review current literature on the epidemiology, acute, and chronic effects of synthetic and natural cannabinoid-based drugs. Synthetic drugs contain a mixture of psychoactive compounds that mostly bind cannabinoid receptors with high potency. These synthetic drugs replicate the effects of natural cannabis and ∆9-tetrahydrocannabinol but they induce more severe adverse effects including respiratory difficulties, hypertension, tachycardia, chest pain, muscle twitches, acute renal failure, anxiety, agitation, psychosis, suicidal ideation, and cognitive impairment. Chronic use of synthetic cannabinoids has been associated with serious psychiatric and medical conditions and even death. Given the growing popularity in the use of cannabinoid-based drugs and their harmful potential, there is a need for further research in this field.

Keywords: cannabis, synthetic cannabinoids, novel psychoactive drugs, drug abuse, addiction

INTRODUCTION

Cannabis is the most widely available and used drug across the world (1, 2). According to the United Nations Office on Drugs and Crime (UNODC) ~4% of the global adult population have used cannabis in their life. In the United States of America (USA) alone, 11% (36 million people) of adults used cannabis at least once in their past (3). In addition, the therapeutic use of cannabis and its derivatives is increasing and has been evaluated for various health conditions including pain, anorexia, side-effects of chemotherapy, multiple sclerosis, and muscle spasms (4–6). The primary psychoactive constituent within cannabis is ∆9-tetra-hydro-cannabinol (THC), which interacts with CB1 and CB2 receptors and it consequently elicits its main effects (7–9). Novel Psychoactive Substances (NPS) which contain Synthetic Cannabinoids (SCs) have recently started to be used recreationally, especially by young adults (10, 11). In contrast to the decline in use of many NPSs such as the cathinones and piperazines, it appears that the number of SC users is increasing (12). Although SC drugs mimic the psychotropic effects of cannabis, their undesired effects are unpredictable and more severe than those associated with cannabis (10, 13–16). Although, there is an increasing interest on the therapeutic potential of cannabinoid-based medications (6, 17) repeated exposure to cannabinoid-agonists in either organic or synthetic forms is associated with both physically and psychological adverse effects (2, 10, 15, 18).
The most notorious psychological side effects are mental disorders including psychotic-states, schizophrenia, and affective disorders (1, 2, 10). The aim of the current review is to describe the available knowledge regarding acute and repeated consumption of both organic and synthetic cannabinoid drugs and their side effects from a public health prospective.

**EPIDEMIOLOGY AND PATTERN OF USE OF CANNABINOIDS**

According to national and regional representative surveys, lifetime prevalence of SC use in the general population is between 0.2 and 4% (19). By comparison, lifetime use of cannabis tends to be greater; and to range between one-quarter to one-third of the population (1). However, Winstock and Barratt reported that SC products are widely popular among recreational cannabis users (20). Among high school seniors in USA, the annual prevalence of SC usages was higher than any other drugs, with the exception of cannabis (21). Evidence accumulated from several surveys shows that between 6 and 17% of college students in USA have used SC drugs at least once during their study period (22, 23). Other than that, SC use was relatively frequent among adolescents and young-teenagers. Approximately 1% of European people between the ages of 14–18 used SC drugs at least once in their lifetime (24). This is especially important since both clinical and preclinical studies indicate that exposure to SC as well as THC during adolescence is associated with an increased risk of developing schizophrenia later in life (25–27) (see Table 1 for comparison of cannabis and SC adverse effects).

Prompted by the alarming growth of the SC drugs phenomenon, legal measures to control the distribution of these drugs have been taken in many countries (57, 58). For example, in the United Kingdom (UK), “first generation” SCs were controlled in 2009 and further legislation to control so-called “second generation” of SCs drugs was enacted in 2013. Yet, subsequent manipulation of the chemical structure of these compounds has resulted in a novel generation of SCs that are not currently legally controlled in the UK (57). Unfortunately, a similar pattern was observed in other countries as well, manufacturers of SCs are aware of the chemical analog loopholes in the law and continue to manipulate SCs as necessary to keep them legal for distribution (26, 57–59). In line with this, a recent epidemiological study by Waugh et al. (57) reported substantial increase in SC drug use in 2011 despite prior legislation efforts. Suggesting, that legislation efforts alone have an insufficient effect on the distribution and use of SC drugs, and further prevention efforts are required to control this phenomenon (57).

Naive consumers typically report using SCs for various reasons, such as curiosity, high availability, easy access, and lower costs compared with cannabis. Since SCs are mostly undetectable via a simple urine test, a major motivation for consuming SC drugs is the desire to experience “cannabis-like” effects without the danger of being detected (11). Other motivations to use SCs are their relatively high availability and low prices (11, 19). In contrast to cannabis, these synthetic drugs are typically not designed to be mixed with tobacco, probably to achieve the most intense effects (13).

**PSYCHOACTIVE INGREDIENTS OF CANNABINOIDS**

The main psychoactive ingredient in cannabis is THC, which is a CB1 and CB2 receptors partial-agonist and the most potent cannabinoid that is present in the organic forms of cannabis (8, 27). Besides THC, organic cannabis products contain additional cannabinoids which do not induce psychoactive effects, such as Cannabinol, Δ8-Tetrahydrocannabinol, and Cannabidiol (CBD) (9, 60, 61). CBD is considered a non-psychoactive cannabinoid that also moderates the psycho tropic effects of THC (32, 62). Moreover, evidence is increasing that CBD has anxiolytic and antipsychotic properties (17, 62). In a broader context, CBD appears to have the ability to counteract psychotic symptoms and cognitive impairment associated with cannabis use as well as with acute THC administration (17, 63–65).

In contrast to cannabis, which contains mostly a mixture of agonist and antagonist cannabinoids (1, 7), SC’s compounds show differences in their selectivity, their potency and their function (10, 26, 27, 66), in general they are more potent and efficacious cannabinoid receptor agonists than THC (11, 67). In addition, SC drugs have additional ingredients such as preservatives, additives, fatty acids, amides, esters, benzodiazepines, and O-desmethyltramadol- an active metabolite of the opioid medication tramadol (26, 31, 68). It is suggested that these additional compounds are probably added to these drugs in purposely to induce greater psychoactive effect, act as masking agents to confuse the identification of the main psychoactive substances within these drugs (31, 68).

Since 2008, at least 200 different types of SCs have been isolated from herbal mixtures in several countries (27, 69, 70). This wide variability of psychoactive compounds is probably a result of (a) the impermanent production processes of these drugs, and (b) again their ever-changing compositions in an attempt to dodge prevention and legal actions (31).

One of the earliest compounds that was identified as a psychoactive component in SC drugs is JWH-018. Contrary to THC, JWH-018 has four times the affinity for CB1 receptors and 10 times the affinity for the CB2 receptors (67). Later-on, additional cannabinomimetic compounds such as CP 47,497, cannabicyclolhexanol, HU-210, and the fatty acid, oleamide have been detected in samples of SC drugs in different areas around the globe (10, 11). Prior studies examined and indicated the therapeutic potential of SCs; HU-210 proposed to have anti-depressant effects (71), HU-211 proposed to have anti-inflammatory effect on brain trauma (72), and nabilone has antiemetic and analgesic effects (73, 74). However, while these studies report an effect that is induced by exclusive compound, within SC based-drugs, a mixture these cannabinoids as well as additional psychoactive ingredients generates a condition that incudes synergistic interactions which may
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ADVERSE HEALTH EFFECTS OF

CANNABINOIDS

Acute Effects of Cannabinoids

The intoxication effects of cannabis are characterized by cannabis
users as; mild euphoria, relaxation, and a general pleasant feeling
(1, 7). These desired psychotropic effects are considered to be
related to the presence of THC (8, 9). In laboratory settings,
cannabis and THC induce dose-related impairment in several
functions including; motor coordination and executive function
(38, 75–78).

Further undesired symptoms including anxiety, panic
attacks, and psychotic episodes were associated with cannabis
intoxication, all of which are most often reported by naive users
and vulnerable individuals (56, 79). Similar to cannabis, the
intoxication of SCs may induce reactions such as relaxation,
euphoria, perceptual alteration, altered sense of time, and mild
cognitive impairments (80).

These cognitive alterations increase the risk of road accidents
if cannabis or SC users drive while intoxicated (1, 15). Epidemiological
evidence demonstrates that cannabis is the most
common illicit drug to be detected in drivers involved in fatal
road accidents or stopped for dangerous driving (1). Accordingly,
cannabis use by drivers is associated with an increased risk
of being involved in motor vehicle crashes (81). There is less
epidemiological data on the association between SC drugs and
road accidents, yet, several case studies have documented driving
under influence of SCs. Musshoff et al. reported 8 drivers in
a Norwegian study conducted during a 7-week period, about

underline their extrema and unpredicted adverse effects (10,
31).

**TABLE 1 | Summary of acute and long-term clinical side-effects of cannabinoid-based drugs.**

| Symptoms          | Type of effect†                  | Type of drug                        |
|-------------------|----------------------------------|-------------------------------------|
|                   | **Synthetic Cannabinoids**        | **Cannabis**                        |
|                   | Acute                            | Perceptual alterations including:   |
|                   |                                  | hallucinations and distortion of    |
|                   |                                  | spatial perception are typical      |
|                   |                                  | effects (7, 30), Paranoia,         |
|                   |                                  | aggressiveness, and prolonged       |
|                   |                                  | psychosis were observed in          |
|                   |                                  | vulnerable users and are dose-related (1, 2, 7). |
|                   | Long-term                        | An increased risk of psychotic      |
|                   |                                  | disorders in vulnerable             |
|                   |                                  | individuals and naive users (2, 25, |
|                   |                                  | 27, 32).                            |
|                   | Affect                           | Anxiety and panic attacks; especially in naive users (1). |
|                   | Acute                            | An increased risk for developing    |
|                   |                                  | anxiety (34, 35), and mood          |
|                   |                                  | disorders (1, 36, 37).              |
|                   | Long-term                        | Wide range of dose-related cognitive |
|                   |                                  | deficits including; attention,      |
|                   |                                  | working-memory, cognitive inhibition, |
|                   |                                  | and psychomotor function (38–41).   |
|                   |                              |                                      |
| Cardiovascular    | Acute                            | Impairments of set-shifting, verbal |
|                   |                                  | learning, attention, short-term     |
|                   |                                  | memory and psychomotor functions    |
|                   | Long-term                        | (39, 42).                           |
|                   |                                  | An increase of cardiovascular       |
|                   |                                  | activity, increase heart rate, and   |
|                   |                                  | decrease blood pressure (40, 44).   |
|                   |                                  | An increased risk of cardiovascular  |
|                   |                                  | disease after prolong use           |
|                   |                                  | (1, 44, 46).                        |
| Neurologic        | Acute                            | Dizziness, somnolence, and muscle   |
|                   |                                  | tension (38, 40).                   |
|                   | Long-term                        | Structural and functional abnormalities |
|                   |                                  | in a range of brain areas including |
|                   |                                  | the hippocampus and amygdala (49, 50). |
| Gastrointestinal  | Acute                            | Hyperemesis, and increase appetite   |
|                   |                                  | (1, 7, 20).                         |
|                   | Long-term                        | Low body weight among regular users |
|                   |                                  | (51).                               |
| Other             | Acute                            | Bronchodilation (55), impairments of |
|                   |                                  | driving ability (1, 7).             |
|                   | Long-term                        | An increased risk of obstructive   |
|                   |                                  | lung disease including lung-cancer  |
|                   |                                  | (1, 7, 55), an increased risk of    |
|                   |                                  | cancers of the oral cavity, pharynx |
|                   |                                  | and esophagus (56), cannabis        |
|                   |                                  | addiction, tolerance, and withdrawal |
|                   |                                  | (1, 7).                             |

†Acute effect denotes 0–6 h after last drug use; Long-term effects denotes 3 weeks or longer after last drug use.

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2.2% of 726 blood samples that were collected from drivers that were suspected to drive under the influence of drugs, confirmed positive for SCs and majority of the drivers were involved in vehicle accidents (54). Taken together it seems that as with driving under the influence of cannabis (1, 81), driving after SCs may also increase the risk of being involved in road accidents (10, 15).

Despite the resemblances, there are major differences between the effect of cannabis and SC drugs, both in terms of spectrum and intensity of these effects (13). Case report studies indicate a wide range of undesired somatic effects ranging in intensity from nausea to more severe symptoms such as psychomotor agitation, diaphoresis, and palpitations (13, 29). Some symptoms such as seizures; agitation, hypertension, emesis, and hypokalemia are features of SC intoxication and are not present even after consuming high doses of organic cannabis (29, 31, 33).

Psychotropic effects of SC intoxication vary significantly. Some users report a feeling of sedation while others experience agitation, fatigue, and flushes (29). This variation may occur due to different concentrations of SCs within different brands (27). Compared with the intoxication of organic cannabis products which have a slow effect and gradually fade (7, 82), SCs have a shorter duration and peak earlier (83). For example, the effects of JWH-018 last approximately for 1–2 h, while CP-47,497 induce effects for ~5–6 h (20). Moreover, some adverse effects such as anxiety, hallucinations, insomnia, and psychotic episodes may be experienced for days and weeks after consuming SC products (84).

**Chronic Effects of Cannabinoids**

Several studies demonstrate an association between repeated cannabis use and long-lasting cognitive impairments (2, 39, 85, 86), and an increase in risk for developing a variety of mental disorders. These include anxiety (34, 35), bipolar disorder (36), depression (37), and schizophrenia (2, 25, 32). There is growing evidence that SC drugs are associated with severe negative psychiatric and medical conditions (10, 15, 29, 31). This evidence demonstrates that repeated exposures to SCs induce overall negative side-effects which are more severe and long-lasting than those related with THC (10, 15, 29, 31).

A recent study by Cohen et al. shows deficiencies in a variety of high-order cognitive functions observed among SC users compared with recreational cannabis users including working memory, attention and recall (18). Another study indicates that SC users who had acute psychotic disorder induced by SC drugs, show cognitive impairments similar to those of schizophrenic patients (87). These results are compatible with evidence from rodent studies that show that repeated exposures to SCs induces long-lasting behavioral and cognitive impairments that resemble rodent models of schizophrenia (88, 89).

There is evidence indicating adverse effects of cannabis on cardiovascular function (1, 44, 46). Studies demonstrate that cannabis use can increase the risk of serious cardiovascular condition, including artery thrombosis, vasospasm, and myocardial infarction (90). Cannabinoid agonists, as well as THC, increase heart rate in a dose-dependent manner (1). Therefore, it is likely that these effects are mediated through cannabinoid-agonist's increase in catecholamines and increased cardiac workload together with a decreased supply of oxygen (91). Since SC drugs contain psychoactive compounds which have much higher affinity at CB1 receptors (67), it is not surprising that there are several reports that indicate an association between SC use and serious cardiovascular problems such as myocardial infarction and tachycardia in both adults and adolescents (92, 93).

**Cannabinoids and Psychosis**

The association between cannabinoids and psychosis is reported and it is well-recognized (2, 77, 79, 94), yet, casual relations between these two factors were not established (2, 79). However, converging evidence suggests that cannabis use has the potential for inducing psychosis (31, 77, 79, 95–98). SC products contain compounds which act as highly potent CB1 and CB2 full agonists, and in contrast to natural cannabis, contain no CBD (27, 31, 79). Due to the psychoactive features of SC drug ingredients it is not surprising that there are numerous reports on healthy and vulnerable individuals who suffer from recurrent psychosis after an acute or repeated consumption of SC drugs (15, 45, 99). Recent reports in Europe suggest that 15% of SC users who report to emergency departments present psychotic symptoms (100). These figures are far greater compared to those using other types of psychoactive substance (100). In addition, compared with cannabis, psychotic symptoms that are associated with SC are more severe and gross, in some cases they can even last for weeks following last use (10, 99).

**Effects of Cannabinoids on the Central Nervous System**

A large number of recent studies present a range of functional and structural neuronal abnormalities associated with regular use of cannabis (32, 49, 50). Generally, cannabis users show volumetric, gray matter, and white matter structural changes in the brain, particular within limbic and prefrontal areas (49, 50, 101). In addition, pharmacological studies draw a link between cannabis use and alterations of dopamine synthesis (102). Greater dose of THC, and an earlier age of onset area associated with these neuronal alterations (2, 32).

Compared with cannabis, there are fewer brain imaging studies exploring the neural correlates of SC use. Nurmedov et al. compared 20 males who used SC products with 20 healthy control participants and reported that SC users showed smaller gray-matter volume in the thalamus and the cerebellum (47). Recently, Zorlu et al. found a reduction of white matter volumes in several brain regions including the left temporal lobe and subcortical structures among SC users (48). In another single case study, a young SC user reported severe symptoms induced following a voluntary abstinence from SC drugs. In this patient, dopamine D2 and D3 receptors availability was lower in the striatum and in extra-striatal regions in comparison with healthy control participants during abstinence but it recovered after treatment (103). These initial studies highlight some the neurotoxic potential of SC products but since they are still preliminary. Further research is warranted.
Health Hazards and Withdrawal
In contrast to cannabis, the use of SC has been associated with severe hazardous health effects on multiple systems and with death (28, 104, 105). During the last 8 years in the United Kingdom, there were 510 reports associated with SC use that required urgent medical intervention (57). In USA there were 37,500 reported cases of seizures and 3,682 reported cases of poisonings related to SC use during 2014 (106). In addition, while there is no available documentation on an overdose death as a result of cannabis use (1), there are numbers of reports indicating a fatal outcome following consumption of SC drugs. Tait et al. identified at least 26 cases of individuals who used SC products and exhibited side-effect complications that have led to their death. The major complications were cardiovascular events, respiratory depression, pulmonary complications and acute kidney injury (107). Prolonged consumption of SC is associated with serious withdrawal symptoms including; agitation, irritability, anxiety, and mood swings (43). Some of these symptoms are similar to cannabis, yet, the differences in presentation may reflect the presence of extraneous psychoactive compounds, including amphetamine-like stimulants, and the high affinity of these SCs (43, 45).

CONCLUSIONS

Cannabinoid based drugs became increasingly popular despite the risks associated with their use (31, 45, 57). While the psychotropic effects associated with natural cannabis are related to the presence of THC (1), SC products contain a wide range of high-potent full agonists of the cannabinoid receptors that induce "THC-like" effects, but they are more severe and enduring (10, 15, 29, 31). While cannabis use usually induces psychotropic effects such as euphoria, relaxation, and a general pleasant feeling, it is associated with severe side-effects (1). The use of SC drugs is associated with more undesired effects including; agitation, irritability, confusion, hallucinations, delusions, psychosis, and death (28, 104, 105).

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