HHS Public Access

Author manuscript

Trends Pharmacol Sci. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

Trends Pharmacol Sci. 2017 March ; 38(3): 257–276. doi:10.1016/j.tips.2016.12.003.

Synthetic Pot: Not Your Grandfather's Marijuana

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Abstract

In the early 2000's in Europe and shortly thereafter in the USA, it was reported that "legal" forms of marijuana were being sold under the name K2 and/or Spice. Active ingredients in K2/Spice products were determined to be synthetic cannabinoids (SCBs), producing psychotropic actions via CB_1 cannabinoid receptors, similar to those of Δ^9-THC, the primary active constituent in marijuana. Often abused by adolescents and military personnel to elude detection in drug tests due to their lack of structural similarity to Δ^9-THC, SCBs are falsely marketed as safe marijuana substitutes. Instead, SCBs are a highly structural diverse group of compounds, easily synthesized, which produce very dangerous adverse effects occurring by, as of yet, unknown mechanisms. Therefore, available evidence indicates that K2/Spice products are clearly not safe marijuana alternatives.

Keywords

Synthetic Cannabinoids; K2; Spice; CB_1 Cannabinoid Receptor; Marijuana Substitute

Synthetic cannabinoids (SCBs): Not simply fake marijuana

Synthetic cannabinoids (SCBs) are a growing class of highly potent, highly efficacious cannabinoid agonists that, until recently, have been falsely marketed as "safe" and "legal" alternatives to marijuana [1]. As early as 2004, SCBs were promoted by Internet retailers and European "head shops" as meditation potpourris and tropical incense products under names such as K2 and Spice [2]. It was not until late 2008 that K2/Spice products were investigated by the European Monitoring Center for Drugs and Drug Addiction for their psychoactive properties [3, 4]. Upon analysis of these herbal mixtures, the synthetic cannabimimetics JWH-018 and CP 47,497-C8 were identified as the primary psychoactive

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Conflicts of Interest:
The authors have no significant conflicts of interest to declare.

components [1]. Since then, several structural classes of SCBs have quickly evolved and diversified to avoid forensic detection and legislative scheduling [1, 5]. Individual users have sought after SCBs to avoid detection in standardized drug testing as well as to achieve a more intense high than that associated with marijuana [3]. The purpose of this review is to summarize reported literature demonstrating that SCBs are neither similar nor suitable substitutes for marijuana and that use of these compounds can result in tolerance and dependence, as well as numerous other documented adverse, toxic and potentially fatal effects.

Evolution of Cannabinoid Nomenclature

The term “cannabinoid” originally referred to a number of structurally related C21 aromatic hydrocarbon compounds isolated from the *Cannabis Sativa* plant [6]. However, following characterization of Δ^9-THC, the principal psychoactive constituent in cannabis [7], and cloning of cannabinoid receptors [8, 9], the term “cannabinoid” instead came to be associated with drugs sharing pharmacological profiles similar to Δ^9-THC and exhibiting affinity for cannabinoid receptors, apart from any structurally similarity to compounds originally isolated from the cannabis plant [10]. Therefore, currently accepted nomenclature for “cannabinoids” are ligands that bind to and modulate the activity of cannabinoids receptors [11]. Cannabinoids are structurally diverse and range from compounds that are endogenously produced (endocannabinoids) [12], to plant-derived (phytocannabinoids) [13] and synthesized compounds (synthetic cannabinoids) [14]. This review will focus on the growing epidemic of synthetic cannabinoid abuse, sought primarily for agonist actions of these compounds at CB_1 cannabinoid receptors [15].

History of emerging SCB abuse and progression of SCB structural scaffolds

Cannabis sativa, commonly known as marijuana, has had an extensive history of medicinal and recreational use dating back to 2600 BC [16]. It was not until 1965 that Dr. Raphael Mechoulam and colleagues discovered the primary psychoactive compound in marijuana, Δ^9-tetrahydrocannabinol (Δ^9-THC) [17]. Upon this finding, significant advancements were made in the cannabinoid field including the characterization of the endocannabinoid system and the identification and cloning of the CB_1 and CB_2 cannabinoid receptors [8, 9]. As cannabinoid research progressed, production of high affinity synthetic CB_1 and CB_2 cannabinoid receptor ligands began to emerge. Alongside classic plant-derived phytocannabinoids, novel synthetic cannabinoid classes such as the aminoaklylindoles (*e.g.,* WIN-55,212-2) and bicyclic cannabinoids (*e.g.,* CP-55,940) contributed to the structural diversity of cannabinoid pharmacology [18, 19]. Questions of how structurally distinct molecules like Δ^9-THC and WIN-55,212-2 bind to CB_1 and CB_2 cannbinoid receptors with high affinity led to the development of novel cannabimimetics by substituting the morpholino group of aminoalkylindoles with the C3 pentyl side chain of Δ^9-THC [20]. Synthesis of pyrrole and indole-derived cannabinoids with the substituted *n*-pentyl group lead to the discovery of the high affinity, full CB_1 cannabinoid receptor agonist JWH-018 [1-pentyl-3-(1-naphthoyl)indole] [21, 22].

More than twenty years following the synthesis of JWH-018, over 150 SCBs have been identified [3]. Aside from the major chemical classes of SCBs, including classical cannabinoids, cyclohexyl-substituted phenols, naphthoylindols, and benzoylindoles, newer SCB structures such as tetramethylcyclopropylindoles, adamantoylindoles, indazole carboximides and quinolinyl esters have been popularized in K2/Spice products [5, 23] (Figure 1). While these SCBs have been advertised as “synthetic marijuana,” when compared to Δ^9-THC, they are structurally heterologous. Of the five structural components that contribute to the high affinity and partial agonism of Δ^9-THC at CB_1 and CB_2 cannabinoid receptors — including the C3 side chain, phenolic hydroxyl, and three rings: aromatic A-ring, pyran B-ring, and the cyclohexenyl C-ring — only one of the pharmacophores are shared with SCBs, that being the C3 side chain [16]. Although SCBs are highly diverse molecules, primary structural motifs that comprise SCBs reveal common pharmacophores. These common pharmacophores include 1) an indole or indazole core, 2) an amide, ketone, or ester linker, 3) a ring consisting of a naphthyl, quinolinyl, adamantyl, tetramethylcyclopropyl moiety, and 4) a hydrophobic alkyl group attached to the nitrogen atom of the indole or indazole ring [5]. Many SCBs such as JWH-018, UR-144, AKB48, and PB-22 have also been subjected to the addition of molecular substituents like halogenation of corresponding alkyl chains and stacking of aromatic naphthoyl and indole groups in order to increase affinity and maximize *in vivo* cannabimimetic effects at CB_1 cannabinoid receptor [23, 24]. Continuous manipulation and modification of these compounds by clandestine laboratories has accelerated the evolution of unique and potentially toxic SCBs, while legislatures have been working vigorously to ban the active constituents in K2/Spice products [2].

Evidence of K2/Spice usage in the USA was first reported in 2009. However, it was not until late 2010 that the National Forensic Laboratory Information System (NFLIS) — under the guidance of the USA Drug Enforcement Administration (DEA) — reported tremendous spikes in K2/Spice product usage. As shown in Figure 1, the major SCBs found in seized K2/Spice products during 2010 were JWH-018, JWH-073 and CP-47,497. While actions were taken to have the naphthoylindole- and cyclohexylphenol-like analogues regulated by the DEA as Schedule I compounds (*e.g.,* having no currently accepted medical use and thus illegal to possess, except for researchers with schedule I licenses), the new, chemically distinct SCBs UR-144, XLR-11 and AKB48 emerged on the market simultaneously and were not captured by these legislative actions. By July 9, 2012, legislation was able to permanently schedule the naphthoylindole- and cyclohexylphenol-like analogues under 1152 FDASIA. Since then, two separate legislative cases, 78 FR 28735 (May 6, 2013) and 79 FR 7577 (February 10, 2014), successfully resulted in the scheduling of numerous novel SCBs (*e.g.,* UR-144, XLR-11, AKB48, AB-FUBINACA and PB-22) found in K2 products. Unfortunately, the development of novel SCBs has remained ahead of the legislative scheduling process and continues to diversify to escape coverage by existing laws and to elude forensic detection, with no apparent end in sight [2].

SCB Toxicity in humans - comparison to Δ^9-THC

While often advertised as “safe” and/or “legal” alternatives to marijuana on the internet, SCBs have proved to be dangerous novel chemicals that are structurally distinct from Δ^9-

THC, and their use results in a constellation of adverse effects that are distinct from, and markedly more toxic than, those produced by marijuana (Table 1). In particular, reports from a number of clinical case studies have documented markedly greater toxicity following acute use of K2/Spice than marijuana, across a broad number of organ/tissue systems, including gastrointestinal [1, 3, 25–27], neurological [3, 26, 28–42], cardiovascular [34, 36, 37, 43–46] and renal [47–49]. Furthermore, although development of dependence to marijuana is rare, chronic use of SCBs can lead to tolerance, dependence, and withdrawal [50–52]. Most alarming, however, are reports that SCB abuse in some individuals can result in death [53]. Taken collectively, clinical cases reported in recent scientific literature clearly indicate that SCBs found in K2/Spice products are not simply safe or alternative forms of “synthetic marijuana”.

Distinct SCB toxicity in humans - issues for special concern

Pro-convulsant effects

Despite current interest in medical cannabis as a treatment for epilepsy and other seizure disorders (recently reviewed in [54], for example), the clinical literature is rife with reports of seizures and convulsions elicited by SCBs in humans ([44, 55–58]), and in one case, their exposed pets [59]. As may be expected from case reports, forensic determination of the specific SCBs responsible for these effects occurs only rarely, and the co-use of other drugs often confounds the causal attribution of these convulsant effects to SCBs. Nevertheless, controlled laboratory studies in animals have recently been performed and support the notion that high efficacy SCBs exhibit unexpected pro-convulsant effects. For example, the SCB AKB48 and its fluorinated analogue 5F-AKB48 [23] as well as the aminoalkylindoles JWH-015 and JWH-073 [60] all induced impaired visual, acoustic and tactile sensorimotor responses, convulsions, myoclonia and hyperreflexia in mice. Similarly, the aminoalkylindole SCBs JWH-018, JWH-073, JWH-210, AM-2201 and JWH-167 all increased central nervous system excitability in a functional observation battery in mice, with JWH-018 being “especially active” in this regard [61]. Further characterization of the pro-convulsant effects of the SCBs is clearly warranted.

Pro-psychotic effects

SCBs are typically much more potent and efficacious than Δ^9-THC at both CB_1 and CB_2 cannabinoid receptors, suggesting a capacity to induce far more intense *in vivo* effects than cannabis. This is sometimes – but not always – the case. With regards to toxicity of cannabinoid agonists, epidemiological studies suggest that cannabis use, particularly in adolescence, increases risk for psychotic episodes later in life [62, 63], and preclinical studies have also demonstrated pro-psychotic effects of Δ^9-THC in rodents treated during the adolescent period [64]. Alarmingly, reports of acute and lasting psychosis elicited by use of SCBs are rapidly accumulating in the clinical literature [4, 34, 35, 38, 50, 65–72], but the mechanism of psychosis remains poorly understood and no controlled studies have yet characterized the pro-psychotic effects of SCBs in humans. Even acute use of SCBs can elicit psychosis-like symptoms of paranoia, disorganized behavior, visual and auditory hallucinations, and suicidal thoughts which persist much longer than more typical cannabinoid effects of motor depression and anxiety [65]. Interestingly, SCBs induce these

effects in users with previous histories of psychosis and schizophrenia, as well as in users with no previous morbidity. Pro-psychotic effects of the low-efficacy cannabinoid agonists Δ^9-THC, dronabinol, and nabilone have been studied under controlled laboratory conditions in humans (reviewed by [73]); however, evidence for a causal relationship between SCB use and re-emergence of previous psychotic symptoms or induction of new-onset psychosis is hampered by the fact that the literature surrounding this topic consists entirely of case reports. Indeed, differences in patient assessment methods, the general lack of forensic confirmation of which exact SCB compound was used, the possible confound of co-use of SCBs with prescribed therapeutics or other drugs of abuse, and the potential for preexisting mental illness should give one pause in attributing a causative link between SCB exposure and psychosis.

SCB abuse liability, tolerance, dependence and withdrawal

Abuse liability

The “gold standard” for preclinical abuse liability testing is the intravenous self-administration assay [74], where an animal subject within a modified cage or experimental chamber can self-inject a drug through a surgically-implanted venous catheter after a specific behavior has been emitted (typically a lever press or a nose poke; for more details of the procedure, see [75]). Thus, these studies directly assess the reinforcing effects of drugs. Importantly, not all drugs which are abused by humans maintain cointingent responding in laboratory species. For example, serotonergic hallucinogens are not reliably reinforcing in self-administration studies in laboratory animals [74], and the psychotropic effects of cannabinoids may be similar to those of the psychedelics. Thus, despite constant recreational use and abuse of cannabinoids throughout human history, the reinforcing effects of cannabinoids have not been widely investigated in laboratory animals. Some of the earliest studies on the reinforcing effects of cannabinoids failed to establish intravenous self-administration of Δ^9-THC in rhesus monkeys [76] or in rats [77]. In later years, attempts were made to compensate for the relatively slow-onset, long-lasting behavioral effects of existing cannabinoids by establishing self-administration procedures with widely spaced drug deliveries, but these efforts also failed to establish reliable responding maintained by either Δ^9-THC or CP-55,940 [78], leading to the widespread perception that cannabinoids, like serotonergic hallucinogens, were simply ineffective in self-administration assays. However, it was eventually noted that these previous studies utilized intravenous unit doses which were higher than those calculated from human studies, perhaps indicating that the unit doses available for self-administration would be aversive to laboratory animals. Similarly, the lipophilic nature of Δ^9-THC and its poor solubility in water suggested that the Δ^9-THC solutions used were, at best, in suspension and therefore not likely to be biologically active. Indeed, the use of lower doses of Δ^9-THC which clearly dissolve in solution, allowing the drug to rapidly penetrate the brain after intravenous administration, seems to readily maintain self-administration in squirrel monkeys [79, 80]. Additionally, self-administration of endogenous cannabinoids anandamide [81] and 2-arachidonoylglycerol [82] by squirrel monkeys has also been demonstrated. To date, Δ^9-THC has not been reported to maintain reliable self-administration behavior in rodents, although the higher efficacy cannabinoids WIN 55,212 and HU-210 have been reported to maintain intravenous self-administration

behavior in mice and rats [83–85]. These data may suggest that other high efficacy cannabinoids, such as those present in K2/Spice products, might also display reinforcing effects in self-administration procedures, but thus far, no published reports bolster this supposition. Indeed, a recent paper failed to demonstrate reinforcing effects with JWH-030, JWH-175 or JWH-176 in rats [86]. Nevertheless, the majority of self-administration reports in squirrel monkeys and rats demonstrate that the reinforcing effects of intravenous cannabinoids are significantly attenuated by pretreatment with CB_1 cannabinoid receptor antagonists, strongly suggesting that the abuse-related effects of these substances are indeed mediated by central cannabinoid systems.

Another way to indirectly assess abuse-related effects of cannabinoids in experimental animals is to study their capacity to elicit a conditioned place preference. After a few pairings of a drug with a novel context, an increase in time spent in the drug-paired context relative to control is deemed a “conditioned place preference” and may indicate that the drug has positive motivational properties, while a decrease in time spent in the drug-paired context is termed a “conditioned place aversion” and may indicate that the drug has aversive stimulus properties [87]. Presumably, the learned association between the context and the interoceptive stimulus properties of the drug dictates both the magnitude and directionality of the place conditioning effect. Studies investigating the capacity of cannabinoids to induce conditioned place preference present a complex and contradictory picture. For example, administration of high dose Δ^9-THC or higher efficacy cannabinoids (including CP 55,940, WIN 55,212, and HU 210) to rodents typically produces either no effect in place conditioning assays, or induces place aversion (reviewed in [88] and [89]). Nevertheless, robust preferences for Δ^9-THC-paired contexts have sometimes been reported in rats [90] and mice [91–93] if the animals have been “pre-exposed” to cannabinoids prior to beginning conditioning trials. These results probably indicate that methodological factors within place conditioning experiments are critical mediators of the magnitude and directionality (preference versus aversion) of the effects observed with cannabinoids. Interestingly, as previously demonstrated with Δ^9-THC, prior exposure to Δ^9-THC was required to “unmask” rewarding effects of JWH-018 [94] and pre-exposure to HU-210 prior to CPP conditioning sessions was necessary to obtain place preference with HU-210. [95]. At the time of this writing, very few SCBs have been tested in CPP experiments. With the exception of JWH-018 (described in [94]), only CP 55,940, WIN 55,212, and HU 210 have been tested for rewarding or aversive effects using place conditioning methods, and the results of such studies have been highly variable ([88, 89]). Given the general failure of cannabinoids to elicit reinforcing effects in laboratory animals, it may be the case that place conditioning could be more sensitive to abuse-related effects of these compounds. Further efforts to characterize newly emerging novel SCBs should consider profiling these drugs in place conditioning assays.

Tolerance

A recent survey [96] finds prevalent use of SCBs among cannabis smokers (*e.g.,* 32.3%), including a subset of individuals reporting daily use of SCBs. This agrees with previous reports that most college students who abuse SCBs also regularly use marijuana [30, 97], raising the possibility of cross-tolerance between Δ^9-THC and the SCBs. Repeated

administration of cannabinoid agonists has been shown to result in tolerance to several central and peripheral effects in laboratory animals [98–100], and to cellular effects observed *in vitro* (reviewed by [10]). In human marijuana users, tolerance to numerous cannabinoid effects has also been reported following smoked [101–103] and oral [104–106] administration of Δ^9-THC. Thus, a history of Δ^9-THC administration might also render individuals less sensitive to some effects of the higher efficacy SCBs through the phenomenon of cross-tolerance. This is especially important because drug users often increase the amount of drugs they consume in an attempt to surmount tolerance to desired psychoactive effects, and any factors which lead SCB users to escalate dose will necessarily increase the risk for adverse effects. Thus, if it is the case that non-cannabinoid receptors prove to be involved in some of the adverse effects of SCBs, tolerant individuals might be particularly susceptible to these effects as they escalate their drug doses.

The role of intrinsic efficacy in tolerance and cross-tolerance among the cannabinoids is underdeveloped, and the data in this domain are often contradictory. For example, some studies show similar tolerance to hypothermic effects of Δ^9-THC and the high efficacy cannabinoids CP-55,940 and WIN 55,212-2 following a Δ^9-THC pretreatment regimen [107], while others show these same high efficacy cannabinoids to partially surmount Δ^9-THC-induced tolerance to locomotor suppression, hypothermia and antinociception [108]. More recently, the high efficacy SCBs JWH-018 and JWH- 073 were unable to induce hypothermia in mice previously made tolerant to hypothermic effects of low efficacy Δ^9-THC, suggesting that cross-tolerance developed to the hypothermic effects of the high efficacy SCBs, despite the relatively large disparity in intrinsic activity [109]. In other words, unlike what is typically observed with other drugs (such as the opioids), tolerance to an effect induced by low efficacy Δ^9-THC was not surmounted by administration of higher efficacy SCBs. Furthermore, cross-tolerance was still present 14 days after Δ^9-THC cessation, suggesting that this cross-tolerance may be as persistent as the tolerance induced by repeated administration of the high efficacy SCBs themselves [109]. Indeed, chronic treatment with high efficacy SCBs results in rapid and persistent tolerance to some, but not all, *in vivo* effects, accompanied by region-specific down-regulation and desensitization of central CB_1 cannabinoid receptors [109–111] (Figure 3).

In the case report literature, there are a few published instances of what might seem to be a paradoxical hyperthermic response to SCB use in humans. One report describes the clinical course of 11 patients exposed to the SCB MAB-CHMINACA [58]. For the most part, the symptoms reported are consistent with known SCB effects, including altered consciousness, severe agitation, seizures and death, however, a 20-year-old male patient developed a malignant hyperthermia and died on his seventh day in the hospital. Similarly, another report (which did not forensically determine the specific compound ingested) described hyperthermia in a patient who reportedly had smoked a commercial SCB preparation known as “Mr Big Shot” [112] and was successfully treated after 60 minutes of evaporative cooling and ice pack exposure. At present the mechanism for SCB-induced hyperthermia – if indeed SCBs were the cause of these two reported instances – remains unknown.

Dependence and Withdrawal

Drug dependence cannot be directly observed *in vivo*, but it is assumed to be present when either sudden abstinence from chronic drug use or administration of an antagonist elicits a withdrawal syndrome. Most studies indicate that simple cessation of chronic Δ^9-THC administration does not cause spontaneous signs of withdrawal in laboratory animals [113], but robust withdrawal signs are reported after discontinuing SCBs in human users [114]. Unfortunately, clinical reviews of withdrawal following SCB discontinuation in humans (see, for example, [52, 96, 114–116] do not report specific SCB compounds used, most likely because the users themselves do not know the identity of the specific drugs. However, in mice, CB_1 cannabinoid receptor antagonist-precipitated withdrawal is reliably characterized by readily quantifiable signs, including wet dog shakes, head shakes, front paw tremor, and motor hyperactivity [113, 117]. Importantly, withdrawal contributes to relapse to drug use for a wide range of abused substances. Thus, if withdrawal from high efficacy SCBs is exacerbated compared to Δ^9-THC, this implies that SCB users attempting to cease SCB use may be powerfully motivated to relapse to escape aversive withdrawal effects. However, it is not currently known whether abuse of high-efficacy SCBs would result in a more extreme abstinence syndrome than typically observed following discontinuation of cannabis use, but reports of SCB withdrawal are accumulating in the literature [52, 114–116]. Given the adverse effects associated with acute and long-term abuse of SCBs [118–120] it is increasingly apparent that research into potential therapeutics is warranted. Currently, there is no accepted medical treatment for cannabinoid dependence. The most well-researched pharmacotherapeutic for the treatment of cannabinoid dependence is the CB_1 cannabinoid receptor antagonist / inverse agonist rimonabant [121], however, the inverse agonist properties of this drug result not only in blockade of the pharmacological effects elicited by cannabinoid agonists, but also in disruption of constitutive CB_1 cannabinoid receptor activity. This fundamental difference between inverse agonists (which decrease signaling below levels observed in normal physiology) and what are conceptualized as neutral antagonists (which block agonist-elicited stimulation in signaling, but preserve constitutive activity) has pharmacological relevance within the cannabinboid system, as rimonabant has been shown to increase cAMP levels in a forskolin-stimulated cAMP assay [122, 123], while the neutral CB1R antagonist AM4113 has no effect on forskolin-stimulated cAMP production [123]. Systems-level behavioral differences between inverse agonists and neutral antagonists have also been demonstrated, where AM4113 did not induce conditioned gaping in rats or emesis in ferrets, both of which occur with inverse agonists, such as rimonabant and AM251 [124, 125]. In humans, adverse events reported after rimonabant exposure, including suicidal ideation, nausea, seizure [126], anxiety and depression [127], eventually led to withdrawal of the drug from the European market and importantly, these adverse events have been ascribed to the inverse agonist properties of rimonabant at CB_1 cannabinoid receptors in the CNS [117, 128]. This suggests that cannabinoid withdrawal precipitated by rimonabant, and the direct adverse effects of rimonabant in subjects not previously exposed to exogenous cannabinoids, may not be solely attributed to blockade of CB_1 cannabinoid receptors, but may also be exacerbated by rimonabant's negative efficacy at those binding sites. Development of a truly neutral CB_1 cannabinoid receptor antagonist as a possible pharmacotherapeutic for cannabis dependence

is currently an active area of research, and may be useful in treatment of cannabinoid dependence.

Factors potentially contributing to greater SCB toxicity relative to Δ⁹-THC

In vitro pharmacodynamics of SCBs

The mechanisms responsible for the enhanced toxicity of SCBs relative to Δ^9-THC (see Table 1) are currently unknown. Many factors may contribute, including potential off-target action of SCBs at non-cannabinoid receptors [61], a complete lack of quality control in abuse-ready smoking products [129], and the absence of potentially toxicity-mitigating non-psychoactive phytocannabinoids in SCB products, as compared to those co-occurring endogenously in *cannabis sativa* [130]. However, the following section will focus on reported differences in CB_1 cannabinoid receptor affinity, potency and efficacy between SCBs and Δ^9-THC, for which the most quantitative data are available.

SCBs exhibit higher CB_1 cannabinoid receptor affinity than Δ⁹-THC

Δ^9-THC produces psychotropic actions by activating CB_1 cannabinoid receptors in the CNS [131]. SCBs also bind and activate CB_1 cannabinoid receptors (see following discussion), and thus the abuse liability of both Δ^9-THC and SCBs likely results from their agonist actions at these receptors. Therefore, this review will limit discussion of recent reports that have examined the affinity of SCBs for CB_1 cannabinoid receptors. Almost all SCBs studied to date have higher affinity for CB_1 cannabinoid receptors than Δ^9-THC. Depending on the radioligand or specific assay conditions employed, the affinity (or Ki) of Δ^9-THC has been reported to range from 3.87 [5] to 41 nM [132]. In contrast, SCBs contained in seized K2/Spice products often exhibit sub-nanomolar CB_1 cannabinoid receptor affinity (*e.g,* 5F-PB-22 [133], AK-B48 [133], AB-FUBINACA [134], ADB-FUBINACA, [134], JWH-122 [24], JWH-210 [21]). Newer SCBs derived from the indazole carboxamide scaffold, including AB-CHIMINACA [135] and AKB48 [23, 133], also have sub-nanomolar affinity for CB_1 cannabinoid receptors. In addition to such “ultra-high affinity” compounds, many other SCBs also bind with high affinity to CB_1 cannabinoid receptors, exhibiting Ki values between 1 and 20 nM (*e.g.,* JWH-018 [136], AB-PINACA [135], JWH-250, [137], STS-135 [133]). Importantly, since the majority of SCBs bind to CB_1 cannabinoid receptors with higher affinity relative to Δ^9-THC, it might be anticipated that these compounds may also more potently modulate signaling pathways, potentially contributing to increased toxicity observed for SCBs.

SCBs exhibit high potency and greater efficacy for modulation of CB_1 cannabinoid receptor-mediated signaling than Δ⁹-THC

In addition to exhibiting higher affinity for CB_1 cannabinoid receptors than Δ^9-THC, most SCBs also modulate intracellular signaling pathways via cannabinoids receptors with high potency and full efficacy when compared to the partial agonist Δ^9-THC (Figure 2). CB_1 and CB_2 cannabinoid receptors are G-protein coupled receptors that, upon agonist binding, activate $G_{i/o}$-proteins [138, 139] that then proceed to inhibit activity of the downstream intracellular effector adenylyl cyclase (AC), resulting in reduction in cAMP levels [140]. Therefore, most studies quantify the intrinsic activity of SCBs by measuring the potency

(*e.g.,* EC_{50}/IC_{50}) and efficacy (*e.g.,* E_{max}/I_{max}) of these compounds to activate G-proteins and/or inhibit AC-activity in brain homogenates (G-protein activation) or whole cells expressing native or transfected CB_1 cannabinoid receptors (AC-activity). Activation of CB_1 cannabinoid receptors by Δ^9-THC results in potent activation of G-proteins (ED_{50} values 81 [141] to 167 [136] nM), but only as a partial agonist. SCBs examined in this assay instead act full CB_1 cannabinoid receptor agonists when compared to Δ^9-THC (*e.g,* JWH-018 [136], 5F-PB-22 [133], MAM-2201 [142], JWH-250 [137], STS-135 [133], XLR-11 [143]). Δ^9-THC also potently inhibits AC-activity via CB_1 cannabinoid receptors (*e.g.,* IC_{50} values ranging from 5.0 [140] to 44 nM [23]), although with reduced efficacy indicative of a partial agonist. In marked contrast, almost all SCBs examined in this assay also inhibit AC-activity with high potency in the nM range, but similar to modulation of G-protein activity, act as full agonists (*e.g,* 5F-PB-22 [133], AB-PINACA [142], EAM-2201 [142], MAM-2201 [142], JWH-250 [137], PB-22, AK-B48 [133], STS-135 [133] and XLR-11 [143]). Similar full agonist activity for SCBs at CB_1 cannabinoid receptors has been demonstrated by use of additional methods including a fluorometric assay to measure membrane potential [144] and in primary hippocampal neurons by quantifying calcium transients [142]. As would be expected if SCBs are modulating G-protein activation and AC-inhibition via CB_1 cannabinoid receptors, in most instances, the rank order of affinity of the investigated SCBs for CB_1 cannabinoid receptors parallels the potency of these compounds to modulate CB_1 cannabinoid receptor-mediated signaling pathways [135] and those CB_1-mediated functional effects induced by SCBs can be reversed by CB_1 cannabinoid receptor antagonists [23, 135, 144]. Importantly, the higher efficacy of SCBs likely results in not only greater acute effects that may contribute to toxicity, but also in enhanced chronic effects occurring at both cellular and whole animal levels that perhaps lead to tolerance and dependence.

SCB *in vivo* Pharmacodynamics

The higher *in vitro* efficacy of SCBs as compared to Δ^9-THC is intriguingly recapitulated at the systems level for some endpoints, but not for all endpoints. Administration of cannabinoid agonists from multiple structural classes elicits a characteristic cluster of effects in laboratory animals. This cluster of the four classical endpoints of hypothermia, analgesia, catalepsy, and locomotor suppression has been termed the cannabinoid tetrad [18, 145]. Consistent with the higher *in vitro* efficacy of SCBs as compared to Δ^9-THC, multiple laboratories reliably report that hypothermic effects obtained with SCBs are greater in magnitude than those observed after administration of maximally effective doses of Δ^9-THC in mice [109, 146, 147]. In contrast, multiple research groups consistently demonstrate that Δ^9-THC elicits a similar degree of locomotor suppression as higher efficacy SCBs [109, 148] [135]. No consistent efficacy-dependent results are obtained with the cannabinoid tetrad endpoints of analgesia and catalepsy, presumably due to numerous methodological variables associated with data collection across laboratories.

Perhaps the most vexing finding with regards to the relationship between intrinsic efficacy and behavioral effects comes from the realm of drug discrimination. In humans, cannabinoids exert numerous effects on perception and other unobservable psychological endpoints, thus, drug discrimination is useful as an animal model of these subjective effects. The drug discrimination assay can be thought of as an *in vivo* drug detection procedure

whereby animals are trained to recognize the stimulus effects of a given dose of a particular training drug. Once trained, animals may be administered different doses of the same training drug, or different doses of a novel compound suspected to have similar subjective effects to the training drug. Indeed, SCBs reliably induce Δ^9-THC-like effects in animals trained to discriminate Δ^9-THC. For example, full substitution for Δ^9-THC was observed with JWH-018 and JWH-073 in mice [149], which is consistent with the notion that a full agonist would substitute for a partial agonist in this assay. However, instead of a partial-substitution profile expected from the study of other drugs as discriminative stimuli, Δ^9-THC reliably produces ***full substitution*** for the training stimulus across rodent and non-human primate species trained to discriminate a variety of full CB_1 cannabinoid receptor agonists. For example, Δ^9-THC fully substituted for the high efficacy SCB JWH-018 in rhesus monkeys [150] and in rats [151]. This same pattern of results was also obtained in squirrel monkeys trained to discriminate the full CB_1 cannabinoid receptor agonist AM4054 [152]. It is clear that the role of intrinsic cannabinoid efficacy in systems-level effects is poorly understood, and likely to be a fertile topic for research for some time.

SCB Pharmacokinetics

SCBs are metabolized to many active phase I and II metabolites, Δ^9-THC is not

Mounting evidence indicates that SCBs can cause severe, adverse responses in users (Table 1), but little is known about the potential influence of metabolism on the toxicological effects of these novel compounds. It is recognized that oxidative metabolism (Phase I) generally terminates the activity of the parent compounds and functionalizes them for future conjugation reactions (Phase II) such as glucuronidation and sulfation [153], considered the final step for terminating biological activity. Δ^9-THC metabolism has been well studied and is extensively metabolized by cytochrome P450 enzymes CYP2C9 and CYP3A4, but only to a single major active metabolite (11-OH-Δ^9-THC) with equivalent CB_1 cannabinoid receptor affinity [154] and slightly higher potency in antinociceptive assays [155] as compared to the parent drug. 11-OH-Δ^9-THC is subsequently oxidized to an inactive intermediate 11-nor-9-carboxy-Δ^9-THC that is conjugated to form the O-ester glucuronide, the major metabolite detected in urine [156]. In marked contrast, it has been reported that numerous hydroxylated metabolites of the SCBs JWH-073, JWH-018 and AM-2201 bind to CB_1 and CB_2 cannabinoid receptors with affinity similar to that of the parent compound, and possess biological activity in both *in vitro* and *in vivo* assays [157–159]. Furthermore, several of the hydroxylated compounds detected following administration of the SCBs JWH-018, AM-2201, JWH-122, JWH-210, PB-22, MAM-2201, EAM-2201 and 5F-PB-22 [158, 160] are the major phase I metabolites formed, and importantly retain higher *in vitro* affinity and activity than Δ^9-THC. Although a major glucuronide conjugate of JWH-018 exhibits reduced affinity for CB_1 cannabinoid receptors, this metabolite still binds to CB_1 cannabinoid receptors in the high nM range and acts as a competitive CB_1 cannabinoid receptor antagonist [161]. Therefore, in susceptible individuals (see following genetic polymorphism section), metabolism to active CB_1 cannabinoid receptor metabolites may contribute to increased half-life, efficacy and toxicity of SCBs compared to Δ^9-THC, while metabolism to competitive CB_1 cannabinoid receptor antagonists could lead to increased SCB consumption in an attempt to overcome blunted psychoactive effects. In any case, since

many hydroxylated and conjugated derivatives of SCBs (but not Δ^9-THC) retain biological activity, defining the metabolic processing of SCBs is required to fully understand the pharmacokinetic and pharmacodynamic properties of known and future novel classes of these abused compounds.

Genetic polymorphisms of P450 and UGT metabolic enzymes may contribute to idiosyncratic SCB toxicity

Based on the reported complex metabolism of SCBs to potentially pharmacologically relevant metabolites (see previous section), identifying specific phase I and II enzymes involved in SCB biotransformation is critical to provide essential direction for future pharmacokinetic and pharmacogenetic studies of current and future classes of these virtually unknown compounds. Without this information, understanding of adverse drug reactions potentially related to polymorphisms of drug metabolizing enzymes and drug-drug interactions cannot be achieved. For example, CYP1A2 and CYP2C9 are the major cytochrome P450 enzymes responsible for metabolism of the SCB JWH-018 [158], while CYP3A4 is most important for oxidation of AKB-48 [162]. SCBs of the napthoylindole class inhibit [163], while cigarette smoking induce [164], CYP1A activity. Several clinically relevant polymorphisms that affect activity of both CYP1A2 and CYP2C9 also have been reported [165]. Furthermore, two human brain UGT isoforms (UGT1A3 and UGT2B7) show relatively high activity toward two metabolites of the SCB JWH-018 commonly found in human urine (JWH-018-ω-OH and JWH-018-ω-COOH) [166], implying that these UGT enzymes may control neuronal concentrations of glucuronidated conjugates available for interaction with CB_1 cannabinoid receptors after SCB exposure. In summary, genetic polymorphisms of drug metabolizing enzymes in susceptible individuals may contribute to unique idiosyncratic toxicity often observed following abuse of SCBs.

SCB toxicity - CB_1 versus non-CB_1 cannabinoid receptor targets

To develop efficacious treatments for SCB toxicity, it is important to first determine potential targets responsible for mediating the adverse effects produced by these drugs. Since SCBs were originally synthesized to exhibit high affinity and activity at CB_1 and/or CB_2 cannabinoid receptors, it might be expected that many of the adverse effects produced by these drug occur via action at cannabinoid receptors. Indeed, as discussed previously in this review, SCBs exhibit several distinct *in vitro* and *in vivo* pharmacodynamic properties when acting at CB_1 cannabinoid receptors that likely contribute to the different and greater toxic effects of these drugs relative to Δ^9-THC. In support of this suggestion, SCBs examined to date (AM-2201, JWH-018, JWH-073, JWH-081, JWH-210, JWH-167 and JWH-391) lack appreciable affinity for a number of non-CB_1 cannabinoid receptor targets including norepinephrine, histamine, opioid, sigma, $GABA_A$ or benzodiazepine receptor subtypes [61]. The selective CB_1 cannabinoid antagonist rimonabant reverses the effects of these SCBs in a functional observational battery in mice (*e.g.,* muscle tone, equilibrium, sensorimotor activity, alertness, ease of handling and autonomic effects). Furthermore, sensorimotor dysfunction in mice produced by JWH-018, JWH-250 and JWH-073 [60, 167], and impaired motor activity and seizures resulting from JWH-018 and JWH-018-Br [168] are all normalized by co-administration with CB_1 cannabinoid receptor antagonists

rimonabant and AM-251. Finally, antinociception and hypothermic effects produced by the SCBs CP-55,950, WIN-55,212-2, JWH-073, A-834,735D and CP-47,497 are absent in CB_1 cannabinoid receptor knockout mice [169]. These *in vitro* and *in vivo* studies collectively indicate that many SCB adverse effects observed in humans are likely mediated via CB_1 cannabinoid receptors.

SCBs also exhibit high affinity and activity at CB_2 cannabinoid receptors, the second major cannabinoid receptor subtype [159, 170, 171]. Although CB_2 cannabinoid receptors are expressed in relatively low levels in the CNS [172] and are not directly associated with psychoactive effects produced by SCBs [173], prolonged activation of CB_2 cannabinoid receptors has been shown to upregulate 5-HT_{2A} serotonin receptors in mouse prefrontal cortex [174, 175]. 5-HT_{2A} serotonin receptors are the primary site of action for hallucinogenic drugs [176] and 5-HT_{2A} serotonin receptor dysfunction has been associated with mental disorders including anxiety [177] and psychosis [178]. Common adverse effects of SCBs, but not Δ^9-THC, are anxiety and psychosis [179] (Table 1). Based on the reported interaction between CB_2 cannabinoid and 5-HT_{2A} serotonin receptors, it is possible that chronic activation of CB_2 cannabinoid receptors by SCBs results in an enhancement of 5-HT_{2A} serotonin receptor function that contributes to anxiety and psychosis often observed following exposure to SCBs.

SCBs are structurally diverse (Figure 1) and produce many toxic effects that are not observed with Δ^9-THC (Table 1). Therefore, it might be anticipated that these uncharacterized compounds might also exhibit appreciable affinity and activity for cellular targets other than CB_1 or CB_2 cannabinoid receptors that contribute to the distinct toxicity associated with SCB abuse. In support of this suggestion, some (AM-2201, JWH-018, JWH-073, JWH-167 and JWH-391), but not other (JWH-081 and JWH-210) SCBs act as low potency (EC_{50} > 3 mM), but high efficacy (> 59%) inhibitors of hERG channels [61]. hERG channel inhibition contributes to prolonged QT intervals and ventricular tachycardia [180], and thus may underlie cardiovascular toxicity reported following SCB use [34] (Table 1). Although potential links to toxicity are currently unknown, SCBs have also been shown to inhibit currents through $5HT_3$ receptors in the high nanomolar (nM) range (100–600 nM) [181], and at high micromolar (μM) concentrations inhibit monoamine oxidase activity [182], antagonize $5HT_{2B}$ serotonin receptors [61], and activate strychnine-sensitive α_1 glycine receptors by direct and allosteric mechanisms [183]. In summary, although more research is required, the distinct toxicity profile observed with abuse of SCBs relative to Δ^9-THC likely results from actions at both CB_1 and non-CB_1 cannabinoid receptor targets.

“Antidote” for acute SCB toxicity – selective CB_1 cannabinoid receptor antagonists?

Since SCBs lack appreciable affinity for non-CB_1 cannainoid receptor targets [61] and almost all acute SCB responses in animals are blocked by co-administration with CB_1 cannabinoid receptor antagonists (*e.g.,* rimonabant or AM-251) [60, 61, 167–169], it is unfortunate that clinical studies to examine the potential use of CB_1 cannabinoid receptor antagonists for treatment of acute SCB overdose in emergency departments have not been

conducted. The CB_1 cannabinoid receptor antagonist/inverse agonist rimonabant was withdrawn from clinical trials for use in obesity by the European Medicines Agency in October of 2008 due to adverse psychiatric consequences [184]. Following this decision, all major pharmaceutical companies developing CB_1 cannabinoid receptor antagonist/inverse agonists quickly discontinued ongoing clinical research of drugs in this class. As might be expected, these safety concerns have likely limited investigation of CB_1 cannabinoid receptor antagonists for treatment of acute or chronic SCB toxicity in humans. However, since the most serious adverse effects of rimonabant were primarily observed following chronic therapy, and in a relatively small subset of patients [185], the important and potential life saving use of CB_1 cannabinoid receptor antagonists for treatment of acute SCB overdose should perhaps be examined.

Concluding Remarks

SCBs were originally synthesized to aid in the development of therapeutically useful cannabinoid receptor ligands [18–21]. Unfortunately, since the early 2000's, SCBs have been synthesized by clandestine labs and marketed to vulnerable populations as safe and legal alternatives to marijuana, despite the numerous serious adverse effects posed to human health (Table 1). Although production and usage of K2/Spice products has significantly increased over the years, very few mechanistic studies have established direct mechanisms responsible for the increased toxicity of these high affinity, high efficacy "marijuana substitutes" at CB_1 and/or non-CB_1-cannabinoid receptor targets (Outstanding Questions 1 and 2). In addition to lack of mechanistic insight, very little continues to be known concerning potential contributions of phase I and II metabolism of SCBs to toxicity observed following K2/Spice use (Outstanding Question 3). As reviewed here, the consequences of acute and chronic K2/Spice abuse have been examined in studies ranging from basic science reports to clinical cases [5, 21, 24, 44, 55–58, 133, 134]. Although much useful information has been gained, unfortunately, many important questions remain; such as, why adolescents appear to be more susceptible to the pro-psychotic actions of SCBs (reviewed in, for example, [186] and in [64]) (Outstanding Question 4). Additionally, it is curious why current treatment of SCB toxicity is purely supportive, lacking clinically available efficacious antidotes for serious life-threatening situations (Outstanding Questions 5 and 6)? Upon review of the structural diversity, distinct pharmacodynamic, pharmacokinetic and clinical effects produced by these compounds, it can readily be concluded that SCBs are neither similar, nor safe, substitutes for marijuana. As shown in Figure 4 (Key Figure) by comparing several characteristics of SCBs reviewed here with marijuana, distinctions between the pharmacological and clinical actions are quite dramatic. Although scheduling of SCBs has been a priority by the DEA since 2010, the inability for legislation to stay ahead of the production of novel SCBs continues to fail in preventing the ongoing abuse of these very dangerous and occasionally deadly drugs (Outstanding Question 7).

Acknowledgments

This work was supported in part by NIDA/NIH grant number DA039143.

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Outstanding Questions Box

- Why is there an apparent lack of research directed toward determination of non-CB_1 receptor-mediated targets possibly responsible for human toxicity produced by SCB, but not Δ^9-THC abuse?
- Does high affinity and efficacy of SCBs at CB_1 receptors, when compared to Δ^9-THC, contribute to greater toxicity associated with use of K2/Spice products?
- Do genetic polymorphisms of drug metabolizing enzymes, potentially producing pharmacologically active phase I and phase II metabolites, contribute to SCB toxicity in susceptible individuals?
- Does brain development during adolescence make K2/Spice users in this group more susceptible the potential psychotic and/or pro-convulsant effects of SCBs?
- Why is no research being conducted to examine the potential use of the CB_1 receptor antagonist/inverse agonist rimonabant for cases of acute K2/Spice overdose in emergency departments?
- Why is there an apparent lack of research toward development of other safe and widely available antidotes for treatment of SCB overdose?
- What legislative steps can be taken to stay ahead of production of novel SCBs by clandestine laboratories?

Trends Box

- Synthetic cannabinoids (SCBs) are a large collection of man-made chemicals, reported in the scientific literature over decades of research to have affinity for CB_1 and CB_2 cannabinoid receptors.
- Products known as K2 or Spice contain a mixture of SCBs that have been illicitly synthesized and sprayed onto inert plant material, in order to mimic the appearance and psychotropic effects of Δ^9-THC in marijuana.
- K2/Spice products are falsely marketed to adolescent and other vulnerable populations as “safe” and/or “legal” alternatives to marijuana, and are widely known to avoid detection in standard drug screens due to their lack of structural similarity to Δ^9-THC.
- SCBs present in K2/Spice products produce a variety of dangerous acute and chronic adverse effects, including psychosis, seizures, tolerance, dependence and death, with a greater severity and frequency than observed following marijuana use.
- Very little is known concerning the mechanisms underlying the distinct toxic effects of SCBs compared to Δ^9-THC, but it is likely that they result from actions at both CB_1 and non-CB_1 cannabinoid receptor targets.

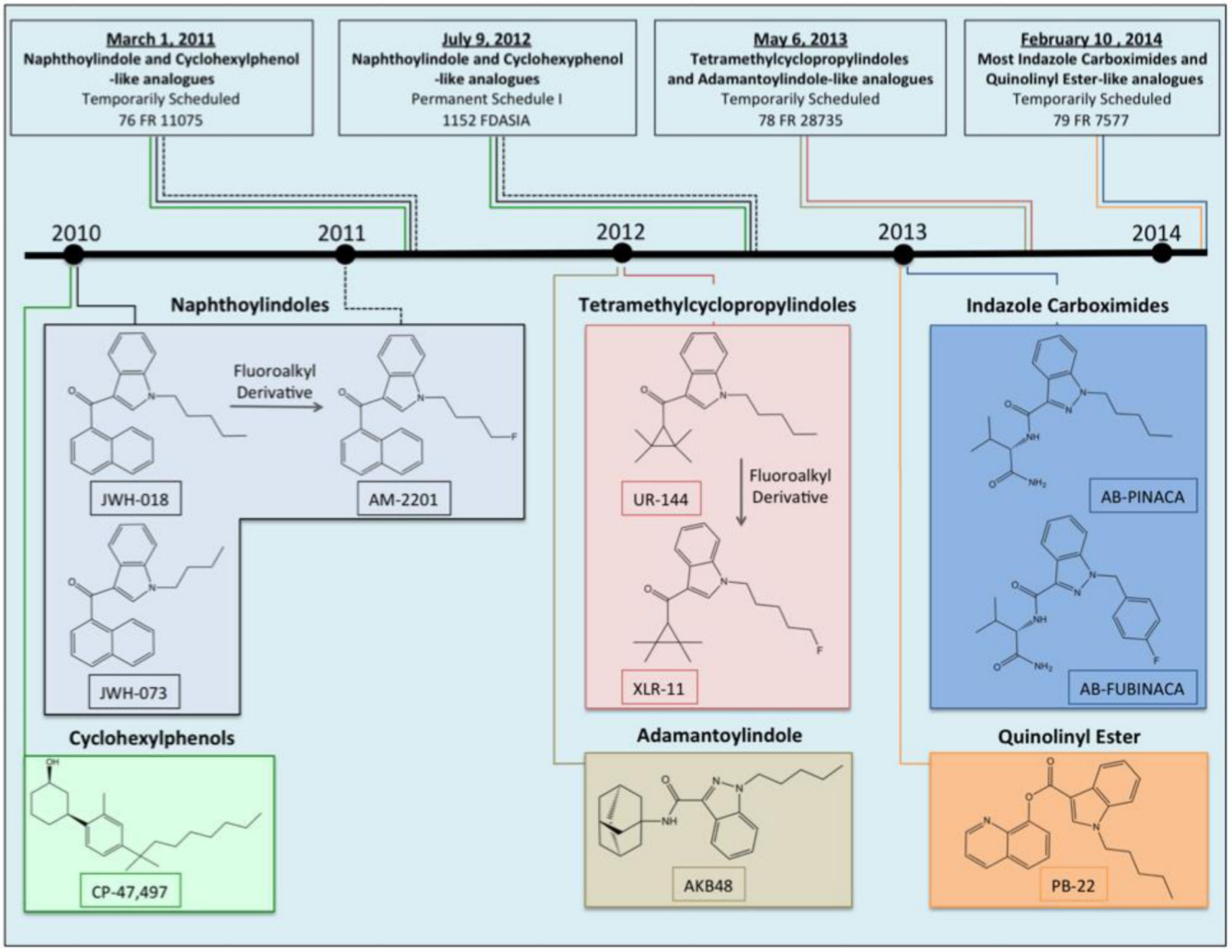

Figure 1. Structural evolution and legislative scheduling of SCBs between 2010 and 2014

Schematic illustration shows the prevalent SCB structural classes and corresponding compounds available in K2/Spice products. In 2010, naphthoylindoles, such as JWH-018 and JWH-073, and cyclohexylphenols, like CP-47,497, were the primary SCBs found in seized K2/Spice products. Use of these SCBs continued throughout 2011, with the addition of the flouroalkyl derivative of JWH-018, AM-2201. On March 1, 2011 legislation under the 76 FR 11075 act temporarily scheduled numerous SCBs (many not shown) that were structurally similar to naphthoylindole and cyclohexylphenol classes. Although numerous SCB analogues within these two classes were permanently scheduled July 9, 2012 under the 152 FDASIA act, new, structurally diverse classes of SCBs were subsequently identified in K2/Spice products. These novel classes included the tetramethylcyclopropylindoles, *e.g.,* UR-144 and its fluorinated analogue XLR-11, as well as adamantoylindoles, *e.g.,* AKB48. Because these structurally distinct SCBs were not included in section the 1152 of FDASIA scheduling act in 2012, May 6, 2013, legislation temporarily scheduled compounds associated with the tetramethylcyclopropylindole and adamantoylindole classes under the 78 FR 28735 act. As previous trends suggested, before completion of the 78 FR 28735

scheduling act, new SCBs had once again emerged in K2/Spice products that were also not included in section the 1152 of FDASIA scheduling act. The new classes of SCBs were the indazole carboximides, AB-PINACA and AB-FUBNACA, and quinolinyl esters, PB-22 and its fluorinated analogue 5F-PB-22 (not shown). Although, most of the compounds in these classes (excluding AB-PINACA) were temporarily scheduled on February 10, 2014 under the 78 FR 28735 act, it can only be assumed that new classes of SCBs will emerge in the future [2].

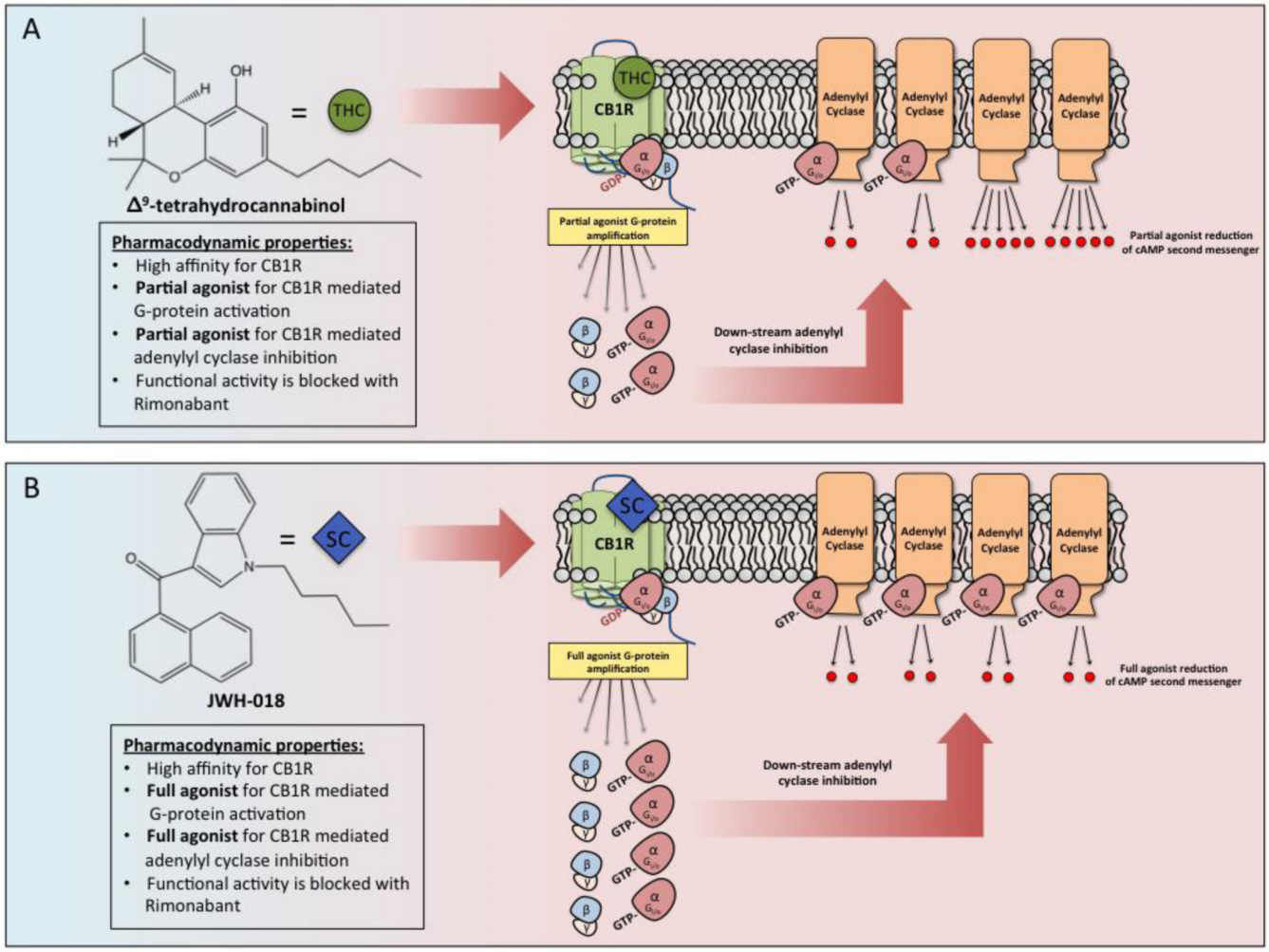

Figure 2. The SCB JWH-018 is a full agonist at CB_1 cannabinoid receptors when compared to Δ^9-THC at the cellular level

In panel **A**, Δ^9-THC (green circles) binds and stabilizes the active confirmation of CB_1 cannabinoid receptors with high affinity. Δ^9-THC induces amplification that results in highly potent, and moderately efficacious coupling to $G_{i/o}$ proteins, that then proceed to inhibit activity of the downstream intracellular effector, adenylyl cyclase [138–140]. Δ^9-THC in marijuana is classified as a partial CB_1 cannabinoid receptor agonist due to its sub-maximal recruitment of $G_{i/o}$ proteins and inhibition of adenylyl cyclase. Comparatively, in panel **B**, the SCB, JWH-018 (blue diamonds) also binds to CB_1 cannabinoid receptors with a very high affinity and couples $G_{i/o}$ proteins to inhibit adenylyl cyclase. The major distinction between Δ^9-THC and JWH-018 is the efficacy of JWH-018-induced $G_{i/o}$ coupling and adenylyl cyclase inhibition. As depicted, binding of JWH-018 to CB_1 cannabinoid receptors results in marked increases in $G_{i/o}$ protein coupling and inhibition of adenylyl cyclase when compared to the partial agonist Δ^9-THC. As such, JWH-018 present in K2/Spice products can be classified as a full CB_1 cannabinoid receptor agonist [136].

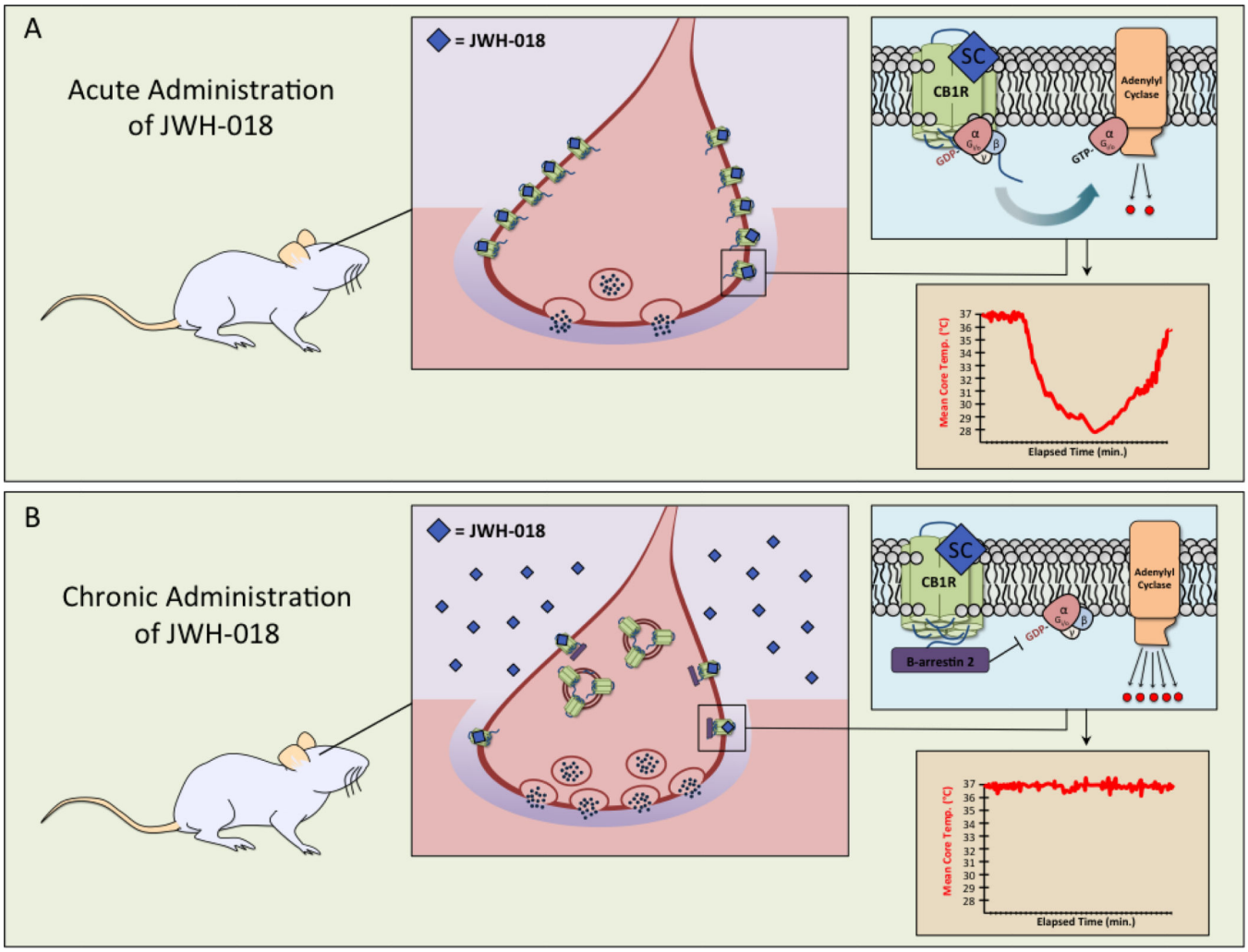

Figure 3. Chronic administration of JWH-018 results in cellular desensitization and down-regulation of CB_1 cannabinoid receptors, as well as tolerance to SCB-induced behavioral responses in animals

In panel A, the SCB JWH-018 (blue diamonds) is administered to a naïve rodent. JWH-018 binds CB_1 cannabinoid receptors on pre-synaptic neurons and mediates full agonist $G_{i/o}$ protein coupling, adenylyl cyclase inhibition and modulation of other effectors including ion channels (not depicted). A single behavioral end-point demonstrates that acute administration of JWH-018 also results in a marked, time-dependent decrease in core body temperature in a SCB-naïve rodent. In panel B, JWH-018 is administered chronically. Complex molecular signaling reveals significant desensitization of CB_1 cannabinoid receptors by phosphorylation and recruitment of β-arrestin 2 (purple rectangles), marked down-regulation and internalization of the receptor, and finally dis-inhibition of quantal release of neurotransmitter by the pre-synaptic neuron. Attenuation of CB_1 cannabinoid receptor signaling via desensitization, down-regulation and receptor internalization contributes to the blunting of JWH-018-induced hypothermia. The complexity of these cellular mechanisms and how they translate to reduced behavioral responses (such as

hypothermia) is indicative of tolerance in the rodent following chronic administration of JWH-018 [187].

Key Figure 4. SCBs present in K2/Spice products are not safe alternatives to marijuana

SCBs in K2/Spice products are structurally diverse psychoactive compounds, exhibiting distinct pharmacodynamic, pharmacokinetic and clinical effects when compared to Δ^9-THC in marijuana. The studies reviewed here clearly demonstrate that SCBs are neither similar, nor suitable, substitutes for marijuana and that use of these compounds can result in tolerance and dependence, as well as numerous other documented adverse, toxic and potentially fatal effects.

Table 1

SCB Toxicity in Humans: Comparison with Marijuana

Adverse Effects and Toxicities	Observed with K2/ Spice Products (SCBs)	Observed with Marijuana (THC)	Citations
Gastrointestinal			
• Nausea	Common	Rare	[1, 3, 25, 26]
• Vomiting	Common	Rare	
• Hyperemesis Syndrome	Common	Rare	[1, 3, 25, 26] [27]
Neurological			
• Euphoria	Common	Common	[26, 29, 30]
• Appetite Stimulation	Common	Common	
• Nystagmus	Reported	Reported	[26, 31]
• Slurred Speech	Reported	Reported	[32]
• Ataxia/Lethargy	Reported	Reported	[33]
• Psychosis in Susceptible Individuals	Extreme	Mild	[34] [3, 35]
• Hypothermia	Reported	None Reported	
• Hallucinations	Common	Rare	[188]
• Delusions	Common	Rare	[3, 36]
• Confusion	Common	Rare	[3]
• Anxiety	Common	Rare	[33]
• Panic Attacks	Common	Rare	[37, 38]
• Agitation	Common	Rare	[34]
• Irritability	Common	Rare	[3, 34]
• Confusion	Common	Rare	[39]
• Memory Disturbances	Reported	Common	[33]
• Self-Mutilation	Reported	None Reported	[26]
• Seizures	Reported	None Reported	[40]
• Catatonia	Reported	Very Rare	[41]
• Acute Cerebral Ischemia	Reported	None Reported	[42] [28]
Cardiovascular			
• Tachycardia	Reported (can lead to Tachyarrhythmia)	Reported (devoid of Tachyarrhythmia)	[34, 37, 43]
• Hypertension	Reported	None Reported	
• Hypotension	None Reported	Reported	[44]
• Chest Pain	Reported	None Reported	[45]
• Cardiotoxicity (i.e. Myocardial toxicity)	Reported	None Reported	[36] [46]
Renal			
• Acute Tubular Necrosis	Reported	None Reported	[47, 48]

Adverse Effects and Toxicities	Observed with K2/ Spice Products (SCBs)	Observed with Marijuana (THC)	Citations
• Acute Interstitial Nephritis	Reported	None Reported	[48]
• Acute Kidney Failure	Reported	Non Reported	[49]
Effects of Chronic Use			
• Tolerance	Common	Common	[50, 51]
• Marked Withdrawal	Reported	Mild	[52]
• Dependence	Reported	Rare	[51, 52]
Deaths (between 2011–2014)	Over 20 deaths reported	None Reported	[53]