CHAPTER FOUR

# Spicing Up Pharmacology: A Review of Synthetic Cannabinoids From Structure to Adverse Events

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## Abstract

Recreational use of synthetic cannabinoids (SCB), a class of novel psychoactive substances is an increasing public health problem specifically in Western societies, with teenagers, young adults, and the prison population being the most affected. Some of these SCB are analogs of tetrahydrocannabinol, aminoalkylindoles, and other phytocannabinoid analogs have been detected in herbal preparations generically called "Spice." Spice, "K2" or "fake cannabis" is a general term used for variable herbal mixtures of unknown ingredients or chemical composition. SCB are highly potent $CB_1$ cannabinoid receptor agonists falsely marketed and sold as safe and legal drugs. Here, we present an overview of the endocannabinoid system, CB, and SCB chemical structures and activity at CB receptors. Finally, we highlight the psychological effects of SCB, particularly on learning and memory, and adverse clinical effects including on the cardiovascular system, kidneys, and CNS, including psychosis. Taken together, it is clear that many SCB are extremely dangerous and a major public health problem.

## 1. THE CANNABINOID SYSTEM, PHYTOCANNABINOIDS, ENDOCANNABINOIDS, AND SYNTHETIC CANNABINOIDS

The plant *Cannabis sativa* produces more than 100 chemical compounds that are named cannabinoids or, more specifically, phytocannabinoids (Andre, Hausman, & Guerriero, 2016; Ligresti, De Petrocellis, & Di Marzo, 2016; Verrotti, Castagnino, Maccarrone, & Fezza, 2016). These terpenophenolic compounds have different relative abundance depending on the cannabis variety, but among them, Δ9-tetrahydrocannabinolic acid (THCA), cannabidiol acid (CBDA), and cannabinolic acid (CBNA) are relatively elevated, followed by cannabigerolic acid (CBGA), cannabichromenic acid (CBCA), cannabinodiolic acid (CBNDA), Δ9-tetrahydrocannabivarin (Δ9-THCV), and cannabidivarin (CBDV) (Andre et al., 2016; Izzo, Borrelli, Capasso, Di Marzo, & Mechoulam, 2009). THCA is the major cannabinoid in the drug-type *Cannabis*, while CBDA predominates in fiber-type hemps. Both THCA and CBDA slowly lose their acidic function (decarboxylate) in the plant on heating and become tetrahydrocannabinol (THC) and cannabidiol, acquiring psychoactive properties, in the case of THC.

Phytocannabinoids are described in detail elsewhere (see chapter "Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads" by Russo and Marcu in this book). Among them, Δ9-THC accounts for most of the psychoactive effects of *Cannabis*. This compound was isolated, described and later synthesized in the 1960s (Mechoulam & Hanus, 2000) opening the door to the identification of the specific receptors for this substance in

animals in the 1980s and 1990s (Devane, Dysarz, Johnson, Melvin, & Howlett, 1988; Matsuda, Lolait, Brownstein, Young, & Bonner, 1990; Munro, Thomas, & Abu-Shaar, 1993). It has been demonstrated that THC binds to G coupled-protein receptors at cell membranes. These receptors, named $CB_1$ and $CB_2$, are widely distributed throughout the body, $CB_1$ being predominately expressed in the central nervous system and $CB_2$ in the immune system. As such, the $CB_1$ receptor is responsible for the psychoactive effects of THC, while the $CB_2$ receptor is involved in immune function (Pacher & Kunos, 2013; Pertwee et al., 2010). A more detailed review on the pharmacology of $CB_1$ and $CB_2$ receptors can be found in the chapter "$CB_1$ and $CB_2$ Receptor Pharmacology" by Howlett and Abood.

The description of cannabinoid receptors led to the finding of their endogenous ligands, termed endocannabinoids, among which two have been more widely studied: *N*-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG). Both endocannabinoids are formed on demand from membrane lipid precursors by specific synthesizing enzymes. For a wider description on the turnover of endocannabinoids, please see the chapter "Endocannabinoid Turnover" by Fowler et al.

The ensemble of cannabinoid receptors, their endogenous ligands (endocannabinoids), and their enzymatic machinery form the core of what is called the endocannabinoid system (ECS). It must be taken into consideration, however, that this definition of the ECS is currently under debate and may only reflect the axis of a more complex structure. In a wider sense, the ECS may also include other members structurally related to anandamide and 2-AG, but that do not bind to $CB_1$ or $CB_2$ receptors with high affinity. These compounds (for example, palmitoylethanolamine, oleamide, or *n*-arachidonoyl dopamine) may behave as allosteric modulators of $CB_1/CB_2$ receptors, or modulate synthesis, degradation, or uptake of anandamide or 2-AG (Di Marzo & Piscitelli, 2015; Ligresti et al., 2016). Both phytocannabinoids and endocannabinoids may also activate receptors other than $CB_1$ and $CB_2$, as with the transient receptor potential cation channels—TRP or GPR55 (Di Marzo & Piscitelli, 2015; Ligresti et al., 2016). These receptors and their natural ligands are also considered related to the wider endocannabinoid family.

The description of cannabinoid receptors and enzymatic machinery triggered the development of whole families of synthetic compounds in the search for new pharmacological tools and new potential therapeutic drugs. Among these synthetic compounds developed are (1) new $CB_1/CB_2$ receptor agonists and antagonists; (2) inhibitors of the hydrolase enzymes (FAAH and MAGL) or of endocannabinoid transport and uptake, in order to

potentiate EC signaling; (3) silent allosteric modulators of $CB_1/CB_2$ receptors. A detailed description of the current status of all these compounds may be found in other chapters of the current book (see chapter "$CB_1$ and $CB_2$ Receptor Pharmacology" by Howlett and Abood, chapter "Functional Selectivity at Cannabinoid Receptors" by Priestley et al., and chapter "Endocannabinoid Turnover" by Fowler et al.).

Some of these synthetic compounds (analogs of Δ9-THC, aminoalkylindoles, and other cannabinoid analogs) have been detected in preparations of the new type of drug generically called "Spice." Spice or "fake cannabis" is a general term used for various herbal mixtures of unknown exact ingredients or chemical composition (Seely, Lapoint, Moran, & Fattore, 2012; Vemuri & Makriyannis, 2015). Product testing of Spice formulations shows that cannabinoid constituents and dosages can vary greatly between products, lots, and even within the same package (Seely et al., 2012). Some of the synthetic cannabinoids (SCB) detected in Spice belong to the "JWH" series initially synthesized by Huffman and Padgett (2005), such as JWH-018 (1-pentyl-3-(1-napthoyl)indole). JWH-018 can be easily synthesized and shows high efficacy at $CB_1$ receptors (Huffman & Padgett, 2005). Other compounds detected in Spice include HU-210, developed at the Hebrew University in the 1960s, and the cyclohexylphenol (CP) cannabinoids developed by Pfizer in the 1970s (Seely et al., 2012), both of which have some structural similarities to Δ9-THC but are more potent, full agonists at $CB_1$ receptors. Compounds first synthesized by Alexandros Makriyannis (AM compounds) have also been detected in Spice (Hudson & Ramsey, 2011). Different preparations of Spice have highly variable content including compounds like JWH-018, JWH-073, CP-47,497, JWH-081, JWH-122, JWH-210, and AM-2201. In addition, endocannabinoid-like molecules such as *N*-palmitoylethanolamine (PEA, endogenously synthesized by the same enzyme as anandamide, NAPE-PLD), have been identified in Spice preparations (Seely et al., 2012).

## 2. SIGNALING PATHWAYS ASSOCIATED TO SCB

While the cannabinoid $CB_1$ receptor is one of the most abundant G protein-coupled receptors present in the central nervous system (Matsuda et al., 1990), the $CB_2$ receptor is located predominantly in the immune system (Munro et al., 1993) and is barely found in the CNS. Both $CB_1$ and $CB_2$ receptors are preferentially coupled to pertussis toxin-sensitive

Gi/o proteins to inhibit adenylate cyclase and cyclic AMP–protein kinase A (PKA) signaling (Howlett, Johnson, Melvin, & Milne, 1988). However, coupling to Gs or Gq/11 of $CB_1$ receptors has also been reported (Glass & Felder, 1997; Lauckner, Hille, & Mackie, 2005).

The signaling pathways triggered by natural-, synthetic-, and *endo*-cannabinoids, through $CB_1$ receptors, have been the focus of extensive research efforts. Upon receptor engagement, cannabinoids activate, among other cascades, phosphatidylinositol 3-kinase/Akt (PI3K/Akt) and mitogen-activated protein kinases (MAPK) such as extracellular signal-regulated kinase (ERK1/2), p38 MAPKs, and JUN N-terminal kinases (JNKs) involved in cell proliferation and survival (Piomelli, 2003). Activation of $CB_1$ receptors in the neuronal presynaptic terminal inhibits L, N, and P/Q type voltage-activated calcium channels and stimulates inwardly rectifying potassium channels to reduce neurotransmitter release (Kano, Ohno-Shosaku, Hashimotodani, Uchigashima, & Watanabe, 2009). Thus, depolarization of a postsynaptic neuron induces short-term depression of GABA release from axon terminals innervating the same postsynaptic neuron. Further, antagonists of $CB_1$ receptors block this depolarization-induced suppression of inhibition (DSI) at hippocampal GABAergic synapses, suggesting that an endocannabinoid was the retrograde messenger involved in this synaptic plasticity (Katona & Freund, 2012). In addition, $CB_1$ receptors also signal from glial cells to neurons to modulate neurotransmission. In fact, in hippocampal astrocytes $CB_1$ receptors are activated by SCB ligands as well as by endocannabinoids released by neurons (Navarrete & Araque, 2008). This activation increased astrocyte calcium levels from internal stores and the intracellular signaling pathway underlying this effect exhibited specific characteristics. In contrast to the canonical coupling to Gi/o proteins, the calcium elevations are mediated by $CB_1$ receptors coupled to Gq/11 proteins that activate phospholipase C and produce inositol triphosphate (Navarrete, Díez, & Araque, 2014).

Cannabinoids promote ERK phosphorylation in the hippocampus, $CB_1$-transfected CHO cells, and human astrocytoma cells (Galve-Roperh, Rueda, Gómez del Pulgar, Velasco, & Guzmán, 2002). In primary cortical neurons, the $CB_1$ receptor agonist methanandamide evoked a biphasic model of ERK activation and required activation of Gq/11 (PLC/PKC) and Gi (Src, Fyn), the magnitude and duration of ERK activation have been causally linked to specific cellular responses in neurons and neural cells such as the induction of cell proliferation and neuronal maturation (Asimaki & Mangoura, 2011).

The SCB agonists WIN 55,212-2 and HU-210 protect primary astrocytes from ceramide-induced apoptosis via activation of the PI3K/Akt pathway, this prosurvival effect also depends on the modulation of the ERK pathway (Gomez del Pulgar, de Ceballos, Guzman, & Velasco, 2002). Whereas in N1E-115 mouse neuroblastoma cells ERK activation by WIN 55,212-2 is mediated by $CB_1$ receptor signaling, but required several basally activated pathways including PI3-kinase, Src, and protein phosphatases, but receptor-stimulated inhibition of adenylate cyclase/PKA is absolutely required for ERK activation (Davis, Ronesi, & Lovinger, 2003). In oligodendrocytes, a role for the ERK/MAPK cascade in endocannabinoid-induced oligodendrocyte maturation has been proposed (Gomez et al., 2010), while the synthetic agonists ACEA, JW133, and HU-210 accelerated oligodendrocyte progenitor differentiation through a mechanism dependent on the activation of the PI3K/Akt and mTOR signaling pathways (Gomez et al., 2011). Moreover, the proliferative action of the PI3K/Akt cascade has been investigated in detail in neural stem cells. In cerebellar granule cell precursors HU-210-induced proliferation requires PI3K/Akt/GSK3β signaling. $CB_1$ receptor activation phosphorylates and inhibits GSK3β thus β-catenin is stabilized and translocates to the nucleus, modulating the expression of genes such as cyclin D1, which is involved in the regulation of cell proliferation (Trazzi, Steger, Mitrugno, Bartesaghi, & Ciani, 2010).

Finally, receptor desensitization has been proposed as a mechanism that terminates cannabinoid agonist signaling and requires phosphorylation by a G protein-coupled receptor kinase and interaction of the phosphorylated receptor with β-arrestins. However, recent reports indicate that β-arrestins, while hindering G-protein signaling, act as scaffold proteins for the endocytic machinery and signaling molecules such as the MAP family of kinases and initiate a second wave of signaling at the cell surface (Nogueras-Ortiz & Yudowski, 2016). In addition, a final wave emerges from receptors localized at intracellular compartments, such as endosomes and lysosomes (Rozenfeld & Devi, 2008).

## 3. STRUCTURAL CLASSIFICATION OF SCB

Synthetic cannabinoids (SC) have gone through numerous iterations of modification to their chemical structures making their forensic detection and identification difficult (Presley, Gurney, Scott, Kacinko, & Logan, 2016). In

2008, the European Monitoring Centre for Drugs and Drug Abuse (EMCDD; http://www.emcdda.europa.eu/publications/drug-profiles/synthetic-cannabinoids) formally monitored these SCB products in order to control the synthesis, trade, distribution, and human consumption of these substances due to their detrimental health effects (Castaneto et al., 2014; EMCDDA, 2009). To date, novel psychoactive substances (NPS) have been detected in over 100 countries/territories (Schifano, Orsolini, Duccio Papanti, & Corkery, 2015), with a specific high impact in the European teenage population (over 5% of 19–24 years old) (EMCDDA, 2014). At present, the EMCDD and the United Nations Office on Drugs and Crime (UNODC) monitor over 450 NPS of which over 160 substances are SCB (EMCDDA, 2015; Scocard, Benyamina, Coscas, & Karila, 2017; Zawilska & Wojcieszak, 2014). Over 10 recognizable chemical families of SCB are known. Forensic/toxicological analysis, identification, and characterization of the new and/or relatively unknown SCB is performed by using advanced analytical tools such as nuclear magnetic resonance (NMR), bioinformatics, computational chemistry, electrospray ionization, and high-resolution liquid-chromatography tandem mass-spectrometry (HR-LC–MS/MS) tools (Adamowicz & Tokarczyk, 2016; Dunne & Rosengren-Holmberg, 2016; Ford & Berg, 2016; Sahai et al., 2016).

The use of in silico and chemical biochemistry approaches are essential in predicting and identifying the metabolites of SCB and drug subclasses that continue to appear (Presley et al., 2016; Strano-Rossi et al., 2014). A chemoinformatic approach permit a broad screening of SCB to manage and unify analytical data from multiple techniques and instruments, and combine it with chemical and structural information (Lobo Vicente et al., 2016; Sahai et al., 2016).

The compound CP47497 and other indoles were first used as analgesics, in different medicinal chemistry programmes from Sterling Winthrop and Charles Pfizer (CP) company (now Pfizier Inc.) in the 1970s–1980s. The fact that many of these compounds bind to cannabinoid receptors was discovered subsequently (Seely, Prather, James, & Moran, 2011) but have only recently found their way into Spice blends (Calles, 2013).

As described earlier, the synthesis of structurally distinct molecules that bind with high affinity to cannabinoid receptors is a relatively recent phenomena that started with the synthesis of the $CB_1$ full agonist naphtoyindole JWH-018 (1-pentyl-3-(1-naphtoyl)indole) (Huffman, Dai, Martin, & Compton, 1994; Huffman and Padgett, 2005).

In March 2011, the Drug Enforcement Agency (DEA, USA) classified as schedule class I, five SCB: JWH-018, JWH-073, JWH-200, CP-47,497, and Cannabicyclohexanol (Drug Enforcement Administration, 2010).

As the synthesis of novel SCB is an area in constant development, it is difficult to establish a clear structural classification. Moreover, to date, SCB can be classified into several major structural groups as shown later, depending on their structural evolution as described in Table 1 (Figs. 1–6).

Furthermore, there are several analytical difficulties posed by the task of identifying SCB (i.e., forensic data are limited) because these SCB are not controlled substances in most EU Member States (EMCDDA, 2009). In the United Kingdom, the Physchoactive Substances Act (2016) effectively banned the production, sale, and possession of so-called legal highs including SCB.

A common structural feature of the SCB is a side-chain, where optimal activity for binding $CB_1$ cannabinoid receptors for psychotropic activity requires more than four and up to nine saturated carbon atoms (see Pertwee et al., 2010, for review). An interesting on-line resource from the EMCDDA, *Interactive* can be found at the following link: (http://www.emcdda.europa.eu/topics/pods/synthetic-cannabinoids). The resource is helpful in facilitating understanding of the chemistry of the SCB and explains the chemical make-up of these compounds.

The structure of the majority of SCB can be divided into four key parts: the core (indole or indazole core) and substituents, the link section (amide, ketone, or ester linker), the ring (naphthyl, quinolinyl, adamantyl, or tetramethylcyclopropyl ring) and substituents, and the tail section.

**Table 1** Structural Classification of Synthetic Cannabinoids

1. *Naphthoylindoles*, *Naphthylmethylindoles*, *Naphthoylpyrroles*, *Naphthylmethylindenes*: JWH-007, JWH-018, JWH-073, JWH-200, JWH-398, AM-1221, AM-2201 (*Fluoroalkyl* derivative from JWH018), AM-694, Win-55,212-2
2. *Phenylacetylindoles* (i.e., *benzoylindoles*): JWH-250, RCS-8
3. *Cyclohexylphenols*: CP-47947, CP-55940
4. *Tetramethylcyclopropylindoles*: UR-144, XLR-11 (*Fluoroalkyl* derivative from UR-144)
5. *Adamantoylindoles*: 5F-AKB-48, STS-135
6. *Indazole carboxamides*: AB-PINACA, AB-FUBINACA
7. *Quinolinyl ester*: PB-22

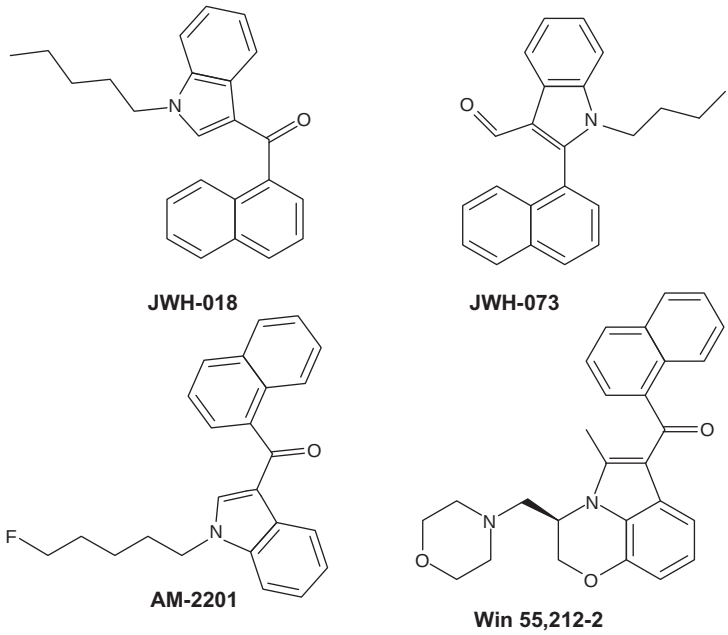


**Fig. 1** The structures of four naphthoylindoles with varying degrees of functional selectivity for $CB_1$ and $CB_2$ cannabinoid receptors: JWH-018, JWH-073, AM2201, and Win 55,212-2.

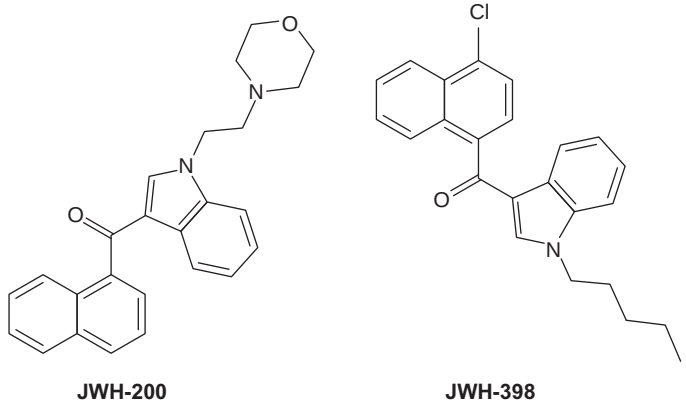


**Fig. 2** The structures of the aminoalkylindole JWH-200 and the synthetic cannabinoid JWH-398.

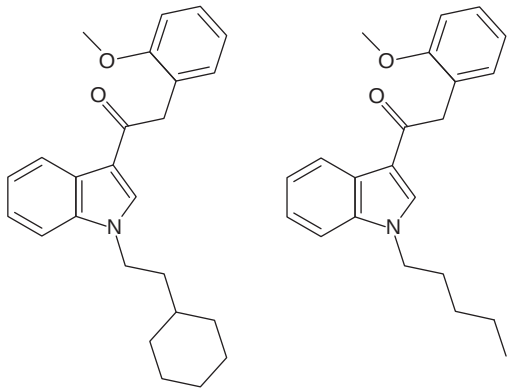


**Fig. 3** The structures of the phenylacetylindoles RCS-8 and JWH-250.

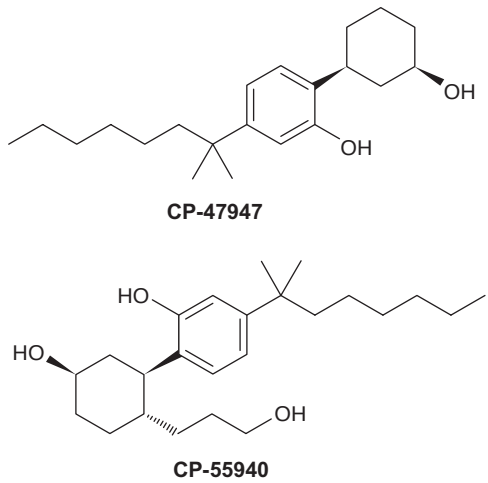


**Fig. 4** The structures of two cyclohexylphenols with varying degrees of selectivity for cannabinoid receptors: CP-47947 and CP-55940.

Other common features of the SCB include a hydrophobic alkyl group attached to the indole or indazole ring (Ford, Tai, Fantegrossi, & Prather, 2017).

Adamantyl-cannabinoids are currently the most frequently used class of SCB in the United Kingdom, particularly AKB-48, 5F-AKB-48, and STS-135 (McIlroy, Ford, & Khan, 2016).

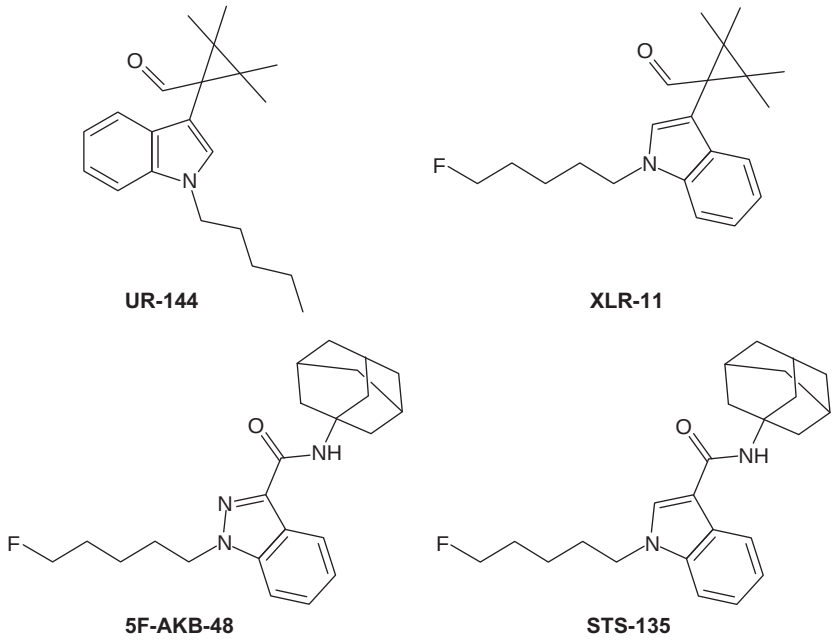


**Fig. 5** The structures of two tetramethylcyclopropylindoles (UR-144 and XLR-11) and two adamantoylindoles (5F-AKB-48 and STS-135) with varying degrees of selectivity for cannabinoid receptors.

## 4. CANNABINOID/$CB_1$ RECEPTORS INVOLVEMENT IN MEMORY REGULATION AND PSYCHOSIS

### 4.1 $CB_1$ Receptor Role in the Regulation of Memory and the Effects of Exogenous Cannabinoids

Endocannabinoids (endocannabinoid) and their central $CB_1$ receptors are richly present within the brain, including the basal ganglia subregions, hippocampus, amygdala, and cerebellum, which is indicative of the wide-ranging roles for endocannabinoid and $CB_1$ receptors in animals and humans (e.g., Herkenham et al., 1991; Mackie, 2008). The distribution of $CB_1$ receptors is consistent with their regulatory roles in the brain, as $CB_1$ receptors are involved in a range of important physiological functions such as movement control, pain processing, brain development and maturation, and learning and memory (Mackie, 2008; Svízenská, Dubový, & Sulcová, 2008).

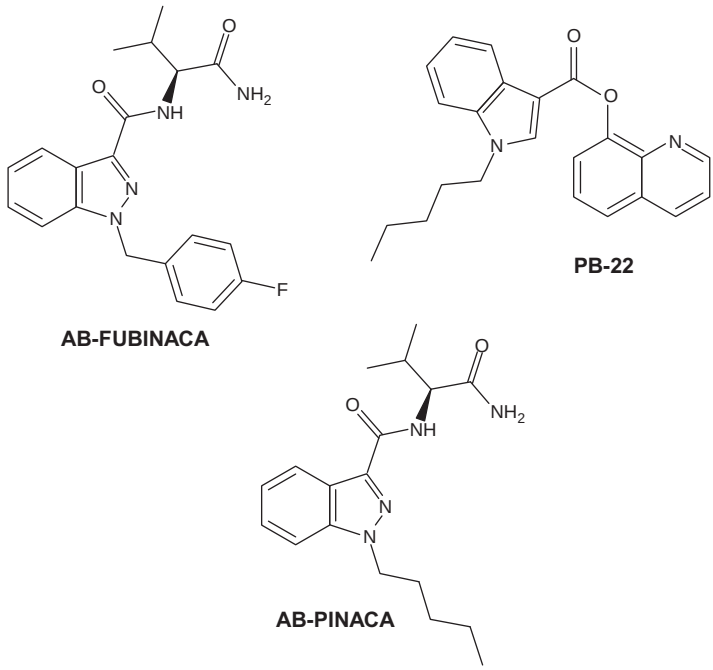


**Fig. 6** The structures of two indazole carboxiamides (AB-PINACA and AB-FUBINACA) and one quinolinyl ester (PB22).

Learning and memory regulation involves neuronal networks that operate by means of glutamate (excitatory) and GABA (γ-aminobutyric acid, inhibitory) and that are modulated by endocannabinoids. Endocannabinoids act within both presynaptic and postsynaptic neuronal compartments and exert neuroplastic changes of synaptic function in glutamatergic and GABA-ergic pathways. It has been established that neuronal activity triggers postsynaptic synthesis and release of endocannabinoids that act retrogradely across the synapse and bind to presynaptic $CB_1$ receptors; it is the nature of the neural network involved that decides about the various neurobiological effects of endocannabinoids mediated by $CB_1$ receptors. Thus, their actions in the brain regions involved in learning and memory, such as the hippocampus (Davies, Pertwee, & Riedel, 2002), amygdala, and dorsal striatum (Goodman & Packard, 2015) necessarily translate into changes in learning and memory-related functions. Of relevance to memory regulation, endocannabinoid release is affected by glucocorticoids as hormonal mediators of the response to stress, which act at glucocorticoid receptors richly expressed in the hippocampus and amygdala. Glucocorticoids activate postsynaptic

glucocorticoid receptors that trigger the postsynaptic synthesis of endocannabinoids, which then act retrogradely via presynaptic $CB_1$ receptors on glutamatergic terminals and this triggers a signaling cascade which inhibits glutamate transmission, leading to a reduction in the neural activity in the hippocampus and amygdala (Di, Malcher-Lopes, Halmos, & Tasker, 2003). It should be said at this stage that not only can endocannabinoids act at $CB_1$ receptors but also exogenous cannabinoids, including THC and their synthetic forms.

While it has been accepted that presynaptic hippocampal $CB_1$ receptors play a role in learning and memory, in line with the fact that the hippocampus has long been implicated in these phenomena, there is a growing interest in the function of mitochondrial cannabinoid receptors as $CB_1$ receptors are located not only in the presynaptic membrane but also in neuronal mitochondria. Activation of mitochondrial $CB_1$ receptors can cause an acute change in the energy status, with reductions in the rate of mitochondrial respiration and further long-term consequences of mitochondrial dysfunction, including neuronal aging and degeneration. Thus, the role of mitochondrial $CB_1$ receptors has emerged as an interesting aspect in the neurobiology of learning and memory (Hebert-Chatelain et al., 2016).

Activation of presynaptic $CB_1$ receptors affects the release of neurotransmitters such as glutamate or GABA in both short-term and long-term (e.g., review by Puighermanal, Busquets-Garcia, Maldonado, & Ozaita, 2012). Experimental rodent studies in vivo or in vitro, using brain tissue—most often hippocampal sections, are essential in explaining the role of the ECS in memory regulation, and the effects of $CB_1$ receptor agonists and antagonists, acute or chronic. Experimental in vitro approaches have demonstrated that short-term endocannabinoid actions involve synaptic plasticity responses such as depolarization-induced suppression of inhibition (DSI) or depolarization-induced excitation (DSE) (Heifets & Castillo, 2009; Kano et al., 2009). A long-term inhibition of transmitter release also induces neuroplasticity as it associates with long-term depression (LTD) of synaptic activity; LTD at inhibitory synapses can lead to long-term potentiation (LTP) downstream (Carlson, Wang, & Alger, 2002). The finding that endocannabinoids can facilitate LTP induction in neurons augments our understanding of the behavioral effects of endocannabinoids in health and under the influence of exogenous cannabinoids.

Exogenous cannabinoids such as of THC administered in the course of experimental interventions in animal and human studies, or as recreational

drugs in humans, are presumed to interact with the brain ECS at higher concentrations than those of endogenous modulators. Thus exogenous cannabinoids, including new SCB that bind to $CB_1$ receptors, can affect endocannabinoid-dependent synaptic plasticity including LTP or LTD, and change behavioral learning processes as observed in acute and long-term treatments (Puighermanal et al., 2012).

A single dose of THC has been shown to abolish endocannabinoid-induced LTD in rat hippocampus, while chronic administration of THC abolishes LTP generated by high-frequency stimulation in vitro, with reductions in glutamate release in rat hippocampal slices. In the hippocampus in vivo, THC preferentially decreases GABA release and has less effect on glutamate release, as there are more $CB_1$ receptors in GABA-ergic neurons and those $CB_1$ receptors have a higher sensitivity to cannabinoid agonists. Therefore, memory impairment caused by exogenous cannabinoids could be predominantly a consequence of a disruption of hippocampal network function that is mediated by synchronized GABAergic activity (for review, see Puighermanal et al., 2012).

A useful experimental tool in studies on the role of the ECS in learning and memory is a genetic modification whereby the *Cnr1* gene that encodes the $CB_1$ receptors is deleted in mice. Mice lacking $CB_1$ receptors have increased hippocampal LTP and improved memory retention when compared with the wild strain (Bohme, Laville, Ledent, Parmentier, & Imperato, 2000; Martin, Ledent, Parmentier, Maldonado, & Valverde, 2002). Interestingly, mature and old Cnr1 knockout mice, unlike young ones, tend to display deficits in procedural learning, spatial memory, and social recognition abilities. These cognitive deficits associate with neuronal losses in the hippocampal areas CA1 and CA3 that are involved in memory consolidation, consistent with the neuroprotective effects mediated via the $CB_1$ receptor. On the other hand, $CB_1$-deficient mice show significantly impaired short-term and long-term extinction of memory, as tested in auditory fear-conditioning paradigms, although no effects have been found in their memory acquisition and consolidation (Marsicano et al., 2002). Similar effects have been observed in control (wild strain) mice treated with the $CB_1$ receptor antagonist SR141716A (rimonabant), which confirms that the $CB_1$ receptor is paramount in the process of memory extinction (Marsicano et al., 2002). Extinction of traumatic/aversive memories is essential in the recovery from posttraumatic stress disorder (PTSD) and maladaptive rumination in clinical depression, where persistent negative memories can cause retraumatization and relapse of mental illness. There is growing evidence that exogenous

cannabinoids could exert normalizing effects on aversive memories in PTSD and phobias.

While there is consensus that $CB_1$ receptors located in the hippocampus play a necessary role in the memory impairments caused by cannabinoid agonists, including THC (e.g., Wise, Thorpe, & Lichtman, 2009) other brain regions also contribute to memory regulation with their $CB_1$ receptors. For example, the prefrontal cortex plays a role in $CB_1$ receptor-mediated memory as demonstrated in a study where THC infusion into the prefrontal cortex disrupted rat memory in a radial arm maze (Silva de Melo et al., 2005). It should be said, however, that in situ infusion of exogenous cannabinoids may bring about different effects to those observed after a systemic administration (for review, see Zanettini et al., 2011).

## 4.2 Cannabinoids and Dorsal Striatal Memory

$CB_1$ receptors are also present in the striatum; they are localized on presynaptic terminals of glutamatergic corticostriatal projection neurons and GABA-ergic medium spiny neurons. $CB_1$ receptors have not been found on cholinergic interneurons in the striatum nor nigrostriatal projections to the striatum. The ECS plays an important role in the types of learning and memory mediated by the dorsal striatum, which includes stimulus–response (S–R) habit memory. Studies of this kind of memory involve maze learning and instrumental learning tasks in mostly rodents although they can be adapted to humans. There is a growing body of evidence that manipulating the ECS by means of either infusion or a chronic exposure to exogenous cannabinoids can alter dorsal striatum-dependent habit memory (for review, see Goodman & Packard, 2015). Exogenous cannabinoid agonist or antagonist administration associates with impairment of dorsal striatum-dependent S–R habit memory, while THC tolerance can associate with enhancement of that type of memory. It is a complex area of research as appetitive paradigms also engage the ventral striatum. As in the case of hippocampal memory, endocannabinoid-dependent striatal memory implicates $CB_1$ receptors with synaptic plasticity (Goodman & Packard, 2015).

It is appropriate to note that the very wide range of endocannabinoid roles superimposes with the complexity of the neuronal circuits involved with their other neurotransmitter systems that respond to *endo*- and *exo*cannabinoid actions as a matter of secondary effects. This justifies an opinion that the effects of the ECS also depend on environmental conditions when it comes to memory impairment produced by exogenous

cannabinoids (Zanettini et al., 2011). On the basis of the limited human studies on the effects of SCB on learning and memory, it would be fair to say that SCB bioactivity is mediated via $CB_1$ receptor agonism in humans (Gunderson, Haughey, Ait-Daoud, Joshi, & Hart, 2012).

## 4.3 Cognitive Changes in SCB Users

A recent study by Cohen et al. (2017) has assessed executive functions in a group of participants comprising SCB users, recreational cannabis users and nonusers by means of cognitive function tests, the Stroop word-color task, and the n-back and free-recall memory tasks. SCB users have performed significantly worse than the other participants in all the tests applied. In addition, they have had higher depression and anxiety scores when compared with the two other groups. Thus, executive functions were impaired in SCB users (Cohen et al., 2017). It is consistent with $CB_1$ receptor involvement.

## 4.4 Role of $CB_1$ Receptors in Psychosis

Synaptic activity closely involves membrane potential changes and gives rise to transmembrane currents that can be measured in the extracellular field to which all neuron types contribute; they time their action potentials with millisecond precision depending on their membrane potential fluctuations (Buzsáki & Wang, 2012). The spatial alignment of neurons and the temporal synchrony of neuronal firing determine the strength of the extracellular field. The synchrony, which results from network oscillations, determines the different magnitudes of local field potentials that represent different brain states (Buzsáki, Anastassiou, & Koch, 2012). In the intact brain, endogenous oscillations result in high-frequency patterns, of which most ubiquitous are rhythms in the gamma-frequency range (30–90 Hz) (Buzsáki & Wang, 2012). Another rhythm of relevance to psychosis is theta oscillations (4–7 Hz) that represent the net activity of the hippocampus; they are generated mainly by the entorhinal cortical inputs. Theta rhythm is thought to be critical for temporal coding and decoding of active neuronal ensembles and modifications of synaptic strength (Buzsáki, 2002). It has been known that high level cognitive activities, such as working memory, closely associate with gamma oscillations in the prefrontal cortex (Fries, 2009). Typically, patients with schizophrenia who show working memory impairments have also reduced gamma and theta oscillations; deficits in cortical oscillations and impairments of memory

associate in schizophrenia and psychosis (Minzenberg et al., 2010; Skosnik, Cortes-Briones, & Hajós, 2016). There is consensus that abnormal neural synchrony and impaired auditory gating indicate of distorted information processing in patients with psychosis.

Interestingly, exogenous cannabinoids, such as THC can also lead to disruptions in neural oscillations, as shown in human studies (for review, see Skosnik et al., 2016). It is of direct relevance to psychotic-like behavior observed after exogenous cannabinoid exposure in humans and can be explained by the fact that oscillations in the cortical and limbic brain areas, including the hippocampus, are controlled by $CB_1$ receptors. There are lines of evidence derived from animal experiments that activation of $CB_1$ receptors interferes with neuronal network oscillations and impairs sensory gating function in the cortical and limbic brain areas, including the hippocampus. For example, a $CB_1$ receptor agonist, CP-55940, has been found to disrupt auditory gating and interrupt theta field potential oscillations in the hippocampus and entorhinal cortex in anesthetized and awake rats. In addition, novelty-induced theta and gamma activities were also significantly diminished by CP-55940 in the same material (Hajós, Hoffmann, & Kocsis, 2008). Findings of this kind have a translational value and support the idea that activation of $CB_1$ receptors by exogenous cannabinoids impairs theta and gamma oscillations that are known to be affected in cannabis abuse-related psychosis spectrum disorders in vulnerable subjects (Skosnik et al., 2016). Case studies of psychotic SCB users are described later.

To sum up, there are similarities between disruptions of neuronal network oscillations in psychosis and those in psychosis-like conditions triggered by exogenous cannabinoids (e.g., THC). There is evidence that activation of $CB_1$ receptors disrupts neuronal network oscillations. Exogenous cannabinoids that act as $CB_1$ receptor agonists, which includes new synthetic forms, can trigger psychosis-like behavior through this mechanism.

## 5. CLINICAL ADVERSE EFFECTS OF SCB

The health risks associated with using SCB cannot be assumed to be similar to those from taking cannabis because, as described elsewhere, SCB tend to be much more potent at $CB_1$ receptors and do not contain cannabidiol or cannabinol (among others), which mitigates against many

adverse effects. The adverse clinical effects of SCB have previously been reviewed by Cooper (2016), and case reports are the main source of information. The main findings are that acute SC intoxication is usually characterized by tachycardia, hypertension, visual and auditory hallucinations, mydriasis, agitation and anxiety, tachypnea, nausea, and vomiting (Heath, Burroughs, Thompson, & Tecklenburg, 2012; Schneir, Cullen, & Ly, 2011). However, in some cases SC misuse can precipitate stroke, seizures (Harris & Brown, 2013; Hermanns-Clausen, Kneisel, Szabo, & Auwarter, 2013; Hoyte et al., 2012; McQuade, Hudson, Dargan, et al., 2013; Spaderna, Addy, & D'Souza, 2013; Winstock & Barratt, 2013) and what appears to be serotonin syndrome, possibly mediated through mild MAOI (Rosenbaum, Carreiro, & Babu, 2012).

## 5.1 Adverse Cardiovascular Effects

Although quite uncommon, the use of cannabis is associated with some serious cardiovascular conditions (Thomas, Kloner, & Rezkalla, 2014) and case studies highlighting coronary artery thrombosis, vasospasm, and myocardial infarction have been reported (Gunawardena, Rajapakse, Herath, & Amarasena, 2014; Mittleman, Lewis, Maclure, Sherwood, & Muller, 2001; Tatli, Yilmaztepe, Altun, & Altun, 2007). It is likely that these effects are mediated through TCH evoked increases in catecholamines, increased cardiac workload (with increased heart rate and blood pressure) with decreased supply of oxygen (Aryana & Williams, 2007). Given that SC have much higher affinity at $CB_1$ receptors, and potentially have effects at other receptors, we may expect more frequent cardiovascular problems with SC. SC use is associated with acute myocardial infarction, found in both adults and children (Ibrahim, Al-Saffar, & Wannenburg, 2014; McKeever et al., 2015; Mir, Obafemi, Young, & Kane, 2011; Tse, Kodur, Squires, & Collins, 2014).

The SC "K2" is associated with tachycardia (Chinnadurai, Shrestha, & Ayinla, 2016). McKeever et al. (2015) reported a 16-year-old male who had taken the SC "K2" 60–120 min prior to complaining of sustained substernal pressure, dyspnea, nausea, and vomiting; ECG revealed ST elevations and increased troponin and creatinine kinase MB. The SC "Black Mamba," smoked 3 h prior to symptoms onset, led to myocardial infarction with ST elevation and high Troponin-T levels. Analysis revealed that the substance ingested was an adamantyl SC (McIlroy et al., 2016).

## 5.2 Adverse Pulmonary Effects of SCB

Long-term SCB users have reported chronic coughs with pneumothorax and diffuse pulmonary infiltrates were also reported (Froberg & Bauer, 2012). Alhadi et al. (2013) reported on a 21-year-old male with a cannabis habit who had been using SC for 4 months prior to presenting with a 2 month history of chronic cough. Laboratory workup suggested that the diffuse pulmonary infiltrates were probably inflammatory-mediated, possibly through macrophage activation. The authors confirmed SC presence through blood, urine, and saliva testing with AM-2201, JWH-122, JWH-210, and JWH-018 all present, but could not rule out allergic alveolitis caused simply by heat or smoke particulate inhalation. Similarly, Bajantri et al. reported the case of a 21-year-old woman, also a long-term cannabis user, who had started smoking SC (K2) in the last 2 months and who presented with nausea, vomiting, and upper abdominal pain. Chest CT revealed pneumomediastinum, hypothesized to be secondary to SC use and increased alveolar pressure leading to barotrauma. Another case report described a 29-year-old man presenting with severe agitation after smoking "K2." Tests revealed fever and tachycardia, but also leukocytosis and interstitial infiltrates on chest radiography (Chinnadurai et al., 2016). Taken together, these studies suggest that SC can cause adverse pulmonary events not seen with cannabis use.

## 5.3 Acute Kidney Injury From SCB

In a case series, Bhanushali, Jain, Fatima, Leisch, and Thornley-Brow (2013) described four males, aged 20–30 who had been using "spice" for weeks up to 2 years, two of whom recently changed supplier, all presenting with nausea and vomiting for more than 2 days. Renal biopsy in three of the patients revealed acute tubular necrosis. The Centre for Disease Control and Prevention (USA; 2013) also describe a case series of 16 SC users from a variety of US states presenting with nausea and vomiting and either flank or abdominal pain and were found to have high creatinine levels. Patients were aged between 15 and 33 years and toxicological analysis (urine, blood, or serum) from seven patients revealed XLR-11 *N*-pentanoic acid metabolites in four of these seven patients, who had taken the SC products Phantom Wicked Dreams, Mr. Happy, Clown Loyal, Lava, or Flame 2.0. In another case series, Buser et al. (2014) identified nine persons (all males, 15–27 years) who presented to Oregon and Southwest Washington hospitals (USA)

during May–October 2012 with acute kidney injury after smoking SCB products. The first patient presented to the emergency department after 4 days of flank pain, emesis, and oliguria examinations revealed hypertension and bilaterally enlarged hyperechoic kidneys. Symptoms began after smoking an SC product called "Clown Loyal." The second patient presented to an emergency department complaining of abdominal pain, nausea, and lower back discomfort lasting 3 days. He was euvolemic, but hypertensive. A renal ultrasound revealed bilateral hyperechoic kidneys with poor corticomedullary differentiation. In cases who recalled their last exposure, they reported symptom onset between approximately 30 min and 24 h (median: 8–12 h) after smoking a SC product. The SCs were marketed as Spice, Mad Monkey, Clown Loyal, Jonny Clearwater, Feel Good, Lava, and Orgazmo. At least two of these products contained XLR-11. The authors suggest that this drug is a potent and long-acting agonist at $CB_2$ receptor and that this effect may underlie its kidney toxicity.

## 5.4 Adverse Neurological Effects of SCB: Psychosis and Catatonia

An increase in susceptibility to schizophrenia has long been hypothesized with cannabis use, with clear data finally confirmed in Swedish conscripts in 1987 (Andréasson, Engström, Allebeck, & Rydberg, 1987). It is then no surprise that SCB have been associated with psychotic events in users and there are numerous case studies in this area (e.g., Glue, Al-Shaqsi, Hancock, et al., 2013). Papanti et al. (2013) have reviewed these cases and coined the term "spiceophrenia" to describe the psychotic symptoms associated with SCB or "Spice" use. In addition to hallucinations, SCB users can exhibit violent and self-injuring behavior (Thomas, Bliss, & Malik, 2012). More recent studies in Europe suggest that 15% of SCB users who report to emergency departments exhibit psychotic symptoms (Vallersnes et al., 2016), interestingly this was a lower percentage of patients compared those taking tryptamines, methylenedioxypyrovalerone, methylphenidate, LSD, or mushrooms.

Catatonia has been seen with SCB use in two patients (Khan, Pace, Truong, Gordon, & Moukaddam, 2016). One patient (21-year-old male) used SC (Kush) almost daily for 18 months, while the other (17-year-old male) used a large quantity of SCB (Spice) over a 2-week period. Both were admitted with catatonia but no mood disturbance or psychosis. To our knowledge, there have been no studies linking cannabis use to catatonia.

## 5.5 Adverse Neurological Effects of SCB: Seizures, Epilepsy, and Tremor

Rosenberg, Tsien, Whalley, and Devinsky (2015) have recently reviewed the role of cannabinoids in epilepsy; highlighting proconvulsive effects (e.g., THC) and anticonvulsive effects (e.g., cannabidiol). The mechanisms of action of cannabidiol in epilepsy have also been recently reviewed (Reddy & Golub, 2016). Much work with SCB in epilepsy has focused on WIN55,212-2. WIN55,212-22 potentiated the effects of four antiepileptic drugs (carbamazepine, phenytoin, phenobarbital, and valproate) in mice (Luszczki et al., 2011). However, the authors also caution that impairment of motor coordination, long-term memory, and a reduction of skeletal muscular strength was also seen with these combination treatments. The same group found WIN 55,212-2 in combination with lamotrigine, pregabalin, and topiramate and second- and third-generation anticonvulsants gabapentin, levetiracetam but not lacosamide, oxcarbazepine, pregabalin, and tiagabine to potentiate anticonvulsant effects in mice (Florek-Luszczki et al., 2015; Luszczki, Wlaz, Karwan, Florek-Luszczki, & Czuczwar, 2013).

Clinical cases are now being described where SC users are presenting with seizures or convulsions. In the United States, there have been reports of seizure activity after smoking various SCB and these were likely JWH-018, JWH-081, JWH-250, and AM-2201 (Lapoint et al., 2011; Schneir & Baumbacher, 2012; Simmons, Cookman, Kang, & Skinner, 2011). In Europe, McQuade et al. (2013) reported a 20-year-old male who had smoked "Black Mamba" and quickly went into tonic–clonic convulsions. Urine analysis revealed metabolites of AM-2201.

More recently, seizure-like activity has been seen following SCB use. Schep, Slaughter, Hudson, Place, and Watts (2015) described a 23-year-old male, with a history of daily SCB misuse, who had smoked a SCB (K2) and 6 h later appeared to exhibit generalized tonic–clonic seizures. Blood analysis revealed that the patient had ingested SCB BB-22, AM2233, PB-22, 5F-PB-22, and JWH-122.

Cannabinoids have long been considered as potential treatments for tremors associated with various CNS disorders, e.g., multiple sclerosis, Parkinson's and Huntington's disease (Arjmand et al., 2015) and this is described later. However, some studies suggest caution in the use of SCB in these diseases and in mice the synthetic CB receptor agonists CP55,940 and HU-210 evoked motor impairment (DeSanty & Dar, 2001). The phytocannabinoid nabilone increases choreatic movements in

Huntington's disease (Müller-Vahl, Schneider, & Emrich, 1999). The motor centers of the brain including the basal ganglia and the cerebellum contain very high $CB_1$ receptor levels and thus one might expect SCB to have a significant effect on such symptoms as tremor.

## 5.6 SCB Withdrawal Effects

In addition to acute toxic effects of SCB, described earlier, there are serious withdrawal effects, recently reviewed by Macfarlane and Christie (2015) in a sample of 47 New Zealanders presenting at detoxification centers. The most common withdrawal symptoms described were agitation (89% of inpatients), irritability (83%), anxiety (55%), and mood swings (55%) and these typically appeared within 1–2 h of last use but peaked on day 2 of withdrawal and remain high for at least 5 days. Other common withdrawal symptoms include nausea and vomiting (44%) and loss of appetite (17%). Elsewhere, a chronic SCB use withdrawal syndrome has also been described where symptoms include drug craving, sweating, insomnia, headache, depression, and anxiety (Nacca et al., 2013; Rominger et al., 2013; Seely et al., 2012; Vandrey, Dunn, Fry, & Girling, 2012; Zimmermann et al., 2009). There have been no longitudinal studies so long-term health risks can only be suggested.

## 5.7 SCB-Associated Deaths

A small number of drug-related deaths have been reported after SCB ingestion; sometimes with SCB ingested alone, or more often in combination with other drugs. There are some analytically confirmed reports. The National Program for Substance Abuse Deaths (np-SAD) reports on such deaths annually. Their most recent report (2014) reveals only about 5–6 SC-related deaths in the United Kingdom with STS-135 present in three cases (Corkery, Claridge, Loi, Goodair, & Schifano, 2014). In a US case series in 2012, three males (29, 52, and 57 years old) were found to have JWH-018 or JWH-073 postmortem (Shanks, Dahn, & Terrell, 2012). In Japan, a 59-year-old man was found to have MAM-2201 postmortem (Saito et al., 2013). In Germany, a 36-year-old male was taken to hospital suffering from seizures, but died shortly after admission. He had been smoking an SC (Mary Joy Annihilation) which was found to contain JWH-018 and JWH-210. However, blood analysis revealed JWH-018,

JWH-122, AM-2201, MAM-2201, UR-144, and amphetamine (Schaefer et al., 2013). These case studies hint at a possible susceptibility to SC-related deaths in older users.

## 5.8 Potential Therapeutic Use of SCB

It may not all be bad news. Cannabis preparations are reported to be analgesic, antiemetic, antiinflammatory, antineoplastic (Patil, Goyal, Sharma, Patil, & Ojha, 2015), and sedative and more recently have been associated with lower body mass index and lower incidence of diabetes (Penner, Buettner, & Mittleman, 2013). As mentioned earlier, SCB were originally developed for medicinal reasons; to increase analgesic effects seen with THC. Hill, Williams, Whalley, and Stephens (2012) have reviewed the use of THC in preclinical animal models and suggest potential use in epilepsy, neurodegenerative diseases, and affective disorders. The role of CB receptor ligands in disease and their potential therapeutic effects have recently been reviewed (Alexander, 2016; Arevalo-Martin, Molina-Holgado, & Garcia-Ovejero, 2016; Gómez-Gálvez, Palomo-Garo, Fernández-Ruiz, & García, 2016; Mursaleen & Stamford, 2016; Velasco, Hernández-Tiedra, Dávila, & Lorente, 2016) with therapeutic potential found in numerous diseases including cancer, spinal cord injury, and Parkinson's disease.

Admittedly, most of the therapeutic effects are mediated via $CB_2$ receptors but one should never discount the possibility of new therapeutic agents from unlikely places (Davidson & Molina-Holgado, 2016). For example, Nutt and colleagues (Danforth, Struble, Yazar-Klosinski, & Grob, 2016) are advocating MDMA for the treatment of anxiety-related disorders, while ketamine may be a fast acting antidepressant (Rasmussen, 2016). More research is needed on these SC, not only to better understand their adverse effects, but also to assess therapeutic potential, particularly in those drugs with a better activity profile at $CB_2$ receptors compared to $CB_1$ receptors. We recently wrote a speculative review where we considered which NPS might have potential therapeutic value (Davidson & Schifano, 2016). With respect to SCB such as WIN-55,212-2 and HU-210, they have been found to be neuroprotective in animal models of Parkinson's disease (More & Choi, 2015) and may be useful in Alzheimer's disease through blocking microglia activation (Ramírez, Blázquez, Gómez del Pulgar, Guzmán, & de Ceballos, 2005).

## 6. CONCLUSION

In this overview, we have reviewed the structure and pharmacology of SCB and highlighted the detrimental psychological effects of SCB, particularly on learning and memory and psychosis, and adverse clinical effects including on the cardiovascular system, brain, and kidneys. However, further work is required to identify the downstream targets, which may include different cellular targets, cell cycle regulatory transcription factors, or interaction with other signaling pathways. Taken together, it is clear that many SCB are extremely dangerous and a major public health problem, especially in Western societies.

Our present knowledge of SCB highlights important differences between the detrimental effects of SCB and the physiological relevance of the ECS as a neuromodulatory network with several protective actions in the human body. This is not simply related to differential activities at $CB_1$ and $CB_2$ receptors. We would advocate a ban on the recreational use of SCB but suggest that much has yet to be learned from the study of cannabinoids (including SCB), which will undoubtedly be of clinical use.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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