

Hijacking of Basic Research: The Case of Synthetic Cannabinoids

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Hijacking of Basic Research: The Case of Synthetic Cannabinoids

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Abstract

Gathering and communicating knowledge are important aspects of the scientific endeavor. Yet presentation of data in public forums such as scientific meetings and publications makes it available not only to scientists, but also to others who may have different ideas about how to use research findings. A recent example of this type of hijacking is the introduction of synthetic cannabinoids that are sprayed on herbal products and subsequently smoked for their marijuana-like intoxicating properties. Originally developed for the legitimate research purpose of furthering understanding of the cannabinoid system, these synthetic cannabinoids are being abused worldwide, creating issues for regulatory and law enforcement agencies that are struggling to keep up with the growing number of compounds of various structural motifs. Basic and clinical scientists need to provide advice now to facilitate decision-making about the health threats posed by this emerging problem.

Contents

Introduction	2
The Hijacking	2
Herbal Incense and Its Regulation	2
Origins of the Synthetic Cannabinoids in Herbal Incense	3
Previous Cases of Designer Drugs	5
Clinical Effects of Synthetic Cannabinoids	5
Research Needed	6
Concluding Remarks	7
References	7
Acknowledgments	Inside back cover

Introduction

Work as a bench scientist often involves long hours spent in a laboratory, talking with other scientists and having little contact with the outside world. Under these circumstances, losing sight of potential applications in the “real” world is easy—until an external event occurs that serves as a reminder that the work of scientists is not done in isolation. This paper presents a case study of the hijacking of findings from basic research on cannabinoids and the use of them to create products that may harm human health. This situation provides a valuable perspective on cannabinoid chemistry and its potential impact on human health and behavior. Further, examination of this situation highlights opportunities for research related to health issues caused by the new products.

The Hijacking

The story starts with John Huffman, professor emeritus of chemistry at Clemson University in South Carolina. After graduating with a doctorate in chemistry from Harvard University, Huffman accepted a faculty position at Clemson and spent much of his career following a traditional academic scientist path of teaching chemistry to graduate and undergraduate students while maintaining a grant-supported program of research. His major research area involved the synthesis of novel cannabinoids, drugs that possessed some of the properties of Δ^9 -tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis.

A few years ago, Huffman began receiving phone calls from law enforcement agencies, the military, and panicked parents, a situation that has continued since his retirement at the end of September 2010. The cause of this consternation was JWH-018, one of the cannabinoids Huffman designed and synthesized in his laboratory, because forensic scientists had identified it in herbal mixtures being marketed over the Internet as incense. Rather than using these herbal blends (e.g., Spice Gold, Spice Diamond, Purple Haze, K2, Skunk, and Smoke; see Figure 1) as incense, people were apparently smoking them for their marijuana-like effects (Vardakou, Pistos, & Spiliopoulou, 2010).

Figure 1. Purple Haze is one of the many herbal incense products containing synthetic cannabinoids



Herbal Incense and Its Regulation

While the packaging for these products lists only natural herbs as ingredients, analysis has revealed that they contain synthetic cannabinoids, including JWH-018, JWH-073, CP 47,497 (a bicyclic cannabinoid), and HU-210 (a tetrahydrocannabinol cannabinoid) (Auwarter et al., 2009; Lindigkeit et al., 2009; Teske et al., 2010; Uchiyama, Kikura-Hanajiri, Ogata, & Goda, 2010). With the exception of HU-210, the cannabinoid constituents of these herbal blends are structurally distinct from THC and, until recently, were not treated as controlled substances in most states in the United States. Hence, they provided an alternative to cannabis for people seeking to avoid potential legal consequences of marijuana use or for those wanting to become intoxicated and still pass a drug test.

As knowledge of the intoxicating effects of these herbal products spread over the Internet, their use in the United States increased to the point that the Drug Enforcement Agency (DEA) issued an emergency edict late in November 2010 proposing to place JWH-018 and four related compounds under Schedule I control (DEA, 2010). The final order (effective March 1, 2011) made these drugs, and products that contain them, illegal to manufacture or possess without a Schedule I license.

Groups of retailers are contesting this rule (see, for example, *L.P.O.E., Inc. v. United States Drug Enforcement Administration*, 2010) because the products are labeled “not for human consumption.” Enforcement is difficult due, in part, to the widespread availability of the products and the insufficient manpower of enforcement agencies. For example, in an unsystematic survey, we found at least one of the banned substances in products we purchased in North Carolina after this new regulation became effective (Cox et al., in press).

In Europe, where use of synthetic cannabinoids in herbal preparations was first seen in 2006 (European Monitoring Centre for Drugs and Drug Addiction [EMCDDA], 2009), several countries have already banned the sale and use of JWH-018 and similar synthetic cannabinoids. While these actions will undoubtedly help restrict access to the cannabinoids covered under these regulations, hundreds of compounds, in several chemical classes, have good cannabinoid receptor affinity and activity, and new substances will likely continue to appear in various formulations intended for use as intoxicants.

Thus, the situation presents a constant challenge for scientists tasked with the forensic and toxicological identification of new synthetic cannabinoid substances or formulations, as well as for public health and law enforcement agencies responsible for the rapid assessment of risk and, where necessary, implementation of control measures.

As one step in this process, RTI International forensic scientist Peter Stout and his team have set up a searchable forensic database (<https://www.forensicdb.org/index.htm>) into which they are entering results of analysis of some of the original JWH compounds synthesized by Huffman (and provided by Jenny Wiley, a coauthor of this paper). This database is publically available to forensic scientists. One of the coauthors, Brian Thomas, and his RTI colleague Megan Grabenauer are also taking an active role in analyzing these compounds.

Origins of the Synthetic Cannabinoids in Herbal Incense

Although the abuse of JWH indole-derived cannabinoids is relatively recent, the original design of many of the compounds occurred more than 20 years ago. Publication of a report on a compound known as pravadoline served as a catalyst for work that eventually led to the creation of the synthetic cannabinoids recently proposed for control by the DEA. Synthesized by scientists at Sterling-Winthrop, pravadoline exhibited promising analgesia preclinically with a mechanism distinct from opioid agonism or cyclooxygenase inhibition (Haubrich et al., 1990).

Researchers later found pravadoline to be nephrotoxic (Everett et al., 1993). In an effort to determine the mechanism through which it worked, researchers designed and synthesized conformationally restrained aminoalkylindole analogs (D'Ambra et al., 1992). From this program, researchers discovered WIN 55,212-2 to be a relatively potent analgesic, but Sterling-Winthrop dropped its research on aminoalkylindoles when it became clear that WIN 55,212-2 and related analogs were cannabimimetic (Compton, Gold, Ward, Balster, & Martin, 1992; Eissenstat et al., 1995).

By then, however, the CB₁ receptor had been identified (Devane, Dysarz, Johnson, Melvin, & Howlett, 1988), and researchers initiated efforts to further explore the structural requirements of cannabinoid receptor binding (Martin et al., 1991). The findings that WIN55,212 2, CP55,940 (a synthetic bicyclic compound), and anandamide possessed cannabinoid activity *in vivo* emphasized the broad structural diversity of cannabinoid agonists.

Within this innovative milieu, Huffman hypothesized that the position of the morpholinoethyl group of WIN55,212-2 might overlay the C3 side chain of THC in the then-accepted 3-point attachment model of cannabinoid receptor binding (Huffman, Dai, Martin, & Compton, 1994; Thomas, Compton, Martin, & Semus, 1991). Based on this model, he and his league of student chemists at Clemson synthesized

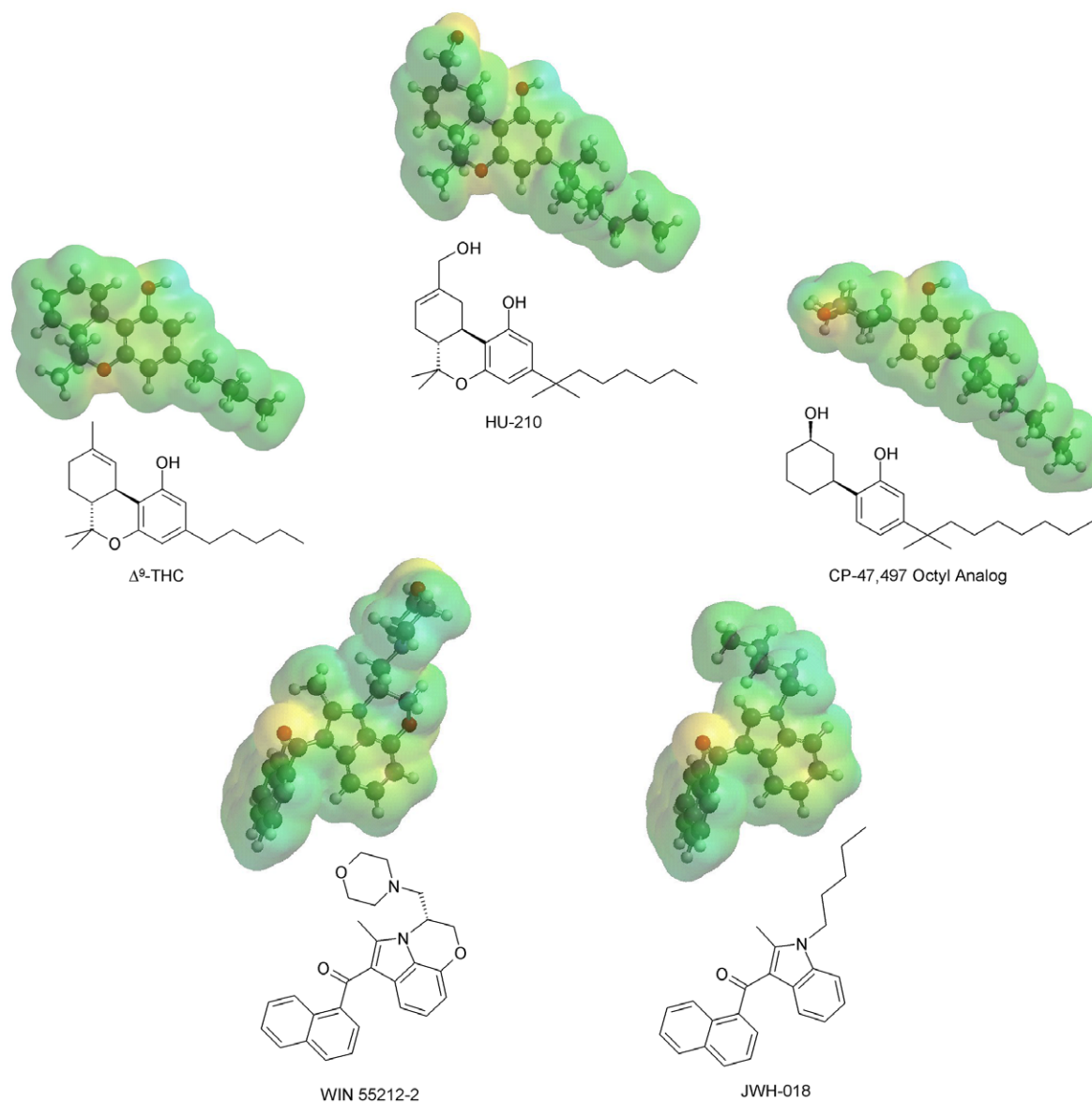
cannabinoids with comparable carbon chains attached to the nitrogen in the indole substituent (Huffman, Dai, Martin, & Compton; Figure 2). They then sent the compounds to pharmacologists Billy Martin and Jenny Wiley at Virginia Commonwealth University (VCU) in Richmond, Virginia, for *in vitro* and *in vivo* evaluation.

Subsequent studies reported an orderly structure-activity relationship between structural variation in these molecules (e.g., length and branching of the chain) and binding to the two identified cannabinoid receptors, CB₁ and CB₂ (Aung et al., 2000; Huffman,

Dai, Martin, & Compton; Lainton, Huffman, Martin, & Compton, 1995).

CB₁ receptors are the predominant type found in the brain and have been shown to mediate the intoxicating effects of THC in humans and in animal models (Huestis et al., 2001; Wiley, Lowe, Balster, & Martin, 1995). Use of synthetic cannabinoids such as those synthesized by Huffman's group has vastly increased scientific knowledge of the characteristics of the interaction between cannabinoids and their receptors. This type of knowledge garnered from basic research has led to greater understanding of the

Figure 2. Chemical structures of THC, the aminoalkylindole WIN55,212-2, and some of the synthetic cannabinoids identified in herbal incense products



functioning of the endogenous cannabinoid system (i.e., a system that communicates through use of cannabinoids that are synthesized in the body) and may assist in more precise design of medications that can be used to treat disruptions of normal functioning of this system.

Ironically, one of the goals of Huffman's later program of research on indole-derived cannabinoids was to develop compounds that selectively activated CB₂ receptors (Huffman, 2000). (THC binds to both types of receptors [Showalter, Compton, Martin, & Abood, 1996].) Selective CB₂ receptor agents would have potential use as anti-inflammatory analgesics and would not be expected to produce marijuana-like intoxication (Patel, Davison, Pittman, & Sharkey, 2010). The potential effects of this aspect of the pharmacology of indole-derived synthetic cannabinoids on peripheral physiological systems of abusers, however, are unknown and have received even less research than their centrally mediated effects.

Such is the foundation of basic science: hypothesis generation and testing followed by publication of the results. Although interdisciplinary cooperation that is the hallmark of basic and clinical research today was key to the long-standing collaboration between the groups at Clemson and VCU, possible clinical implications of the basic science research that resulted in development of JWH cannabinoids were usually confined to a few concluding sentences in each publication.

However, the fact that people are now abusing JWH cannabinoids has taken cannabinoid research to the public marketplace without the aid of clinical trials or regulatory oversight, with currently unknown implications for human health and behavior. Furthermore, it has primed the area for initiation of additional research, garnering the attention of researchers who heretofore had never read any of the original publications on indole-derived cannabinoids. Interestingly, the compounds that have been appearing in herbal products are those with the best CB₁ receptor affinities, suggesting that the suppliers of these products *have* been reading the scientific literature to determine which compounds are most likely to produce the effect of interest (intoxication)

with the least likelihood of adverse effects (e.g., law enforcement interference). Indeed, perusal of the scientific literature is the likely method through which illicit manufacturers of synthetic cannabinoids discovered their existence and potential abuse liability.

Previous Cases of Designer Drugs

This situation is not the first—nor the last (e.g., witness the recent emergence of products containing cathinone analogs, stimulants that have been marketed as “bath salts” or “plant food”)—instance where research on novel synthetic drugs conducted by legitimate scientists, often with support from the National Institutes of Health, has led to compounds that have subsequently been subject to abuse.

The phenethylamine analogs of mescaline and amphetamine and the tryptamine analogs of LSD became known as “designer drugs” because they were made and abused prior to their regulatory control, often for many years (Shulgin & Shulgin, 1991, 1997). Indeed, people used one of these designer drugs, methylenedioxymethamphetamine (MDMA, or ecstasy), for years before it became illegal. Another interesting example is the drug phencyclidine (PCP). Although abuse reports did not begin until the early 1970s, the street name, PCP, was based on an abbreviation for the chemical name 1-(1-phenylcyclohexyl) piperidine that was published over 10 years earlier (Chen, Ensor, Russell, & Bohner, 1959).

Clinical Effects of Synthetic Cannabinoids

Although researchers have not conducted systematic studies of the clinical effects of synthetic cannabinoids, anecdotal reports and case studies (primarily from visits to the emergency room) reveal that many, but not all, of the effects of synthetic cannabinoids resemble those of marijuana. Similar effects include subjective intoxication, tachycardia (fast pulse rate), and conjunctival injection (red eyes) (Auwarter et al., 2009). In addition, at least one case study has been published that documents dependence and associated withdrawal in an individual following

chronic (8 month) use of synthetic cannabinoids (Zimmermann et al., 2009).

According to some reports, the intoxication produced by synthetic cannabinoids is more intense than that produced by cannabis, while others report that it is milder (Vardakou, Pistos, & Spiliopoulou, 2010). Previous findings that WIN 55,212-2 and some indole-derived synthetic cannabinoids have better affinity for the CB₁ receptor and may activate it more strongly (i.e., have higher efficacy) than THC (Atwood, Huffman, Straiker, & Mackie, 2010; Griffin, Atkinson, Showalter, Martin, & Abood, 1998; Huffman et al., 2005) are consistent with the idea that synthetic cannabinoids have greater potency in vivo than marijuana; hence, people smoking either marijuana or herbal incense with an identical amount of active cannabinoid (THC or synthetic) would be expected to show greater intoxication with synthetic cannabinoids such as JWH-018 and JWH-073.

In addition, studies have reported a few differences in the clinical effects of THC and synthetic cannabinoids. Whereas marijuana tends to decrease blood pressure, individuals smoking herbal incense with synthetic cannabinoids have had high blood pressure upon admission to the emergency department. Other symptoms that tend to be more pronounced in users of synthetic cannabinoids include increased anxiety or agitation (Schneir, Cullen, & Ly, 2010), nausea and vomiting (Schifano et al., 2009), and psychiatric disturbance (e.g., suicidality, exacerbation of preexisting psychosis) (Every-Palmer, 2011; Müller et al., 2010).

Several caveats apply to these observations. First, many published reports on the clinical effects of synthetic cannabinoids derive primarily from persons seeking treatment in a hospital emergency department. Consequently, effects that are described may be characteristic of only the most severe cases of intoxication. Second, published reports have not always verified the content and purity of the synthetic cannabinoids contained in herbal incense. In addition, studies have neither identified other substances in the plant material of the incense product nor evaluated their potential contribution to intoxication (or to modulation of the effects of synthetic cannabinoids).

Research Needed

Formulation of a workable solution for handling the issue of abuse of non-controlled synthetic cannabinoids or herbal products containing them will require collaborative input from all interested parties, including basic and clinical scientists, legislative bodies, regulatory agencies, parents, and other concerned citizens. Like the creation of the problem itself, the foundation of its solution starts with science. Despite increasing incidence of use of synthetic cannabinoids, no controlled clinical studies have examined their pharmacological effects in humans, and research on their behavioral effects in animals is sparse, with only a few studies that have examined the acute in vivo effects of a small percentage (less than 10 percent) of the entire series of over 200 indole- and pyrrole-derived cannabinoids synthesized in Huffman's lab (Huffman, Dai, Martin, & Compton, 1994; Vann et al., 2009; Wiley et al., 1998; Wiley, Huffman, Balster, & Martin, 1995), not to mention synthetic cannabinoids developed by other researchers.

Anecdotal reports from users of these herbal products suggest identifiable differences in the degree of intoxication, dependent upon the "flavor" (and presumably upon the specific synthetic cannabinoids contained therein). Research is needed to learn more about the possibly subtle differences in the effects of these synthetic cannabinoids and/or in the various plant materials upon which the chemicals are sprayed. Indeed, to preemptively control some of these products instead of reacting to abuse situations after they occur, regulatory authorities need data on the chemistry and pharmacology of cannabinoid receptor agonists.

Efficient forensic methods for detection of the numerous cannabinoid variants contained in the herbal products and their probable metabolites are also lacking (Dresen et al., 2010). Collaborative work among scientists and researchers to examine the effects of these synthetic compounds in animals and in human users would provide health care workers with additional information on potential impact of acute and repeated use of these substances on health, including addiction, and would give policy makers a

scientific basis for regulation of the content of these potent products.

In the process of this work, comparison of synthetic cannabinoids or herbal preparations with their closest referents, THC or marijuana, will be essential. Coincidentally, simultaneous with the appearance of these herbal products, several states were challenging the legal status of marijuana. Although California voters recently rejected a proposition to legalize recreational use of marijuana, decriminalization remains the trend there and in some, but not all, other states. In addition, prescription of marijuana for medicinal purposes is widespread in California and some other states. Examining comparative prevalence of marijuana use versus use of synthetic cannabinoid herbal preparations across states and globally, particularly data from the period when these herbal products still served as a legal alternative to marijuana, would present a potentially valuable source of information on the effects of different regulatory approaches on demand of these formulations.

In fact, although little is known about the extent to which smoking mixtures containing synthetic cannabinoids has replaced cannabis smoking in the United States or globally, a preliminary survey conducted among 1,463 students aged 15 to 18 years at schools providing general and vocational training in Frankfurt, Germany, found that around 6 percent of respondents reported having used Spice

at least once (EMCDDA, 2009). Determining the extent to which the population of users of synthetic cannabinoids overlaps with that of marijuana users would indicate whether the availability of these products serves as an incentive to a new group of substance abusers or is primarily an alternative for marijuana smokers.

Concluding Remarks

While it is too soon to discern the overall public health impact of the abuse of synthetic cannabinoids, previous experience with other designer drugs shows that making synthetic drugs illegal does not prevent them from being made and abused. In addition, many hundreds of other compounds that could have cannabimimetic effects are not yet specifically regulated, so some of them may factor in as well. We may be on the verge of another ecstasy-like problem, although the relatively easy availability of natural cannabis products worldwide may make abuse of synthetic cannabinoids less profitable.

On the other hand, it is interesting to note that the advertized price of these synthetic herbal mixtures on the Internet of \$10 to \$12 per gram is about the same as typical prices for high-quality medical marijuana sold in legal dispensaries, so if the price of legally obtainable cannabis products remains high, a market for these synthetic variants may remain. Most important is the need for scientific investigation of the health consequences of synthetic cannabinoid abuse.

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