Synthetic cannabinoid JWH-018 and psychosis: An explorative study

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A B S T R A C T

Background: Aroma, Spice, K2 and Dream are examples of a class of new and increasingly popular recreational drugs. Ostensibly branded “herbal incense”, they have been intentionally adulterated with synthetic cannabinoids such as JWH-018 in order to confer on them cannabimimetic psychoactive properties while circumventing drug legislation. JWH-018 is a potent cannabinoid receptor agonist. Little is known about its pharmacology and toxicology in humans. This is the first research considering the effects of JWH-018 on a psychiatric population and exploring the relationship between JWH-018 and psychotic symptoms.

Method: This paper presents the results of semi-structured interviews regarding the use and effects of JWH-018 in 15 patients with serious mental illness in a New Zealand forensic and rehabilitative service.

Results: All 15 subjects were familiar with a locally available JWH-018 containing product called “Aroma” and 86% reported having used it. They credited the product’s potent psychoactivity, legality, ready availability and non-detection in drug testing as reasons for its popularity, with most reporting it had replaced cannabis as their drug of choice. Most patients had assumed the product was “natural” and “safe”. Anxiety and psychotic symptoms were common after use, with 68% of users experiencing or exhibiting symptoms consistent with psychotic relapse after smoking JWH-018. Although psychological side effects were common, no one reported becoming physically unwell after using JWH-018. Three subjects described developing some tolerance to the product, but no one reported withdrawal symptoms.

Conclusion: It seems likely that JWH-018 can precipitate psychosis in vulnerable individuals. People with risk factors for psychosis should be counseled against using synthetic cannabinoids.

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1. Introduction

While cannabis use has a long history, the emergence of synthetic cannabinoids such as JWH-018 is recent. This article explores the relationship between JWH-018 and psychotic symptoms and reports 15 forensic inpatients’ experiences with synthetic cannabinoid containing products (SCCPs).

1.1. Background: SCCPs emerge as a new drug trend

Spice, Aroma, K2 and Dream are examples of a large and evolving group of smokable products branded as ‘herbal incense’, but found by users to have potent cannabis-like properties. Spice first started appearing on internet sites and in specialized shops around 2004 (Dresen et al., 2010). Warning messages on the product stating it was not intended for human consumption contrasted with sophisticated packaging and marketing, promoting the product as a cannabis alternative which was undetectable by conventional drug testing methodology.

It was not until December 2008 that researchers reported the reason for Spice’s cannabis-like properties: Spice had been ‘laced’ with undeclared synthetic cannabinoids JWH-018 and CP 47,497 (Auwärter et al., 2009). It is believed that these synthetic cannabinoids were dissolved in a solvent which was then sprayed on a plant-derived base for delivery (Vardakou et al., 2010). The herbal ingredients cited on Spice’s packaging did not appear to contribute to its psychoactivity; in fact they were not even present in most of the samples tested (Piggee, 2009).

Since being identified in “herbal” products JWH-018 and CP 47,497 have been banned in a number of European countries and some American States (Vardakou et al., 2010). Three weeks after CP-compounds and JWH-018 were banned in Germany, second generation products (e.g., analogues such as JWH-073) appeared on the market, suggesting the manufacturers had anticipated prohibition and had already synthesized an array of alternatives (Lindigkeit et al., 2009). Currently “headshops” and the internet offer an ever-expanding array of synthetic cannabinoids originating from 3 chemically distinct groups...
JWH compounds (e.g., JWH-018, JWH-015 and JWH-073) are currently unregulated in New Zealand and are widely available in ‘headshops’ and over the internet. New Zealand may be a particularly opportune market for cannabimimetic drugs with an annual prevalence of cannabis use at 14.6%, one of the highest in the world (United Nations Office on Drugs and Crime, 2010). Cannabis use is particularly prevalent in criminal populations with 55% of New Zealand prison inmates qualifying for lifetime diagnoses of cannabis abuse or dependence (New Zealand Department of Corrections, 1999).

In forensic psychiatric services, substance use is prohibited, and abstinence is monitored by urine drug screens. However, the arrival of unregulated synthetic cannabinoids into the market is posing new challenges to forensic and other mental health services.

1.2. Synthetic cannabinoids and psychosis

Little data is available on the psychological and other risks of synthetic cannabinoids. Psychotic relapses following the use of a JWH-018 product in 5 patients in our forensic service have already been reported (Every-Palmer, 2010). There is one published case report of tolerance and withdrawal phenomena in the literature (Zimmermann et al., 2009) and another of drug induced psychosis (Müller et al., 2010). Both these cases were attributed to Spice, which at the time contained JWH-018 and CP 47,497.

There is also an increasing number of reports describing patients presenting for emergency medical care after using “Spice” products. Common features of many of these presentations have included anxiety symptoms, agitation, tachycardia, paranoia and hallucinations (Banerji et al., 2010; Bebarta et al., 2010; Piggee, 2009; Vearrier and Osterhoudt, 2010). Inter-batch variation in the type and quantity of cannabinoids present has also resulted in accidental overdosing requiring hospitalization (Auwärter et al., 2009).

A number of self-reports of users experiencing anxiety and psychotic symptoms following the use of JWH-018 and other cannabinoids can be found on the internet (e.g., http://www.erowid.org/experiences/subs/exp/JWH018.shtml#Train_Wrecks_&_Trip_Disasters).

1.3. Synthetic cannabinoid use in New Zealand

Five of the 15 subjects recruited had previously been identified by staff as experiencing psychotic relapses in the context of synthetic cannabinoid use, becoming objectively agitated, disorganized and delusional after smoking the product. The study had ethical approval from the New Zealand Central Regional Ethics Committee.

2.2. Recruitment

The interviewer visited the two inpatient units where the research was conducted on 7 occasions. A brief explanation of the study was provided to patients. Subjects who were interested in participating were individually provided with written and oral information about the study and informed oral consent was obtained.

2.3. Interviews

Semi-structured interviews were conducted by the author in a private interview room within the inpatient units. The interview explored the subjects’ experience with synthetic cannabinoids, including knowledge, personal use, subjective experience and their observations of how these substances appeared to have affected others. A formal inquiry into each subject’s current mental state was not conducted, but the interviewer noted her observations of the subject’s presentation immediately after the interview, including whether the subject seemed thought disordered. Interviews took place in March and April 2010.

2.4. Data collection and analysis

Short-hand notes recording the subjects’ responses were taken during the interview. Patients were not willing to consent to audio recording due to the sensitive nature of the material discussed, and fears about confidentiality. Following the interview, short-hand notes were transcribed into long-hand and were annotated with the interviewer’s observations from the interview. The transcripts were analyzed manually in order to identify key themes and recurrent ideas. Data were coded and indexed in terms of similarity and contrast of content. All data recorded was de-identified to preserve confidentiality.

Quotations in Section 3 are used to illustrate emergent trends. Interviewee quotes are identified by: (a) a number between 1 and 15 to differentiate among respondents, and (b) the letter N, O or H to denote the subject’s reported frequency of synthetic cannabinoid use over the preceding year (N: never, O: occasional-less than weekly; H: high-use daily or weekly).

2.5. Urinalysis

All patients had been subject to regular random urine drug testing for cannabinoids, opiates, opioids, amphetamines and benzodiazepines. The urine drug screen results from the last 18 months were reviewed.

3. Results

3.1. Patient demographics

All 15 participating subjects were male. At the time of the study the service had a 5:1 male to female ratio, and no female patients met the inclusion criteria.

All patients had a history of psychotic illnesses and had been compulsorily treated with therapeutic doses of antipsychotic medication, with active monitoring of compliance, for at least 6 months prior to the study. Five patients were also taking mood stabilizers. They had all achieved stable mental states prior to the decompensations reported in this study. The demographics of the subjects are summarized in Table 1.

All subjects had been within the service for some years, and had been referred to a low security rehabilitation facility as their mental states had improved. They all had unescorted leave off the unit, although in three cases leave privileges had been temporarily revoked due to the patients’ recent deterioration in mental state. All participants had used cannabis in the past. None of the participating patients had tested positive for THC in their most recent urine drug screens. Review of urine drug screens for the cohort over the previous 18 months showed a positive result for cannabinoids was a low probability event. Of 153 urine tests, only 7 (from

Footnote: Random drug screening used an immunoassay technique, based on the KIMs method.
4 different patients) were positive for cannabinoids. No patient tested positive for amphetamines or opioids, and positive tests for benzodiazepines and opiates correlated with prescribed medicine.

3.2. Trends

On analysis and coding of the interview transcripts four common themes were identified relating to the use of synthetic cannabinoids in the service: their popularity, psychoactivity, effects on mental state and pleasurable feelings of rebellion associated with their use. Results are summarized in Table 2.

3.2.1. Popularity. All subjects were familiar with a locally available SCCP, Aroma. Four patients had some historical experience with similar products called Kronic Skunk, Dream and Spice. All these products consist of a base of unidentified plant matter which has been shown to contain JWH-018 (personal correspondence. Mark SCPS, Aroma. Four patients had some historical experience with similar products called Kronic Skunk, Dream and Spice. All these products consist of a base of unidentified plant matter which has been shown to contain JWH-018 [Wilkins and Sweetser, 2006]). Patients credited Aroma’s legality, easy availability, product consistency, non-detection in drug tests and perceived safety as reasons to favour it over marijuana.

“Aroma has cancelled out all the cannabis here. No one smokes cannabis anymore. Why would you? It [Aroma]’s a good substitute, its legal, it’s not in urine and it’s easier to go to [name of local shop that sells Aroma] than to go down to a tinny house [cannabis dealer].” (8-H)

3.2.2. Psychoactivity. All 13 patients who acknowledged having smoked Aroma said that they used it as a cannabis substitute. “[Aroma]’s like marijuana, but health wise it’s better. …It’s strong. It gets you real whacked and makes you high.” (2-H)

Five subjects commented that they preferred Aroma to cannabis due to its potency. One subject preferred cannabis and the others were indifferent. A common complaint was that the SCCPs “did not last as long as cannabis”, with the psychoactive effects being consistently described as having a rapid onset of action and a duration of 1–2 h following inhalation.

Patients did not know what conferred Aroma its psychoactive properties. Three patients correctly speculated that it ‘had been sprayed with chemicals’, the others were either unsure or described it as a “natural” or “herbal” product. Aroma won’t interfere with medication. Aroma won’t interfere with medication. It’s a better buzz than marijuana. It’s quite safe” (10-O)

3.2.3. Effects on mental state. Five patients reported experiences consistent with a psychotic relapse within 24 h of smoking Aroma which lasted “2 days” to “several weeks”. Two of these patients also reported pronounced anxiety symptoms. They attributed these symptoms to Aroma. However, of the 5 patients in this study who had previously been identified by clinical staff as suffering a probable JWH-018-induced psychotic relapse (Every-Palmer, 2010), only 1 subjectively acknowledged the effects Aroma had on their mental state. The other 4 had little insight into their mental illnesses and denied being adversely affected by SCCPs, for example one man who objectively became floridly psychotic and aggressive after admittedly smoking Aroma reported:

“Staff say we’re not allowed to smoke it, because it would cause risks. But they don’t know. It doesn’t cause risks to me. It just makes me cool, calm and collected. …to clients who are sick, it causes risks to them.” (3-O)

Table 2

Summary of subjects’ experiences with synthetic cannabinoid containing products (SCCPs).

<table>
<thead>
<tr>
<th>Experience</th>
<th>Yes</th>
<th>No</th>
<th>Unsure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Of all subjects who participated in the study (n = 15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familiar with synthetic cannabinoid containing products (SCCPs)</td>
<td>15/15 (100%)</td>
<td>0/15 (0%)</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td>Admitted using SCCPs over the last year</td>
<td>13/15 (87%)</td>
<td>2/15 (13%)</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td>Admitted using SCCP ‘Aroma’ over the last year</td>
<td>13/15 (87%)</td>
<td>2/15 (13%)</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td>Admitted using other SCCPs (e.g., Kronic Skunk, Dream, Spice,)</td>
<td>4/15 (27%)</td>
<td>10/15 (67%)</td>
<td>1/15 (7%)</td>
</tr>
<tr>
<td>Of the subjects who reported SCCP use (n = 13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Described psychoactive effects from SCCP</td>
<td>13/13 (100%)</td>
<td>0/13 (0%)</td>
<td>0/13 (0%)</td>
</tr>
<tr>
<td>Considered SCCP a “herbal” or “natural” product</td>
<td>7/13 (54%)</td>
<td>3/13 (23%)</td>
<td>3/13 (23%)</td>
</tr>
<tr>
<td>Reported or exhibited psychotic symptoms following SCCP use</td>
<td>9/13 (69%)</td>
<td>3/13 (23%)</td>
<td>1/13 (7%)</td>
</tr>
<tr>
<td>Reported experiencing anxiety symptoms following SCCP use</td>
<td>7/13 (54%)</td>
<td>5/13 (38%)</td>
<td>1/13 (7%)</td>
</tr>
<tr>
<td>Reported tolerance (requiring increasing amounts to achieve the same effects)</td>
<td>2/13 (15%)</td>
<td>10/13 (77%)</td>
<td>1/13 (7%)</td>
</tr>
<tr>
<td>Reported withdrawal symptoms</td>
<td>3/13 (23%)</td>
<td>10/13 (77%)</td>
<td>0/13 (0%)</td>
</tr>
</tbody>
</table>

4. Discussion

4.1. Limitations of the study

This was a small study (n = 15) of a highly select patient group. The participants were all men with serious mental illness with risk profiles mandating intensive supervision in a forensic service. This group is particularly vulnerable to psychosis, but paradoxically may also currently have some degree of protection (compared to vulnerable people in the community), as all subjects were receiving assertive treatment and environmental support. The experiences of this group cannot necessarily be extrapolated to a wider population, particularly those without mental illness, females and adolescents.

This study describes only the subjective experiences that subjects chose to share with the interviewer and as such is subject to bias including selection bias, under-reporting and exaggeration. Although patients and staff report deteriorations in the subjects’ mental states in relation to synthetic cannabinoid use, this study only suggests, but does not prove a causal link.

4.2. Discussion of findings

In this cohort of forensic inpatients in a low-secure setting all the subjects were familiar with synthetic cannabinoids and 86% reported having used them. They credited the products’ potent psychoactivity, legality, ready availability and non-detection in drug testing as reasons for their popularity, reporting they had replaced cannabis as the drugs of choice in our service. Synthetic cannabinoids do not appear in conventional urine drug testing so users could evade detection and sanction by their care team. This had engendered a conspiratorial culture in which users took some pleasure in small acts of insurrection, in an environment where the balance of power usually resides on the side of the health professionals.

Furthermore, most patients assumed SCCPs were “herbal”, “natural” and “safe”. This may be due to by their legality, easy availability and marketing as “organic”. However, synthetic cannabinoids are not herbal, natural nor safe. Nine patients experienced symptoms consistent with a psychotic relapse after using JWH-018 containing products (5 self reported, 4 reported by health professionals). Three patients reported tolerance, but nobody endorsed withdrawal symptoms.

Substance abuse is a robust predictor of an increased probability of violence and criminality in the mentally disordered (Soyka, 2000). Whether JWH-018, like cannabis, is a potential mediator of antisocial behaviour is at this stage unclear, but the unfettered use of psychoactive compounds in high risk patients is concerning for both individual and societal reasons.

4.3. Pharmacology of Aroma

All patients were smoking the same product, a SCCP marketed as Aroma. This product comprises a dried herb material which is a vehicle for high concentrations of JWH-018 and oleamide. Of 46 products tested by Uchiyama et al. (2010) Aroma contained the highest concentration of oleamide and the second highest concentration of JWH-018. (See Table 4.)

4.4. JWH-018 and psychosis

Although to date there is little data about the possible psychiatric sequelae of synthetic cannabinoids, the link between cannabis and psychosis is well established and has been extensively reviewed (e.g., Henquet et al., 2005; Fergusson et al., 2006; Moore...
et al., 2007; Murray et al., 2007). Cannabis contains at least 90 different cannabinoids, with THC being the primary psychoactive ingredient (Gaoni and Mechoulam, 1964). In experimental studies, THC produces transient and dose related psychotic symptoms (D’Souza et al., 2004) and impaired memory (Solowij and Michie, 2007). Consumer surveys (e.g., Thomas, 1996) provide further evidence that cannabis intoxication can produce transient psychotic experiences. Large prospective epidemiological studies (e.g., van Os et al., 2002; Zammit et al., 2002; Arseneault et al., 2002) show a link between cannabis use and the development of chronic psychotic illnesses such as schizophrenia.

All the patients in this study had established psychotic illnesses. Cannabis use in such patients is common (Green et al., 2004; Boydell et al., 1999) and has been associated with poor clinical and functional outcomes including: an earlier disease onset (Foti et al., 2010); more positive symptoms (Bühler et al., 2002; Mauri et al., 2006); a higher relapse rate (Swofford et al., 1996), and a reduced treatment response (Foti et al., 2010). In first-episode schizophrenia cannabis use is associated with a greater reduction in cerebral grey matter volume in users compared with non users over time (Rais et al., 2008).

It cannot be assumed that the psychiatric risks of synthetic cannabinoids will equate to those associated with cannabis, however, it is hypothesized that JWH-018 may pose comparable or even greater risks due to the following observations:

1. JWH-018 produces similar effects to THC in animal experiments (EMCDDA, 2009).
2. There are an emerging number of reports of users experiencing psychotic symptoms in the context of JWH-018 use on the internet and in the literature (Müller et al., 2010; Every-Palmer, 2010).
3. The pharmacological profile of JWH-018 raises the theoretical possibility of increased cognitive and psychiatric side effects compared to cannabis.

(a) In vitro data suggests that JWH-018 possesses approximately a four-fold higher affinity to the CB₁ receptor and ten-fold affinity to CB₂ receptor compared with THC (Aung et al., 2000; Huffman et al., 2005). CB₁ receptors are abundant in central nervous system, particularly in the basal ganglia, hippocampus and cerebellum (Howlett et al., 2004; Fergusson et al., 2006). These receptors regulate the release of several key neurotransmitters, including dopamine and serotonin. It is thought that cannabis may lead to psychosis through THC’s effects on dopaminergic and serotonergic pathways via CB₁ receptors (Fergusson et al., 2006). While THC exerts only partial CB₁ agonism, JWH-018 is a full and potent agonist at CB₁ receptors (Atwood et al., 2010).

(b) Unlike cannabis, SCCPs do not contain cannabidiol. Cannabidiol and THC are the two major components of cannabis, and they exhibit opposing pharmacological and physiological actions. Cannabidiol is a CB₁ and CB₂ antagonist which appears to have antipsychotic (Leweke et al., 2009; Zuardi et al., 2006; Morgan and Curran, 2008) and anxiolytic properties (Guimarêas et al., 1990) and may be neuroprotective in humans (Herrmann et al., 2007; Morgan et al., 2010). While cannabidiol may afford cannabis users some inherent protection against psychotic symptoms (Morgan and Curran, 2008) and cognitive impairment (Morgan et al., 2010) this protection is lacking in SCCPs.

(c) Some SCCPs like Aroma also contain oleamide, a fatty acid demonstrated to functionally activate CB₁ cannabinoid receptors in vitro (Leggett et al., 2004), which may have potentiating effects.

4. SCCPs may appeal to vulnerable populations who might not otherwise smoke cannabis including those who have suffered adverse effects from cannabis or have been warned against using cannabis (e.g., a possible predisposition to psychotic illness) and those being monitored for drug use (e.g., in prisons, forensic hospitals). There are increasing reports of young people using SCCPs (e.g., EMCDDA, 2009; http://www.stuff.co.nz/national/4279640/Parents-worried-by-legal-weed). In the forensic population studied in this research, the base rate of ongoing cannabis use was low due to institutional deterrents and education regarding the risks of cannabis. However, those disincentives did not exist to the same extent with SCCPs, which were being consumed in greater quantities than cannabis had previously been. Although it is likely that most people who smoke SCCPs will not experience psychotic symptoms, the risks are much higher for these vulnerable populations.

4.5. Management

It is known that in forensic populations drug treatment programs associated with the best outcomes are assertive and use some form of leverage, such as mandatory drug testing (Lamb et al., 1999). Currently there are no widely available drug testing methods to identify JWH-018 use, although laboratory techniques have recently been developed for identifying JWH-018 in serum (Teske et al., 2010) and JWH-018 metabolites in urine (Sobolevsky et al., 2010). Until these techniques become more widely available clinicians will need to rely on clinical skills. These include: specifically asking patients about “herbal highs”; being alert to the physiological and effects of SCCP use such as conjunctival injection and tachycardia (Auwärter et al., 2009; Sobolevsky et al., 2010) and having a high index of suspicion in the context of an unexplained deterioration in mental state in the context of a negative urine drug screen. Health professionals need to be cognizant and responsive to novel drug trends in order to counsel their clients appropriately.

In countries where synthetic cannabinoids remain legal, there needs to be ongoing review and monitoring of their safety at a national level. Discussion also needs to be held around the accurate labeling of products containing psychoactive compounds, so that users are aware of the potential risks.

5. Conclusion

Synthetic cannabinoids pose difficult social, political and health challenges. There are more than 100 known compounds with cannabinoid receptor activity, and no doubt more will be synthesized in the future. Almost nothing is known about the pharmacology and toxicology of compounds such as JWH-018, however, it seems that they can cause psychosis in vulnerable individuals. Health professionals need to maintain a high degree of vigilance for novel substance use, and the possible psychiatric consequences. People with risk factors for psychosis should be counseled against using synthetic cannabinoids.

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Conflict of interest

No conflict declared.

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References


