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Synthetic Marijuana and Current Treatment: A Literature Review

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Review Article

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ABSTRACT

Introduction: The number of users of synthetic marijuana is rising, and is responsible for many of the emergency room visits and inpatient psychiatric admissions in the United States. A unique characteristic of this substance is its varying composition from containing JWH-018 to new derivatives like JWH-081, JWH-122 and AM-220 in attempts to avoid regulations. Compounds such as JWH-018 can cause psychosis in vulnerable individuals. Individuals with a history of psychosis, family history of psychosis and limited resources are vulnerable to experience psychosis after smoking synthetic marijuana.

Methods: This research paper is a comprehensive literature review to determine if successful pharmacological treatments have been developed to treat synthetic marijuana induced psychosis. The online databases, PubMed, Cinahl PLUS with full text, Ebscohost, and Google Scholar were all used to search for articles published after the year 2010. Any synthetic marijuana identified differently such as K2, spice, or JWH-018 was all used for inclusion. Exclusions to the study were articles that described cannabinoid or marijuana induced psychosis.

Results: After reviewing abstracts for 80 articles, nine articles conducted in the US, UK and Australia met inclusion criteria; which included either pharmacological treatment for synthetic marijuana induced psychosis or symptoms experienced related to synthetic marijuana use. Antipsychotics such as risperidone, haloperidol, Clopixol-Acuphase and clozapine were used to treat the psychosis. Clozapine was used in cases where other antipsychotics were ineffective. Benzodiazepines such as lorazepam and diazepam were used to treat agitation, and quetiapine was used for agitation as well. Lorazepam was used for catatonia, and ECT was used for treatment refractory catatonia not resolved by lorazepam.

Conclusions: Treatment for synthetic marijuana toxicity is mainly supportive. The most common symptoms of synthetic marijuana toxicity were tachycardia, agitation, nausea/vomiting and hallucinations. Withdrawal symptoms after using synthetic marijuana were described as anxiety and mood swings making relapse more likely. Also, synthetic marijuana may catalyse psychotic symptoms; making treatment more complex. Treatment for psychotic symptoms related to synthetic marijuana use may warrant treatment with high potency antipsychotics like haloperidol and clozapine. Also, severe catatonia from synthetic marijuana use can be treated with benzodiazepines and electroconvulsive therapy (ECT).

INTRODUCTION

Spice, K2, and Black Mamba are street names for the synthetic marijuana that is responsible for many of the emergency room visits and inpatient psychiatric admissions in the United States. The synthetic marijuana is legal due to its branding as “herbal incense” or “potpourri”. Since 2004, herbal mixtures were available via internet in many European countries as a substitute for marijuana and labeled as air fresheners [1]. The herbal mixtures soon crossed overseas to the United States. Due to the availability of synthetic marijuana on the internet and branding, the substitute for marijuana was easily obtainable. The American Association of Poison Control Centers track human exposure to synthetic marijuana by documenting phone calls from users who experience

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adverse effect from the substance. In 2011, there were 6,968 cases reported, followed by 7,779 in 2015 and 2,695 in the year 2016 [2]. The users of synthetic marijuana are rising. The drop in number of calls in the year 2016 can be attributed to different reasons including tighter regulation of these substances. In 2012, the synthetic drug abuse prevention act added twenty-six types of cannabinoids and cathinones into Schedule I of the Controlled Substances Act. This legislation was in an effort to reduce the availability of these drugs in gas stations, smoke shops, and on the street. The efforts on the national level allowed states to also introduce bills in their own state legislature to ban the different compounds of synthetic marijuana. In 2015, the Texas Senate Bill 173 designated criminal prosecution of certain chemicals referred to as synthetic cannabinoids as controlled substances under their own Controlled Substance Act. The state of New York has also issued health advisories annually since 2014, and in 2015, the mayor in New York signed K2 legislation into laws punishing retailers for selling K2. For example, Intro 917-A criminalizes the sale of K2 a misdemeanor punishable by up to one year in jail and up to $5,000 in fines. Efforts on national and state levels may be responsible for the lower numbers of exposures to synthetic cannabinoids. The decreasing availability of synthetic marijuana due to legislation is imperative; especially since the chemicals have been changed frequently in order to escape legislation. In addition to this, synthetic marijuana is undetectable with conventional drug testing, which makes it appealing as a substitute to marijuana. Another cause for concern is the teenage population who may find synthetic marijuana easier to obtain because it can be bought on the internet.

One unique characteristic of Spice or synthetic marijuana is its varying composition from containing JWH-018, to new derivatives like JWH- 081, JWH-122, and AM-2201, probably in attempts to avoid regulations [3]. John W Huffman is the chemist who synthesized the chemicals that affected the endocannabinoid system, hence the acronym, JWH. The HU series (developed at the Hebrew University), the CP series (from the Pfizer Inc.) and the JWH series (developed by JW Huffman) are the major groups of synthetic cannabinoids [4]. Newer derivatives of the synthetic cannabinoids make regulating this substance difficult because unlike other illicit substances, the composition changes while the packaging under herbal products is maintained. These compounds are high affinity, full agonists of brain cannabinoid receptors and are between 10–200 times more potent than THC [5]. Therefore, regulation of these substances in the United States is minimal and can pose a threat to the safety of users. The use of synthetic marijuana also puts the mental health of users at risk. Data suggests that JWH-018 possesses higher affinity than conventional marijuana to the CB1 receptors, hippocampus, and cerebellum which regulates release of dopamine and serotonin. The neurotransmitters dopamine and serotonin are known to play significant roles in psychosis. It seems compounds such as JWH-018 can cause psychosis in vulnerable individuals [6]. Individuals with a history of psychosis, family history of psychosis, and limited resources are vulnerable to experience psychosis after smoking synthetic marijuana.

PROJECT PURPOSE

Synthetic marijuana use can precipitate psychosis in vulnerable individuals, and current providers in the field of psychiatry are faced with this challenge. A substance disguised as herbal and safe in its packaging is undetectable in urine, yet causing psychotic symptoms in users. This project is a comprehensive literature review to determine if successful pharmacological treatments have been developed to treat synthetic marijuana induced psychosis. This question serves to provide information and identify current gaps in knowledge for the provider administering psychiatric treatment to patients with substance-induced psychosis who have been smoking synthetic marijuana.

BOYER'S SCHOLARSHIP MODEL

In addition to identifying current gaps in knowledge in treating synthetic marijuana induced psychosis, a discussion of how this research contributes to the discipline of nursing is explained here. Master's prepared nurses in the field of psychiatry prescribe and treat patients in the inpatient and outpatient settings. With increasing emphasis on evidence-based practice, research is directly impacting current practice guidelines that help to guide treatment decisions for providers. Performing research is one of the best ways to advance the knowledge base of nursing. The Boyer's scholarship is a model explaining research as scholarly work that functions in four ways. The work of a scholar should have functions that include the scholarship of discovery, integration, application, and teaching. In my research endeavor, application of knowledge is the primary purpose of this study. Within the scholarship of application, theory and practice vitally interact and renew each other [7]. Theoretical knowledge and practice are synergistic in the ability to produce best practice within the psychiatric field. The literature review will synthesize treatments for synthetic marijuana induced psychosis, and can influence practice for providers in the psychiatric field. Synthetic marijuana has caused adverse outcomes in the mental health of its users. These adverse outcomes are bringing these users into the emergency rooms and inpatient psychiatric settings. Expanding the knowledge of synthetic marijuana and treatment for the induced psychosis is a process of application in advanced practice nursing care.

PICO QUESTION

Further clarification as to what this literature review is attempting to discover will be explained by turning the clinical question into PICO format. This acronym stands for four separate entities, and is explained here: P-problem/patient population, I-intervention, C-comparison, and O-outcome of interest. The PICO question is: Has successful pharmacological treatment been developed to treat adult patients with acute psychosis induced by synthetic marijuana? The patient population in this question is adult pa-

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tients or patients over the age of 18 years. The intervention is successful pharmacological treatment, more specifically, psychiatric pharmacological treatment. The comparison is current treatment specific to psychosis induced by synthetic marijuana. Lastly, the outcome of interest is acute psychosis induced by synthetic marijuana. In order to understand if treatments have been developed or are being developed, a review of literature is performed, and the methods used to do this are explained in the next section.

METHODS

Literature was searched and included in this research study based on relevance to the topic and year of publication. The online databases, PubMed, Cinahl PLUS with full text, Ebscohost, and Google Scholar were all used to search for articles published after the year 2010. Terms used for the search are listed as follows: Synthetic marijuana psychosis, synthetic marijuana toxicity, synthetic cannabinoid psychosis treatment, synthetic marijuana psychosis treatment, and treatment for synthetic cannabinoid. Case reports, conference abstracts, retrospective studies, cohort studies, review articles, literature reviews, treatment guidelines, and results from clinical research trials were reviewed and included in this study. References within retrieved articles were also searched. Studies were eligible if the treatment described in the study was used for, or related to the treatment of psychosis induced by synthetic marijuana. Any synthetic marijuana identified differently such as K2, spice, or JWH-018 was all used for inclusion. Research articles that were related to treatment of psychotic symptoms as a result of either synthetic marijuana intoxication or withdrawal were included as well. Exclusions to the study were articles that described cannabinoid or marijuana induced psychosis. After screening titles in the search databases for articles that contain treatment for synthetic marijuana substance induced psychosis, 80 articles were found. After reviewing abstracts for 80 articles, nine articles were chosen. Two articles were excluded because they only contained symptoms induced by synthetic marijuana, but not treatments. Seven articles met inclusion criteria; which included pharmacological treatment for synthetic marijuana induced psychosis.

LITERATURE DESCRIPTION

The purpose of this review was to examine current research on successful treatment options for synthetic marijuana induced psychosis. In review of this research, no treatment guidelines have been established to treat psychosis induced by synthetic marijuana. The treatment has been primarily supportive for psychiatric symptoms after use of synthetic marijuana. These symptoms in addition to the knowledge that this substance cannot be readily tested in the urine promote accurate diagnosis. In describing the literature reviewed, symptoms and treatments related to synthetic marijuana will be explained as follows in systematic reviews, cohort analyses, and case reports.

A systematic review of 106 publications included patients that presented to the emergency department, hospital, and drug rehabilitation centers for adverse events following synthetic marijuana use. One hundred and six papers, letters, and conference abstracts representing over 4000 of these cases were reviewed in this study. The publications included cases from U.K, USA, and Australia. These patients presented for various behavioral abnormalities like agitation, psychosis, and anxiety. In addition to both physical and psychiatric symptoms, the most common symptoms were tachycardia, agitation, and nausea. This systematic review searched online databases: Medline, PsycInfo, Embase, Google Scholar, and PubMed up to December 2014. The publications were reviewed to include synthetic cannabinoids, or synthetic marijuana and adverse events recorded by medical staff. Benzodiazepines and haloperidol have been used to treat agitation, IV fluids have been used for the dehydration, and onitoring for airway, cardiac, and cerebral ischemia is also maintained. Also, agitation is one of the most common symptoms; in addition to psychosis and anxiety. Majority of the publications reviewed had patients treated with intravenous fluids, benzodiazepines (lorazepam, diazepam, and midazolam), and antipsychotics. In treatment of agitation, sometimes present with psychosis, can be treated with benzodiazepines and antipsychotics. Antipsychotics used included haloperidol, risperidone, clozapine, olanzapine, quetiapine, and chlorpromazine. Mood stabilizers such as valproic acid were also used for agitation [4]. This was a large systematic review representing over four-thousand cases related to adverse events from synthetic marijuana use. This systematic review on pharmacological treatment is helpful because the study pulls from 106 studies and lists the treatments given in each study.

The next study included is a retrospective cohort study of twenty clients admitted into an inpatient unit in a detoxification center in Auckland, New Zealand from May 2013 to 2014. These twenty clients were separated from another set of twenty-five patients that were admitted into another inpatient unit for medical supervision after synthetic marijuana use. The symptoms were measured via Cannabis Withdrawal Assessment Scale (CWAS) by nursing staff twice a day for five days, and then daily. The most commonly reported withdrawal symptoms in the forty-seven patients were: Agitation, 89% (n = 16); Irritability, 83% (n = 15); Anxiety, 55% (n=10) and Mood swings 55% (n = 10) [8]. Patients were reporting more than one symptom in this data. Medications utilized to attenuate these withdrawal symptoms in this detoxification center consisted of Diazepam (5-25 mg), which was always prescribed first for an average of four days and then if ineffective, quetiapine (25-475 mg) was prescribed on an average of eight days. Diazepam, a benzodiazepine, and quetiapine, an atypical antipsychotic, would be used to treat anxiety and mood swings in this cohort of patients. Patients reported that quetiapine was more effective than diazepam at alleviating agitation, irritability and anxiety; and associated with synthetic cannabinoid withdrawal [8]. Diazepam had been used for fewer days then the quetiapine, and the reason for this was not mentioned in the study. Instead diazepam was tried first; and if it did not work, quetiapine was administered. This regimen may be helpful in patients who do not require medical intervention, but do require inpatient hospitalization due to withdrawal symptoms of anxiety, agitation, and irritability.

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This next study is an analysis of past data for 214 patients obtained from the ToxIC Registry (registry of patients seen by medical toxicologists at 50 sites in the USA) who were exposed to synthetic marijuana. The ToxIC Registry contains data from all clinical cases cared for in-person by medical toxicologists and these cases are entered by clinicians with specialty training in the care of poisoned patients [9]. Medical toxicologists use an online interface to enter patients into the registry and they upload the following: Substance involved demographics, encounter circumstances, toxidrome, signs and symptoms, treatment, and outcomes. In this study, the nedical toxicologists extracted 353 cases from a total of 39,925 cases in the years between 2010 and 2015. The 353 cases were coded as synthetic marijuana (Black Mamba, K2, Crazy Clown, etc.) and descriptive statistics were used to characterize demographics, clinical features, and treatment characteristics. Three hundred fifty-three cases were due to synthetic marijuana toxicity and 214 of these patients required treatment for toxicity. Linear regression was used to determine correlation between continuous variables and two-sided chi-square with odds ratios were used to determine correlation between categorical variables; p-value was <0.05 [9]. Correlations were made between symptoms and treatment after synthetic marijuana exposure in these 214 patients. In this multi-center cohort analysis of patients treated in the emergency department, medical floors, and intensive care, out of the 214 patients, 131 of them were treated with benzodiazepines, 36 treated with antipsychotics, and 31 treated with both. In this study of patients admitted to various units in the inpatient hospital, majority of patients received treatment with benzodiazepines, and antipsychotics. The study also studied correlations, and found that patients who had seizures were more likely to receive benzodiazepines (OR=3.0; 95% CI=1.7-5.3) and anticonvulsants (OR=4.2; 95% CI–1.1-16.2). Also, there was no evidence that benzodiazepines or antipsychotics caused significant heart rate or blood pressure decline. The specific benzodiazepines or antipsychotics were not mentioned in this study, but the most common pharmacological intervention were benzodiazepines followed by antipsychotics [9]. This data exposes which treatments were used for synthetic marijuana exposure, and also finds that benzodiazepines and antipsychotics did not induce bradycardia or hypotension in this withdrawal period.

Another study includes a case report of an 18-year old male, never tried on an antipsychotic, treated with an antipsychotic that was effective in treating his synthetic marijuana induced psychosis. This case is unique in that this patient has experienced first-episode of psychosis after synthetic marijuana use, and has not been tried on any antipsychotics before. This patient was smoking synthetic marijuana for three to four weeks presenting for treatment because of paranoid auditory hallucinations, delusions, and insomnia. Treatment for two weeks with Lorazepam 2 mg orally as needed improved his stiffness, and risperidone resolved his paranoid ideation, abnormal thought processes, and stiffness. Also, as the risperidone was titrated, the need for lorazepam progressively decreased; and oral benzotropine helped improve the extrapyramidal symptoms (EPS) from the risperidone [10]. In addition to this, the patient relapsed in using synthetic marijuana again and experiencing a second episode of psychosis following recovery. Risperidone was successful a second time for this patient, which is a significant finding when psychotic symptoms may be difficult to treat when related to a substance like synthetic marijuana. The strong response to risperidone both as an initial treatment and following relapse provides additional information that it can be used for relapse of synthetic cannabis-induced psychosis [10]. Stiffness is characteristic of catatonia, which was managed with lorazepam and risperidone. Risperidone helped to minimize the need for lorazepam in this patient. Also, benzotropine mitigated EPS that was caused by risperidone. The efficacy of risperidone in treating initial psychosis and subsequent psychosis following relapse in the use of synthetic marijuana makes it a viable option.

A comparison of two antipsychotics: Clopixol-Acuphase, an atypical antipsychotic and haloperidol, typical antipsychotic were compared for efficacy in treating hallucinations in seventy-two patients with psychotic disorders due to synthetic cannabinoid use. These patients were divided into two groups, and thirty-seven were treated with haloperidol and thirty-five were treated with Clopixol-Acuphase (an atypical antipsychotic from the thioxanthene group). The study compared psychomotor excitement and hallucinatons; and found Clopixol-Acuphase to decrease psychomotor excitement after approximately four hours while haloperidol took approximately eight hours. Hallucinations stopped in an average of thirty-six hours with Clopixol-Acuphase, and haloperidol took forty-eight hours to stop hallucinations [11]. This medication belongs to the thioxanthene group, in which medications from that class is used in the United States. However, Clopixol-Acuphase is not FDA approved to be used in the United States. Synthetic marijuana use has been established as potentially causing hallucinations and agitation or psychomotor excitement. Inclusion of this study is based on comparing two medications from two different classes in treating these two symptoms as a result of synthetic marijuana exposure.

In another study, different antipsychotics are presented here in attempting to treat psychotic behavior in two patients that used synthetic marijuana. The publication by Rahmani Paul & Nguyen (2014) presented two case reports of two males experiencing psychotic and disorganized behavior who received risperidone and haloperidol that did not control their symptoms, but required the use of clozapine [12]. The two seventeen-year old males were using synthetic marijuana and presenting to an inpatient psychiatric unit in Florida with psychotic and disorganized behaviors. The risperidone and haloperidol were used for on average of twenty days for one patient before switching to clozapine, which allowed for stabilization of psychotic symptoms and stepdown into an outpatient rehabilitation program. One patient returned to the hospital after successful treatment with risperidone because he had relapsed on synthetic marijuana which was refractory to risperidone and haloperidol at the second admission. Clozapine was used in this patient at his second admission because of his more severe psychotic symptoms. Further speculation in this study is that symptoms catalyzed by substance use were more refractory to treatment than “typical psychotic symptoms, thus requiring the use of clozapine [12]. If synthetic cannabinoids can make psychosis an even more severe presentation than typical psychosis,

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treatment may need to escalate in potency. This speculation may be true for the two clients in this publication, but this cannot be generalized to all patients presenting with psychotic symptoms after using synthetic marijuana.

In another case report of a male with schizophrenia, cannabis dependence, and recent onset of synthetic cannabis use, the patient experienced his first onset of psychosis. This patient had been using marijuana for years, but started smoking synthetic marijuana for about two weeks and presented with motor slowing with posturing in addition to illogical speech, paranoia, and auditory hallucinations. He was given clozapine for the psychotic symptoms, and started on lorazepam IM up to 12 mg per day until day 15 of hospitalization. Life threatening catatonia persisted after treatment with clozapine and lorazepam; requiring the use of electroconvulsive therapy (ECT) which improved his catatonia immediately. This case report described severe catatonia that was not improving with lorazepam. He had psychotic episodes before, but had never experienced life-threatening catatonia. ECT has been shown to decrease catatonic symptoms, such as mutism, rigidity, and decreased food intake [13]. ECT may therefore be another treatment option for a patient with synthetic marijuana induced catatonia that was not controlled on other medications. In this case, the other medications used to treat the catatonia were lorazepam. This case report described life-threatening catatonia superimposed on psychotic symptoms after recent synthetic marijuana use. This catatonia was refractory to usual treatment with lorazepam, and ECT helped to treat this patient. A factor that may skew results is his past psychiatric history and use of marijuana in the past. These factors may play a part in causing more severe psychosis, in which catatonia was present.

SUMMARY & SIGNIFICANCE

In this comprehensive literature review, findings include symptoms related to synthetic cannabinoid use and treatments that target these symptoms. There are no current practice guidelines on treatment of synthetic cannabinoid induced psychosis. Symptoms related to synthetic marijuana use include psychotic symptoms in individuals that have never experienced psychotic symptoms that are susceptible or individuals with a history of psychosis. Psychotic symptoms include hallucinations, paranoia, and delusions. In one case report, the patient presented with psychosis after using synthetic marijuana also experienced life-threatening catatonia. Agitation was the most common psychiatric symptom reported, and anxiety was also a common symptom reported in people who used synthetic marijuana.

Treatments for psychosis due to synthetic cannabinoid are supportive, and agitation is frequently treated with benzodiazepines. Benzodiazepines like lorazepam and diazepam have been used to control agitation, especially in the initial presentation [14]. Anticonvulsants, such as valproic acid have also been used to help control mood lability.

Risperidone, quetiapine, haloperidol, Clopixol-Acuphase, and clozapine were the antipsychotics used to treat psychotic symptoms in this literature review. Risperidone was used to treat initial psychosis, and subsequent psychosis effectively after relapsing on synthetic marijuana [15,16]. Clopixol-Acuphase has been compared with haloperidol in decreasing psychotic symptoms at a quicker rate. Clozapine has been used to treat refractory symptoms of psychosis in patients after using synthetic marijuana. It has also been used after trials of risperidone and haloperidol did not work; and decreased psychotic symptoms effectively. Electroconvulsive therapy (ECT) has also been used in addition to lorazepam to treat catatonia from synthetic marijuana use. ECT has been examined in patients that experienced synthetic marijuana induced catatonia, and it has been effective.

IMPLICATIONS FOR NURSING PRACTICE

Synthetic marijuana is a substance that comes in the form of marijuana mixed with other chemicals that have been disguised as “herbal incense” or “potpourri,” presenting an easier and more feasible option to marijuana. Synthetic marijuana is changing in composition, and poses risks to consumers that view this substance as a “natural” form of marijuana. The risks are psychotic symptoms, including but not limited to delusions, paranoia, and hallucinations that may be more refractory to conventional treatment. Also, increasing agitation, mood lability, anxiety, and various physical consequences (tachycardia, seizures and heart attack) are adverse effects of synthetic cannabinoid use [17]. Psychosis has been correlated with synthetic cannabinoid use, but there are no established guidelines in treating these symptoms specifically from this cause. Benzodiazepines have been used for the agitation that presents with patients using synthetic marijuana. Antipsychotics have shown efficacy in treating the new onset psychosis directly related to synthetic marijuana, and clozapine and ECT have been used to treat more severe psychosis.

Clinicians need to be aware of the effects of synthetic marijuana use, and inability to detect the substance in urine. The understanding that a more severe, treatment refractory psychosis can present in patients who have not been using other illicit substances, may be using synthetic marijuana is important. It is important to understand that this substance that is constantly changing in composition poses a threat to consumers. The consumers are at risk for various complications, and the severity of these complications needs to be understood by clinicians. The adverse effects of synthetic marijuana use should be disseminated amongst clinicians in various settings, including psychiatric hospitals and emergency rooms. Benzodiazepines and antipsychotics are used in treating patients that present to psychiatric hospitals and emergency rooms. Clozapine and ECT have also been used to treat more treatment refractory psychotic symptoms. Educating the public should be a priority for clinicians who witness the deteriorating effects of synthetic marijuana. Furthermore, application of new and effective treatment strategies should be a part of practice when treating synthetic marijuana induced psychosis **(Table 1)**.

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Table 1. Matrix of articles.

Citation, Author, Title	Design/ Method	Sample/ Setting	Major Variables Of Study	Statistical/ Data Analysis	Study Findings	Strengths/ Weaknesses	Level of Evidence
1. Monte AA, Calello DP, Gerona RR, Hamad E, Campleman, SL, Brent J, Wax P, & Carlson RG (2017). Characteristics and Treatment of Patients with Clinical Illness Due to Synthetic Cannabinoid Inhalation Reported by Medical Toxicologists: A ToxIC Database study. *J. Med Toxicology, 13*. 146-152.	Multi-center cohort study/ Analysis of 214 patients seen by medical toxicologists	Patients Exposed to synthetic marijuana in emergency departments, hospital floors, and ICUs using the ToxIC Registry.	Patient demographics, clinical features, and treatment characteristic (pharmacological treatments). 214 patients (60.1%) out of the 353 required treatment for synthetic marijuana toxicity.	Descriptive statistics characterized patient demographics, clinical features, and treatment characteristic. Linear regression determined correlation between categorical variables using continuous variables and two-sided chi-square with odds ratios. A *p* value less than 0.05 was statistically significant.	1. Benzodiazepines are the most common pharmacological intervention (n=131, 37.1%) 2. Antipsychotics are the second most common pharmacological intervention (n=36, 10.2%) 3. Both benzodiazepines and antipsychotics were used (n=31, 9%). 4. Naloxone was given in 12 patients, or (3.4%) of them. 5. Anticonvulsants were given in 9 patients, or 2.5% of them. 6. Neuromuscular blockers and mechanical ventilation in 8 (2.3%) patients.	Weakness: The Toxic Registry is specifically designed to capture consequential effects of drug exposure. This may overestimate the severity of cases in this study, including the more severe ones. Strength: The ToxIC registry identifies cases of synthetic marijuana toxicity seen by medical toxicologists.	Level IV: Cohort study
2. Roberto, A. J., Lorenzo, A., Li, K. J., Young, J. Mohan, A., Pinnaka, S., & Lapidus, K. A. B. (2016). First-Episode of Synthetic Cannabinoid-Induced Psychosis in a Young Adult, Successfully Managed with Hospitalization and Risperidone. *Case Reports in Psychiatry, 2016.* 1-4.	Case Report	Single Case report of an 18-year old antipsychotic naïve African-American male presenting to ER with first time psychotic episode.	First episode Psychosis related to use of synthetic cannabinoids, psychotic symptoms, catatonic symptoms, lorazepam, risperidone	No statistical analysis performed in this case report.	1. A strong response to risperidone both as an initial treatment and following relapse provides additional information that it can be used as a previously effective antipsychotic for relapse of synthetic cannabis-induced psychosis 2. Lorazepam was also used for catatonic symptoms.	Weakness: This study was a case report on a single patient, limiting its applicability to a larger population. Strength: The treatment of subsequent relapse with risperidone, a second time.	Level V: Case report
3. Bokhan, N. A., Abolonin, A. F., & Mandel, A. I. (2015). Use of Traditional and Atypical Neuroleptics in Therapy of Psychoses Caused by Use of Synthetic Drugs. *European Psychiatry, 30*(1). 489.	Controlled trial	72 patients admitted with acute psychotic disorders due to synthetic cannabinoids	Group 1 (n=37): Haloperidol used to stop psychotic disorder. Group 2 (n=35): Clopixol-Acuphase (zuclopenthixol acetate) used to stop psychotic disorder	Carried-out analysis of the two medications and the efficacy for each in treating acute psychoses.	1. The use of Clopixol-Acuphase, an atypical antipsychotic treats psychomotor excitement and hallucinatory disorders quicker than haloperidol.	Weakness: Reduction of psychomotor excitement and hallucinatory manifestations was observed subjectively and documented by number of hours; introducing observer bias. 2. Strength: Both groups were relatively equal in size, and separated randomly.	Level III: Controlled trial without randomization

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4. Tait R. J., Caldicott, D., Mountain, D., Hill, S. L., & Lenton, S. (2015). A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. *Clinical Toxicology, 54*(1). 1-13.	Systematic Review of reports	106 papers, letters, and conference abstracts representing over 4000 cases.	1. Target substance was any synthetic cannabinoid 2. Adverse events had to be recorded by medical staff or specialists at the Poison Center. 3. Both self-reported and analytically confirmed use of synthetic cannabinoids were eligible. 4. Presentations involving synthetic cannabinoids and other drugs were included.	Descriptive analysis included the symptoms of synthetic cannabinoid toxicity and supportive care.	1. Patients presented in ED because of behavioral abnormalities like agitation, psychosis, and anxiety. 2. Patients also presented due to acute critical illness, such as seizures, AKI, myocardial ischemia, and infarction. 3. The most common symptoms were tachycardia, agitation, and nausea. 4. Treatments included: Benzodiazepines and haloperidol for agitation, IV fluids for dehydration, airway control, and monitoring for cardiac or cerebral ischemia.	Weakness: 1. The methods to detect, identify, and confirm new synthetic cannabinoids makes it more difficult to address. Strength: 1. The study delineated which treatments were used to manage the symptoms.	Level I: Systematic review
5. Macfarlane, V. & Christie, G. (2015). Synthetic cannabinoid withdrawal: A new demand on detoxification services. *Drug and Alcohol Review, 34*. 147-153.	Retrospective audit of electronic and paper files for clients presenting for treatment with synthetic cannabinoid use.	Between May 2013 and May 2014, 47 clients with problematic synthetic cannabinoid use were either referred by an addictions counselor or self-referred.	1. A recording template with 68 items was used to record information. This information is listed here: demographic information, other substance dependence, other DSM-IV Axis I diagnoses, reported synthetic cannabinoid use, reported adverse effects, withdrawal symptoms and CWAS scores, treatment information and outcome, and medication used if admitted into the detoxification unit.	1. Standard descriptive statistics were used to summarize the characteristics of the audit sample. 2. Following data collection, a random sample of 20% of files were reviewed by the second investigator to check for data entry inaccuracies.	1. The mean age of clients was 31 years, and 62.5% were males. 2. All clients presenting reported daily use. 3. The most commonly reported problem as a result of the use of synthetic cannabinoid was the withdrawal symptoms: anxiety(n=29), mood swings(n=30), nausea and loss of appetite(n=5). 4. Other clients reported intoxication (n=2), self-harm (n=7), and psychosis (n=9). 5. Diazepam (5-25 mg) was always prescribed first for withdrawal symptoms, and then if ineffective, quetiapine (25-475 mg) was prescribed.	Weakness: 1. This study did not give clear evidence base for pharmacological treatment of synthetic cannabis withdrawal. Strength: The delineation of withdrawal symptoms reported by patients may help providers understand reason for relapse of synthetic cannabinoid use.	Level IV: Retrospective cohort study
6. Rahmani, M., Paul, S., & Nguyen, M. L. (2014). Treatment of refractory substance-induced psychosis in adolescent males with a genetic predisposition to mental illness. *Int J. Adolescent Med Health, 26*(2). 297-301.	Two case reports	Two adolescent males admitted into an inpatient psychiatric unit.	1. Both patients presented with psychotic, disorganized behavior. 2. Both males had a genetic vulnerability to mental illness 3. Both males reported significant synthetic cannabinoid use. 4. Both males possessed symptoms refractory to treatment, and required the use of clozapine.	No statistics were used in these case reports.	1. After risperidone and haloperidol did not control the persistent psychotic symptoms in both cases, clozapine was used for its efficacy. 2. Symptoms catalyzed by synthetic cannabinoid use were more refractory to treatment than typical psychotic symptoms.	Weaknesses: 1. Both patients had history of schizophrenia, depression, or anxiety in a first degree relative causing higher risk of a psychotic break. Strength: 1. Both patients presented with cases that were not responsive to FDA-approved medication, risperidone in treating psychotic symptoms.	Level V: Case report

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7. Leibu, E., Garakani, A., McGonigle, D. P., Liebman, L. S., Loh, D., Bryson, E. O., & Kellner, C. H. (2013). Electroconvulsive Therapy (ECT) for Catatonia in a Patient with Schizophrenia and Synthetic Cannabinoid Abuse. *Journal of ECT, 29*(4). e61-e62.	Case Report	One patient presenting to the inpatient psychiatric hospital.	1. 36- year old male previously diagnosed with schizophrenia and cannabis dependence. 2. Patient and his mother reports this is his first time smoking synthetic cannabinoids this past two weeks before hospitalization. 3. Patient was treated with clozapine for psychotic symptoms, with good effect. 4. Patient was treated with up to 12 mg /day of lorazepam for catatonia, without improvement.	No statistics were used in this case report.	1. After life threatening catatonia persisted after treatment with clozapine and lorazepam, ECT was given which caused immediate improvement. 2. ECT can be used for drug-induced catatonia, especially if benzodiazepines have failed. 3. Severe and life-threatening catatonia is related to his recent onset of synthetic cannabinoid consumption.	Weakness: 1. In addition to starting to smoke synthetic cannabis, this patient also stopped taking his antipsychotic medications before admission into the hospital. This discontinuation of medicine may also contribute to the catatonia. Strength: 1. This case presents severe and life-threatening catatonia related to synthetic cannabinoid use, that was resolved with ECT.	Level V: Case report

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