

SYNESTHESIA OCCURRING AFTER THE USE OF JAPANESE KIKEN DRUGS: A CASE REPORT

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INTRODUCTION

“Kiken drugs”*, which literally means “dangerous drugs” in Japanese, are designer drugs widely abused in Japan. They have been reported to contain synthetic cannabinoids (SCs) (Kikura-Hanajiri et al. 2011) and are sold under labels such as “herbs,” “bath salts,” and “aromatic liquids” in street shops, on the Internet, or from vending machines (Tanibuchi et al. 2013, Fuse-Nagase et al. 2015). Due to their novelty and repetitive chemical modifications, their use is not yet legally controlled, also earning these drugs the name “Dappou drugs”**, meaning “drugs that evade the law” (Matsumoto et al. 2014). Few studies have investigated these novel drugs utilizing Japanese data, and two surveys estimated their prevalence. One involving Japanese university students reported that 1.0% of students knew of their close acquaintances taking the drugs (Fuse-Nagase et al. 2015). Data from the 2012 National Mental Health Survey on Drug-related Psychiatric Disorders, in which all Japanese psychiatric health centers participated, reported 1,161 cases of drug-related disorders. Among these, the number of cases diagnosed as mental and behavioral disorders due to psychoactive substance use, based on the Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (World Health Organization 1993), included 126 diagnoses related to a designer drug like *Kiken* drugs, 138 related to hypnotics/anxiolytics, and 86 related to methamphetamine (Matsumoto et al. 2014).

Kiken drugs have received media coverage in the Republic of Korea (hereafter, Korea), warning of its spread within the nation. However, there are no reports of psychiatric cases in Korea about them. The current study details the relief from perceptual symptoms obtained in a patient with bipolar I disorder experiencing synesthesia after the use of *Kiken* drugs and also intends to alert health professionals to their use.

**Kiken* drugs - 危險

***Dappou* drugs - 脱法

CASE REPORT

A 30-year-old single Korean male student visited a university health center with complaints of “mixed senses,” recurrent visual and auditory hallucinations, and depression in May 2, 2017. His symptoms started as a major depressive episode in October 2014 while working in Japan. Without treatment, the episode improved, but a manic episode occurred in April 2015. He worked excessively without fatigue and argued frequently with his superior at work. In October, he started to smoke *Kiken* herbs of a single type by rolling them in a cigarette paper, which he and colleagues purchased from “herb” shops on the street in order to supply social context for continued conversations about work, and felt relaxed after the consumption. In the same month, he began to experience a sense of loss. He felt depressed, fatigued, and began experiencing insomnia and decreased concentration. During this second major depressive episode, he continued to use *Kiken* herbs with varying degrees of frequency from daily to once every other week.

In October 2016, while still in the depressive episode, he began to experience various perceptual disturbances. He started to experience “mixed senses” continuously for 30 minutes daily. The patient described different colors producing distinct, corresponding pitches of whistling sounds lasting 2 to 3 seconds. When he heard speech, the patient reported that spoken sentences appeared as black letters, 3 to 4 mm thick and 2 cm tall, on a pink background above his eyebrows. After a time lag lasting the length of one word, these letters disappeared. He described the experience as if he was looking at movie subtitles. Because the letters were fixed in space, they disappeared if he looked away. The patient reported that these “mixed senses” did not affect his mood. In addition, he perceived several dispersed colors similar to a prism at the edges of objects, and straight lines of objects appeared curved. Concurrently, he reported visual hallucinations consisting of metallic drains and computer screens “as if seen through sunglasses,” and auditory hallucinations of persecutory and humiliating content.

He was prescribed aripiprazole in January 2017 for perceptual disturbances and stopped using *Kiken* herbs that February, when he returned to Korea. In April, venlafaxine was added to ameliorate his depressive symptoms. In a psychiatric examination in May, he appeared tidy and exhibited age appropriate behavior with adequate self-care and good eye contact. He demonstrated a restricted affect, responded with simple answers and denied using any other illicit substance. Non-contrast brain magnetic resonance imaging, waking electroencephalography, and blood tests (complete blood count, electrolytes, glucose, and liver, kidney, and thyroid function) indicated no abnormalities. The patient met the diagnostic criteria for bipolar I disorder, in a current depressed episode of moderate severity, with mood-congruent psychotic features, based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5) (American Psychiatric Association 2013). At this time, his Clinical Global Impressions-Severity (CGI-S) score was 5.

Despite the use of aripiprazole up to 17 mg/day and venlafaxine up to 300 mg/day, his symptoms did not improve. They were discontinued, and risperidone was initiated at 1 mg/day and increased to 2 mg/day after a week. Divalproex sodium was added at 250 mg/day to alleviate his depressive symptoms and increased weekly by 250 mg/day to 750 mg/day with a blood level of 68.2 µg/mL. After two weeks of the new regimen, his perceptual disturbances started to decrease, and at the end of the fifth week, they completely disappeared. Although he still felt depressed, he reported that the severity of his depression had lessened by half. He no longer complained of insomnia or difficulty concentrating. At the last visit, his CGI-S score was 3.

This study was approved by an institutional review board and conformed to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). The patient signed a written informed consent form.

DISCUSSION

This is the first Korean case of synesthesia that developed after the consumption of Japanese *Kiken* herbs. Shortly after initiating *Kiken* herbs, the patient's first manic episode abruptly switched to his second major depressive episode and persisted over one year, during which he continued to use the substance. Since the patient was experiencing moderate impairments in schoolwork and a major depressive episode with hallucinations, considering his history of a manic episode, his diagnosis was seemingly, bipolar I disorder, current episode depressed, moderate severity, with mood-congruent psychotic features by DSM 5. However, the average duration of bipolar depression is reported to be only 15.8 weeks (Lev-Ran et al. 2014); hence, the duration of his episode appeared unusually long. Moreover, a diagnosis of substance/medication-

induced mental disorder can be made if a disorder develops under the influence of substance (American Psychiatric Association 2013). Thus, given his abrupt mood change after he began using the substance and the following uncommonly long-lasting episode, the episode seemed to be partly attributable to the herbs, suggesting concurrence of another substance-induced depressive disorder. A meta-analysis that heavy cannabis users had increased risk of depressive disorders supports this view (Lev-Ran et al. 2014). On the other hand, a PubMed literature, with the search terms synesthesia/synaesthesia, bipolar, manic, and depressive, search revealed no studies regarding synesthesia in bipolar disorders; it is presumed to be scarce. Moreover, cannabis consumption may result in chronic psychosis, lasting even after abstinence and yet usually ending with complete recovery (Johns 2001, Hall & Degenhardt 2000); our patient presented perceptual disturbances for several months after abstinence but showed no residual psychotic symptoms after treatment. Owing to lack of previous reports and the clinical course, the patient's perceptual abnormalities imply manifestations of co-existing cannabis-induced psychotic disorder (American Psychiatric Association 2013) rather than that of bipolar depression only.

Synesthesia is a phenomenon in which one stimulated sensory percept is experienced as another sensory percept that is internally produced (Sinke et al. 2012). The prevalence of all known types was reported to be 4.4% (Simner et al. 2006), and it is classified into 3 different types, by etiology: developmental (symptoms appear in early childhood under genetic influences), acquired (e.g. brain injury), and pharmacological synesthesia (Grossenbacher & Lovelace 2001). Our patient complained of 'ticker-tape' synesthesia, a very rare type in which the patient sees words while they are being heard, similar to movie subtitles (Holm et al. 2015), as well as color-sound synesthesia. Because these symptoms emerged following the use of *Kiken* herbs, they were classified as pharmacological synesthesia. It is well documented that psychedelic agents cause synesthesia, especially lysergic acid diethylamide, mescaline, and psilocybin, all of which share a feature of serotonergic agonism (Luke & Terhune 2013). However, other non-serotonergic drugs with inherent psychedelic characteristics, including cannabis, can also reportedly induce synesthesia (Luke & Terhune 2013). Substance-induced synesthesia is usually auditory-visual (Luke & Terhune 2013), which has been demonstrated in at least one case report related to cannabis (Marks 1975). According to a survey of cannabis users, more than half of the respondents noted music-color synesthesia, a type of auditory-visual synesthesia. The symptoms that this patient experienced under the influence of the herbs, including 'ticker-tape' auditory-visual synesthesia, correspond with the results of earlier studies (Marks 1975, Luke & Terhune 2013).

Many SCs are based on an indole scaffold (Banister et al. 2015). Because indole structurally resembles serotonin, it is speculated that it may act as a serotonin 5-HT_{2A} receptor agonist (Hamid et al. 2017). According to the literature, given that 5-HT_{2A} receptor signaling is an important site of action for hallucinogens, an upregulation of 5-HT_{2A} receptors after long-term activation of the cannabinoid receptor type 2 by SCs might, presumably, lead to perceptual disturbances (Tai & Fantegrossi 2017, Amodeo et al. 2014). Because synesthesia is also a type of perceptual abnormality and has been associated with 5-HT_{2A} receptor agonism (Luke & Terhune 2013), this mechanism might explain the induction of synesthesia by SCs. Risperidone, an antagonist with a high affinity for 5-HT_{2A} receptors, presumably, effectively blocked their activation, consequentially reducing perceptual disturbances (Amodeo et al. 2014).

Psychiatric disorders often entail long-lasting impairments of function. According to the literature, users of designer drugs including *Kiken* drugs were young, and had greater educational and occupational experiences compared with methamphetamine users (Tanibuchi et al. 2013), and suffered from more psychotic disorders than methamphetamine or hypnotics/anxiolytics abusers (Matsumoto et al. 2014). As these novel substances attract a young population, costs will be enormous. Therefore, prevention should be given a priority. In a survey of Japanese students, 70.7% responded that they were knowledgeable of *Kiken* drugs, but only a half of them were aware of the risk of psychotic symptoms (Fuse-Nagase et al. 2015). Education regarding the recognition of new psychoactive substances and their consequences is necessary, and resources should be mainly allocated to a young population with high socioeconomic status. Health professionals should be aware of the possible spread of these substances not only from Japan to Korea, but also globally, as international travel has become routine.

CONCLUSION

We described a case with perceptual disturbances called synesthesia occurring after the use of Japanese *Kiken* drugs and successfully treated with mood stabilizer and antipsychotics. This case emphasizes the inquiry of a history of using synthetic cannabinoids in patients presenting synesthesia and education about their detrimental effects on perception. By reviewing Japanese policies on preventing the spread of these new drugs, establishment of a nation-specific strategies is warranted. Further studies are needed to clarify the pathophysiology of synesthesia induced by synthetic cannabinoids.

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Contribution of individual authors:

C. Hyung Keun Park: Research idea, design of the study, patient's care, literature searches, manuscript preparation, writing the paper, approval of the final version;
SeulA Kim: Literature searches, manuscript preparation, writing the paper, approval of the final version;
Joon Sung Shin, Daewook Kim: Literature searches, manuscript preparation, approval of the final version;
Yong Min Ahn: Design of the study, manuscript preparation, approval of the final version;

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