CASE REPORT

Withdrawal Phenomena and Dependence Syndrome After the Consumption of "Spice Gold"

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SUMMARY

Background: "Spice" and other herbal blends were marketed in Germany until January 2009 as substances purportedly exerting similar effects to cannabis, yet containing no cannabinoids. These products were recently forbidden in Germany under the provisions of the German Narcotics Law after they were found to contain undeclared, synthetic cannabinomimetic substances. The authors describe physical withdrawal phenomena and a dependence syndrome that developed after the consumption of "Spice."

Case presentation and course: A 20-year old patient reported that he had smoked "Spice Gold" daily for 8 months. He developed tolerance and rapidly increased the dose to 3 g per day. He felt a continuous desire for the drug and kept on using it despite the development of persistent cognitive impairment. His substance use led him to neglect his duties in his professional training position. Urinary drug screens were negative on admission to the hospital, as they were again on discharge. On hospital days 4–7, he developed inner unrest, drug craving, nocturnal nightmares, profuse sweating, nausea, tremor, and headache. His blood pressure was elevated for two days, with a maximal value of 180/90 mm Hg accompanied by a heart rate of 125/min. The patient stated that he had experienced a similar syndrome a few weeks earlier during a phase of abstinence owing to a short supply, and that it had quickly subsided after he had started consuming "Spice" once again.

Conclusions: The authors interpret the symptoms and signs described above as a dependence syndrome corresponding to the ICD-10 and DSM-IV criteria for this entity. The physical withdrawal syndrome closely resembles that seen in cannabis dependence. The authors postulate that the syndrome in the patient described was due to an admixture of synthetic cannabinomimetics such as JWH-018 and CP 47497 in "Spice Gold," in combination with the patient's daily consumption in very large amounts.

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Pre-packed herbal blends were sold in Germany and other European countries until January 2009. The smoke of these products is supposed to have cannabinoid-like effects when inhaled, although they do not contain any cannabis. Several names have been given to these products, such as "Spice," "Smoke," "Scence," "Yucatan Fire," or "Skunk." As this drug had spread rapidly by the end of 2008, there was an intensive discussion about any possible risk. In December 2008, several laboratories detected an admixture of the synthetic cannabinomimetic substances JWH-018 and CP-47-497. These are in all probability the sole cause of the psychotropic effects of these smoked products (1). Therefore, the German Federal Ministry of Health made all products containing these substances subject to the Narcotics Law, by fast-track legislation on 22 January 2009. For this reason, production, trade and possession are prohibited. There is still no reliable scientific information on the actions of these substances in man. We have observed withdrawal phenomena after regular consumption of these substances in the form of "Spice Gold."

Medical history

A youth care worker presented a 20-year-old patient (165 cm, 50.8 kg). She had been taking care of him as part of a professional rehabilitation measure. He had not participated in practical work for four weeks and now he was threatened with losing his professional training position. As regards his drug history, the patient reported that he had been consuming illegal drugs for about three years. At the beginning, he had only consumed hashish. After that he had also begun to take hallucinogenic mushrooms and Salvia divinorum, a type of sage with the hallucinogenic active substance salvinoin A. He drank alcohol very rarely; he had never regularly consumed opiates or other illegal drugs than the above mentioned and had not done this at all in recent years. Besides ten cigarettes per day, he has only been consuming "Spice Gold," initially 1 g daily, for eight months. Due to decreasing effect, he had rapidly increased the dose to a final value of 3 g daily—split into 3 to 4 doses, with the first dose early in the morning. For this purpose, he inhaled the smoke from the herbal mixture burned in a glass pipe ("bong"). Owing to the consumption of the substance, he had often recently been listless and had had problems in thinking clearly. A few weeks ago

during a phase of abstinence owing to shortages in supply, he had developed symptoms in the form of profuse sweating during the day and especially in the night, as well as internal unrest, tremor, palpitation, insomnia, headache, diarrhea, nausea, and vomiting. Additionally he had suddenly felt depressed and desperate. This had lasted for two days and had only abruptly disappeared after taking the drug again. Therefore, he no longer had the courage to discontinue the drug by himself. In the last month, he had additionally unintendedly lost 5 kg in weight and could only sleep about five hours in the night. As a result, the primary care physician initially prescribed zopiclone four days earlier. The patient stated that he had taken 7.5 mg of this drug for the night.

History

The patient fell ill from Langerhans cell histiocytosis at the age of four months. When he was two years old, he was successfully treated with chemotherapy and operated for chronic otitis media. He subsequently developed pituitary deficiency, which required substitution of growth hormone up to the age of 18 and permanent treatment of diabetes insipidus with vasopressin (desmopressin nasal spray). This constellation allows the conclusion that the patient had been suffering from the Hand-Schüller-Christian disease.

He received psychotherapy as an outpatient from the age of three to ten and again at the age of 16, due to social withdrawal and occasional eating disorders. The responsible psychiatrist reported that he had already diagnosed attention deficit/hyperactivity disorder (ADHD) and this had improved during treatment with unretarded methylphenidate at up to 2 x 15 mg/d. However, the patient denied any positive effect and reported that he had in fact discontinued this treatment after six months because of frequent impulsive and aggressive behavior. He stated that he had felt internal unrest and nervousness in a disturbing way since early childhood and that this had been the trigger for his drug consumption, too. His experience had been that the unrest could only be improved by cannabis or "Spice Gold." The patient's half-sister was addicted to methamphetamine ("Crystal") and had committed suicide at the age of 31. The rest of the family's medical history was unremarkable. Due to his previous experience of withdrawal phenomena, the patient requested medical treatment for detoxication of "Spice Gold" and therefore was admitted to hospital on a voluntary basis.

Findings on admission

The patient's very slim build and his spinal scoliosis were striking during the examination. The internal and neurological findings were unremarkable. From the psychopathological point of view, the patient acted in an appropriate manner to the situation, although he was slightly anxious and insecure. Otherwise, the alcohol breath test was normal. Immunological rapid tests for cannabinoids, benzodiazepines, amphetamines, cocaine, opiates and methadone in urine were negative. In routine laboratory tests, normal values were found apart from borderline anemia with Hb 8.5 mmol/L (normal: >8.6). The heart rate (HR) was 82/min, the blood pressure 130/70 mm Hg and the ECG was unremarkable.

Clinical course in hospital

The first abstinent day of treatment (day 1) was symptom-free. In the evening of day 2, the patient complained about increasing internal unrest. As requested by the patient, zopiclone was nevertheless reduced from 7.5 mg to 3.75 mg and discontinued after one single dose. In the following night, the patient started to sweat profusely for the first time.

From day 4, the patient started to develop increasing internal unrest, strong desire for "Spice," nightmares, profuse sweating, nausea, tremor, and headaches. These symptoms did not improve after a renewed single administration of 7.5 mg zopiclone, either. Additionally the patient reported that "he had stood beside himself." He had also developed the familiar intermittent feeling of electrical shocks and "twitches" around the shoulder, followed by a feeling of numbness in the right arm, radiating into the fingers and lasting for approximately one minute. The blood pressure increased to a maximum of 180/90 mm Hg with a maximum heart rate of 125/min. For two days, the blood pressure was mostly 140/90 mm Hg with a heart rate of 95/min. Oral single administrations of promethazine 25 mg and clonidine 0.175 mg decreased the blood pressure. However, they hardly changed the other symptoms.

From the morning of day 7, the symptoms disappeared and the patient felt well despite further hypertension around 140/85 mm Hg with HR around 100/min, lasting till his release on day 21. From day 10 of treatment, he was clearly irritable and reported that he had had several arguments with his parents. This was contrary to his normal friendly behavior. An EEG on day 14 showed an alpha-beta-mixed type without epileptiform potentials.

From day 8 of treatment, the patient complained about the familiar increasing internal unrest and nervousness. This was especially disturbing in the night and kept him from falling asleep. Because of the unfavorable prior experience with methylphenidate and with the suspicion of hypofunction of the dopaminergic system, the patient was treated off-label (after prior explanation) from day 11 with 0.175 mg pramipexole for the night. This brought a slight improvement. The patient reported that the unrest and his sleep at night had effectively improved after increasing the dose to 0.35 mg on day 18. He had only been able to sleep so well when consuming the drug. No adverse events were reported or observed.

A second immunochemical drug screening in urine on the day of release was negative for cannabis metabolites, amphetamines, cocaine metabolites, and opiates. The patient fully participated in a structured and addiction-specific psychotherapeutic program with group meetings using a cognitive behavioral therapy approach, taking place four times weekly. Four days after his release, the patient returned to the hospital. He was still well. Nevertheless, he did not take advantage of further outpatient

meetings offered to him. Four months after his release, he returned to the hospital as an outpatient and reported that he felt well and that he was abstinent from Spice products. However, he had consumed cannabis about four times since his release. He stated that he had discontinued pramipexole after approximately one month, as he could now sleep well enough without either this drug or zopiclone.

Discussion

In accordance with the experience of other consumers discussed in relevant Internet forums, the patient described how "Spice Gold" acted similarly to cannabis and was relaxing and sedative. It produced ravenous cravings. However, the main difference between "Spice" and cannabis was that "Spice" produced less euphoria. Overall he felt that the effect of "Spice" was stronger than that of hashish. A sample of "Spice Gold" was bought through the Internet and then examined by gas chromatography and mass spectroscopy. No cannabinoids or other familiar ingredients of illegal drugs could be detected. The psychotropic effect of the sample was confirmed by two experienced consumers of cannabis through inhaling the smoke.

The symptoms described can be interpreted as a physical withdrawal syndrome as a consequence of the discontinuation of "Spice Gold." This has several similarities with withdrawal symptoms after discontinuing cannabis. A zopiclone withdrawal syndrome is also a theoretical possibility; this would resemble benzodiazepine withdrawal (2). However, the following points argue against this:

- the very short-term and low dosage administration of zopiclone,
- the patient's spontaneous request for dose reduction,
- the lack of observable difficulty in falling asleep and sleeping through,
- the persistence of withdrawal symptoms despite renewed zopiclone administration, and
- their reproducible occurrence after discontinuation of "Spice Gold."

For this reason, this differential diagnosis was excluded as cause of this withdrawal syndrome.

Besides the withdrawal symptoms, the following other addiction criteria are also present in the described case:

- dose increase,
- strong desire for the substance with an urgent need for consumption,
- continuous consumption despite the consequences ("often listless and problems with thinking clearly"),
- Neglect of other interests or duties (participation in practical work).

Therefore, five dependency criteria have been fulfilled within a period of eight months, justifying the diagnosis of a dependency syndrome according to both ICD-10 and DSM-IV.

In December 2008, different synthetic substances were detected in "Spice" and other products mentioned before. These substances act agonistically on the cannabinoid receptors CB1 and CB2. They exhibit much higher receptor affinity than natural cannabinoids. These cannabinoids are JWH-018, CP-47-497, and homologs and stereomers of these, as well as oleamide (1). For this reason, the addictive disease of our patient is in all probability based on the action of these cannabinomimetics. However, it must be pointed out that no body fluids were stored when he was admitted to hospital and therefore the detection of the actual consumption of these substances is lacking.

With this limitation, the authors' observations serve as further evidence for the cannabinoid withdrawal syndrome—which has long been a controversial topic (3). This syndrome could only be established with absolute certainty as a separate clinical entity after two new developments (4). On the one hand, the THC content (THC, tetrahydrocannabinol) of the commercially available cannabis products has doubled in the last twenty years through targeted culture and artificial lighting of the plants (5). According to other sources, the content has even increased by factor of four (6). On the other hand, consumption habits have changed, in that more and more hashish is burned in a "bong" and inhaled in a single breath, instead of being mixed with tobacco and then smoked as a joint over a period of several minutes. Then the ingredients rapidly flood into the body and produce more intensive psychotropic effects. This typically leads to consumption of higher amounts, more intensive withdrawal symptoms and higher risk of addiction (7). The patient described here used a "bong." This form of consumption was connected with the use of high amounts of "Spice Gold" (3 g daily). Together this may have led to a fully developed and manifest addiction disease, which is theoretically expected for these cannabinomimetic substances. The probable ADHD may have enhanced this process, as the patient used the substance for self-treatment of his lasting disrupting unrest, nervousness and sleep disturbances.

The observations confirm the necessity of the planned classification of the mentioned synthetic cannabinomimetics as narcotic in January 2009. The special feature of the phenomenon "Spice" is that for the first time a synthetic drug has been commercially distributed disguised as "herbal blend." This must be seen as a malicious deception of the consumer. What makes this particularly alarming is that neither JWH-018 nor CP-47-497 has been examined with respect to its safety when used in man. The same applies to about 100 other cannabinomimetica with similar chemical structures which have been synthesized in recent years (8). Here the possibility of a wave of other cannabinomimetic "designer drugs" must be considered. Due to the increasing knowledge about the utilization of cannabinoids for treatment of therapy resistant symptoms (9), this should not be used as an excuse to neglect scientific studies of innovative cannabinomimetic substances.

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Conflict of interest statement
The authors declare that there is not conflict of interest in the sense of the guidelines of the International Committee of Medical Journal Editors.

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