# Unresponsive and mute after he smoked 'Spice'

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Mr. R, age 19, who has no psychiatric history, experiences new-onset catatonia after ingesting a synthetic cannabinoid with the street name 'Spice.' How would you care for him?

## How would you handle this case?

Answer the challenge questions throughout this article

## CASE Mute and nonresponsive

Mr. R, a 19-year-old African-American man, is brought to the emergency room (ER) because he has reduced oral intake and mutism, and is not attending to activities of daily living (ADL). His family reports gradual onset of symptoms over the past month after he began using "Spice," a synthetic cannabinoid (***Box, page 66***[1-8]).

Mr. R has been using marijuana regularly for a few years. He has no history of psychiatric illness. The family history is positive for schizophrenia (mother).

Mr. R slowly stopped speaking and eating, and no longer responds to verbal stimulation. On examination, he responds only with unintelligible mumbling. Mr. R exhibits blunted affect and fails to maintain eye contact, looking to the side of the interviewer. He exhibits severe psychomotor retardation but without posturing or waxy flexibility. It takes him approximately 3 minutes to transfer between chairs, and he is incontinent of bladder and bowel.

Mr. R has not experienced a similar episode in the past, although he had exhibited brief paranoia while intoxicated with marijuana.

Before this episode, Mr. R had been moving between his grandmother's and father's homes and was attending high school classes. Recent stressful events include his brother's incarceration and his father having re-entered his life after a long absence.

**Which treatment would you initiate for Mr. R's symptoms of catatonia?**

a) dantrolene
b) a benzodiazepine
c) an antipsychotic
d) electroconvulsive therapy (ECT)

## The authors' observations

Catatonia is a common complication in a variety of psychiatric and medical contexts. It can be a feature of mood disorders, schizophrenia, metabolic disturbances, drug intoxication, neuroleptic malignant syndrome (NMS), and encephalopathy. The most common psychiatric comorbidity is bipolar disorder; as many as 25% of cases are caused by a medical or neurological condition.[9] When accompanied by fever and autonomic instability, so-called malignant catatonia

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## Clinical Point

**Synthetic cannabinoid-containing products have been reported to cause psychotic symptoms and either relapse or worsening of existing psychosis**

Box

### The emerging problem of synthetic cannabinoids

Spice and other synthetic cannabinoid-containing products (SCCP) can lead to an array of psychiatric and physical symptoms (***Table 2, page 68***). Catatonic features, including mutism and rigidity, are well described in the literature.[1] The incidence of SCCP-induced catatonia or psychosis is unknown; most estimates come from data from poison control centers and emergency rooms, which could be skewed toward more extreme presentations. It is likely that most cases are mild and self-limiting.[2]

Spice is the second most commonly used illicit substance among American high school seniors, after *Cannabis*.[3] Hu et al[4] reported that 8% of college students had used Spice or other SCCPs within the past year. Hurst et al[5] reported 10 cases of first-episode psychosis after synthetic *Cannabis* use. Most patients recovered in 5 to 8 days after admission; 3 continued to have psychotic symptoms 5 months after presentation.

Synthetic cannabinoids are full agonists at cannabinoid-1 and cannabinoid-2 receptors, unlike tetrahydrocannabinol (THC), which is a partial agonist. Emergence of high-potency synthetic compounds parallels increasing levels of THC found in *Cannabis*. Different forms of the *Cannabis sativa* plant contain varying amounts of the main cannabinoids, THC and cannabidiol (CBD). Traditional "grass" or "hash," which predominated Western markets through the 1990s, contain approximately 4% THC and CBD, respectively. Because of innovative indoor cultivation, sinsemilla, or "skunk" *Cannabis*, which contains 16% to 20% THC and minimal CBD, now is widely available.

Although THC has been shown to cause at least transient psychosis and memory impairment in a dose-dependent manner, CBD appears to be protective against these effects. CBD has anxiolytic properties and protects against the cognitive impairment and psychotic symptoms produced by THC.[6,7] Synthetic cannabinoids do not contain CBD and therefore lack these protective qualities.

SCCPs have been reported to cause psychotic symptoms and either relapse or worsening of existing psychosis. The mechanism by which these substances induce psychosis has not been elucidated but is thought to be similar to that of naturally occurring *Cannabis*. A growing body of literature has linked *Cannabis* use to schizophrenia. Among patients with a psychotic disorder, those who use *Cannabis* have an earlier onset of symptoms by 2.7 years.[8] Researchers and clinicians are concerned that this phenomenon also will be seen with newly developed synthetic cannabinoids.

Testing for synthetic cannabinoid exposure continues to be a moving target. Spice and related products do not cross-react with traditional THC immunoassays but, starting in 2008, tests have been developed to detect metabolites of SCCPs in urine. Many SCCPs are detectable by liquid chromatography tandem mass–spectrometry and enzyme-linked immunosorbent assays, but novel undetectable compounds are being created all the time.

Because of the dangers associated with Spice, robust screening measures and early intervention for at-risk patients are recommended. Integrated treatment modalities are preferred for concomitant psychotic disorders and substance abuse. Reducing exposure should be a public health priority; government agencies have made efforts to curb availability of SCCPs. There were no laws pertaining to SCCPs until the U.S. Drug Enforcement Agency banned several of them in 2010. More than 10 states and Puerto Rico followed suit. In July 2012, President Obama signed the Synthetic Drug Abuse Prevention Act, which outlawed a number of synthetic cannabinoids and components of "bath salts" and permanently relegated them to Schedule I status along with all other "cannabimimetic agents." Although this makes SCCPs illegal, frequent changes in chemical structure make enforcement difficult. The availability of inexpensive, potent, and often undetectable synthetic cannabinoids is likely to remain a public health hazard.



can lead to respiratory failure, coma, and death.

Catatonia is characterized by ≥3 of the elements outlined in ***Table 1***.[10]

In DSM-5, catatonia is no longer considered a subtype of schizophrenia, but is a specifier in the following disorders: brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, and substance-induced psychotic disorder. In addition, catatonia not otherwise specified is reserved for cases when the cause is not apparent; this diagnosis is intended to lead to greater recognition of catato-

nia and prompt initiation of treatment. DSM-5 stops short of classifying catatonia as an independent syndrome, however. Changes in clinical status can be charted with instruments such as the Bush-Francis Catatonia Rating Scale.

## Workup and treatment

The initial workup of patients with catatonia is extensive. A basic metabolic panel can detect electrolyte disturbances and acute renal failure. Monitoring creatine kinase (CK) allows clinicians to assess for rhabdomyolysis. Patients should also undergo an infectious workup, including complete blood count (CBC) and chest radiography, because patients can develop pneumonia due to atelectasis or aspiration. Additional workup could include EEG, erythrocyte sedimentation rate, D-dimer, urinalysis, urine drug screen, antinuclear antibodies, magnetic resonance imaging, cerebrospinal fluid analysis, anti-*N*-methyl-D-aspartate receptor antibodies, and serum iron, which could predict development of NMS in patients treated with an antipsychotic.[11]

**Table 1**

### DSM-5 diagnostic criteria for catatonia

| Catatonia is defined as the presence of ≥3 of the following: |
|---|
| 1. Catalepsy (ie, passive induction of a posture held against gravity) |
| 2. Waxy flexibility (ie, slight and even resistance to positioning by examiner) |
| 3. Stupor (no psychomotor activity; not actively relating to environment) |
| 4. Agitation, not influenced by external stimuli |
| 5. Mutism (ie, no, or very little, verbal response [Note: not applicable if there is an established aphasia]) |
| 6. Negativism (ie, opposing or not responding to instructions or external stimuli) |
| 7. Posturing (ie, spontaneous and active maintenance of a posture against gravity) |
| 8. Mannerisms (ie, odd caricature of normal actions) |
| 9. Stereotypies (ie, repetitive, abnormally frequent, non-goal directed movements) |
| 10. Grimacing |
| 11. Echolalia (ie, mimicking another's speech) |
| 12. Echopraxia (ie, mimicking another's movements) |

**Source:** Reference 10

**Treatment.** In addition to supportive measures, the initial treatment of choice for catatonia is a benzodiazepine, lorazepam being the most commonly used agent; dramatic improvement in symptoms can be seen within minutes of IV administration. A high dosage of lorazepam (14 to 16 mg/d) sometimes is required for symptomatic relief. Zolpidem also has been used successfully to treat catatonia, although the supporting literature is less extensive.[12]

Antipsychotics generally are held during the initial stages of catatonia treatment because they can exacerbate symptoms and increase the likelihood of NMS. Glutamate antagonists, such as amantadine and memantine, also are being investigated for treating catatonia.[9]

ECT is effective but is reserved for when pharmacotherapy has failed or when a rapid response is required. ECT is associated with cognitive and medical complications, although current techniques have greatly mitigated the risks. Mortality is estimated to be 1 in every 10,000 patients or 1 for every 80,000 treatments, most often due to a cardiac or pulmonary cause.[13] Patients receiving ECT could experience temporary anterograde amnesia and confusion as well as retrograde amnesia, particularly memories formed around the time of treatment.

Response to benzodiazepine therapy varies: Some patients experience significant improvement after 1 dose; others require a high dosage for an extended period. More than 70% of cases remit with benzodiazepines; ECT should be considered after several days or earlier if indicated.[9] Some patients with catatonia

**Clinical Point**

**In addition to supportive measures, the initial treatment of choice for catatonia is a benzodiazepine**

Table 2

**Adverse effects of synthetic cannabinoids**

| Category of symptom | Adverse effects |
|---|---|
| General symptoms | Tremor, blurred vision, dizziness, insomnia, sedation, combativeness, psychomotor retardation |
| Mood disturbance | Depression, euphoria, irritability |
| Psychosis | Prolonged episodes, hallucinations, delusions, paranoia, thought blocking, blunted affect, alogia, catatonia |
| Anxiety symptoms | General anxiety, panic attacks |
| Cognitive effects | Memory impairment |

**Clinical Point**

**Patients with catatonia are at risk of dehydration and malnutrition, and might require IV fluids or parenteral nutrition**

require a slow benzodiazepine taper to prevent symptoms from recurring.

Patients with catatonia are at risk of dehydration and malnutrition, and might require IV fluids or parenteral nutrition. These patients also are at risk of constipation, ileus, decubitus ulcers, deep vein thrombosis, and pulmonary embolism. Encourage early ambulation and consider prescribing an antithrombotic. Some patients might require physical therapy to prevent or treat muscle contractures.

## TREATMENT Benzodiazepines, ECT

Mr. R is admitted for stabilization of catatonic symptoms. A basic metabolic panel, CBC with differential, urine drug screen, urinalysis, folate level, thyroid-stimulating hormone level, vitamin $B_{12}$, EEG, and a stool culture are unremarkable. Ammonia level is slightly elevated at 40 µmol/L.

Mr. R is started on IM lorazepam, 1 mg every 8 hours. Antipsychotics are held in part because of an elevated CK level (614 U/L). CK is rechecked daily and increases to 5,681 U/L by the second week. Internal medicine is consulted because Mr. R could develop NMS. However, the treatment team thinks that CK elevation is caused by immobility, because Mr. R remains afebrile, normotensive, and without leukocytosis.

After 4 days of treatment, Mr. R can follow simple commands. He nods or shakes his head when questioned. IV fluids are started because of limited oral intake. As the month progresses, Mr. R's CK levels slowly trend downward, toward 500 U/L.

Mr. R progresses slowly with benzodiazepine therapy. He begins to ambulate, make eye contact, and look at interviewers. Lorazepam is slowly titrated to 4 mg IM every 8 hours. On hospital Day 20, his functioning reaches a plateau; Mr. R's cognition continues to fluctuate with periods of unresponsiveness, immobility, and incontinence.

The treatment team obtains consent from the family to begin ECT. On hospital Day 24, bilateral transtemporal ECT is initiated and continued 3 times a week. Mr. R tolerates the procedure without complications. After the first treatment, he demonstrates spontaneous speech for the first time since admission. He continues to improve overall but has a variable clinical course.

By Day 30, Mr. R can state the day, month, year, and that he is in the "psych" unit. He remembers being on the unit for a long time and says that he had been attempting to talk but "it wasn't coming out." When further questioned about substance use, he admits to using Spice for the month before admission and marijuana regularly over several years. He denies using other illicit drugs or alcohol.

Mr. R is started on olanzapine, 2.5 mg/d, titrated to 15 mg/d. He becomes increasingly interactive, although with occasional bouts of confusion, and regains bladder and bowel control. He receives a total of 12 ECT

treatments. The family is adamant that Mr. R should not receive more ECT treatments, and is not interested in maintenance therapy. Mr. R's father and grandmother visit and believe that he is back to baseline functioning. After 51 days of inpatient treatment, Mr. R is discharged on olanzapine, 15 mg/d, and oral lorazepam, 1 mg/d.

Nine days later, Mr. R is brought to the ER because of unresponsiveness, poor oral intake, refusal of medication, bowel and bladder incontinence, and inability to perform ADL. His father reports that he administered olanzapine but, because he only recognized the brand name of lorazepam, he did not get that prescription filled. Mr. R slowly decompensates and, by the time of readmission, refuses all medications.

Over the next few months, Mr. R is readmitted several times for similar symptoms. Again, the family states they do not want further ECT; the father believes that these treatments have caused his son's condition. Complicating the matter is that the father had been out of his son's life for an extended period and is unaccustomed to his son's display of psychiatric symptoms.

## The authors' observations

The use of ECT for drug-induced psychosis is not well described in the literature because substance abuse is exclusionary in many trials. The safety and efficacy of ECT has been established for adolescents with first-episode psychosis[14] and with catatonia.[15,16]

The use of ECT in Spice-induced catatonia has been reported in 2 case studies.[17,18]

**Case 1.** A 36-year-old man with schizophrenia and *Cannabis* dependence was admitted for auditory hallucinations, disorganization, paranoia, and manic symptoms, which progressed to catatonia.[17] His symptoms were profound, including psychomotor retardation, rigidity, posturing, waxy flexibility, and inability to perform ADL.

The patient later reported that, 3 weeks prior, he had stopped taking his psychotropic medications and started smoking "K2," a synthetic cannabinoid, because it was cheaper and easier to obtain than *Cannabis*. He had never experienced disturbances in motor function or speech in the past, even during episodes of *Cannabis* use and medication non-adherence.

After clozapine and benzodiazepine treatment (as high as 12 mg/d of lorazepam) did not resolve his symptoms, the patient received 6 bilateral ECT treatments over 16 days, with complete resolution of catatonic symptoms. He showed marked improvement, including resumption of speech after the first treatment, although he required an additional 20 days of inpatient care. As in our case, exposure to synthetic cannabinoids was self-reported; no confirmatory tests were performed.

**Case 2.** A 17-year-old male with no history of psychosis exhibited catatonic symptoms after smoking an estimated 2 to 3 g/d of K2 over 2 months.[18] Similar to the case of Mr. R, he plateaued after lorazepam treatment, and then received 6 ECT treatments, which resulted in complete resolution of symptoms. He was discharged with olanzapine.

As our patient, and the 2 cases cited, show, ECT seems to be an effective option for Spice-induced catatonia. Unlike those published cases, however, our patient achieved only brief resolution of symptoms after an acute course of ECT. There appears to be a subset of patients who require maintenance ECT or prolonged benzodiazepine therapy after Spice-induced catatonia.

### Clinical Point

**ECT for drug-induced psychosis is not well described in the literature because substance abuse is exclusionary in many trials**


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continued

## Clinical Point

**There may be a subset of patients who require maintenance ECT or prolonged benzodiazepine therapy after Spice-induced catatonia**

## Related Resources

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**Drug Brand Names**

Amantadine • Symmetrel
Clozapine • Clozaril
Dantrolene • Dantrium
Lorazepam • Ativan
Memantine • Namenda
Olanzapine • Zyprexa
Zolpidem • Ambien


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# Bottom Line

The use of synthetic cannabinoids is on the rise because of availability, cost, and problems with detection. They are full agonists at the cannabinoid receptors, and contain no protective cannabidiol—making them potentially more dangerous than *Cannabis*. Spice has been implicated in several cases of first-onset catatonia. Electroconvulsive therapy is an effective treatment for catatonia when benzodiazepines fail.