Exacerbation of psychosis triggered by a synthetic cannabinoid in a 70-year-old woman with Parkinson disease

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Cite as: *CMAJ* 2018 January 15;190:E50-2. doi: 10.1503/cmaj.170361

Psychosis developed in a 70-year-old woman with a 12-year history of Parkinson disease after she ingested nabilone, a synthetic cannabinoid. The patient had chronic and painful dystonia in both feet that occurred as her medications were wearing off; this was resistant to management with frequent and multiple antiparkinsonian medications. She was advised by a friend with Parkinson disease to try medical marijuana for the dystonia. Her family physician prescribed nabilone, and the patient took two doses (1 mg) that resulted in intrusive visual hallucinations, panic and paranoia within hours. Despite stopping treatment with nabilone after the two doses, the patient's psychosis worsened over the next three weeks. She had delusions that her neighbours were engaged in illegal and dangerous activities.

Before the ingestion of nabilone, the patient had had occasional nonintrusive visual hallucinations for many years; insight was preserved. Although she had mild cognitive concerns, these did not interfere with her daily function, and she lived independently at home with her husband. She had scored 27 out of 30 on the Montreal Cognitive Assessment (www.mocatest.org/) two months before taking nabilone, with points lost for visuospatial and executive function.

The patient had no other active concurrent medical problems and had made no changes to her other medications, which included levodopa–carbidopa (1000/250 mg per day), entacapone (1000 mg per day), pramipexole (4.5 mg per day) and amantadine (300 mg per day).

She was assessed and managed as an outpatient by her primary specialists in Parkinson disease. On repeat Montreal Cognitive Assessment testing three weeks after using nabilone, the patient scored 23 out of 30, losing points for attention, abstraction, delayed recall and orientation. Despite ending treatment with amantadine, which has been associated with psychosis, the patient's delusions and visual hallucinations persisted. Quetiapine (12.5 mg) was added at bedtime, and her evening dose of pramipexole was reduced (from 1.5 to 0.75 mg).

Despite these adjustments, the patient's psychosis worsened. About two months after first ingesting nabilone, the patient reported seeing two figures drag a body — whom she believed to be her daughter — into her neighbour's shed. She became so agitated that she broke into the shed. A video taken at home by her daughter shows generalized dyskinesia, pressured and tangential speech, and delusions (a video [Appendix 1], is available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.170361/-/DC1.)

Because of the patient's acute psychosis, we admitted her to hospital the following day. Our goal was to rapidly stop treatment with the dopamine agonist in a monitored setting, to consider adding clozapine if this did not improve her psychosis and to provide in-hospital support to our patients' family members, who were overburdened with her care.

On admission, a general medical workup was unremarkable. We tapered and stopped pramipexole, but the patient's psychosis persisted. We started clozapine, which resulted in symptomatic orthostatic hypotension that required the addition of fludrocortisone. Over two weeks, the dyskinesias subsided, but her nonmotor symptoms of wearing off persisted. We added controlled-release levodopa–carbidopa at bedtime and reduced the dose interval to every 2.5 hours. Eventually, the patient's psychosis diminished, and we discharged her to home with levodopa–carbidopa (1000/250 mg/d), entacapone (1000 mg/d), controlled-release levodopa–carbidopa (100/25 mg/d), fludrocortisone (0.1 mg in the morning) and clozapine (37.5 mg at bedtime).

Three months after discharge, the patient's visual hallucinations and delusions were still present but less severe despite taking clozapine (12.5 mg in the morning and 50 mg at bedtime).

KEY POINTS

- Evidence for the therapeutic use of medical marijuana and cannabinoid derivatives in patients with Parkinson disease is heterogenous and of low quality.
- Cannabinoids may precipitate psychosis, even in patients without a psychiatric history.
- Patients with Parkinson disease have an inherent risk of psychosis and cognitive impairment, and may be more susceptible to the psychomimetic and cognitive effects of cannabinoids.

Box 1: Information for patients on the adverse effects of cannabinoid use for Parkinson disease and parkinsonism[4,5,12]

There is conflicting evidence about the effect of cannabinoids (inhaled marijuana and cannabis extracts taken orally that combine variable amounts of Δ9-tetrahydrocannabinol and cannabidiol) on symptoms of Parkinson disease and parkinsonism (e.g., multiple system atrophy, progressive supranuclear palsy, corticobasal syndrome). For example, there are some claims of improvement in tremor or drug-induced dyskinetic (involuntary) movements. However, there is little good scientific evidence to support these claims. Furthermore, all cannabinoids have adverse effects that may be detrimental to people with Parkinson disease. Owing to the widespread interest of our patients and their families in cannabinoids, the lack of good evidence that these agents are effective in controlling symptoms, and our concern that people are ignoring the wide array of possible adverse effects, which we believe largely outweigh the potential benefits in most patients, we provide a list of the adverse health effects of cannabinoids.

Nonneurological effects

Inhaled marijuana

Respiratory:
- Bronchitis, asthma, cough
- Increased risk of lung cancer

Cardiovascular:
- Heart attack
- Stroke
- Vasculitis

Possible increased risk of cancers of the oral cavity, throat or esophagus

Inhaled cannabinoids and oral cannabinoids

Cardiovascular:
- Increased heart rate
- Decreased blood pressure*
- Fainting*

Immune system:
- Suppression (risk of infection)
- Increased inflammation

Reproduction:
- Potential harm to fetus
- Decreased fertility in men
- Passes into breast milk

Gastrointestinal:
- Nausea
- Cannabis hyperemesis syndrome (vomiting)

Neurological effects

Acute effects

Cognition:
- Impairment of short-term memory*
- Impairment of attention*
- Impairment of executive functioning*
- Impairment of visual perception*

Mood:
- Anxiety,* panic attack
- Depression*
- Suicidal ideation

Psychiatric/behavioural:
- Hallucination*
- Fatigue*
- Drowsiness*
- Low motivation*
- Psychosis* (e.g., paranoid thinking)
- Feelings of intoxication

Psychomotor:
- Impaired driving*
- Increased weakness
- "Zombie"-like state

Potential permanent effects
- Psychosis*
- Development of schizophrenia or bipolar disorder
- Dependence or addiction*
- Stroke or brain hemorrhage

*People with Parkinson disease and parkinsonism commonly experience these symptoms even before using cannabinoids and, therefore, may be more susceptible to these adverse effects.

We arranged for home care to help with evening medications. She had no new cognitive concerns and scored 26 out of 30 on the Montreal Cognitive Assessment, which was reassuring because worsening psychosis often coincides with the onset of dementia from Parkinson disease.

Discussion

This case illustrates the potential for the synthetic cannabinoid, nabilone, to trigger psychosis in a susceptible patient. The psychomimetic action of even single doses of nabilone are well described, as are the extended effects of a single dose because of the long half-life of active metabolites.[1]

Psychosis in Parkinson disease — its timing in relation to disease progress and severity of symptoms — exists on a spectrum.[2] Patients may have well-formed visual hallucinations with insight into these experiences, but in more severe psychosis, insight can be lost and patients may act in response to their hallucinations. Delusional beliefs may also crystalize around the experiences. Psychosis may occur as part of the natural history of Parkinson disease or it may be due to exogenous triggers, such as medical illnesses (notably infections) and dopaminergic drugs.[3]

Synthetic oral cannabinoids (nabilone, dronabinol and tetranabinex/nabidiolex) are licensed in Canada for selected medical conditions, including the management of nausea and neurologic symptoms such as pain and spasticity.[4] The use of cannabinoids to manage motor symptoms in Parkinson disease including tremor, bradykinesia and dyskinesia, as well as other movement disorders, is not well-supported by current evidence, which is heterogenous, of low quality and often observational.[5] Nevertheless, because many motor and nonmotor symptoms of Parkinson disease are incompletely or poorly responsive to medical and surgical treatments, patients desperate for relief have begun to turn to medical marijuana and cannabinoids, often encouraged by the belief that marijuana is a "natural remedy" and by the positive anecdotes of peers or videos on the Internet. Unfortunately, patients and their families are often unaware of the potential adverse effects of marijuana and cannabinoids.[6]

There is evidence that use of cannabis can precipitate or exacerbate psychosis even in patients without a relevant psychiatric

history.[7] Cannabinoids, including Δ9-tetrahydrocannabinol (THC), cannabidiol and cannabinol, are pharmacologically active compounds isolated from the cannabis plant. Although THC is thought to be the most psychoactive, all cannabinoids bind to the same endocannabinoid receptors (cannabinoid receptor types 1 and 2); however, cannabidiol acts as a functional antagonist at these receptors. Some studies have suggested that cannabidiol has an antipsychotic effect, but these studies did not include participants with Parkinson disease.[8] In addition, other mechanisms not mediated by cannabinoid receptor 1 are implicated, and possibly associated with, variable risk of psychosis, including interaction with glutamate and dopamine neurotransmission, among others.[9] Nabilone is a mixture of cannabinoids, primarily cannabinol, but it also contains THC and cannabidiol. Although potentially less psychoactive, its mechanism of action is similar to that of THC.[10]

We suggest that the potential risks of the use of cannabis outweigh the benefits in patients with Parkinson disease, because these patients are susceptible to many of the possible neurologic and nonneurologic adverse effects caused by cannabis use. Cognitive impairment, in the form of executive and attentional dysfunction, is common in Parkinson disease, and cannabinoids can cause distractibility and executive dysfunction in some users.[4,7] Use of cannabis can also lower upright blood pressure, and patients with Parkinson disease commonly have orthostatic hypotension, which may be detrimental to both cognition and disease progression.[11]

Our patient had symptoms of mild parkinsonian psychosis — hallucinations with preserved insight — which is not uncommon. Her symptoms were stable for many years, until she ingested nabilone. She used this drug only twice, but on each occasion she had anxiety, hallucinations without insight and paranoia. Even after she stopped taking nabilone, she continued to have progressively worsening psychotic symptoms. Although the patient's Parkinson disease, antiparkinsonian drugs and previous psychiatric symptoms may have provided a predisposition to the development of psychosis, ingestion of nabilone was the clear trigger that caused her psychotic symptoms to become established and then spiral out of control. The association of her paranoid delusional state with generalized dyskinesia, and pressured and tangential speech suggest that a hyperdopaminergic state may have contributed to her psychosis.

We have developed a patient information sheet to inform our clinic population of the potential adverse effects that can occur with the use of cannabinoids (Box 1).[4,5,12]

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Please see the following video online:

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www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.170361/-/DC1

Competing interests: Susan Fox has received consultant fees and research frunding from Avanir Pharmaceuticals, Biotie Therapies, Britannia, C2N, Cynapsus, Eisai, Kyowa Kirin, Orion, Sunovion and Zambon; honoraria from the International Parkinson and Movement Disorder Society, CHDI Foundation and the American Academy of Neurology; research funding from the Michael J. Fox Foundation for Parkinson's Research, National Institutes of Health, Parkinson Canada and Toronto Western Hospital Foundation; and salary from the University Health Network Department of Medicine Practice Plan. Anthony Lang has received personal fees from AbbVie, Acorda, Biogen, Bristol–Myers Squibb, Corticobasal Solutions, Medichem, Medtronic, Merck, Paladin, Sunovion and Sun Pharma, outside the submitted work. No other competing interests were declared.

This article has been peer reviewed.

The authors have obtained patient consent.

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Contributors: Sean Udow was responsible for compiling the case report, writing the discussion and creating the patient handout. Maria Eliza Freitas was responsible for literature review and creating the patient handout. All of the authors revised the manuscript crtically for important intellectual content, provided final approval of the version to be published and agreed to be accountable for all aspects of the work.

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