Synthetic Δ-9-Tetrahydrocannabinol (Dronabinol) Can Improve the Symptoms of Schizophrenia

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Abstract: We are reporting improvement of symptoms of schizophrenia in a small group of patients who received the cannabinoid agonist dronabinol (synthetic Δ-9-tetrahydrocannabinol). Before this report, cannabinoids had usually been associated with worsening of psychotic symptoms. In a heuristic, compassionate use study, we found that 4 of 6 treatment-refractory patients with severe chronic schizophrenia but who had a self-reported history of improving with marijuana abuse improved with dronabinol. This improvement seems to have been a reduction of core psychotic symptoms in 3 of the 4 responders and not just nonspecific calming. There were no clinically significant adverse effects. These results complement the recent finding that the cannabinoid blocker rimonabant does not improve schizophrenic symptoms and suggest that the role of cannabinoids in psychosis may be more complex than previously thought. They open a possible new role for cannabinoids in the treatment of schizophrenia.

Key Words: cannabinoid hypothesis of schizophrenia, endocannabinoid stimulation

(*J Clin Psychopharmacol* 2009;29: 255–258)

We are reporting the response to the cannabinoid agonist dronabinol (synthetic Δ-9-tetrahydrocannabinol [Δ-9-THC]) of a small group of patients with refractory, chronic psychosis diagnosed as schizophrenia.

The idea for our use of dronabinol in this population came from the surprisingly good response of 1 patient. He was grossly psychotic, assaultive, disorganized, and highly refractory to multiple medication trials. However, in reviewing his history, we noted that he had a history of several years of calm behavior when he was using marijuana. We determined that trying a marijuana congener was a reasonable therapeutic option. Remarkably, he became calm, logical, nonviolent, and cooperative within days and was discharged within weeks. This prompted us to try dronabinol on other patients who fit this profile: having a diagnosis of chronic refractory schizophrenia, together with a history of marijuana use during which they reported some improvement.

Dronabinol is synthetic Δ-9-THC, an endocannabinoid agonist approved by the Food and Drug Administration in 1992 as an appetite stimulant for the treatment of weight loss in patients with human immunodeficiency virus/acquired immunodeficiency syndrome. It also has antinausea properties and is used as an antiemetic in chemotherapy patients. Dronabinol stimulates primarily the major brain endocannabinoid receptor, cannabinoid type 1 (CB1),[1] although it may have some effect on the other endocannabinoid receptor, CB2, found mostly in the periphery. Although naturally occurring Δ-9-THC seems to be the main active ingredient of marijuana, it is nevertheless only one of many components of marijuana, and its synthetic version, dronabinol, does not seem to have significant addictive potential or withdrawal in clinical practice.[2,3]

METHODS

This was a clinical case series. Impressed by the dramatic response of our first patient, we were interested in determining if that response was purely idiosyncratic or might be generalizable to help any other patients with refractory psychosis in our state hospital population. Approval was obtained from the joint institutional review board of the Rockland Psychiatric Center and Nathan S. Kline Institute for Psychiatric Research to prescribe dronabinol clinically in a limited number of appropriate cases, whose number was to be determined by our parent agency, the State of New York Office of Mental Health. We received permission to try dronabinol on 3 patients, and that permission was later expanded to include an additional 2 patients.

Recognizing that cannabinoid agonists may worsen schizophrenic symptoms, we were careful to select only patients whose long-standing, severe, refractory condition, weighed against a history of improvement when using marijuana, made the possible benefits outweigh the risks. From approximately 200 patients with chronic psychosis, we identified 5 patients who met the inclusion criteria: a history of sustained improvement with past chronic marijuana use as related by the patient and confirmed by chart review or family; marijuana being their substance of choice and otherwise an absence of significant polysubstance abuse or dependence; good physical health; a diagnosis of schizophrenia, undifferentiated type meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria; and severe, long-standing illness refractory to standard treatment. All of the subjects had experienced schizophrenia for many years and carried that diagnosis since their teens or early adulthood. All had numerous adequate antipsychotic medication trials, including clozapine, with minimal or no response. Ages ranged from 21 to 43 years. Although all the patients were on ongoing antipsychotic medications, their conditions had been essentially unchanged for months or years, and there were no significant medication changes in the months before starting the dronabinol. Aside from the dronabinol titration, there were no changes or adjustments of their medications during the trial period. Although all patients were in the supportive setting of the hospital, they had been in that setting for years without significant improvement, and there were no recent changes in the milieu or the staffing.

To track the response, the Clinical Global Impression (CGI)[4] and 18-item Brief Psychiatric Rating Scale,[5] both

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ISSN: 0271-0749
DOI: 10.1097/JCP.0b013e3181a6bc3b

TABLE 1. Outcomes as Measured by CGIs and Brief Psychiatric Rating Scale

			CGI-S		CGI-I	Brief Psychiatric Rating Scale	
Patient	Age, yr	Antipsychotic Medication(s)	Baseline	Endpoint	Endpoint	Baseline	Endpoint
1	21	Olanzapine and risperidone	7	2	1	48	30
2	21	Clozapine and haloperidol	5	2	1	47	29
3	27	Fluphenazine	5	3	2	57	42
4	43	Ziprasidone and quetiapine	6	5	3	56	52
5	41	Olanzapine	5	5	4	46	44
6	30	Clozapine and quetiapine	6	6	5	88	99

Endpoints were at weeks 2, 4, 8, 8, 4, and 3 for patients 1, 2, 3, 4, 5, and 6, respectively.
CGI-I indicates Clinical Global Impression, global improvement; CGI-S, Clinical Global Impression, severity of illness.

observer rated, were done at baseline and then weekly. Both instruments are used routinely to track the clinical course of all patients in our facility. In view of the well-known stimulation of appetite with cannabis and the primary Food and Drug Administration approval of dronabinol as an appetite stimulator, we also followed weekly weights. Patients were assessed daily for adverse effects by their treating psychiatrist. Dronabinol was initiated at 2.5 mg twice a day and subsequently raised to 5 mg twice a day at week 2 and to 10 mg twice a day at week 3. We received permission for a trial period of up to 8 weeks, with the possibility of compassionate use continuation treatment for responders. The study was uncontrolled.

RESULTS

We followed up 6 adults, 5 men and 1 woman. Four of the 6 patients improved to a clinically significant extent (Table 1).

Three of the 6 patients (1 of them being the index case) had a robust response, with modest to marked reductions in core psychotic symptoms (Table 2). Patients 1 and 2 showed improvement within several weeks of beginning the medication, whereas patient 3 required 8 weeks to reach significant improvement. In addition, robust improvement in overall functioning was also observed, with patients 1 to 3 changing from being gravely ill to being functioning individuals able to be discharged. Patient 4 had more limited improvement in that he was calmer, cooperative, and less aggressive but had persistence of his core psychosis. Nevertheless, his overall functioning was significantly improved. When his dronabinol was later discontinued, he decompensated within 1 week, returning to his baseline aggressive behavior. When the dronabinol was restarted, his behavior rapidly improved.

Subjectively, the patients who improved explained that they felt calmer. Patient 2 noted, "My thinking is no longer scrambled." All subjects made the point that the medication did not feel like real marijuana and did not give them a high.

The 2 patients who did not respond had profound agitated psychosis with prominent assaultiveness at baseline. Of note, patient 6, whose symptoms worsened, was the only female and also the only patient whose history of improvement with marijuana was questionable.

We saw no significant adverse effects and no abnormalities in the laboratory results. Surprisingly, no patient gained weight. We did not do formal assessment of cognition function but noted no clinical signs of cognitive deterioration.

DISCUSSION

Heretofore, stimulation of the endocannabinoid system in patients with schizophrenia has only been reported with worsening of psychosis,[6,7] and it has been observed that even some people with no history of mental illness who use marijuana develop psychotic symptoms.[8,9] However, not all patients with schizophrenia worsen with *Cannabis sativa*, and it has been hypothesized that it is mainly a genetically predisposed or vulnerable subgroup that shows worsening of symptoms.[10–12] One recent study demonstrated that Δ-9-THC, the same component of marijuana that we used in our study, also exacerbates the symptoms of schizophrenia.[7] These results are opposite to our findings. However, the authors of that study noted that they did not include patients with a history of cannabis use, and they opined that this may have excluded candidates likely to improve with cannabinoids. By contrast, our study specifically enrolled patients with a history of improvement with cannabis use.

It is postulated that some types of schizophrenia may be caused by hyperactivity of the endocannabinoid system in the brain, the so-called cannabinoid hypothesis of

TABLE 2. Outcomes for the Robust Responders as Measured by the Brief Psychiatric Rating Scale Items of Conceptual Disorganization, Hallucinatory Behavior, Suspiciousness, and Unusual Thought Content

	Conceptual Disorganization		Hallucinatory Behavior		Suspiciousness		Unusual Thought Content	
Patient	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
1	4	3	5	1	4	2	5	3
2	6	3	4	1	5	2	6	3
3	5	3	4	2	3	2	4	3

Endpoints were at weeks 2, 4, and 8 for patients 1, 2, and 3, respectively.

schizophrenia.[10,13–15] According to this hypothesis, stimulation of the endocannabinoid system should cause psychotic symptoms, whereas blockade of that system might treat schizophrenia. Endocannabinoid stimulation may cause psychosis through cannabinoid-induced blockade of sensory gating.[15,16] Gating, the filtering out of extraneous environmental stimuli, is required to allow a manageable amount of stimuli to impact the brain. The theory that inadequate filtering of sensory input may cause schizophrenia is well known.[17,18] It is intuitive that a person flooded by auditory stimuli may become overwhelmed and develop misperceptions such as auditory hallucinations, ideas of reference, and paranoia.

Preclinical research supports the hypothesis that excessive endocannabinoid activity causes loss of sensory gating. The exogenous CB1 receptor agonist WIN55,212-2 abolished sensory gating in the rat hippocampus.[15] Conversely, blocking CB1 receptors in rats with the CB1 antagonists rimonabant and AM251 increased sensory gating; the rats had their phencyclidine-induced sensorimotor deficits reversed to an extent that mimicked the antipsychotic profile of clozapine.[16] It was therefore expected that rimonabant would improve schizophrenic symptoms in humans. However, this did not occur. The one clinical trial of rimonabant (SR141716) in patients with schizophrenia showed no effect on their symptoms.[19] Our findings seem to complement this observation: some of our patients improved rather than worsened on the CB1 stimulant dronabinol. Thus, it seems that in some patients with schizophrenia, blocking CB1 receptors may have no effect on symptoms, whereas stimulating those receptors may lead to amelioration of psychosis. This is contrary to the endocannabinoid theory of schizophrenia, in which blocking CB1 receptors should have improved schizophrenia and stimulating those receptors should have worsened it. The endocannabinoid theory of schizophrenia may be more complex than it had previously appeared.

One might argue that the improvement in our patients was nonspecific, coming only from the well-known calming effect of cannabinoids and not from any direct antipsychotic efficacy of the dronabinol. There is evidence that the calming effect of cannabinoids can be therapeutic in several conditions. The CB1 receptor agonist WIN55,212-2 exerts strong antidepressantlike activity in the rat forced-swim test.[20] Dronabinol has been shown to relieve nighttime agitation in demented patients.[21] Similarly, the oral cannabinboid nabilone has been shown to reduce pain and anxiety in fibromyalgia.[22] Moreover, studies on the endocannabinoid receptor 1 blocker rimonabant, designed to decrease appetite, actually caused some patients to drop out of clinical trials because of anxiety and depression, presumably caused by blocking the endocannabinoid system.[23] Consistent with the evidence mentioned, all 4 of the patients in our series who improved stated they were calmer. However, only the improvement in patient 4 seemed primarily related to calming. The improvement in patient 3 seemed only partially linked to calming, and the improvement in patients 1 and 2, our 2 most robust responders, showed an apparent direct and primary lysis of their core psychosis, above and beyond any nonspecific calming or relief of depression.

The fairly high response rate in our patients was surprising, given that we were treating a chronic, refractory population in which success with any intervention might be unlikely. It is possible that the good response rate was a self-selection artifact. We specifically recruited patients who had a history of calming with marijuana, presumably making the likelihood of a good response to a cannabinoid stimulator more likely. However, self-reports of past cannabis use are only moderately reliable in research patients,[24] and self-reported improvement with marijuana use in patients with schizophrenia often correlates with actual clinical worsening.[25] Other possible reasons for the relatively high response rate include our including the index case and not using blind or controlled conditions. In addition, it is possible that our population of chronic, refractory patients in a state hospital may include a subgroup that uniquely responds to cannabinoids. Precisely because these patients have not responded to standard dopamine-blocking antipsychotic medication, their psychotic symptoms may be generated by abnormalities in other systems, such as the endocannabinoid system. In any case, any subgroup of patients with schizophrenia who respond to dronabinol is likely to be small, and identifying such patients may be difficult, even with a history of past improvement on marijuana. Future studies on dronabinol will need to carefully identify such a subgroup to demonstrate a statistically significant response. In addition, given recent evidence that marijuana and tetrahydrocannabinol can cause cognitive impairment,[7] future studies should assess serial cognitive function.

Given the increased mortality in patients with dementia, given standard antipsychotic medications for psychosis and agitation,[26] there is an urgent need to find a safe and efficacious treatment for this patient population. If further study proves our findings valid, dronabinol might become an alternative adjunctive treatment for at least some of these patients.

A caveat is the risk of drug abuse. Even if dronabinol has minimal abuse and addicting potential in and of itself, the psychological reminder of marijuana might cue ex-users back to using it. Although our case series of patients did not suggest it, we cannot rule out this possibility, and we recommend that this risk be weighed against the therapeutic benefits and that future studies monitor this risk.

CONCLUSIONS

Adjunctive dronabinol may be efficacious in reducing core psychotic symptoms in patients with treatment-refractory schizophrenia. The results of this open-label case series need to be followed up with a controlled study.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the assistance of Khaja Moinuddin, MD and Hong Tao Zhang, MD of Rockland Psychiatric Center in the collection of data; the assistance of Scott Clark, MD, former clinical director of Rockland Psychiatric Center, in obtaining approval from the institutional review board and the Office of Mental Health; and the assistance of Les Citrome, MD of the Nathan S. Kline Institute, Orangeburg, New York, in reviewing the manuscript.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflict of interest.

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