Case report

Cannabidiol was ineffective for manic episode of bipolar affective disorder

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Abstract

The pharmacological profile of cannabidiol (CBD) has several characteristics in common with drugs known to benefit bipolar affective disorder (BAD), leading to the hypothesis that CBD may have therapeutic properties in BAD. Therefore, the aim of the present report was to directly investigate for the first time the efficacy and safety of CBD in two patients with BAD. Both patients met DSM IV criteria for bipolar I disorder experiencing a manic episode without comorbid conditions. This was an inpatient study, and the efficacy, tolerability and side effects were assessed. Both patients received placebo for the initial 5 days and CBD from the 6th to 30th day (initial oral dose of 600 mg reaching 1200 mg/day). From the 6th to the 20th day, the first patient (a 34-year-old woman) received adjunctive olanzapine (oral dose of 10–15 mg). On day 31, CBD treatment was discontinued and replaced by placebo for 5 days. The first patient showed symptoms improvement while on olanzapine *plus* CBD, but showed no additional improvement during CBD monotherapy. The second patient (a 36-year-old woman) had no symptoms improvement with any dose of CBD during the trial. Both patients tolerated CBD very well and no side-effects were reported. These preliminary data suggest that CBD may not be effective for the manic episode of BAD.

Key words
affective disorder; bipolar; cannabidiol; cannabis; CBD; mania

Introduction

The treatment of bipolar affective disorder (BAD) remains problematic and often involves a combination of drugs, including lithium, anticonvulsants, antidepressants, antipsychotics and benzodiazepines. All such treatments have their disadvantages such as low acceptance, occurrences of mania on withdrawal, risks in women of childbearing age and careful dosage control (Goodwin, 2003; Ashton, *et al*., 2005). Thus, there is a clear need to explore new pharmacological possibilities of managing BAD.

Anecdotal reports suggest that some patients use marijuana to relieve both depression and mania symptoms (Henquet, *et al*., 2006; Gruber, *et al*., 1996), although no systematic studies of their therapeutic use in BAD were described in the scientific literature.

Cannabidiol (CBD), a major *Cannabis sativa* component, was formerly proposed as a cannabinoid devoid of the typical psychological effects of marijuana in humans. Potential antipsychotic, anticonvulsive, antidepressant, hypnotic, anxiolytic and antioxidant properties of CBD have been suggested based on preclinical and clinical data (Zuardi, *et al*., 2006a; Mechoulam, *et al*., 2007). Such pharmacological profile has several characteristics in common with drugs known to benefit BAD, leading to the hypothesis that CBD may have therapeutic properties in BAD (Ashton, *et al*., 2005).

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Because CBD does not seem to induce significant adverse effects in humans (Consroe, *et al*., 1991), we decided to directly investigate, for the first time to the best of our knowledge, the efficacy and safety of CBD in two patients with BAD.

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Procedure

This was an inpatient study with rater-blind evaluations. The protocol was approved by the local Ethical Committee (HCRP – nº 11734/03) and informed consent was obtained both from the patient and also from their next of kin.

Two female adult patients recruited from the psychiatric ward of the University Hospital of the Faculty of Medicine of Ribeirão Preto (Brazil) were included in the study. They were identified among patients requiring inpatient admission. Diagnosis of BAD I experiencing a manic episode with psychotic features, without comorbid conditions was confirmed using the Portuguese version (Del-Ben, *et al*., 2001) of the Structured Clinical Interview for DSM-IV (SCID-IV; First, *et al*., 1997). The neurological examination of both patients was normal. Both patients had previous history of being responsive to mood stabilising treatment (lithium, anticonvulsants and antipsychotics).

During the study, the patients participated in the usual non-pharmacological therapeutic procedures on the ward, such as psychotherapeutic groups, occupational therapy, individual interviews and programmed physical activities. In cases of agitation or severe insomnia, the patients received midazolam, on an as-required basis.

Patients were assessed simultaneously and independently by two psychiatrists (both rater-blind) who completed the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) using the version by Bech, *et al*. (1986), translated to Portuguese and validated by Zuardi, *et al*. (1994). The manic symptoms were assessed by the Young Mania Rating Scale (Young, *et al*., 1978 – YMRS), translated to Portuguese and validated by Vilela, *et al*. (2005). The Intraclass correlation coefficient between the two evaluators was very good (0.9 for BPRS and 0.75 for YMRS). The evaluators also used the UKU Side Effect Rating Scale for psychotherapeutic drugs (Lingjaerde, *et al*., 1987) to investigate possible side-effects and the tolerability of CBD. The assessment and the drug adjustment were made weekly.

Case 1

Ms A, a 35-year-old woman, was referred to the inpatient unit because of elated mood, aggressiveness, insomnia, talkativeness difficulty in concentrating, increased drive, grandiosity delusions and auditory hallucinations. She had a BAD diagnosis since 25 years old with two previous manic and two depressive episodes, which had been successfully treated with carbamazepine, antipsychotics and antidepressants. During the first 5 days of hospitalisation, Ms A received placebo plus usual environmental support measures. From the 6th to 30th day (inclusive) she received CBD twice a day (initial oral dose of 600 mg reaching 1200 mg/day). Since it was the first time that the CBD would be used in manic patients in crisis, to ensure that it would not stay without effective treatment, for ethical reasons, we chose to associate olanzapine and after 2 weeks withdraw it checking if the CBD alone maintains the achievements of the association. Thus, from the 6th to the 20th day, she received adjunctive olanzapine (oral dose of 10–15 mg). On day 31, CBD treatment was discontinued and replaced by placebo for 5 days. The doses of the drugs were given in Table 1.

Case 2

Ms B, a 36-year-old woman, was referred to the inpatient unit because of elated mood, delusions with mystic and grandiose content, excessive speech, racing thoughts, impaired attention, difficulty with concentrating, impulsiveness, aggressiveness and reduced sleep. She had a BAD diagnosis since 17 years old with three manic and one depressive episode previously, who had been successfully treated with lithium and antipsychotics. Ms B received the same scheme of treatment than Ms A, but adjunctive olanzapine was not given, to verify whether the Ms A initial improvement was due to CBD. The doses of the drugs were given in Table 1.

Results

The YMRS and BPRS scores are shown in Table 1. Ms A presented reduction of 37% and 33% in YMRS and BPRS scores, respectively, while on olanzapine *plus* CBD, but showed no additional improvement during CBD monotherapy. Ms B had no symptoms improvement with any dose of CBD during the

Table 1 Scores of the Young Mania Rating Scale (YMRS) and the Brief Psychiatric Rating Scale (BPRS) for two bipolar patients throughout the study

Case	Day of study	Treatment	YMRS	BPRS
A	5	Placebo	27	21
	12	CBD-600 mg OLZ-10 mg	17	14
	19	CBD-600 mg OLZ-15 mg	18	15
	26	CBD-900 mg	22	12
	33	CBD-1200 mg	22	15
	38	Placebo	17	12
B	5	Placebo	23	10
	12	CBD-600 mg	20	8
	19	CBD-900 mg	15	7
	26	CBD-1200 mg	20	11
	33	CBD-1200 mg	17	12
	38	Placebo	28	12

trial. Patients received midazolam on an as-required basis only in placebo periods. Both patients tolerated CBD very well and no side-effects were observed with the UKU scale.

After the trial, both patients initiated treatment with lithium at 600–900 mg/day that was increased to 1200 mg/day, according to clinical response, with serum concentrations of 0.9 and 1.0 mmol/L (case 1 and 2, respectively). They completely remitted from manic episode and psychotic symptoms in about 30 days. The patients have remained psychiatrically stable on lithium treatment use after a 6-month follow-up.

Discussion

Although the efficacy outcome of this trial is mainly negative, these results showed that high-dose CBD is safe to use in patients with BAD. Consistent with other human studies (Consroe, *et al*., 1991; Zuardi, *et al*., 1995, 2006b), CBD was well tolerated and patients did not show any side-effects with CBD use at any dosage, as assessed by the appropriate rating scales, even at a high dosage of 1200 mg/day.

These preliminary data do not support the hypothesis that CBD may have therapeutic properties in BAD (Ashton, *et al*., 2005) at least in patients with manic features.

Acute mania can be modelled in animals using D-amphetamine (AMPH) because mood stabilisers have shown to reverse and prevent hyperactivity induced by daily administration of this compound during 14 days in rats, indicating a good predictive validity (Frey, *et al*., 2006). Using this animal model of mania, our group has observed that CBD neither reversed nor prevented AMPH-induced hyperactivity (unpublished data) in accordance with the results verified in these two patients with BAD.

However, the lack of effect of CBD in the present cases could be due to an insufficient duration of treatment with higher doses and, with this protocol, it was neither possible to evaluate the effects of CBD as an antidepressant nor if this compound is capable to prevent a manic episode.

Therefore, double-blind, controlled clinical trials would be necessary to further investigate these possibilities.

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