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Cannabidiol monotherapy for treatment-resistant schizophrenia

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Abstract

Cannabidiol (CBD), one of the major products of the marijuana plant, is devoid of marijuana's typical psychological effects. In contrast, potential antipsychotic efficacy has been suggested based on preclinical and clinical data (Zuardi *et al.*, 2002). In this report, we further investigated the efficacy and safety of CBD monotherapy in three patients with treatment-resistant schizophrenia (TRS). This was an in-patient study. All patients were given placebo for the initial 5 days, and from the 6th to 35th day (inclusive) they received CBD (initial oral dose of 40 mg reaching 1280 mg/day). On the 36th day, CBD treatment was discontinued and replaced by placebo for 5 days, which was subsequently switched to olanzapine for over 15 days. Efficacy, tolerability and side effects were assessed. One patient showed mild improvement, but two patients didn't show any improvement during CBD monotherapy. All patients tolerated CBD very well and no side effects were reported. These preliminary data suggest that CBD monotherapy may not be effective for TRS.

Keywords

cannabidiol, CBD, schizophrenia, psychosis, treatment

Introduction

Cannabis use appears to act as a risk factor for the onset of schizophrenia or schizophrenia-like psychosis, especially in vulnerable people (Smit et al, 2004). This effect must be attributed to Δ9-tetrahydrocannabinol (Δ^9-THC), the main psychoactive constituent of the plant, since high doses of Δ^9-THC induce psychotic-like symptoms in healthy volunteers and is associated with transient exacerbation in core psychotic symptoms in schizophrenic patients (D´Souza *et al.*, 2005).

Several reports have demonstrated that other components of the plant influence its pharmacological activity (Carlini *et al.*, 1970). Cannabidiol (CBD), one of the major derivatives of Cannabis sativa (Grlie, 1976) is devoid of the typical marijuana psychological effects (Zuardi *et al.*, 1982) but interact with Δ^9-THC effects (Karniol and Carlini, 1973). In healthy volunteers it was verified that CBD, co-administered with Δ^9-THC, significantly reduced anxiety and the psychotomimetic symptoms induced by the latter drug (Zuardi *et al*., 1982).

It has been shown that CBD has potential antipsychotic efficacy in animal models with a pharmacological profile similar to an atypical antipsychotic drug (Zuardi *et al.*, 1991; Guimarães *et al.*, 2004; Moreira and Guimarães, 2005).

Safety of CBD has been studied in humans and the only side effect is sedation, in very high dose (Cunha *et al.*, 1980; Consroe *et al.*, 1991; Zuardi *et al.*, 1993).

Evidences for an antipsychotic effect of CBD were obtained from models used for evaluation of antipsychotic-like activity in

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healthy volunteers, such as the perception of binocular depth inversion and the administration of sub-anaesthetic doses of ketamine (Leweke *et al.*, 2000; Bosi *et al.*, 2003).

Considering the safe profile of CBD administration in humans and laboratory animals, we previously tested CBD in a case study with a 19-year-old schizophrenic female patient who presented serious side effects after treatment with conventional antipsychotics. After a few days of rapidly escalating doses of CBD dissolved in oil, this patient received 1200 mg/day of CBD, for 4 weeks. After this period, CBD administration was interrupted and placebo was administered for 4 days. Finally, the treatment shifted to escalating doses of haloperidol that reached 12.5 mg/day. The psychiatric interviews were video recorded and the symptoms were assessed by a blindfolded psychiatrist using the Brief Psychiatric Rating Scale (BPRS). A significant improvement with no side effects was observed during CBD treatment, which was not increased by haloperidol (Zuardi *et al.*, 1995).

The aim of this study was to investigate effectiveness of CBD in treatment-resistant schizophrenia (TRS), used as monotherapy, since this cannabinoid inhibits hepatic microsomes and potentially interacts with other co-administered drugs (Bornheim *et al.* 1993; McArdle *et al.*, 2001).

Method

The local Ethics Committee fully approved the study protocol, and informed consent was obtained from close relatives of the patients and themselves.

Three male 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 schizophrenia 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).

All patients had previous history of being non-responsive to at least two trials with traditional antipsychotics (haloperidol, chlorpromazine) and also to risperidone (6 mg/day). They fulfilled the criteria for TRS as defined by National Institute for Clinical Excellence (NICE) guidelines (2002). All the patients were offered clozapine treatment initially – however they refused clozapine treatment, given the side effects – and required blood monitoring process.

During the first 5 days of hospitalization, all the patients were given placebo (washout period). From day 6 to 35 of hospitalization they received CBD (GW-Pharm, UK) in two daily doses, starting with 40 mg and increasing the dose depending on tolerance and side effects and also efficacy, observed to a maximum dose of 1280 mg/day. The administration of CBD was then replaced by placebo for 5 days, which was subsequently switched to olanzapine for at least 15 days.

During the study, all 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 evaluated using 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 negative symptoms were assessed by the Negative Sub-scale from the Positive and Negative Syndrome Scale (PANSS-N; Kay *et al.*, 1987), translated to Portuguese and validated by Vessoni *et al.* (1993). The evaluators also used other rating scales: Global Clinical Impression Scale (CGI; National Institute of Mental Health, 1976); UKU Side Effect Rating Scale for psychotherapeutic drugs (Lingjaerde *et al.*, 1987); Simpson-Angus scale for Parkinsonism (Simpson and Angus, 1970); and Akathisia rating scale (Barnes, 1989).

Results

The BPRS scores are shown in Table 1.

Case 1

Mr A, a 23-year-old single male, was referred to the inpatient unit due to aggressiveness, incoherent thoughts, persecutory and reference delusions and prominent auditory hallucinations.

In the present study, from day 6 to 35 of hospitalization he received CBD, starting with 40 mg for 5 days, with the dose being doubled every 5 days, reaching 1280 mg/day. After the second placebo period, the patient received 10 mg of olanzapine that was increased to up to 20 mg/day.

During the use of CBD, after the first placebo period, there was a trend for symptom improvement at dose of 1280 mg/day. After CBD was discontinued, there was a significant worsening of the symptoms, partially improved with olanzapine treatment. The improvement with CBD and worsening after discontinuation were both related to its effect on positive, negative and general symptoms (Table 1). During CBD treatment there were no side effects observed or reported and the patient tolerated CBD very well. Olanzapine treatment, on the other hand, was associated with slight sedation, excess of salivation and weight gain (3 kilograms). The patient has remained psychiatrically stable, on olanzapine treatment use after a 1-year follow-up.

Case 2

Mr B, a 23-year-old single male, was referred due to persistent psychomotor agitation, suspiciousness, physical aggression, auditory command hallucinations, incoherent formal thought, loosening of association and religious, persecutory, reference and bizarre delusions.

His symptoms did not improve with CBD treatment. However, after CBD discontinuation there was worsening of all symptoms, especially the negative ones (Table 1). The use of olanzapine only partially improved the symptoms. Mr B was again offered clozapine and he agreed and started on clozapine treatment (at week 4,

Table 1 Raw scores of the Brief Psychiatric Rating Scale (BPRS) and the percentage of the maximum score of the BPRS factors: positive (+), negative (–) and general factors (G.F.) for three schizophrenic patients throughout the study

Drug	Case 1				Case 2				Case 3			
	BPRS	BPRS Factors (% of the maximum score)			BPRS	BPRS Factors (% of the maximum score)			BPRS	BPRS Factors (% of the maximum score)		
		+	–	G.F.		+	–	G.F.		+	–	G.F.
1st Placebo (Day 5)	19	50%	30%	12.5%	30	80%	30%	31.3%	29	65%	55%	25.0%
Cannabidiol (Day 35)	10	30%	20%	00.0%	28	80%	20%	25.0%	26	50%	45%	37.5%
2nd Placebo (Day 40)	32	80%	50%	25.0%	39	100%	60%	37.5%	26	50%	40%	43.8%
Olanzapine (Day 55)	6	5%	10%	12.5%	26	55%	25%	25.0%	22	50%	45%	12.5%

200 mg/day). He has remained on clozapine treatment over a year as he has shown satisfactory clinical improvement.

Case 3

Mr C is a 22-year-old single male living at home with his parents. He presented in crisis to the service due to the firm belief that people could hear his thoughts, reference delusions and auditory and visual hallucinations. At this time, his speech was incoherent and tangential; he was not able to take care of personal hygiene and presented severe isolation, spending most of the time closed in the bathroom. There was very minimum improvement after CBD treatment in both positive and negative symptoms. He was commenced on olanzapine with no improvement (Table 1). He finally agreed to take clozapine treatment. He received up to 300 mg/day of clozapine, biperiden (4 mg/day) and valproic acid (1500 mg/day), with no improvement and intolerable side effects (excessive sedation, seizures and excessive salivation). As he didn't comply with treatments, he was discharged from the inpatient unit into the community agreeing haloperidol decanoate (150 mg/month) treatment with mild clinical improvement. A 1-year follow-up at the outpatient unit showed no recovery of the psychotic symptoms.

Discussion

The evidence that cannabis derivatives are associated with worsening of psychotic symptoms in schizophrenic patients, together with the discovery of the endocannabinoid system and its possible dysfunction in schizophrenia attracted this system as a possible novel therapeutic target (Zuardi *et al.*, 1995; Leweke *et al.*, 1999; Giuffrida *et al.*, 2004; Meltzer et al, 2004).

Although the efficacy outcome of this trial is mainly negative, these results demonstrated that high dose CBD is safe to use in patients with schizophrenia. Consistent with other human studies, 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 1280 mg/day.

There are several possible reasons for the lack of efficacy in this trial as compared to the trial by Zuardi *et al*. (1995). These are:

1 The therapeutic approach was different as Zuardi *et al*. (1995) initiated a high dose scheme from the beginning of treatment while in the present study a titration was tried, investigating the dose response and the minimum effective dosage possible. Therefore, this lack of effect of CBD could be due to an insufficient length of higher dose.
2 Patients are treatment resistant to conventional antipsychotics and risperidone and one patient did not even respond to clozapine. This find would not exclude the hypothesis that CBD could be effective in non-refractory schizophrenia patients.
3 The duration of treatment was short. Four weeks usually is insufficient for most antipsychotics to have effects on negative symptoms.
4 A final possibility is that CBD has no clinical efficacy in treating schizophrenia. This is difficult to assess at the present moment, mainly when considering the amount of evidence on the contrary. (Zuardi *et al*., 1991, 1995, 2002; Leweke *et al*., 2000; Bosi *et al*., 2003; Guimarães *et al*., 2004; Moreira and Guimarães, 2005).
The mechanism(s) of action whereby CBD produces all these effects remains obscure. This is largely in contrast with the effects of Δ9-THC, which mimics the endogenous cannabinoids in many of its actions. CBD does not bind to known cannabinoid receptors, but the stereospecificity previously observed may indicate that CBD binds to another type of receptor in the brain (Mechoulam *et al*., 2002). This would exclude the idea that CBD would act similarly to other CB1 receptor antagonists that have been shown not to be effective in schizophrenia (Meltzer *et al*., 2004).

We suggest controlled clinical trials with CBD in first episode psychosis and early phases of schizophrenia.

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References

Barnes T R E (1989) A rating scale for drug-induced akatisia. Br J Psychiatry *154*: 672–676

Bech P, Kastrup M, Rafaelsen O J (1986) Mini-compendium of rating scales for states of anxiety depression mania schizophrenia with corresponding DSM-III syndromes. Acta Psychiatr Scand (Suppl) *326*: 1–37

Bornheim L M, Everhart E T, Li J M, Correia M A (1993) Characterization of cannabidiol-mediated cytochrome-p450 inactivation. Biochemical Pharmacology *45* (6): 1323–1331

Bosi D C, Hallak J E C, Dursun S M, Deakin J F W, Zuardi A W (2003) Effects of cannabidiol on (s)-ketamine-induced psychopathology in healthy volunteers. J Psychopharmacol *17*: A55

Carlini E A, Santos M, Claussen V, Bieniek D, Korte F (1970) Structure activity relationship of four tetrahydrocannabinols and the pharmacological activity of five semipurified extracts of Cannabis sativa. Psychopharmacologia (Berl) *18*: 82–93

Consroe P, Laguna J, Allender J, Snider S, Ster L, Sandyr R, Kennedy K, Schram K (1991) Controlled clinical trial of cannabidiol in Huntington's disease. Pharmacol Biochem Behav *40*: 701–708

Cunha J M, Carlini E A, Pereira A E, Ramos Ol, Pimentel C, Gagliardi R, Sanvito Wl, Lander N, Mechoulam R (1980) Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology *21*: 175–185

Del-Ben C M, Vilela J A A, Crippa J A S, Hallak J E C, Labate C M, Zuardi A W (2001) Confiabilidade teste-reteste da Entrevista Clínica Estruturada para o DSM-IV – Versão Clínica (SCID-CV) traduzida para o português. Rev Bras Psiquiatr *23* (3):156–159

D'Souza D C, Abi-Saab, Madonick S, Forselius-Bielen K, Doersch A, Braley G, Gueorguieva R, Krystal J H (2005) Delta-9-Tetrahydrocannabinol effects in schizophrenia: Implications for cognition, psychosis, and addiction, Biol Psychiatry *57*: 594–608

First M B, Spitzer R L, Gibbon M & Williams J B W (1997) Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), Clinician Version. American Psychiatric Press, Washington, DC

Giuffrida A, Leweke F M, Gerth C W, Schreiber D, Koethe D, Faulhaber J, Klosterkotter J, Piomelli D (2004) Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. Neuropsychopharmacology. *29* (11): 2108–2114

Grlie L (1976) A comparative study on some chemical and biological characteristics of various samples of cannabis resin. Bull. Narcot. *14*: 37–46

Guimarães V M C, Zuardi A W, Del Bel E A, Guimarães F S (2004) Cannabidiol increases Fos expression in the nucleus accumbens but not in the dorsal striatum. Life Sciences *75*: 633–638

Karniol I G, Carlini E A (1973) Pharmacological interaction between cannabidiol and delta 9-tetrahydrocannabinol. Psychopharmacologia (Berl) *33*: 53–70

Kay S R, Fiszbein A, Opler L A (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull *13*: 261–276

Leweke F M, Giuffrida A, Wurster U, Emrich H M, Piomelli D (1999) Elevated endogenous cannabinoids in schizophrenia. Neuroreport. *10*: 1665–1669

Leweke F M, Schneider U, Radwan M, Schmidt E, Emrich H M (2000) Different effects of nabilone and cannabidiol on binocular depth inversion in Man. Pharmacol Biochem Behav *66*: 175–181

Lingjaerde O, Ahlfors U G, Bech P, Dencker S J, Elgen K (1987) The UKU side effects rating scale – a new comprehensive rating-scale for psychotropic-drugs and a cross-sectional study of side-effects in neuroleptic-treated patients Acta Psychiatrica Scandinavica *76*: (Suppl. 334): 81–94

McArdle K, Mackie P, Pertwee R, Guy G, Whittle B, Hawksworth G (2001) Selective inhibition of Delta(9)-tetrahydrocannabinol metabolite formation by cannabidiol in vitro. Toxicology *168*: 133–134

Mechoulam R, Parker L A, Gallily R (2002) Cannabidiol: an overview of some pharmacological aspects. J Clin Pharmacol *42* (Suppl. 11): 11S–19S

Meltzer H Y, Arvanitis L, Bauer D, Rein W (2004) Meta-trial Study Group: Placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and schizoaffective disorder. Am J Psychiatry. *161*: 975–984

Moreira F A and Guimarães F S (2005) Cannabidiol inhibits the hyperlocomotion induced by psychotomimetic drugs in mice. European Journal of Pharmacology *512*: 199–205

National Institute for Clinical Excellence (NICE) guidelines (2002) Schizophrenia core interventions in the treatment and management of schizophrenia in primary and secondary care. www.nice.org.uk/pdf/CGINICEguideline.pdf

National Institute of Mental Health (1976) CGI – Clinical Global Impression. In Guy W (ed.) ECDEU Assessment Manual of Psychopharmacology (revised). NIMH, Rockville, MD pp. 534–537

Overall J E, Gorham D R (1962) The brief psychiatric rating scale. Psycol Rep *10*: 799–812

Simpson G, Angus J Á (1970) A rating scale for extrapyramidal side effects. Acta Psychiatr Scand *45* (Suppl. 212): 11–19

Smit F, Bolier L, Cuijpers P (2004) Cannabis use and the risk of later schizophrenia: a review. Addiction *99*: 425–430

Vessoni A L N (1993) Adaptação e estudo da confiabilidade da escala de avaliação das síndromes positiva e negativa para a esquizofrenia no Brasil. Dissertação de Mestrado. Escola Paulista de Medicina

Zuardi A W, Guimarães F S, Moreira A C (1993) Effect of cannabidiol on plasma prolactin, growth hormone and cortisol in human volunteers. Brazilian J Med Biol Res *26*: 213–217

Zuardi A W, Rodrigues J A, Cunha J M (1991) Effects of cannabidiol in animal models predictive of antipsychotic activity. Psychopharmacology *104*: 260–264

Zuardi A W, Guimarães F S, Guimarães V M, Del Bel E A (2002) Cannabidiol: possible therapeutic application. In Grotenhermen, F, Russo, E (eds) Cannabis and Cannabinoids: Pharmacology, Toxicology and Therapeutic Potential. The Haworth Press Inc., New York, pp. 359–369

Zuardi A W, Morais S L, Guimarães F S, Mechoulam R (1995) Anti-psychotic effect of cannabidiol. J Clin Psychiatry *56*: 485–486

Zuardi A W, Shirakawa I, Finkelfarb E, Karniol I (1982) Action of cannabidiol on the anxiety and other effects produced by Δ^9-THC in normal subjects. Psychopharmacology *76*: 245–250

Zuardi A W, Loureiro S R, Rodrigues C R C, Correa A J, Glock S S (1994) A study of the reliability, validity and factor structure of a Portuguese translation and adaptation of the modified Brief Psychiatric Rating Scale. Revista ABP-APAL *16*: 63–68