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Spontaneous, anecdotal, retrospective, open-label study on the efficacy, safety and tolerability of cannabis galenical preparation (Bedrocan)

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Abstract

Objectives Our main aim was to investigate the short-term therapeutic effects, safety/tolerability and potential side effects of the cannabis galenical preparation (Bedrocan) in patients with a range of chronic conditions unresponsive to other treatments.

Methods In this retrospective, 'compassionate use', observational, open-label study, 20 patients (age 18–80 years) who had appealed to our 'Second Opinion Medical Consulting Network' (Modena, Italy), were instructed to take sublingually the galenical oil twice a day for 3 months of treatment. The usual starting dose was low (0.5 ml/day) and gradually titrated upward to the highest recommended dose (1 ml/day). Tolerability and adverse effects were assessed at baseline and monthly thereafter during the treatment period through direct contact (email or telephone) or visit if required. Patients' quality of life was evaluated at baseline and 3 months using the medical outcome short-form health survey questionnaire (SF-36).

Key findings From baseline to 6 months post-treatment, SF-36 scores showed: reductions in total pain ($P < 0.03$); improvements in the physical component ($P < 0.02$); vitality ($P < 0.03$); social role functioning ($P < 0.02$); and general health state ($P < 0.02$). No changes in role limitations ($P = 0.02$) due to emotional state (e.g. panic, depression, mood alteration) were reported. Monthly reports of psychoactive adverse effects showed significant insomnia reduction ($P < 0.03$) and improvement in mood ($P < 0.03$) and concentration ($P < 0.01$).

Conclusions These data suggest that a cannabis galenical preparation may be therapeutically effective and safe for the symptomatic treatment of some chronic diseases. Further studies on the efficacy of cannabis as well as cannabinoid system involvement in the pathophysiology are warranted.

Introduction

In 2011, cannabis-based treatments are approved in many European countries and represent an alternative therapeutic strategy for a wide range of chronic diseases, including spasticity associated with multiple sclerosis (MS), neuropathic pain,[1–3] pain resistant to corticosteroids or opioids[3] and side effects related to chemotherapy (e.g. nausea, vomiting, cachexia and anorexia) in oncologic or acquired immunodeficiency syndrome (AIDS) patients,[4,5] glaucoma resistant to conventional therapies,[6] facial and body movements in Gilles de la Tourette Syndrome.[7]

Cannabis contains more than 60 endogenous and exogenous compounds defined as cannabinoids (CBs) that act primarily through specific cannabinoid receptors: CB_1 and CB_2 receptors. The CB_1 are distributed in the central nervous system and involved in learning, memory and cognitive processes, while the CB_2 receptors are

located in the peripheral nervous system, including brainstem, cerebellum, microglia and the immune system.[8–15] In the past decade, preclinical studies and case reports have shown the therapeutic potential of two main CBs, delta-9-tetrahydrocannabinol acid (Δ^9-THCA) and cannabidiol (CBD) against a range of pathologies.[16,17] Δ^9-THCA is the main constituent in raw cannabis, it converts to Δ^9-THC when heated over a certain temperature, binding at both CB receptors. It is responsible for the psychoactive effects, such as impaired memory and cognitive processing (mediated by CB_1), but acts also on other targets, such as ionic channels and enzymes with potential analgesic, anti-emetic and antikinetosic properties, stimulating muscle relaxation, appetite and acting as an intraocular hypotensive agent.[18–20] CBD is not psychoactive as it has lower CB_1 and CB_2 receptor affinity compared to Δ^9-THC and has anti-epileptic, anti-inflammatory, anti-emetic, muscle relaxing, anxiolytic, neuroprotective and antipsychotic activity and (when co-administered) may reduce the psychoactive effects of Δ^9-THC (euphoria, anxiety), antagonizing CB_1 receptor at low nanomolar concentrations.[21–24] There are several commercially available cannabis galenical products (Table 1) and synthetic cannabinoids (Table 2), approved by European Pharmacopeia and/or US Food and Drug Administration.[25,26]

Italian physicians can legally prescribe different cannabis galenical products including oral products (infusion, sublingual oil, capsule), inhalations (vaporizing) or oromucosal preparations (spray) to users registered on a Ministry of Health database[27] 'when other available medications have proven to be ineffective or inadequate to the therapeutic needs of the patient'.[28] Eligible indications include chronic pain conditions, neuropathic pain, as well as spasticity, cachexia and anorexia among AIDS and cancer patients, ocular hypertension in glaucoma, spasms in Tourette syndrome, some types of epilepsy, fibromyalgia and other severe diseases (Official journal n.279, 30-11-2015, Rome, Italy). The most prescribed preparations are FM2 and Bedrocan (Table 1).

Several studies have shown that cannabinoids pharmacokinetics differ and are dependent on the dose and administration schedule.[29,30] An oral Δ^9-THC bioavailability has a lower bioavailability (10–20%), compared with intravenous administration, probably due to several factors, including low hydrosolubility of the molecule, degradation by stomach acid and/or bio-transformation to metabolites during first passage through the liver.[31] Δ^9-THC is converted in the liver to its equipotent and longer-acting active metabolite 11-Hydroxy-Δ^9-tetrahydrocannabinol (11-OH-Δ^9-THC). After oral ingestion, these metabolites are present in the plasma at approximately equal concentrations.[32]

The safety and efficacy of cannabis therapy has not been completely explored, and this is a barrier to its therapeutic use.[33] Several randomized controlled trials of smoked cannabis have shown efficacy in chronic pain and spasticity,[34–36] but with the bias of short-term treatment period (1–3 weeks) and small sample sizes (n = 20–60 participants); safety and effectiveness of oral galenical products have been studied with a follow-up to 1 year in patients with MS.[37,38]

However, despite the growing interest in the medicinal use of cannabis, there is a paucity of preclinical and clinical trials data. Thus, we conducted a prospective analysis of a case series of patients in Italy treated with a cannabis galenical preparation (Bedrocan) in accordance with the above regulations. Our main aim was to evaluate the therapeutic effect, determine the correct dosage, assess safety/tolerability and identify side effects.

Methods

We enrolled 20 patients, from Northern Italy, with variable pattern of persistent, severe and chronic symptoms,

Table 1 Description of commercially available cannabis galenical products with standardized Δ^9-THC (known also as dronabinol) and several CBD concentrations. All the composts are free of pesticides and heavy metal (<0.5 ppm lead, <0.1 ppm mercury and <0.1 ppm cadmium), with confirmed microbiological purity, absence of aflatoxins, according to EU pharmacopoeia

Type cannabinoid product	Variety cannabis	Concentration Δ^9-THC (%)	Concentration CBD (%)	Therapeutic indications	Reference
Bedrocan	*C. sativa*	22	<1	Analgesic and antidepressant effect, muscle relaxant and sedative effects	[57–60]
Bedrobinol	*C. sativa*	13.5	<1	Analgesic effect	[57, 58]
Bediol	*C. sativa*	6.5	8	Anti-anxiety effect, insomnia treatment, anti-inflammatory effect	[57, 58]
Bedica	*C. indica*	14	<1	Pain treatment	[57, 58]
Bedrolite	*C. sativa*	0.4	9	Anti-anxiety effect, insomnia treatment	[57, 58]
FM2	*C. sativa*	5–8	7–12	Analgesic, muscle relaxant and antidepressant effect	[57, 58]

Table 2 Description of three cannabinoid products derived from isolated synthetics

Type cannabinoid product	Composition	Company	Therapeutic indications	Reference
Marinol	Synthetic form of oral Δ^9-THC (2.5–5 mg/each capsule)	Unimed Pharmaceuticals Inc, Marietta, USA	Reduction in nausea associated with chemotherapy, Appetite stimulation in HIV/AIDS	[61]
Nabilone (marketed as Cesamet)	Synthetic dimethylheptyl analogue of Δ^9-THC (0.25–1 mg/each capsule)	Valeant Pharmaceuticals Int., New Jersey, USA	Anti-emetic effect in chemotherapy, Analgesic effect in neuropathic pain	[62]
Sativex	Oromucosal spray of a formulated extract of the *C. sativa* plant that contains Δ^9-THC and CBD in a 1 : 1 ratio	GW Pharmaceuticals, Cambridge, USA	Reduction in central neuropathic pain in multiple sclerosis, Reduction in cancer pain unresponsive to opioid therapy	[63]

who had successfully appealed to our 'Second Opinion Medical Consulting Network', to receive galenical cannabis. The Second Opinion Medical Network is a consultation referral web and Medical Office System comprising a panel of specialists, to whom any patient affected by any disease or syndrome and not adequately satisfied by the diagnosis or therapy can apply for an individual clinical audit.[39–43]

Inclusion criteria were as follows: (1) aged 18 years or older, (2) prescribed a cannabis galenical preparation and (3) suffering from severe/chronic symptoms for at least 6 months and seeking an effective, adequate therapy. Exclusion criteria were as follows: (1) current treatment with antidepressant and anxiolytic therapy, (2) history of psychotic disorder, (3) presence of significant cardiac or pulmonary disease and (4) pregnant or breastfeeding women.

Following the Italian law (N.38 of 15 March 2010) on the medical use of cannabis, all participants were identified by alphanumeric code and registered in a database to evaluate specific clinical data.[44] The patients were recruited by a researcher, visited and informed during a personal interview, gave their permission, signed an informed consent previously approved by the Local Institutional Review Board under the Helsinki Declaration (Table 3). The Second Opinion Medical Centre confirmed that formal ethical approval for this 'anecdotal, retrospective study "compassionate use" observational study' was not required.

As part of the standard regimen, patients were instructed to take 5 g Bedrocan in 50 ml of olive oil, dispensed by the galenical pharmacy (Pharmacy Dr. Ternelli, Via GB Venturi, Bibbiano, Reggio Emilia, Italy), sublingually twice a day for 3 months, beginning with 0.5 ml/day (15 drops) and titrating upwards to the recommended maximum dose of 1 ml/day (30 drops) followed by a reduction down to 0.5 ml/day (15 drops) at week 12 (Table 4). The tolerability and safety of this dosage had been previously confirmed.[45]

Table 3 Patient's characteristics

No. of patients	20
Gender	8 men and 12 women
Mean age	40.7 aa
Mean weight	55.5 kg
Mean height	1.61 cm
Diseases	Neurologic diseases (n = 4) Cancer (n = 4) Fibromyalgia (n = 3) Multiple sclerosis (n = 3) Dystrophy syndrome (n = 1) Insomnia (n = 3) Chronic obstructive pulmonary disease (COPD) (n = 1) Hernia (n = 1)
Type galenical oil preparation	Bedrocan

Tolerability and adverse effects (including hypertension, palpitation or tachycardia, weight loss or gain, etc.) were assessed monthly during the treatment period through email, telephone or visit if required. Quality of life (QOL) assessment was performed using the Short Form-36 (SF-36). It measures health-related QOL in eight dimensions: vitality, general health perceptions, physical functioning, physical role functioning, emotional role functioning, social role functioning, bodily pain and mental health (Figure S1). Each scale is scored using norm-based methods, with percentage scores ranging from 0% (lowest or worst response) to 100% (highest or best possible response).[46]

These scores were compared, for each patient, at baseline and monthly during the 3-month treatment period and at a 6-month follow-up for cannabis use behaviours, symptoms worsening and neurocognitive performance.

Table 4 Galenical oil preparation's dosage

Bedrocan dosage	
1st week	15 drops/day
2nd week	15 drops/day
3rd week	23 drops/day
4th week	23 drops/day
5th week	30 drops/day
6th week	30 drops/day
7th week	30 drops/day
8th week	30 drops/day
9th week	23 drops/day
10th week	23 drops/day
11th week	15 drops/day
12th week	15 drops/day

We evaluated the onset of 'serious adverse event', defined as 'any untoward medical occurrence that requires admission to hospital, causes congenital malformation, results in persistent or significant disability or incapacity, that is life-threatening or that results in death', according to the definitions recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (1994, Geneva, Switzerland).[47]

Data were entered into an HQCD database by a researcher and analysed using the R software, version 3.1.2 (2015, Vienna, Austria).[48] Statistical tests included the Mann–Whitney test (continuous variables not normally distributed) and the chi-squared test (categorical variables). A commonly used measure of linear correlation, the Pearson correlation coefficient, denoted by r, was reported. Statistical significance was set at a P value < 0.05.

Results

The demography of the participating patients is shown in Table 3 who were of average age 40 years and suffered from a range of chronic conditions. The Bedrocan was administered concomitantly with other therapy for five patients (Table 5).

All the patients completed the study. The main efficacy endpoints, as assessed by the monthly SF-36 questionnaire administered at the end of every month treatment, are reduction in bodily pain ($P < 0.03$), significant improvements in the physical role functioning score ($P < 0.02$), in vitality ($P < 0.03$), in social role functioning ($P < 0.02$) and in general health perceptions (Figures S1–S6). No changes in role limitations ($P = 0.02$) or emotional state (including anxiety, panic, paranoia, depression, mood alteration and altered perceptions etc.) between the first month of treatment and 6 months post-treatment were found (Figures S7 and S8). No adverse effects were reported. The patient with the Rett syndrome reported significant improvement in the control of epileptic seizures, reducing the number from 5 to 2 seizures weekly.

Table 5 Baseline pharmacological therapy administered in addition galenical treatment in five enrolled patients with cancer or neurological disease

No patients	Disease	Pharmacological therapy
2	Rett and epilepsy syndrome	Anti-epileptic drugs: • Lamotrigine
2	Cancer	Palliative care • Tramadol • Enalapril (for hypertension treatment) • Pantoprazole
1	Alzheimer syndrome	Palliative care • Donepezil

Monthly reports on potential psychoactive adverse effects confirmed significant insomnia reduction ($P < 0.03$), mood improvement ($P < 0.03$) and concentration improvement ($P < 0.01$) (Figures S9–S11). At 3 months, a quarter of the participants self-reported an improvement in mental concentration.

Somnolence was the sole self-reported adverse event in three patients during the first month of treatment, but noticed a complete resolution of this symptom over time. During the study period, no serious adverse effects, including respiratory and thoracic disorders (dyspnoea, pneumonia), gastrointestinal disorders (vomiting, diarrhoea, abdominal pain), nervous system disorders (convulsions, dizziness), renal and urinary disorders (urinary tract infection, haematuria) and psychiatric disorders occurred.

Discussion

The findings show that short-term Bedrocan administration was well tolerated and effective in reducing symptoms including pain, stiffness and muscle spams, when administered concomitantly with or without other therapy.

Participants reported an improvement of cognitive function and no psychoactive adverse events potentially connected to cannabinoids, such as euphoria, sleepiness, confusion, short-term memory or concentration loss. Indeed, significant improvements in sleep quality and mood scores are noted in the majority of patients (80%).

A strength of this study is a well-defined and standardized treatment protocol and the inclusion of 'real-world' patients. Limitations include the uncontrolled and retrospective design study, the small clinically heterogeneous cohort and use of the self-administered subjective SF-36 as the main outcome measure.

The safety and tolerability of Bedrocan may be due to oral administration route and type of galenical preparation that contains lower levels of Δ^9-THC (0.18–0.2 mg/ml) and higher levels of Δ^9-THCA (0.26–0.3 mg/ml) (with no psychoactive activity).[49] However, the high concentration of CBG (16 mg/g), a phytocannabinoid known to be an α-2 adrenoreceptor and the serotonin 1A receptor (5- HT1A) agonist, and terpenoid myrcene (5 mg/g) in this formulation could explain the analgesic and myorelaxant effect recorded in most patients (75%). Also, the improvement of neurologic symptoms (improvement in mood and concentration) might be due to this selected formula containing Δ^9-THC and CBD at the ratio of 22 : 1 that could mitigate the beta-amyloid peptide (Aβ) level-evoked neuroinflammatory and neurodegenerative responses.[50] A recent study in vitro evidenced that low doses of Δ^9-THC solution (100 μl at 2× concentrations in each well) added in mouse neuroblastoma cell line (N2a/AβPPswe cells) lowed the Aβ level, the total and phosphorylated GSK-3β levels (protein kinase that has a key role in the pathogenesis of both sporadic and familial AD).[51] Additionally, low doses of Δ^9-THC, when combined with melatonin, could enhance mitochondria function, not inhibiting melatonin's action that is a potential therapeutic for AD.

The significant reduction in pain and stiffness in FM patient could be due to the modulating action of CB receptors in the dysfunctions of the stress system and, particularly, the hypothalamic–pituitary–adrenal axis (HPA axis).[52]

Furthermore the relief of muscle spams and insomnia, common symptoms related to MS could be associated to anti-inflammatory activity of CBD by decreasing transmigration of blood leucocytes and by downregulating expression of VCAM-1, chemokines (CCL2 and CCL5) and pro-inflammatory cytokine IL-1β, as well as by attenuating activation of microglia.[53]

Several vitro/vivo studies showed that CBD in tumour cell lines (e.g. MM cells and A549, H460 lung cancer cells) xenografted in nude mice, inhibited the cell proliferation by blocking cell cycle and inducing apoptotic cell death, and it enhanced the activity of pharmacological therapy.[54,55] For instance, Ward *et al.*[56] evidenced the efficacy of CBD, in breast cancer cells, to downregulate the expression of inhibitor differentiation/DNA binding 1 (Id1), that has a critical role in breast cancer lung metastasis, and to enhance the activity of paclitaxel (Taxol), well-known chemotherapeutic drug.

Conclusions

The findings suggested that patients affected by chronic long-standing (months or years) advanced disease, who had not responded to standard treatment, had improved symptoms when they were treated with Bedrocan. The galenical treatment contributed not only to decreased pain but also to restored physical function in this cohort after 3 months and improvement in overall QOL. There is now a need to confirm these findings in a robust double-blind standardized clinical trials, with a more homogenous clinical group such as cancer or fibromyalgia.

Declarations

Conflict of interest

The authors declared that they have no competing interests and certified that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript. The authors contributed equally to this work.

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Author contributions

The authors have adhered to the ICMJE definition of authorship. The specific contribution is described as following: BP design study, conclusions. CL data collection. MV data elaboration, description of results. All Authors state that they had complete access to the study data that support the publication.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Pain scores before and after galenical preparation' treatment.

Figure S2. Physical functioning level scores before and after galenical preparation' treatment.

Figure S3. Role limitations due to physical health scores before and after galenical preparation' treatment.

Figure S4. Energy scores before and after galenical preparation' treatment.

Figure S5. Social functioning scores before and after galenical preparation' treatment.

Figure S6. General health scores before and after galenical preparation' treatment.

Figure S7. Role limitations due to emotional problems scores before and after galenical preparation' treatment.

Figure S8. Emotional well-being scores before and after galenical preparation' treatment.

Figure S9. Insomnia scores before and after galenical preparation' treatment.

Figure S10. Mood improvement scores before and after galenical preparation' treatment.

Figure S11. Concentrations improvement scores before and after galenical preparation' treatment.