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Letter to the Editor

The challenge of clinical application of FM2 cannabis oil produced in Italy for the treatment of neuropathic pain

Dear Editor,

Cannabinoids mainly contained in the female cannabis flowering tops has proved useful in neuropathic pain modulation inhibiting neuronal transmission in pain pathways though pronounced anti-nociceptive effects[1].

Although most studies up to date have been performed involving a limited number of participants, a series of methodological limitations (e.g. lack of standardized administered preparations or dosages), and an unclear description of the long-term effects, a recent metanalysis study has however shown conclusive and substantial evidence of medical cannabis efficacy for the treatment of patients with chronic neuropathic pain and multiple sclerosis spasticity symptoms[2]. Conversely, the evidence of efficacy on other types of pain is still limited or insufficient[2-4].

The combination of the psychoactive cannabis alkaloid 9-tetrahydrocannabinol (THC) with the non-psychotropic alkaloid cannabidiol (CBD), together with their non-psychoactive carboxylated forms – tetrahydrocannabinolic acid and cannabidiolic acid – has demonstrated a greater activity than THC alone in treating both neuropathic pain and spasticity in multiple sclerosis[5-8]. As heat, oxygen and light progressively decarboxylate the two acidic compounds into THC and CBD, the storage of the flowering tops in closed packets kept in the dark, possibly in a nitrogen atmosphere, is advised. The heating of the flowering tops at a high temperature should also be avoided when preparing cannabis tea or oil products for oral administration[9,10].

From November 2015, the Military Pharmaceutical Chemical Works of Florence, Italy, started autonomous cultivation and production of medical cannabis, authorized by a Decree of the Italian Ministry of Health[11]. From January 2017, the batches of the so-called Cannabis FM2, with standardized amount of 6.5% THC and 8% CBD, came into the market.

The Italian National Institute of Health, committed to evaluate cannabinoid concentration and their stability in cannabis flowering tops, cannabis tea and oil, have recently demonstrated the poor extraction efficiency of water for cannabinoids required for cannabis medical action together with the extremely short stability (e.g. two days) of the same cannabinoids in aqueous preparations. This has pushed towards the preparation of cannabis oil with a maximum extraction yield and a minimum active compound degradation up to one year[9,10].

Indeed, the amount of cannabinoids in Italian FM2 cannabis flowering tops grown at a fixed temperature with light-dark cycles, in oil prepared with a standardized procedure, shows within a year only slight changes, which do not affect therapeutic continuity in treated individuals, therefore assuring a homogeneous product of defined stability[9]. Thus, the cannabis oil prepared by FM2 cannabis flowering tops seems to suit perfectly the multicentre, double blind, placebo controlled clinical trials aimed to definitively assess whether cannabis or cannabinoids used for therapeutic purposes are an effective or ineffective treatment.

The prime unmet need is to establish a therapeutic range of THC/CBD concentrations effective in the treatment of neuropathic pain and associated with an acceptable safety profile. In fact, both in a national and international context, there is an enormous discrepancy between daily-administered dosages and administration times even when only using cannabis oil (Tables I-III).

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In this concern, the main goal should include a study on safety and preliminary efficacy of a minimum of three doses of FM2 oil for sublingual administration with the possibility of increasing the dose to intermediate or high, eventually dividing in two daily administrations. Pharmacokinetic and pharmacodynamics profile of FM2 oil should also be recorded. The treatment should last at least a week to titrate the dose. At the end of this phase, one or more "recommended doses" should be defined to start a second phase. At that point the efficacy of FM2 administered daily, detected in the previous phase, should be evaluated in patients with chronic neuropathic pain refractory to standard therapies by the

Table I. Type of administration and daily doses of medical cannabis for neuropathic pain in the National context (Italian Regions). * Infusion of Flowering tops.

Italian Regions	Type of administration of cannabis flowering tops	Number of administration/die	THC/CBD Dosage mg
Liguria	Vaporization	2	18/25
	Vaporization	1	60/84
	Oral*or vaporization	1	84/100
	Not reported	1	90/110
Piedmont	Oral*or vaporization	1	30/30
Marche	Oral* or vaporization	2	120/150
Lazio	Oral* or vaporization	1	19/20
	Oral*	1	60/75
Tuscany	Not reported	1	15/18
Puglia	Not reported	1	30/30
	Oral*	2	180/220
Trentino-Alto Adige	Oral*	1	18/25

Table II. Type of administration and administration cycles of medical cannabis for neuropathic pain in the International context.

City and country	Type of administration of cannabis flowering tops	THC/CBD Dosage (mg)	References
Ramat Yishai (Israel)	Vaporization	15/20	12
Ottawa (Canada)	Vaporization	90/130	13
	Vaporization	75/120	
	Vaporization	5/50	
	Vaporization	90/130	

Table III. Type of administration and daily doses of medical cannabis for neuropathic pain in the National context (patients treated with cannabis oil since January 2018 and reported to the National Observatory on medical cannabis).

Patients	Type of administration of Cannabis oil (as reported in the patient form)	Number of administration/die	THC/CBD Dosage (mg)
1	80 drops	2	19.2/24.8
2	40 drops	Not reported	4.8/6.2
3	80 drops	Not reported	9.6/12.4
4	40 drops	Not reported	4.8/6.2
5	40 drops	Not reported	4.8/6.2
6	80 drops	2	19.2/24.8
7	80 drops	2	19.2/24.8
8	90 mg THC	1	90.0/116.3
9	30 drops	Not reported	3.6/4.6
10	80 drops	Not reported	9.6/12.4
11	10 mg THC	1	10.0/12.9
12	20 mg THC	1	20.0/28.8
13	20 mg THC	1	20.0/28.8
14	28 mg THC	1	28.0/36.2
15	20 mg THC	1	20.0/28.8
16	20 mg THC	1	20.0/28.8
17	10 mg THC	1	10.0/12.9

administering of oil as an add-on to the basic analgesic treatment for a minimum of one month. The primary end point to be estimated should be an eventual decrease in neuropathic pain using a defined neuropathy pain scale (e.g. clinically significant reduction of equal or more than 30% pain) together with the recording of general life quality, time of pain disappearance and eventual adverse events.

We believe that these are the main challenges of the clinical applications of FM2 cannabis oil and once addressed, there will be additional evidence and a clear understanding of the indications and the dosing of medical cannabis, thereby avoiding the administration of cannabis oil by doctors who, without a scientifically supported rationale, could determine not only an inefficient treatment but also cause an eventual toxicity[14].

Conflict of interest

The authors declare no conflicts of interest.

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