

# Short-Term Efficacy of CBD-Enriched Hemp Oil in Girls with Dysautonomic Syndrome after Human Papillomavirus Vaccination

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**ABSTRACT:** **Background:** Cannabidiol (CBD)-based treatments for several diseases, including Tourette's syndrome, multiple sclerosis, epilepsy, movement disorders and glaucoma, are proving to be beneficial and the scientific clinical background of the drug is continuously evolving.

**Objectives:** To investigate the short-term effect of CBD-enriched hemp oil for relieving symptoms and improving the life quality (QOL) in young girls with adverse drug effects (ADRs) following human papillomavirus (HPV) vaccine.

**Methods:** In this spontaneous spontaneous anecdotal, retrospective, "compassionate-use," observational, open-label study, 12 females (age 12–24 years) with severe somatoform and dysautonomic syndrome following HPV vaccination were given sublingual CBD-rich hemp oil drops, 25 mg/kg per day supplemented by 2–5 mg/ml CBD once a week until a maximum dose of 150 mg/ml CBD per day was reached over a 3 month period. Patients' quality of life was evaluated using the medical outcome short-form health survey questionnaire (SF-36).

**Results:** Two patients dropped out due to iatrogenic adverse events and another two patients stopped the treatment early due to lack of any improvement. SF-36 showed significant benefits in the physical component score ( $P < 0.02$ ), vitality ( $P < 0.03$ ) and social role functioning ( $P < 0.02$ ) after the treatment. The administration of hemp oil also significantly reduced body pain according to the SF-36 assessment. No significant differences from the start of treatment to several months post-treatment were detected in role limitations due to emotional reactions ( $P = 0.02$ ).

**Conclusions:** This study demonstrated the safety and tolerability of CBD-rich hemp oil and the primary efficacy endpoint. Randomized controlled trials are warranted to characterize the safety profile and efficacy of this compound.

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**KEY WORDS:** hemp oil, cannabidiol (CBD), adverse event, vaccine, human papillomavirus (HPV)

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**C***annabis sativa* plant derivatives have long been used in folk medicine as symptomatic treatment for many disorders, including anorexia and pain [1]. Cannabis contains more than 80 phytocannabinoids, but little is known about the potential therapeutic effects of most of these molecules. The major neuroactive components are  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) and cannabidiol (CBD).

$\Delta^9$ -THC activates the endocannabinoid system, a widespread network of G protein-coupled cannabinoid (CB) receptors, synthetic and degradative enzymes, and transporters including anandamide and 2-arachidonoylglycerol, CB1 and CB2 endogenous ligands [2]. In the central nervous system,  $\Delta^9$ -THC influences synaptic communication and modulates eating, anxiety, learning and memory, growth and development. To exert its effects this compound binds to two G protein-coupled cell membrane receptors – cannabinoid type 1 (CB1) and type 2 (CB2) receptors that are found primarily in the brain and in immune and hematopoietic cells, respectively [3]. The potential medical use of whole-plant cannabis extracts is limited by the psychoactive properties and the adverse effects associated with long-term  $\Delta^9$ -THC use [4].

Unlike  $\Delta^9$ -THC, CBD is a multi-target drug: it does not activate CB1 and CB2 receptors, which likely accounts for its lack of psychotropic activity, but it interacts with many other, non-endocannabinoid signaling systems. CBD is a blocker of the equilibrative nucleoside transporter (ENT), the orphan G protein-coupled receptor GPR55, and the transient receptor potential of melastatin type 8 (TRPM8) channel. Conversely, CBD enhances the activity of the 5-HT<sub>1a</sub> receptor, the  $\alpha 3$  and  $\alpha 1$  glycine receptors and the transient receptor potential of ankyrin type 1 (TRPA1) channel, and has a bidirectional effect on intracellular calcium. At higher micromolar concentrations, CBD activates the nuclear peroxisome proliferator-activated receptor- $\gamma$  and the transient receptor potential of vanilloid type 1 (TRPV1) and 2 (TRPV2) channels, also inhibiting cellular uptake and fatty acid amide hydrolase-catalyzed degradation of anandamide [5].

CBD is metabolized extensively by the liver where it is hydroxylated to 7-OH-CBD by P450 enzymes, predominantly by the CYP3A (2/4) and CYP2C (8/9/19) families of isozymes. This metabolite is then further metabolized in the liver, and the resulting metabolites are excreted in the feces and, to a lesser extent, in the urine. The half-life of CBD in humans is estimated to be 18–32 hours, and following single-dose administration in chronic cannabis users the clearance was found to be 960–1560 ml/min [6]. In the last decade several clinical trials of CBD safety showed good tolerance across a wide dosage range. No significant adverse events affecting the central nervous system, or effects on vital signs or mood were

observed with doses of up to 1500 mg/day (p.o.) or 30 mg (i.v.) by both acute and chronic administration [7].

Clinical reports of the 25th Annual Symposium of the International Cannabinoid Research Society (2015) emphasize the therapeutic effect of CBD for kidney fibrosis and inflammation, metabolic syndrome, overweight and obesity, anorexia-cachexia syndrome, and amelioration of osteoarthritic and other musculoskeletal conditions [8]. The common mild or moderate adverse events reported include oral pain, oral mucosal disorder, dry mouth, dizziness, diarrhea, nausea, fatigue, headache, and somnolence, and are likely due to  $\Delta^9$ -THC, which is the CBD component that has almost no side effects. The adverse effects that do occur, rarely (such as somnolence), usually are of low intensity.

To date, no clinical trials have been undertaken to study the efficacy of the non-psychoactive CBD for treating medical conditions such as Gulf War syndrome, fibromyalgia, macrophagic myofasciitis, sick building syndrome, and a group of autoimmune/inflammatory adjuvant-induced conditions (ASIA syndrome), characterized mainly by headache, insomnia, muscle weakness, chronic fatigue, cognitive problems and neuropathic pain. The common feature of these clinical conditions is previous exposure to an external stimulus (including vaccines) that triggers an undefined immune mediated response elicited by its adjuvant properties [9]. Indeed, severe and persistent neurological and/or psychiatric symptoms, defined as adverse drug reactions (ADRs), arose also in young girls after HPV vaccination [10]. Due to the absence of a safe and effective therapy for these girls who were living with their families and having to deal with difficult conditions (such as emotional instability, social problems as well as school obligations), and suspecting that an endogenous cannabinoid network imbalance might be responsible for some of the described symptoms, we selected a natural therapeutic approach based on CBD-enriched hemp oil over a 3 month period in our Italian cohort.

**Table 1A.** Patients' characteristics

No. of patients	21
Mean age	16.7 yrs
Mean weight	56.3 kg
Mean height	162.3 cm
HPV vaccine type	Gardasil® (Merck&Co Inc, USA) (n = 10) Cervarix® (GSK, England) (n = 11)
No. of doses	One dose (n = 4) Two doses (n = 8) Three doses (n = 9)

**Table 1B.** ASIA diagnostic criteria in our case series (n =12)

Patients	Type of HPV vaccine	Major criteria	Minor criteria	Clinical manifestation
#1	Gardasil® (2 doses)	Headache, epileptic seizures, chronic fatigue syndrome (CFS), concentration problems, memory loss	Autoantibodies (anti-VCA IgG, EBNA IgG)	Drug-resistant epilepsy
#2	Cervarix® (1 dose)	Headache, CFS, concentration problems, memory loss	Autoantibodies (anti-VCA IgG, EBNA IgG)	Diabetes mellitus type 1
#3	Gardasil® (2 doses)	Muscle weakness, dry mouth, CFS, concentration problems, memory loss	Autoantibodies (AbTPO, Anti-VCA IgG)	Diabetes mellitus type 1
#4	Gardasil® (3 doses)	Headache, muscle weakness, skin rash, cognitive impairment, CFS	Autoantibodies (anti-VCA IgG)	Fibromyalgia
#5	Cervarix® (2 doses)	Muscle weakness	–	Optic neuritis
#6	Cervarix® (3 doses)	Headache, arthralgia, cognitive impairment, muscle weakness, CFS	Autoantibodies (anti-VCA IgG)	Fibromyalgia
#7	Cervarix® (2 doses)	Arthralgia, muscle weakness, recurrent syncope, asthenia	Autoantibodies (anti-VCA IgG)	Fibromyalgia
#8	Gardasil® (2 doses)	Nausea, asthenia, insomnia, recurrent syncope, abdominal pain	Autoantibodies (anti-VCA IgG, Anti-VCA IgM)	Fibromyalgia, Raynaud's syndrome
#9	Cervarix® (3 doses)	Amenorrhea, abdominal pain, stomach pain	–	–
#10	Gardasil® (3 doses)	Fever, myalgia, myositis, cognitive impairment, CFS	Autoantibodies (Anti-VCA IgG)	Fibromyalgia
#11	Cervarix® (3 doses)	Myalgia, headache, insomnia, CFS	Autoantibodies (Anti-VCA IgG, Anti-EBNA IgG)	Fibromyalgia
#12	Cervarix® (1 dose)	Headache, CFS, concentration problems, memory loss	Autoantibodies (Anti-VCA IgM and IgG)	Fibromyalgia

## PATIENTS AND METHODS

Our study group recruited 21 females aged 12–24 years affected by a clinical syndrome (asthenia, severe pain, skin rashes, sinus tachycardia, amenorrhea, optic neuritis, headache, sleep disturbances) and high titers of autoantibodies such as anti-Epstein-Barr virus (EBV), anti-nuclear antibody (ANA), and HLA. The symptoms appeared in the first hours after the first vaccine injection and worsened with the subsequent challenges in those girls incautiously resubmitted to the trial. The families consulted our “Second Opinion Medical Network” (Modena, Italy) seeking a proper diagnosis and especially an effective therapy for this syndrome, putatively part of the “ASIA syndrome” [Table 1A and B].

The Second Opinion Medical Network is a consultation referral web and Medical Office System recruiting a wide panel

of real-time available specialists, to whom any patient affected by any disease or syndrome and not satisfied with the diagnosis or therapy can apply for an individual clinical audit [11]. Due to the doctor-patient communication gap, most of the patients usually wander around the medical websites looking for proper answers to their health problems. However, this search often becomes compulsive and obsessive and is frequently ambiguous and frustrating. Palmieri et al. [12] describe this borderline or even pathological behavior as the “Web Babel Syndrome” – a psychological imbalance affecting young and elderly patients, especially those with multiple synchronous diseases who receive from their caregivers heterogeneous and misleading information or advice, including confused, contradictory statements and prescriptions [13]. To deal with this problem, the Second Opinion Network aims to be a useful “problem-solving” support revisiting each diagnostic and therapeutic step and properly re-addressing tailored treatments and prognoses, as well as preventing unnecessary investigational procedures and unhelpful and expensive medical and surgical interventions [14].

Considering that every previous attempted medical treatment had worsened the post-vaccination disease, we evaluated the impact of a possible modulation of the endocannabinoid network in a spontaneous anecdotal, retrospective, observational, open-label and “compassionate-use” study [10]. “Compassionate use” is a way to provide an investigational treatment to a patient who has a serious or life-threatening illness for which other pharmacological treatments have not been found effective, allowing the bona fide administration of compounds that have not undergone a clinical registration process [15].

In our study we adopted strictly selective patient inclusion criteria, such as the sudden emergence of clinical symptoms just a few hours after the first vaccine injection, followed by progressive disease within 20 days of the first, second or third HPV vaccination. The exclusion criteria were current treatment with cannabis-based therapy, or women who were pregnant or lactating.

The selected patients and their parents (for the younger patients) were briefed during a personal interview and signed an informed consent. The format explained that a safe nutraceutical hemp extract lacking any psychotropic effect and providing potential benefit for peripheral nerve iatrogenic disorders would be administered in a compassionate-use setting since the previous treatment attempts were not only unsuccessful but had even worsened the symptoms.

Of the 21 enrolled patients, 2 refused the treatment because their ASIA syndrome symptoms had progressively ameliorated with antioxidant and pain killer treatment and another 7 patients refused the treatment, opting for alternative therapies.

For our study, we used CBD-rich hemp oil manufactured, as a nutraceutical, by Elixinol™ (Broomfield, CO, USA) according to our specific formula prescription and whose

**Table 2.** Dosage of CBD-enriched hemp oil (1 drop = 5 mg/ml CBD)

CBD-rich oil dosage	
1th week	5 drops/day
2th week	10 drops/day
3th week	15 drops/day
4th week	20 drops/day
5th week	25 drops/day
6th–7th weeks	30 drops/day
8th week	25 drops/day
9th week	20 drops/day
10th week	15 drops/day
11th week	10 drops/day
12th week	5 drops/day

declared chemical composition had been previously verified on HPLC analysis by our chemical department.

All patients with ADRs following HPV vaccine received this hemp oil administered sublingually and added to the possible baseline drug regimen in some patients. One bottle of hemp oil contained 10 ml hemp oil with 1500 mg (15%) of CBD; later one drop contained 5 mg CBD. The dosage for all the patients was standardized: 25 mg/ml per day divided into twice-daily dosages, then supplemented by 2–5 mg/ml CBD once a week until intolerance or a maximum dose of 150 mg/ml CBD per day was reached [Table 2].

Tolerability and adverse effects were assessed weekly during the treatment period through direct contact (email or telephone) with the patients or their parents. Quality of life (QOL) assessment was performed using the Short Form-36 (SF-36) health survey questionnaire that measures health-related quality of life in eight domains: vitality, general health perceptions, physical functioning, physical role functioning, emotional role functioning, social role functioning, bodily pain, and mental health. The percentage scores range from 0% (lowest or worst response) to 100% (highest or best possible response) [16].

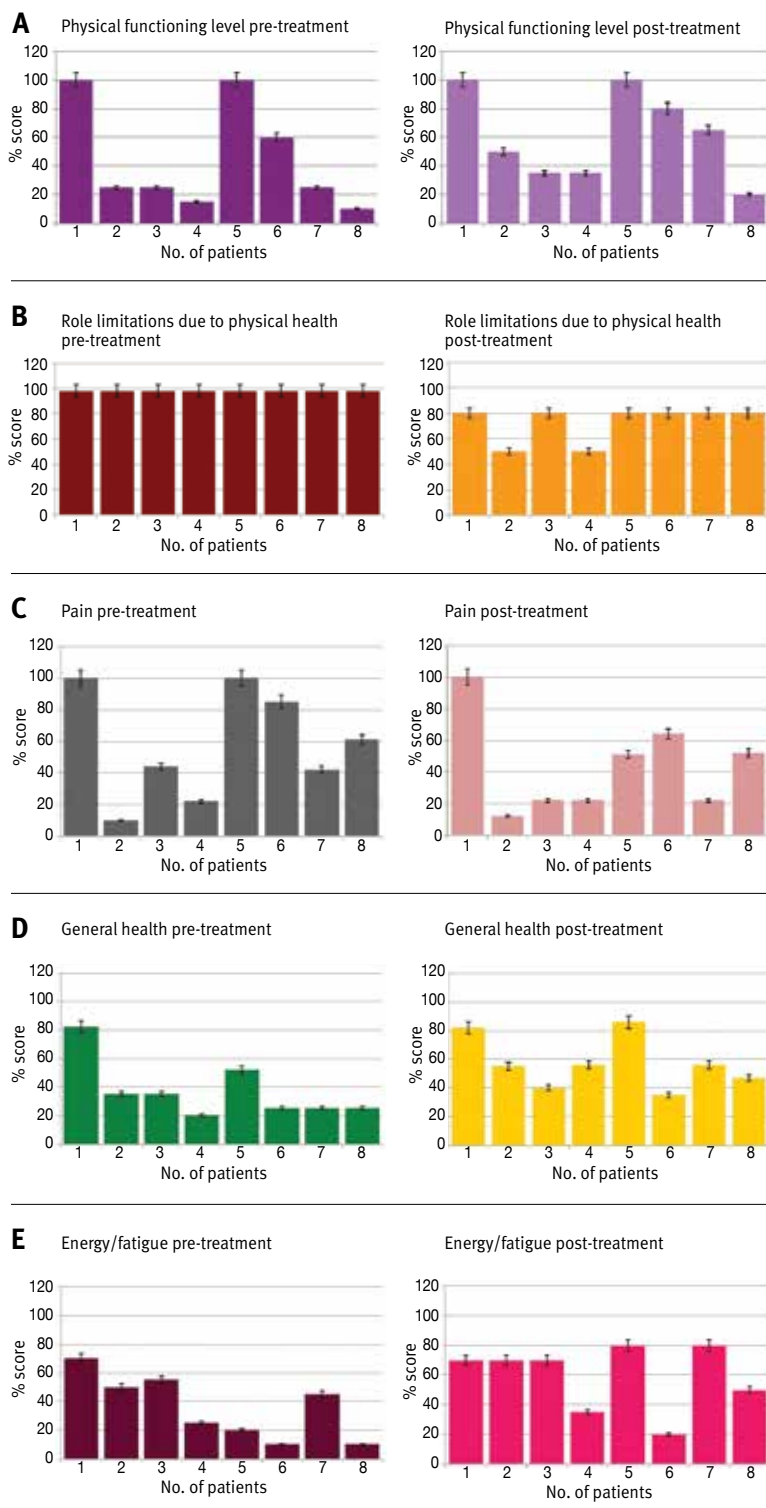
**STATISTICAL ANALYSIS**

The statistical analysis was performed using 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, and all data and graphics were analyzed using the R software, version 3.1.2 [17].

**RESULTS**

Two patients were excluded from the study after the first month of treatment due to complaints of mild side effects: hyperglycemia in one patient with diabetes mellitus, and

**Figure 1.** Graphic illustration of the SF-36 questionnaire in the patients before and after CBD-rich hemp oil treatment for the following domains: **[A]** Physical functioning, **[B]** Role limitations, **[C]** Pain, **[D]** General health, **[E]** Vitality, **[F]** Social functioning, **[G]** Emotional limitations, and **[H]** Mental health



moderate sleepiness and confusion in the second patient. Another two patients decided to withdraw early as they experienced no benefit from the trial.

SF-36 revealed significant improvements in the physical component score ( $P < 0.02$ ), vitality ( $P < 0.03$ ) and social role functioning ( $P < 0.02$ ) after treatment [Figures 1A, E, and F]. The administration of hemp oil also significantly reduced body pain assessed by the SF-36 [Figure 1C]. No significant differences in role limitations due to emotional functioning ( $P = 0.02$ ) for the period before treatment until 3 months post-treatment were found [Figures 1G and H].

## DISCUSSION

Hemp oil is a main source of the two essential fatty acids (EFAs): linoleic acid (18:2 omega-6) and alpha-linolenic acid (18:3 omega-3), in addition to their respective biologic metabolites, gamma-linolenic acid (18:3 omega-6, GLA) and stearidonic acid (18:4 omega-3, SDA) and other polyunsaturated fatty acids (PUFAs) [18].

The recent availability and use of hemp oil in Europe and North America has fostered anecdotal stories on health improvements in a wide range of acute and chronic conditions, including skin conditions (eczema, psoriasis), inflammatory conditions (arthritis, lupus, multiple sclerosis), and others [19]. These claims are attributed to the unique fatty acid profile of hemp oil and to its direct impact on the subsequent metabolism of EFAs to eicosanoids, which include prostaglandins and other metabolites, such as  $\omega$ -6 PUFAs (arachidonic and dihomo-gamma-linolenic acids) and  $\omega$ -9 PUFA (mead acid) [20]. Eicosanoids have been implicated in chronic disease states of the immune system [21]. PUFAs carry out several actions such as inhibiting T lymphocyte activation probably by displacing acylated signaling proteins from membrane lipid rafts and modulating the immune response, and are therefore applied clinically as adjuvant immunosuppressant in the treatment of inflammatory disorders [22,23]. PUFAs also increase bleeding times by decreasing platelet aggregation, with subsequent decreased peripheral blood pressure and clot formation [24].

The level of  $\Delta$ 9-THC in the CBD-enriched hemp oil is definitely below the EU level of 0.2%, with average values  $< 0.10\%$  of the dry weight of mature plants [25]. Indeed, there is no significant psychotropic or toxic effect on human health with such low  $\Delta$ 9-THC levels. In addition, the total absence of emotional reactions such as anxiety, panic attack or irrational distrust after hemp oil administration together with the regular school attendance and no memory or psychological gaps clinically confirm the minimal declared  $\Delta$ 9-THC concentration within the legal limits and without any psychotropic rebound effect.

The action mechanism of the prescribed CBD-enriched hemp oil remains unexplained but is probably due to the

high concentration of CBD (15%), since CBD is an inhibitor of P450 isozymes, primarily CYP2C and CYP3A classes of isozymes, as shown in *in vitro* and *in vivo* studies [26]. With regard to the disruption of learning and memory processes induced by CB receptor activation in addition to euphoria, in the present study we did not observe, for a wide range of CBD doses, any worsening of memory or learning impairment at school or in daily life [27]. The safety and tolerability of CBD-rich hemp oil has been quite acceptable, as only 2 of 12 patients (16%) withdrew from the study due to an adverse event. No significant untoward effects were observed in the patients throughout the trial.

Sleep disorders (especially insomnia), a common symptom in all the girls who usually slept 3 hours or less a night, are significantly alleviated in the first month of treatment, with all the girls sleeping 6–8 hours a night.

The major obvious limitations of our investigation are the type of study and the questionnaire. The study was open-labeled and uncontrolled, and the SF-36 is self-administered which means that the respondents might have reported their subjective health status without an objective checkup.

The trial is still ongoing to evaluate the long-term efficacy of the CBD-enriched hemp oil that might not only relieve the symptoms but in the long term perhaps even be progressively curative, suppressing the symptoms. Hopefully, the patients will be able to discontinue the treatment if the remission of symptoms and functional improvements are steadily achieved.

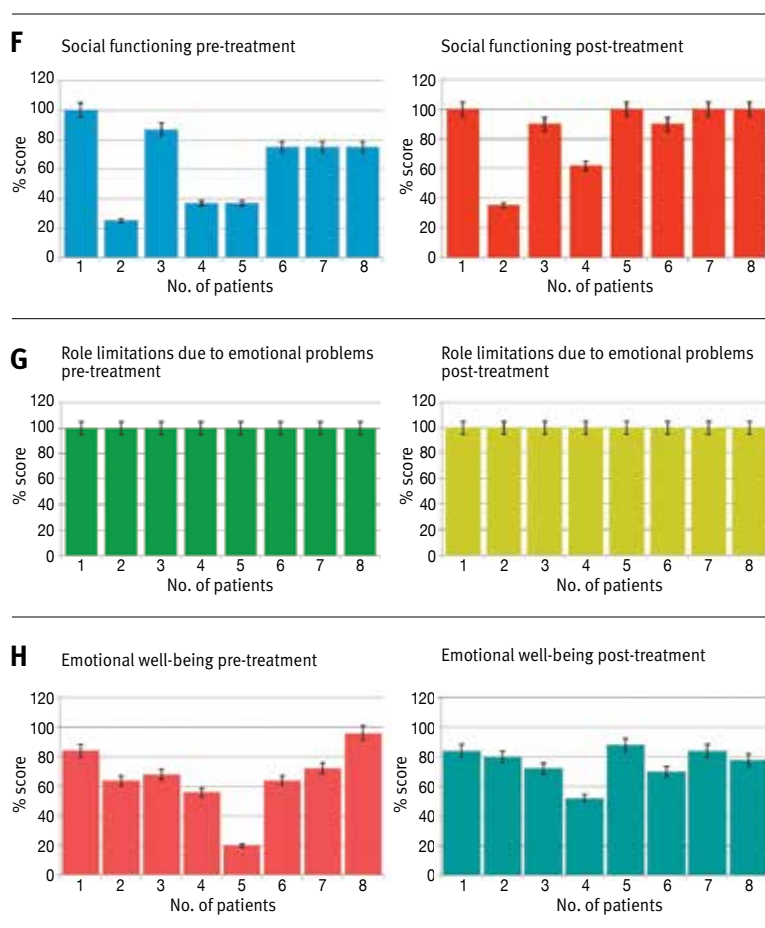
During the study we observed that the sudden interruption of therapy for a week at the end of the first administration month dramatically exacerbated the symptoms, but were immediately ameliorated when resuming the regular previous dose.

**CONCLUSIONS**

CBD displays a broad spectrum of pharmacological effects with multiple potential sites of action in the gastrointestinal, nervous, muscular, and immune systems; these include anti-inflammatory and anti-nociceptive effects, as well as neuro-protective activity. As a pure nutraceutical compound, the CBD-enriched hemp oil in our preliminary ongoing wide-range pilot study is a promising effective strategy for the treatment of several diseases, including neuropathic pain, fibromyalgia, macrophagic myofasciitis, herpetic neuralgia, etc.

Further formal case-control blind clinical investigations are urgently required to introduce regular use of CBD-enriched hemp oil and assess its impact on ADRs subsequent to HPV vaccine, taking into account the general safety and good compliance of long-term administration.

In our Second Opinion Medical Network, we were not able to find any better effective symptomatic treatment and thus we emphasize the advantage of cannabinoid sublingual oil administration for this puzzling orphan disease with a



severely compromised quality of life, as well as school difficulties and social impairment.

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**References**

1. Ben Amar M. Cannabinoids in medicine: a review of their therapeutic potential. *J Ethnopharmacol* 2006; 105 (1-2): 1-25.
2. Di Marzo V, Fontana A. Anandamide, an endogenous cannabinomimetic eicosanoid: 'killing two birds with one stone'. *Prostaglandins Leukot Essent Fatty Acids* 1995; 53 (1): 1-11.
3. Alger BE, Kim J. Supply and demand for endocannabinoids. *Trends Neurosci* 2011; 34 (6): 304-15.
4. Volkow ND, Baler RD, Compton WM, Weiss SRB. Adverse health effects of marijuana use. *N Engl J Med* 2014; 370 (23): 2219-27.
5. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol* 2008; 153 (2): 199-215.
6. Huestis MA. Pharmacokinetics and metabolism of the plant cannabinoids, delta 9-tetrahydrocannabinol, cannabidiol and cannabinol. *Handb Exp Pharmacol* 2005; 168: 657-90.

7. Bergamaschi MM, Queiroz RH, Zuardi AVV, Crippa JA. Safety and side effects of cannabidiol, a Cannabis sativa constituent. *Curr Drug Saf* 2011; 6 (4): 237-49.
8. Starowicz K. Role of endocannabinoid system in pathogenesis of osteoarthritic pain. Proceedings of the 25th Anniversary Symposium of the International Cannabinoid Research Society 2015: 1-7.
9. Shoenfeld Y, Agmon-Levin N. 'ASIA' – autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmun* 2011; 36 (1): 4-8.
10. Palmieri B, Poddighe D, Vadalà M, Laurino C, Carnovale C, Clementi E. Erratum to: Severe somatoform and dysautonomic syndromes after HPV vaccination: case series and review of literature. *Immunol Res* 2016: 1-12.
11. Wunsch A, Palmieri B. The role of second opinion in oncology: an update. *Eur J Oncol* 2013; 18 (3): 3-10.
12. Palmieri B, Iannitti T, Capone S, Arisi E. Second opinion clinic: is the Web Babel Syndrome treatable? *Clin Ter* 2011; 162 (6): 575-83.
13. Palmieri B, Iannitti T. The Web Babel syndrome. *Patient Educ Couns* 2011; 85 (2): 331-3.
14. Di Cerbo A, Palmieri B. The economic impact of second opinion in pathology. *Saudi Med J* 2012; 33 (10): 1051-2.
15. European Medicines Agency (EMA). Guideline on compassionate use of medicinal products, pursuant to article 83 of regulation. *Eval Med Human Use* 2007: 1-8.
16. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). *Med Care* 1992; 30 (6): 473-83.
17. Core R. A Language and Environment for Statistical Computing. R Foundation for Statistical Computing (Vienna, Austria) URL <https://www.R-project.org/> 2015.
18. Callaway JC. Hempseed as a nutritional resource, an overview. *Euphytica* 2004; 140: 65-72.
19. Wilkinson JD, Williamson EM. Cannabinoids inhibit human keratinocyte proliferation through a non-CB1/CB2 mechanism and have a potential therapeutic value in the treatment of psoriasis. *J Dermatol Sci* 2007; 45 (2): 87-92.
20. Kriese U, Schumann E, Weber WE, Beyer M, Matthaes LB. Oil content, tocopherol composition and fatty acid patterns of the seeds of 51 Cannabis sativa L. genotypes. *Euphytica* 2004; 137: 339-51.
21. Kelley DS, Rudolph IL. Effect of individual fatty acids of omega-6 and omega-3 type on human immune status and role of eicosanoids. *Nutrition* 2000; 16 (2): 143-5.
22. Belluzzi A, Brignola C, Campieri M, Pera A, Boschi S, Miglioli M. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. *N Engl J Med* 1996; 334 (24): 1557-60.
23. James MJ, Cleland LG. Dietary n-3 fatty acids and therapy for rheumatoid arthritis. *Semin Arthritis Rheum* 1997; 27 (2): 85-97.
24. Oliwiecki S, Burton JL, Elles K, Horrobin DF. Levels of essential and other fatty acids in plasma and red cell phospholipids from normal controls and patients with atopic eczema. *Acta Derm Venereol* 1991; 71 (3): 224-8.
25. Small E, Marcus D. Tetrahydrocannabinol levels in hemp (Cannabis sativa) germplasm resources. *Econ Bot* 2003; 57 (4): 545-58.
26. Yamaori S, Okamoto Y, Yamamoto I, Watanabe K. Cannabidiol, a major phyto-cannabinoid, as a potent atypical inhibitor for CYP2D6. *Drug Metab Dispos* 2011; 39 (11): 2049-56.
27. Lichtman AH, Varvel SA, Martin BR. Endocannabinoids in cognition and dependence. *Prostaglandins Leukot Essent Fatty Acids* 2002; 66 (2-3): 269-85.