WHO Expert Committee on Drug Dependence Pre-Review

.....

Extracts and tinctures of cannabis

Section 4: Therapeutic use

World Health Organization

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

Acknowledgments

This report was prepared by the Secretariat of the Expert Committee on Drug Dependence (ECDD) within the Department of Essential Medicines and Health Products (EMP) of the World Health Organization (WHO), Geneva, Switzerland. The WHO staff involved in the production of this document, developed under the overall guidance of Mariângela Simão (Assistant Director General, Access to Medicines, Vaccines, and Pharmaceuticals), Suzanne Hill (Director, Essential Medicines and Health Products), Gilles Forte, (Secretary of the Expert Committee on Drug Dependence) were Dilkushi Poovendran (Technical Officer, WHO Essential Medicines and Health Products) and Wil De Zwart (Technical Officer, WHO Essential Medicines and Health Products).

This report was commissioned as a background document for a preliminary review for the 40th Expert Committee on Drug Dependence (ECDD). WHO would like to acknowledge the contributions of the following individuals who authored this report:

Chemistry
Giuseppe Cannazza (University of Modena and Reggio Emilia), Italy
Cinzia Citti (University of Modena and Reggio Emilia), Italy

Pharmacology
Jenny Wiley (RTI International), USA

Epidemiology
Vidhi Thakkar (Centre for Addiction and Mental Health), Canada
Haya Fernandez (Centre for Addiction and Mental Health), Canada
Omer S.M. Hasan (Centre for Addiction and Mental Health), Canada
Jakob Manthey (Institute for Clinical Psychology and Psychotherapy), Germany
Jurgen Rehm (Centre for Addiction and Mental Health), Canada
Astrid Otto (Centre for Addiction and Mental Health), Canada
Charlotte Probst (Centre for Addiction and Mental Health), Canada
Julian Sauer (Centre for Addiction and Mental Health), Canada

Toxicology
Jonathon Arnold (University of Sydney), Australia

Therapeutic Use
Kevin P. Hill (Harvard Medical School), USA
Judith Spahr, (Thomas Jefferson University) USA
Charles V. Pollack. (Thomas Jefferson University) USA
Brock Bakewell (Thomas Jefferson University), USA

The Member State questionnaire report was prepared by Jurgen Rehm, Astrid Otto, and Jakob Manthey.
Technical editing was provided by Ann Morgan and Susan Kaplan.
Administrative support was provided by Afrah Vogel and Christine Berling.

Contents

1. Marketing Authorizations (as a Medicinal Product) 5
2. Listing on the WHO Model List of Essential Medicines 5
3. Therapeutic Applications 5
3.1 Extent of Therapeutic Use 5
3.2 Epidemiology of Medical Use 6
3.3 Effectiveness of Therapeutic Uses 6
3.3.1 Hemp Seed, Evening Primrose Oils 6
3.3.2 Cannabis Sativa Extract 7
3.3.3 Oral mucosal cannabinoid extract 7
3.3.4 Nabiximols 9
4. References 15

1. Marketing Authorizations (as a Medicinal Product)

Nabiximols (trade name Sativex®, GW Pharma) is a cannabis extract with equal proportions of plant-derived tetrahydrocannabinol (THC) and cannabidiol (CBD) available as an oromucosal spray. It was developed in the United Kingdom in response to anecdotal reports of THC as useful in treating multiple sclerosis-related symptoms; CBD was included to modulate the adverse effects of THC.[1]

2. Listing on the WHO Model List of Essential Medicines

Not listed.

3. Therapeutic Applications

3.1 Extent of Therapeutic Use

Nabiximols has received marketing authorization for the treatment of spasticity due to multiple sclerosis (MS) in Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Iceland, Ireland, Italy, Lichtenstein, Luxembourg, Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden, Switzerland and the United Kingdom. It has regulatory approval for MS spasticity in Canada, Australia, New Zealand, Brazil, Colombia, Chile, United Arab Emirates, Kuwait and Israel. Canada and Israel have additionally approved nabiximols for neuropathic pain in MS and for chronic cancer pain. There is an ongoing review of nabiximols data at the United States Food and Drug Administration.

An analysis of data from retrospective registries in the UK, Germany, and Switzerland (N=941) and a prospective safety study in Spain (N=204) found positive benefit to risk ratio in the use of nabiximols. In both studies, after approximately one year of treatment, physicians approved continued use of the agent because of the benefit derived by their patients. There were few adverse events and no evidence of abuse, misuse, or addiction, but it is not clear that these observational data represent a rigorous assessment of these concerns.[2]

3.2 Epidemiology of Medical Use

There are large numbers of patients afflicted with MS or cancer who may be eligible to use nabiximols. As of 2013, MS affects at least 2.3 million individuals globally.[3] Prevalence rates vary by continent and latitude. Prevalence is high (>30 per 100,000) in northern Europe and North America; medium (5-30 per 100,000 in southern Europe and southern US; and prevalence is low (<5 per 100,000) in Asia.[4]

Muscle spasticity is a debilitating symptom that affects many patients with MS. In a registry of more than 20,000 North American patients with MS, the degree and frequency of spasticity were: minimal, 31%; mild, 19%; moderate, 17%; severe, 13%; total, 4%.[5] In a systematic review of pain in more than 7000 adults with MS, the prevalence of neuropathic pain was 26%.[6]

The prevalence of cancer worldwide and the frequency of pain in those suffering from cancer make treatment of cancer-related pain an important clinical consideration. The 2017 World Cancer Report reported that in 2012 there were 14 million new cancer cases. There were 8.7 million people (older than 15 years) alive who had had a cancer diagnosed in the previous year, 22.0 million with a diagnosis in the previous 3 years, and 32.6 million with a diagnosis in the previous 5 years. Globally, nearly 1 in 6 deaths is due to cancer.[7] Up to 75% of patients with cancer may experience chronic pain due directly to their disease[8], about 40% experience neuropathic pain syndromes.[9] As cancer mortality has declined, the number of patients living with cancer-related pain may increase.

3.3 Effectiveness of Therapeutic Uses

(See Table 2&3)

3.3.1 Hemp Seed, Evening Primrose Oils

3.3.1.1 Multiple Sclerosis

In a double-blind, randomized trial, patients with multiple sclerosis who received co-supplemented hemp seed and evening primrose oils had decreased extended disability status scores and lower liver transaminase levels compared to patients treated with a dietary intervention alone.[10]

3.3.2 Cannabis Sativa Extract

3.3.2.1 Dementia

Cannabis oil containing THC as an add-on pharmacotherapy for dementia produced a significant reduction in Clinical Global Impression (CGI) and Neuropsychiatric Inventory (NPI) scores in an open-label trial involving eleven patients, ten of whom completed the study.[11]

3.3.2.2 Motor Neuron Disease

A preliminary report of results from a randomized, double-blind, placebo-controlled multicenter trial of cannabis sativa extract in patients with motor neuron disease, treatment with cannabis sativa extract produced in the modified Ashworth Scale and pain scores. However, while there was a trend for improvement of all outcome measures, most outcomes were not significantly affected.[12]

3.3.2.3 Neurogenic Symptoms

Extracts containing THC, CBD, and THC and CBD in a 1:1 ratio produced a significant reduction in neurogenic symptoms including bladder control, muscle spasms, and spasticity in a series of randomized, double-blind, placebo-controlled crossover studies in 24 patients with chronic medical illnesses (18 were participants with multiple sclerosis) associated with neurogenic symptoms.[13]

3.3.3 Oral mucosal cannabinoid extract

3.3.3.1 Glaucoma

In one small randomized, double-blind, placebo-controlled crossover trial of oral THC extract, cannabidiol, and placebo in six participants with ocular hypertension or early stage glaucoma, oral THC extract and cannabidiol did not separate from placebo on measures of intraocular pressure.[14]

3.3.3.2 Multiple Sclerosis, Spasticity

There have been four randomized, double-blind, placebo-controlled trials of oral cannabinoid extracts for symptoms related to multiple sclerosis. Improvements were modest: one study with 630

participants with MS demonstrated significant improvements in spasticity and pain by self-report, as well as urge incontinence and another study with 249 participants showed that oral cannabinoid extract pharmacotherapy led to reduction in muscle stiffness and improved sleep.[15,16] Two other studies (n=50 and n=14, respectively) failed to demonstrate a difference in spasticity by self-report or Ashworth Scale and no reduction in tremor.[17,18]

3.3.3.3 Nausea and Vomiting Due to Chemotherapy

A considerable evidence base shows that cannabis and specific cannabinoids are effective pharmacotherapy for nausea and vomiting due to chemotherapy. The two United States FDA-approved cannabinoids, dronabinol and nabilone, received indications for nausea and vomiting due to chemotherapy as a result of three randomized controlled trials of dronabinol (and four studies of levonantradol, a synthetic analog of dronabinol) and 14 randomized controlled trials of nabilone for this indication. There have been six studies of oral THC capsules as pharmacotherapy for this indication, five of which used the anti-emetic prochlorperazine as a comparator and one that used the anti-histamine hydroxyzine as a comparator.[19-25] All studies suggested a greater benefit of cannabinoids versus both placebo and active comparators, but these benefits did not reach statistical significance in all studies. Additional studies looking at cannabis with differing ratios of THC to CBD for nausea and vomiting due to chemotherapy are underway and use more contemporary anti-emetic therapy as a control.[26]

3.3.3.4 Parkinson's disease

In 17 patients with Parkinson's Disease, treatment with oral cannabinoid extract did not produce improvements in dyskinesia compared to placebo.[27]

3.3.3.5 Sleep Disorder

Three trials involving oral cannabinoid extracts have evaluated sleep as a secondary outcome measure. All three provided some evidence that oral cannabinoids extracts outperform placebo in measures of sleep.[15-17]

3.3.4 Nabiximols

3.3.4.1 Anxiety Disorder

No studies of cannabis or cannabinoids with anxiety measures as primary outcomes have been conducted. Rog et al. found evidence in a secondary outcome measure that nabiximols reduced anxiety compared to placebo in 66 participants with multiple sclerosis.[28]

3.3.4.2 Attention-deficit/hyperactivity Disorder (ADHD)

Nabiximols oromucosal spray did not produce a difference in the primary endpoint compared to placebo in a randomized, placebo-controlled trial in 30 adults with ADHD. The nabiximols group demonstrated nominally significant improvement in hyperactivity/impulsivity and cognitive measure of inhibition and no difference in adverse events compared to the placebo group.[29]

3.3.4.3 Cannabis Withdrawal, Craving

In an eight-week randomized, double-blind, placebo-controlled trial, treatment with nabiximols significantly reduced cannabis withdrawal symptoms but not craving in nine community-recruited participants with cannabis use disorder. No difference in adverse events was noted.[30]

3.3.4.4 Chronic Pain

In a randomized, double-blind, placebo-controlled trial, nabiximols treatment led to significant improvements in pain on movement, pain at rest, and quality of sleep among 58 patients over five weeks of treatment. It had no effect on morning stiffness, however.[31] Four other randomized controlled trials of nabiximols in patients with advanced cancer pain refractory to opioids failed to produce differences from placebo on the primary study endpoints. Improvement was observed in some secondary endpoints such as overall quality of life.[32-34]

3.3.4.5 Depression

There have been no studies of cannabis or cannabinoids with measures of depression as the primary outcome. Three studies of nabiximols (n= 360, 66, and 666) found no difference between nabiximols and placebo in depression outcomes.[13,28,34]

3.3.4.6 Huntington's Disease

The only randomized, double-blind, placebo-controlled trial of nabiximols for Huntington's Disease failed to demonstrate any difference between nabiximols and placebo on motor, cognitive, behavioral, or functional scores in 26 patients (24 completed the study) treated over twelve weeks.[35] Other cannabinoids, namely nabilone and cannabidiol, not included in this pre-review, have been studied as pharmacotherapy for Huntington's Disease, yielding improvements in chorea and no difference from placebo, respectively.

3.3.4.7 Multiple Sclerosis, spasticity

Two meta-analyses addressed the literature of cannabis and cannabinoids for spasticity in multiple sclerosis. Whiting et al. reported that the pooled odds of patient-reported improvement on a global impression-of-change score was greater with nabiximols than with placebo (OR, 1.44, 95% C.I.= 1.07-1.94).[36] Meanwhile, Koppel et al. concluded that nabiximols is "probably effective" for reducing patient-reported spasticity scores.[37] Both meta-analyses stated that treatment with nabiximols does not produce differences in objective spasticity compared to placebo, although it was noted that the Ashworth Scale is not ideal to detect such differences.

Five randomized, double-blind, placebo-controlled trials of nabiximols for spasticity in multiple sclerosis have been conducted (one utilized a crossover design). Of these trials, three demonstrated that nabiximols treatment led to a significant difference in spasticity[38-40], while nabiximols treatment failed to separate from placebo in the other two trials.[39,41] Further investigation of either secondary endpoints or of those previously in spasticity clinical trials showed decreases in subjective measures of spasticity and a recent observational study of patients with multiple sclerosis on nabiximols showed this as well.[41-43]

3.3.4.8 Neuropathic Pain

Of seven randomized, double-blind, placebo-controlled trials of nabiximols for neuropathic pain, three produced positive results on primary endpoints, and four did not. The three positive trials all showed significant reductions in neuropathic pain while two of the three also showed significant improvements in sleep quality.[28,44] The other studies did show a significant difference between nabiximols and placebo on measures of neuropathic pain.[45-48] All studies demonstrated an increased incidence of adverse events in the nabiximols group compared to placebo.

3.3.4.9 Sleep Disorder

Two studies have evaluated nabilone (not included in this pre-review) as a pharmacotherapy for sleep disorder. Nineteen other placebo-controlled studies for chronic pain and multiple sclerosis have evaluated sleep as an outcome. Thirteen of these studies involved nabiximols, which was associated with greater average improvement in sleep quality and sleep disturbance.[13,28,31,34,38,44,46,47,49-52]

Table 2: Studies of Extracts and Tinctures of Cannabis

Intervention	Administration Method	Dose Evaluated	Comparator	Number of Studies Described in this Report	Indicatio
Hemp Seeds, Evening Primrose Oils	Oil	18-21 g/day	Olive Oil	1	Multiple
Cannabis Sativa Extract	Oil	Maximum 15 g/day	None, Open-Label	1	Dementi
	Spray	Unspecified Dose	Placebo	1	Motor N
	Spray	2.5-120 mg/day	Placebo	1	Neuroge
Oral Mucosal cannabinoid extract	Capsules	5 mg/day	Placebo	1	Glaucom
	Capsules	10-30 mg/day	Placebo	4	Multiple
	Capsules	5-30 mg/day	Prochlorperazine, Hydroxyzine, or Placebo	7	Chemoth nausea a
	Capsules	10 mg/day	Placebo	1	Parkinso
	Capsules	25-30 mg/day	Placebo	3	Sleep Dis

Key: THC= delta-9-tetrahydrocannabinol, CBD= cannabidiol

Intervention	Administration Method	Dose Evaluated	Comparator	Number of Studies Described in this Report	Indication
Nabiximols	Oromucosal Spray	Titrated to a maximum of 48 sprays/Day 2.7 mg THC/2.5 mg CBD per spray	Placebo	1	Anxiety
		Maximum 14 sprays/day			ADHD
		Maximum 40 sprays/day	Placebo	1	Cannabis Withdrawal, Craving
		Maximum 6-16 sprays/day	Placebo	1	Chronic Pain
		Maximum 16-48 sprays/day	Placebo	5	Depression
		Maximum 12 sprays/day	Placebo	3	Huntington's Disease
		Maximum 48 sprays/day	Placebo	1	Multiple Sclerosis, Spasticity

3.4 Table 3: Studies of Extracts and Tinctures of Cannabis cont.

		Maximum 4-40 sprays/day Maximum 48 sprays/day	Placebo Placebo Placebo	7 7 13	Neuropathic Pain Sleep Disorder

Key: THC= delta-9-tetrahydrocannabinol, CBD= cannabidiol

4. References

1. Notcutt, W. G. Clinical Use of Cannabinoids for Symptom Control in Multiple Sclerosis. *Neurotherapeutics* 2015*, 12*, 769-777.

2. Fernandez, O. THC:CBD in Daily Practice: Available Data from UK, Germany and Spain. *Eur. Neurol.* 2016*, 75 Suppl 1*, 1-3.

3. Multiple Sclerosis International Federation Atlas of MS. *https://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf*.

4. Koch-Henriksen, N.; Sorensen, P. S. The changing demographic pattern of multiple sclerosis epidemiology. *Lancet Neurol.* 2010*, 9*, 520-532.

5. Rizzo, M. A.; Hadjimichael, O. C.; Preiningerova, J.; Vollmer, T. L. Prevalence and treatment of spasticity reported by multiple sclerosis patients. *Mult. Scler.* 2004*, 10*, 589-595.

6. Foley, P. L.; Vesterinen, H. M.; Laird, B. J.; Sena, E. S.; Colvin, L. A.; Chandran, S.; MacLeod, M. R.; Fallon, M. T. Prevalence and natural history of pain in adults with multiple sclerosis: systematic review and meta-analysis. *Pain* 2013*, 154*, 632-642.

7. World Health Organization Cancer Fact Sheet. *http://www.who.int/mediacentre/factsheets/fs297/en/*.

8. Portenoy, R. K. Treatment of cancer pain. *Lancet* 2011*, 377*, 2236-2247.

9. Paice, J. A.; Portenoy, R.; Lacchetti, C.; Campbell, T.; Cheville, A.; Citron, M.; Constine, L. S.; Cooper, A.; Glare, P.; Keefe, F.; Koyyalagunta, L.; Levy, M.; Miaskowski, C.; Otis-Green, S.; Sloan, P.; Bruera, E. Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J. Clin. Oncol.* 2016*, 34*, 3325-3345.

10. Rezapour-Firouzi, S.; Arefhosseini, S. R.; Ebrahimi-Mamaghani, M.; Baradaran, B.; Sadeghihokmabad, E.; Torbati, M.; Mostafaei, S.; Chehreh, M.; Zamani, F. Activity of liver enzymes in multiple sclerosis patients with Hot-nature diet and co-supplemented hemp seed, evening primrose oils intervention. *Complement. Ther. Med.* 2014*, 22*, 986-993.

11. Shelef, A.; Barak, Y.; Berger, U.; Paleacu, D.; Tadger, S.; Plopsky, I.; Baruch, Y. Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological Symptoms of Dementia: An-Open Label, Add-On, Pilot Study. *J. Alzheimers Dis.* 2016*, 51*, 15-19.

12. Riva, N.; Mora, G.; Soraru, G.; Lunetta, C.; Falzone, Y.; Marinou, K.; Maestri, E.; Fazio, R.; Comola, M.; Comi, G. The canals study: a randomized, double-blind, placebo-controlled, multicentre study to assess the safety and efficacyon spasticity symptoms of a cannabis sativa extract in motor neuron disease patients. *Amyotrophic lateral sclerosis and frontotemporal degeneration.Conference: 27th international symposium on ALS/MND.Ireland.Conference start: 20161207.Conference end: 20161209* 2016*, 17*, 44.

13. Wade, D. T.; Robson, P.; House, H.; Makela, P.; Aram, J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin. Rehabil.* 2003*, 17*, 21-29.

14. Tomida, I.; Azuara-Blanco, A.; House, H.; Flint, M.; Pertwee, R. G.; Robson, P. J. Effect of sublingual application of cannabinoids on intraocular pressure: a pilot study. *J. Glaucoma* 2006*, 15*, 349-353.

15. Zajicek, J. P.; Hobart, J. C.; Slade, A.; Barnes, D.; Mattison, P. G.; MUSEC Research Group Multiple sclerosis and extract of cannabis: results of the MUSEC trial. *J. Neurol. Neurosurg. Psychiatry.* 2012*, 83*, 1125-1132.

16. Zajicek, J.; Fox, P.; Sanders, H.; Wright, D.; Vickery, J.; Nunn, A.; Thompson, A.; UK MS Research Group Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003*, 362*, 1517-1526.

17. Vaney, C.; Heinzel-Gutenbrunner, M.; Jobin, P.; Tschopp, F.; Gattlen, B.; Hagen, U.; Schnelle, M.; Reif, M. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. *Mult. Scler.* 2004*, 10*, 417-424.

18. Fox, P.; Bain, P. G.; Glickman, S.; Carroll, C.; Zajicek, J. The effect of cannabis on tremor in patients with multiple sclerosis. *Neurology* 2004*, 62*, 1105-1109.

19. Broder, L. E.; Sridhar, K. S.; Selawry, O. S.; Charyulu, K. N.; Rao, R. K.; Saldana, M. J.; Lenz, C. A phase II clinical trial evaluating the use of two sequential, four-drug combination chemotherapy regimens in ambulatory bronchogenic adenocarcinoma patients. *Am J Clin Oncol.* 1992*, 15*, 480-486.

20. Duran, M.; Perez, E.; Abanades, S.; Vidal, X.; Saura, C.; Majem, M.; Arriola, E.; Rabanal, M.; Pastor, A.; Farre, M.; Rams, N.; Laporte, J. R.; Capella, D. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. *Br. J. Clin. Pharmacol.* 2010*, 70*, 656-663.

21. Orr, L. E.; McKernan, J. F.; Bloome, B. Antiemetic effect of tetrahydrocannabinol. Compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. *Arch. Intern. Med.* 1980*, 140*, 1431-1433.

22. Orr, L. E.; McKernan, J. F. Antiemetic effect of delta 9-tetrahydrocannabinol in chemotherapy-associated nausea and emesis as compared to placebo and compazine. *J. Clin. Pharmacol.* 1981*, 21*, 80S.

23. Ungerleider, J. T.; Andrysiak, T.; Fairbanks, L.; Goodnight, J.; Sarna, G.; Jamison, K. Cannabis and cancer chemotherapy: a comparison of oral delta-9-THC and prochlorperazine. *Cancer* 1982*, 50*, 636-645.

24. Frytak, S.; Moertel, C. G.; O'Fallon, J. R.; Rubin, J.; Creagan, E. T.; O'Connell, M. J.; Schutt, A. J.; Schwartau, N. W. Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. A comparison with prochlorperazine and a placebo. *Ann Intern Med* 1979*, 91*, 825-830.

25. Sallan, S. E.; Cronin, C.; Zelen, M.; Zinberg, N. E. Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *N. Engl. J. Med.* 1980*, 302*, 135-138.

26. Mersiades, A.; Haber, P.; Stockler, M.; Lintzeris, N.; Simes, J.; McGregor, I.; Olver, I.; Allsop, D. J.; Gedye, C.; Kirby, A.; Fox, P.; Briscoe, K.; Clarke, S.; Wong, N.; Walsh, A.; Hahn, C.; Grimison, P. Pilot and definitive randomized double-blind placebo-controlled trials evaluating anoral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting (CINV). *Asia-pacific journal of clinical oncology.Conference: annual scientific meeting of the medical oncology group of australia incorporated, MOGA 2017.Australia* 2017*, 13*, 67-68.

27. Carroll, C. B.; Bain, P. G.; Teare, L.; Liu, X.; Joint, C.; Wroath, C.; Parkin, S. G.; Fox, P.; Wright, D.; Hobart, J.; Zajicek, J. P. Cannabis for dyskinesia in Parkinson disease: a randomized double-blind crossover study. *Neurology* 2004*, 63*, 1245-1250.

28. Rog, D. J.; Nurmikko, T. J.; Young, C. A. Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. *Clin. Ther.* 2007*, 29*, 2068-2079.

29. Cooper, R. E.; Williams, E.; Seegobin, S.; Tye, C.; Kuntsi, J.; Asherson, P. Cannabinoids in attention-deficit/hyperactivity disorder: a randomised-controlled trial. *European neuropsychopharmacology* 2017*, 27*, 795-808.

30. Trigo, J. M.; Lagzdins, D.; Rehm, J.; Selby, P.; Gamaleddin, I.; Fischer, B.; Barnes, A. J.; Huestis, M. A.; Le Foll, B. Effects of fixed or self-titrated dosages of Sativex on cannabis withdrawal and cravings. *Drug and Alcohol Dependence* 2016*, 161*, 298-306.

31. Blake, D. R.; Robson, P.; Ho, M.; Jubb, R. W.; McCabe, C. S. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford)* 2006*, 45*, 50-52.

32. Fallon, M. T.; Albert, L. E.; McQuade, R.; Rossetti, S.; Sanchez, R.; Sun, W.; Wright, S.; Lichtman, A. H.; Kornyeyeva, E. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. *British journal of pain* 2017*, 11*, 119-133.

33. Lichtman, A. H.; Lux, E. A.; McQuade, R.; Rossetti, S.; Sanchez, R.; Sun, W.; Wright, S.; Kornyeyeva, E.; Fallon, M. T. Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as a Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain. *J. Pain Symptom Manage.* 2017.

34. Portenoy, R. K.; Ganae-Motan, E. D.; Allende, S.; Yanagihara, R.; Shaiova, L.; Weinstein, S.; McQuade, R.; Wright, S.; Fallon, M. T. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *J. Pain* 2012*, 13*, 438-449.

35. L 'opez-Send 'on Moreno, Jose Luis; Garc 'ia Caldentey, J.; Trigo Cubillo, P.; Ruiz Romero, C.; Garc 'ia Ribas, G.; Alonso Arias, M A Alonso; Garc 'ia de Y 'ebenes, Mar 'ia Jes 'us; Tol 'on, Rosa Mar 'ia; Galve-Roperh, I.; Sagredo, O.; Valdeolivas, S.; Resel, E.; Ortega-Gutierrez, S.; Garc 'ia-Bermejo, Mar 'ia Laura; Fern 'andez Ruiz, J.; Guzm 'an, M.; Garc 'ia de Y 'ebenes Prous, Justo A double-blind, randomized,

cross-over, placebo-controlled, pilot trial with Sativex in Huntington's disease. *J. Neurol.* 2016*, 263*, 1390-1400.

36. Whiting, P. F.; Wolff, R. F.; Deshpande, S.; Di Nisio, M.; Duffy, S.; Hernandez, A. V.; Keurentjes, J. C.; Lang, S.; Misso, K.; Ryder, S.; Schmidlkofer, S.; Westwood, M.; Kleijnen, J. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA* 2015*, 313*, 2456-2473.

37. Koppel, B. S.; Brust, J. C.; Fife, T.; Bronstein, J.; Youssof, S.; Gronseth, G.; Gloss, D. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2014*, 82*, 1556-1563.

38. Collin, C.; Davies, P.; Mutiboko, I. K.; Ratcliffe, S.; Sativex Spasticity in MS Study Group Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. *Eur. J. Neurol.* 2007*, 14*, 290-296.

39. Aragona, M.; Onesti, E.; Tomassini, V.; Conte, A.; Gupta, S.; Gilio, F.; Pantano, P.; Pozzilli, C.; Inghilleri, M. Psychopathological and cognitive effects of therapeutic cannabinoids in multiple sclerosis: a double-blind, placebo controlled, crossover study. *Clin. Neuropharmacol.* 2009*, 32*, 41-47.

40. Novotna, A.; Mares, J.; Ratcliffe, S.; Novakova, I.; Vachova, M.; Zapletalova, O.; Gasperini, C.; Pozzilli, C.; Cefaro, L.; Comi, G.; Rossi, P.; Ambler, Z.; Stelmasiak, Z.; Erdmann, A.; Montalban, X.; Klimek, A.; Davies, P.; Sativex Spasticity Study Group A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex((R))), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur. J. Neurol.* 2011*, 18*, 1122-1131.

41. Leocani, L.; Nuara, A.; Houdayer, E.; Schiavetti, I.; Del Carro, U.; Amadio, S.; Straffi, L.; Rossi, P.; Martinelli, V.; Vila, C.; Sormani, M. P.; Comi, G. Sativex((R)) and clinical-neurophysiological measures of spasticity in progressive multiple sclerosis. *J. Neurol.* 2015*, 262*, 2520-2527.

42. Haupts, M.; Vila, C.; Jonas, A.; Witte, K.; Alvarez-Ossorio, L. Influence of Previous Failed Antispasticity Therapy on the Efficacy and Tolerability of THC:CBD Oromucosal Spray for Multiple Sclerosis Spasticity. *Eur. Neurol.* 2016*, 75*, 236-243.

43. Vermersch, P.; Trojano, M. Tetrahydrocannabinol:Cannabidiol Oromucosal Spray for Multiple Sclerosis-Related Resistant Spasticity in Daily Practice. *Eur. Neurol.* 2016*, 76*, 216-226.

44. Serpell, M.; Ratcliffe, S.; Hovorka, J.; Schofield, M.; Taylor, L.; Lauder, H.; Ehler, E. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *Eur. J. Pain* 2014*, 18*, 999-1012.

45. Selvarajah, D.; Gandhi, R.; Emery, C. J.; Tesfaye, S. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. *Diabetes Care* 2010*, 33*, 128-130.

46. Berman, J. S.; Symonds, C.; Birch, R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain* 2004*, 112*, 299-306.

47. Langford, R. M.; Mares, J.; Novotna, A.; Vachova, M.; Novakova, I.; Notcutt, W.; Ratcliffe, S. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J. Neurol.* 2013*, 260*, 984-997.

48. Lynch, M. E.; Cesar-Rittenberg, P.; Hohmann, A. G. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. *J. Pain Symptom Manage.* 2014*, 47*, 166-173.

49. GW Pharma Ltd A study to evaluate the effects of cannabis based medicine in patients with pain of neurological origin. *ClinicalTrials.gov* 2002.

50. GW Pharma Ltd A double blind, randomised, placebo controlled, parallel group study of Sativex in the treatment of subjects with pain due to diabetic neuropathy. *EU Clinical Trials Register* 2005.

51. Nurmikko, T. J.; Serpell, M. G.; Hoggart, B.; Toomey, P. J.; Morlion, B. J.; Haines, D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain* 2007*, 133*, 210-220.

52. Johnson, J. R.; Burnell-Nugent, M.; Lossignol, D.; Ganae-Motan, E. D.; Potts, R.; Fallon, M. T. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J. Pain Symptom Manage.* 2010*, 39*, 167-179.