Extracts and tinctures of cannabis

Section 4: Therapeutic use
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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:

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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. 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.

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%. In a systematic review of pain in more than 7000 adults with MS, the prevalence of neuropathic pain was 26%.

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. Up to 75% of patients with cancer may experience chronic pain due directly to their disease, about 40% experience neuropathic pain syndromes. 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.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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). Meanwhile, Koppel et al. concluded that nabiximols is “probably effective” for reducing patient-reported spasticity scores. 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, while nabiximols treatment failed to separate from placebo in the other two trials. 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.

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. The other studies did show a significant difference between nabiximols and placebo on measures of neuropathic pain. 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.\textsuperscript{13,28,31,34,38,44,46,47,49-52}
### Table 2: Studies of Extracts and Tinctures of Cannabis

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Administration Method</th>
<th>Dose Evaluated</th>
<th>Comparator</th>
<th>Number of Studies Described in this Report</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemp Seeds, Evening Primrose Oils</td>
<td>Oil</td>
<td>18-21 g/day</td>
<td>Olive Oil</td>
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<td>Multiple Sclerosis</td>
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<tr>
<td>Cannabis Sativa Extract</td>
<td>Oil Spray</td>
<td>Maximum 15 g/day</td>
<td>None, Open-Label</td>
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<td>Dementia</td>
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<tr>
<td></td>
<td>Oil Spray</td>
<td>Unspecified Dose</td>
<td>Placebo</td>
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<td>Motor Neuron Disease</td>
</tr>
<tr>
<td></td>
<td>Capsules</td>
<td>5 mg/day</td>
<td>Placebo</td>
<td>1</td>
<td>Neurogenic Symptoms</td>
</tr>
<tr>
<td>Oral Mucosal cannabinoid extract</td>
<td>Capsules</td>
<td>10-30 mg/day</td>
<td>Placebo</td>
<td>4</td>
<td>Glaucoma</td>
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<tr>
<td></td>
<td>Capsules</td>
<td>5-30 mg/day</td>
<td>Prochlorperazine, Hydroxyzine, or Placebo</td>
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<td>Multiple Sclerosis</td>
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<tr>
<td></td>
<td>Capsules</td>
<td>10 mg/day</td>
<td>Placebo</td>
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<td>Chemotherapy-induced nausea and vomiting</td>
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<td>Capsules</td>
<td>25-30 mg/day</td>
<td>Placebo</td>
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<td>Parkinson Disease</td>
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<tr>
<td></td>
<td>Capsules</td>
<td>10 mg/day</td>
<td>Placebo</td>
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<td>Sleep Disorder</td>
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Key: THC= delta-9-tetrahydrocannabinol, CBD= cannabidiol
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Administration Method</th>
<th>Dose Evaluated</th>
<th>Comparator</th>
<th>Number of Studies Described in this Report</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Nabiximols</td>
<td>Oromucosal Spray</td>
<td>Titrated to a maximum of 48 sprays/Day 2.7 mg THC/2.5 mg CBD per spray</td>
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<td>Anxiety</td>
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<td>Maximum 14 sprays/day</td>
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<td></td>
<td>ADHD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximum 40 sprays/day</td>
<td>Placebo</td>
<td>1</td>
<td>Cannabis Withdrawal, Craving</td>
</tr>
<tr>
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<td></td>
<td>Maximum 6-16 sprays/day</td>
<td>Placebo</td>
<td>1</td>
<td>Chronic Pain</td>
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<td>Maximum 16-48 sprays/day</td>
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<td>Depression</td>
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<td>Maximum 12 sprays/day</td>
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<td></td>
<td></td>
<td>Maximum 48 sprays/day</td>
<td>Placebo</td>
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<td>Multiple Sclerosis, Spasticity</td>
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**3.4** Table 3: Studies of Extracts and Tinctures of Cannabis cont.
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<td>Maximum 4-40 sprays/day</td>
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<td>Neuropathic Pain</td>
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<tr>
<td>Maximum 48 sprays/day</td>
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Key: THC= delta-9-tetrahydrocannabinol, CBD= cannabidiol
4. References


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.; Valdeolivias, 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,


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

