

WHO Expert Committee on Drug Dependence Pre-Review

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Delta-9-tetrahydrocannabinol

Section 4: Therapeutic use



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1. Marketing Authorizations (as a Medicinal Product)

Dronabinol (Marinol®) is produced and sold by AbbVie, Inc. in the United States.

2. Listing on the WHO Model List of Essential Medicines

Not listed.

3. Therapeutic Applications

3.1 Extent of Therapeutic Use

Dronabinol (Marinol®), synthetic THC, has FDA approval in the United States for the treatment of anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS) and for nausea and vomiting associated with cancer chemotherapy (CINV) in patients who have failed to respond adequately to conventional antiemetic treatment. Dronabinol is either approved or available under 'special access rules' in the United Kingdom, Scandinavian countries, and most Western European countries. For example, it is approved in Austria, Denmark and Ireland for CINV unresponsive to conventional treatment in oncology and palliative care and for cancer pain in Denmark. In Ireland, dronabinol is approved for appetite stimulation in HIV. Dronabinol can be prescribed for any type of chronic pain and for any condition in palliative care in Germany.¹

3.2 Epidemiology of Medical Use

It is estimated that over 90% of patients exposed to highly emetogenic chemotherapy and between 30 and 90% of patients exposed to moderately emetogenic chemotherapy will experience acute-phase CINV. Several observational studies have shown that later onset CINV may be incompletely controlled even if acute CINV has been managed.² In a study of 1413 patients, 72% of patients reporting vomiting at the first treatment also reported subsequent vomiting; 31% of these patients experienced emesis at all remaining treatments.³

Neuropathic pain is common with a global prevalence of 7% to 8%. Approximately 20% of people with cancer have cancer-related neuropathic pain, due to either the disease or its treatment.⁴ A systematic review of 19 UK studies found that chronic pain affects between one-third and one-half of the UK's population, almost 28 million adults though not all of these are neuropathic in origin. Two of the studies reviewed found that over 8% of the entire population was suffering from chronic neuropathic pain.⁵

3.3 Effectiveness of Therapeutic Uses

(See Table 4&5)

3.3.1 Pure delta-9-tetrahydrocannabinol

3.3.1.1 *Abdominal Pain*

In 65 participants with chronic abdominal pain after surgery or from chronic pancreatitis, treatment with THC tablets did not produce differences in visual analog scales of chronic pain. No differences were observed on secondary outcome measures, although those receiving THC were more likely to experience adverse events than those receiving placebo.⁶ Analysis of the 24 participants with pain from chronic pancreatitis also failed to show a difference between treatment with THC and placebo.⁷

3.3.1.2 *Dementia*

Pure delta-9-tetrahydrocannabinol has been studied in four randomized controlled trials in participants with dementia. An initial safety crossover study in ten participants with dementia found that treatment with THC was safe in this population; THC did not produce more adverse events than placebo.⁸ Two studies evaluating the effects of THC treatment on neuropsychiatric symptoms in dementia found no difference between THC and placebo. In the first study by Van den Elsen et al., a crossover design of 22 participants receiving up to 3 mg of THC daily yielded no difference between THC and placebo in Neuropsychiatric Inventory (NPI) scores.⁹ A second randomized, double-blind, placebo-controlled trial in 50 participants by the same group showed that 4.5 mg of THC daily also failed to produce a difference from placebo in NPI scores, nor were there differences in secondary outcome measures of agitation, quality of life, or activities of daily living.¹⁰ A third trial by the same group, a randomized, placebo-controlled, crossover study of THC 3 mg daily in 18 participants with dementia showed that THC had no adverse effect upon balance, gait, and adverse events in this population.¹¹

3.3.1.3 *Multiple Sclerosis*

Amerongen et al. assessed the effects of a pure form of THC on spasticity and neuropathic pain in 24 participants with progressive MS and moderate spasticity. Treatment with THC decreased neuropathic pain immediately after administration but not when measured in daily diaries. A similar pattern was observed with subjective muscle spasticity; the THC group was also significantly more likely to experience adverse events than the placebo group.¹²

3.3.1.4 *Nausea and Vomiting*

In a randomized, double-blind, placebo-controlled trial of intravenous THC for postoperative nausea and vomiting in 40 participants, THC did not significantly lessen nausea and vomiting compared to placebo.

Due to significant side effects--primarily sedation and confusion--and uncertain efficacy for postoperative nausea and vomiting, the study was discontinued after 40 participants.¹³

3.3.1.5 Neuropathic Pain

As mentioned above, treatment with a pure form of THC decreased neuropathic pain immediately after administration but not when measured in daily diaries in 24 participants with progressive MS.¹²

3.3.2 (-)-trans-delta-9-tetrahydrocannabinol (dronabinol)

3.3.2.1 Anxiety Disorder

No studies of cannabis or cannabinoids with anxiety measures as primary outcomes have been conducted. Narang et al. found evidence in a secondary outcome measure that dronabinol reduced anxiety compared to placebo in 30 participants with chronic pain.¹⁴

3.3.2.2 Amyotrophic Lateral Sclerosis

In a randomized, double-blind, placebo-controlled trial of dronabinol for amyotrophic lateral sclerosis, treatment with dronabinol yielded no reduction in cramps compared to placebo.¹⁵

3.3.2.3 Anorexia Nervosa

Dronabinol pharmacotherapy induced a small but significant weight gain in 25 women with anorexia nervosa in an add-on, prospective, randomized, double-blind, placebo-controlled crossover study. Dronabinol was safe and well-tolerated in this group, with no difference between dronabinol and placebo in adverse events.¹⁶

3.3.2.4 Appetite Stimulation in HIV Infection/AIDS

Four studies of dronabinol as pharmacotherapy for appetite stimulation in HIV/AIDS infection led to dronabinol earning FDA approval for this indication. In a randomized, double-blind, placebo-controlled trial of 67 participants with HIV infection, both dronabinol and smoked cannabis produced significantly greater weight gain than placebo. This safety study also showed that both dronabinol and smoked cannabis were safe in this population and they did not adversely affect viral load in comparison to placebo.¹⁷ Similarly, treatment with dronabinol was associated with significant weight gain in randomized, double-blind, placebo-controlled trials in 12 and 139 participants, respectively (participants

in the latter study were HIV patients already diagnosed with anorexia).^{18,19} Finally, in an open-label trial of 52 participants with HIV infection, dronabinol, alone and in combination with megastrol acetate, was shown to produce significant weight gain.²⁰

3.3.2.5 *Cannabis Use Disorder*

Dronabinol has been studied as pharmacotherapy for cannabis use disorder in two large clinical trials from the same investigative team. In a randomized, double-blind, placebo-controlled trial of 156 participants with cannabis use disorder, dronabinol at 20 mg twice daily did not differ from placebo in the proportion of participants who achieved 2 weeks of abstinence or in reduction of cannabis use. The dronabinol group was significantly more likely to stay in treatment and to have fewer cannabis withdrawal symptoms.²¹ In another randomized, double-blind, placebo-controlled trial building upon promising human laboratory data, the combination of dronabinol 20 mg three times daily and the alpha-2 agonist lofexidine, did not produce a significant difference in the proportion of participants who achieved three weeks of abstinence during the maintenance phase of the trial compared to placebo.²²

3.3.2.6 *Chronic Pain*

Dronabinol has been studied as an add-on pharmacotherapy chronic pain. Narang et al. carried out a two-phase investigation of dronabinol's efficacy in 30 participants with chronic pain who took opioids for pain management.²³ In Phase I, a randomized, double-blind, placebo-controlled single dose crossover human laboratory study, dronabinol decreased pain intensity and increased patient satisfaction compared to placebo, although there was no difference between 10 mg or 20 mg doses of dronabinol. Phase II, an extended open-label trial of dronabinol added to stable doses of opioids, showed that titration of dronabinol led to significant pain relief, reduced pain bothersomeness, and increased satisfaction compared to baseline.¹⁴ This group of investigators also showed that dronabinol had similar psychoactive effects to smoked marijuana during this trial.²⁴

3.3.2.7 *Depression*

There have been no studies of cannabis or cannabinoids with measures of depression as the primary outcome. One study of dronabinol (n= 30) found no difference between dronabinol and placebo in depression outcomes.¹⁴

3.3.2.8 *Multiple Sclerosis*

Dronabinol pharmacotherapy for multiple sclerosis has been studied in five randomized, double-blind, placebo-controlled trials. Three of these trials evaluated its effects upon spasticity in these participants, one assessed neuropathic pain, and one looked at its effects upon disease progression; one of the trials evaluated both spasticity and pain. Two of the spasticity trials, which enrolled 630, and 13 participants, respectively, found that treatment with dronabinol significantly reduced spasticity by self-report.^{25,26} Killestein et al. found in 16 participants that dronabinol did not separate from placebo in its effects upon spasticity.²⁷ Dronabinol's effects upon neuropathic pain in MS patients has been mixed, with Svendsen et al. showing an effect in 24 participants while Schimrigk did not in 240 participants.^{28,29} The CUPID trial of 493 participants with primary or secondary progressive MS found no evidence that dronabinol has an effect on MS progression.³⁰

3.3.2.9 *Neuropathic Pain*

As mentioned above, dronabinol's effects upon neuropathic pain in MS patients was mixed: Svendsen et al. showed an effect in 24 participants while Schimrigk et al. and did not in 240 participants.^{28,29}

3.3.2.10 *Noncardiac Chest Pain*

In a randomized, double-blind, placebo-controlled trial of thirteen patients with functional chest pain, treatment with dronabinol 10 mg daily increased pain thresholds significantly and reduced chest pain intensity and odynophagia compared to placebo without a difference in adverse events.³¹ An initial randomized, double-blind, placebo-controlled investigation by the same group in the same participants showed that dronabinol does not affect basic metabolic parameters like body mass index, HDL, triglycerides, and insulin after a treatment period of 28 days, clearing the way for additional studies of dronabinol in this population.³²

3.3.2.11 *Obstructive Sleep Apnea*

In the only randomized controlled trial of a cannabinoid as pharmacotherapy for obstructive sleep apnea, dronabinol produced lower scores on the apnea-hypopnea index, improved scores of self-report sleepiness, and greater treatment satisfaction than placebo. There was no difference between dronabinol and placebo in objectives measures of sleepiness or incidence of adverse events.³³

3.3.2.12 Opioid Use Disorder

Treatment with dronabinol 30 mg daily, when added to a buprenorphine detoxification regimen, significantly reduced the severity of opioid withdrawal symptoms compared to placebo in a randomized, double-blind, placebo-controlled trial of 60 participants with opioid use disorder. The dronabinol group, however, was not more likely to be successfully induced on injectable naltrexone nor were they more likely to complete treatment.³⁴

3.3.2.13 Opioid Withdrawal

In an inpatient randomized, double-blind, placebo-controlled trial of dronabinol for opioid withdrawal suppression in twelve participants with opioid use disorder, dronabinol doses from 5 mg to 30 mg failed to significantly suppress symptoms of opioid withdrawal. Dronabinol administration was complicated by dose-dependent increases in euphoria, sedation, and tachycardia. The tachycardia was significant enough for the initial planned maximum dose of 40 mg to be reduced to 30 mg. Furthermore, participants did not prefer dronabinol over placebo and they demonstrated some impairment in cognitive performance after dronabinol administration as well.^{35,36}

3.3.2.14 Tourette Syndrome

In two (n = 12 and 24) randomized, double-blind, placebo-controlled trials of dronabinol in participants with Tourette Syndrome, dronabinol produced either significant improvement in tics or a trend toward such improvement, as well as a significant improvement in obsessive-compulsive behavior in one of the studies.^{37,38}

3.4 Table 4: Studies of Delta-9-tetrahydrocannabinol

Intervention	Administration Method	Dose Evaluated	Comparator	Number of Studies Described in this Report	Indication
Pure delta-9-tetrahydrocannabinol	Capsules, Tablets	15 mg/day	Placebo	2	Abdominal pain
		3-4.5 mg/day	Placebo	4	Dementia
		4.5-15 mg/day	Placebo	1	Multiple Sclerosis
		Maximum 15 mg/day	Placebo	1	Nausea and Vomiting
		4.5-15 mg/day	Placebo	2	Neuropathic Pain
(-)-trans-delta-9-tetrahydrocannabinol (dronabinol)	Capsules (Oral)	20 mg/day	Placebo	1	Anxiety Disorder
		10 mg/day	Placebo	1	Amyotrophic Lateral Sclerosis

		5 mg/day	Placebo	1	Anorexia Appetite Stimulation in HIV/AIDS Infection Cannabis Use Disorder
		2.5- 10 mg/day	Placebo or Megestrol Acetate	4	
		40-60 mg/day	Placebo	2	

Intervention	Administration Method	Dose Evaluated	Comparator	Number of Studies Described in this Report	Indication
(-)-trans-delta-9-tetrahydrocannabinol (dronabinol)	Capsules (Oral)	10-20 mg/day	Placebo	3	Chronic Pain
		10-20 mg/day	Placebo	1	Depression
		7.5-15 mg/day	Placebo	5	Multiple Sclerosis
		7.5-15 mg/day	Placebo	2	Neuropathic Pain
		10 mg/day	Placebo	2	Noncardiac Chest Pain
		10 mg/ day	Placebo	1	Obstructive Sleep Apnea Opioid Use Disorder

3.5 Table 5: Studies of Delta-9-tetrahydrocannabinol cont.

		30 mg/day	Placebo	1	Opioid Withdrawal
		5-30 mg/day	Placebo	2	Tourette Syndrome
		5-10 mg/day	Placebo	2	

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