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Sativex for the Management of Multiple Sclerosis Symptoms

Summary

- **Sativex® is a cannabis-based pharmaceutical product containing Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:1 ratio, delivered in an oromucosal (mouth) spray. It has been approved as adjunctive treatment for neuropathic pain in patients with multiple sclerosis (MS). It is being investigated for the management of other MS symptoms, such as spasticity. THC:CBD spray is regulated as a narcotic.**
- **Five randomized controlled trials (RCTs) compared the benefits and harms of THC:CBD spray with placebo. A total of 368 patients with various neurological conditions (including MS) were recruited.**
- **In some trials, THC:CBD spray significantly reduced neuropathic pain, spasticity, muscle spasms and sleep disturbances.**
- **The most common adverse events (AEs) reported in trials were dizziness, sleepiness, fatigue, feeling of intoxication and a bad taste. Long-term safety and the potential for dependence, abuse, misuse and diversion are unknown.**

The Technology

Sativex® (developed by GW Pharmaceuticals and marketed by Bayer Inc.) contains THC and CBD delivered through an oromucosal (mouth) spray.[1] THC is the main psychoactive cannabinoid of the plant *Cannabis sativa*, commonly known as marijuana.[2] THC primarily acts as an agonist on cannabinoid receptors in the brain (CB1), and to some extent on cannabinoid receptors in peripheral tissues (CB2). Although the cellular mechanism is unclear, it is postulated that the activation of CB1 receptors affects brain synaptic function by inhibiting amino acid and monoamine neurotransmitter release. This affects neurological functions such as psychomotor behaviour, short-term memory, appetite and pain perception.[3] CBD is a non-psychoactive cannabinoid with weak antagonist activity at the CB1 receptors.[2] It may help modulate the response to THC.[4]

Regulatory Status

Sativex® (THC:CBD spray) is the first natural cannabis-based pharmaceutical product (not synthesized) to be considered for marketing approval anywhere in the world.[5] It received a Notice of Compliance with Conditions on April 15, 2005.[6] It is indicated as adjunctive treatment for the symptomatic relief of neuropathic pain in adults with MS.[7] Sativex® is regulated as a narcotic (Schedule II of the Controlled Drug and Substances Act and the Narcotic Control Regulations) (Cynthia Sunstrum, Health Canada, Ottawa: personal communication, 2005 Apr 25).

In March 2003, an application was made in the UK to approve the use of THC:CBC for the relief of spasticity in MS.[8] On December 3, 2004, the UK requested a confirmatory study on the effects of THC:CBD spray on spasticity.[9]

Patient Group

MS, which is a chronic neurological disorder of unknown etiology, causes inflammation and destruction of the myelin sheath and axonal damage of the brain and spinal cord. The disease usually appears in individuals between the ages of 20 to 40 years.[10,11] A diagnosis is based

on history, and clinical and magnetic resonance imaging (MRI) findings.[10,12] In 2004, an estimated 50,000 Canadians had MS.[11]
The symptoms of MS include fatigue; spasticity; pain; bladder, bowel, and sexual dysfunction; visual disturbances; coordination problems; and altered sensation.[10,11] Psychiatric conditions such as major depression and bipolar affective disorder are also common.[13]

Current Practice

There is no cure for MS. Disease-modifying agents such as beta interferons and glatiramer acetate used chronically may reduce relapses and may affect relapse-related outcomes.[14]
Examples of drug treatment used for MS-related symptoms include muscle relaxants (baclofen, dantrolene) for spasticity; antispasmodic agents (oxybutinin, tamsulosin) for bladder dysfunction; antiepileptic agents (gabapentin) for neuropathic pain; and selective serotonin reuptake inhibitors (fluoxetine) for fatigue and depression.[10]

The Evidence

Five RCTs evaluated the benefits and harms of THC:CBD combination therapy administered through a sublingual (under the tongue) or an oromucosal (on the inside of the cheek) spray. The trials were conducted in 368 patients with a variety of symptoms and neurological conditions; four trials included MS patients (Table 1).[15-19] One unpublished phase III, randomized, double-blind, placebo-controlled parallel group trial was conducted in 189 patients with MS, who were experiencing spasticity. Details about the results for this trial are unavailable.[20,21]

Statistically significant improvements were obtained for pain (two of five trials); spasticity (two of two trials); muscle spasms (one of two trials); and sleep disturbance (the number of times woken due to pain) (two of three trials). The trials were conducted in small groups of patients with heterogenic diagnosis and symptoms. Larger trials in better-defined study populations are required.

Adverse Effects

The most frequent AEs reported in the clinical trials are presented in Table 1. The trials were too short to determine long-term safety, although extension studies are in progress.[15,18] In the largest study, withdrawals due to AEs were greater with THC:CBD spray (three of 80) than with placebo (one of 80).[18]

Administration and Cost

THC:CBD combination therapy is administered as an oromucosal spray. It is available in a 5.5 mL vial that delivers ≤51 sprays. Each spray contains 2.7 mg of THC and 2.5 mg of CBD. On the first day, treatment should be initiated at a maximum rate of one spray every four hours, up to a maximum of four sprays. The dosage may be increased as required. There is limited experience with dosages of >12 sprays daily. The vial requires refrigeration and should be used within 28 days once opened.[7]

The drug is available in a package of four vials at a cost of $499.80 (ex-factory cost) (Doug Grant, Bayer Inc., Toronto: personal communication, 2005 Jul 12).

Concurrent Developments

Varying formulations of THC and CBD are being investigated in different delivery systems such as sublingual tablets and inhaled dosage forms for spinal cord injury, peripheral nerve injury, neuroinvasive cancer, dystonias, cerebral vascular accident, spina bifida, and pain and inflammation related to rheumatoid arthritis.[22]

Rate of Technology Diffusion

The rate of diffusion of the THC:CBD spray will depend on the results of ongoing studies assessing clinically meaningful outcomes. Social acceptance of a natural cannabinoid as a legitimate prescription treatment will affect its rate of diffusion. Given its prescription status, THC:CBD spray may be more accessible or acceptable than smoked marijuana.

Table 1: Benefits and harms of THC:CBD spray compared with placebo

Study	Participants	Interventions	Outcomes	Mean Treatment Difference	Adverse Events
Berman *et al.*[15]	48 non-MS patients (brachial plexus root injury)	THC:CBD spray,* THC extract (data not shown) or placebo; 2 weeks in each regimen (cross-over design); concomitant medications for symptoms allowed	Primary: pain; secondary: sleep	**Pain** (BS-11†): -0.58 boxes, p=0.005 **Sleep quality** (BS-11†): +0.6 boxes, p=0.019 **Sleep disturbance** (4 point scale‡): -0.2 boxes, p=0.017	**Dizziness:** THC:CBD n=9, placebo n=4 **Sleepiness:** THC:CBD n=7, placebo n=5 **A bad taste:** THC:CBD n=10, placebo n=1 **Nausea:** THC:CBD n=1, placebo n=3 **Feeling of intoxication:** THC:CBD n=4, placebo n=0
Rog *et al.,*[16] abstract	66 MS patients with central pain	THC:CBD* versus placebo for 1 week run-in plus 4 weeks treatment	Primary: pain and sleep; secondary: disability, anxiety and depression, memory, cognition, attention, ambulation	**Pain** (NPS**): -6.82, p=0.039 **Pain** (NRS§): -1.25 boxes, p=0.005 **Sleep disturbance** (NRS§): -1.39 boxes, p=0.003 **Secondary outcomes:** NS	**Patients with AE:** THC:CBD n=30, placebo n=22
Sharief *et al.,*[17] abstract	70 patients with chronic neuropathic pain, including MS patients	THC:CBD* versus placebo for 1 week run-in plus 3 weeks treatment; escape medication allowed	Pain, sleep	**Pain:** NS **Sleep disturbance** (5 point scale): -0.34 boxes, p=0.052	Not reported
Wade *et al.*[18]	160 patients with MS and one of the following symptoms: spasticity, spasms, bladder problems, tremor, pain	THC:CBD* versus placebo for 6 weeks; concomitant medications allowed	Primary: composite VAS; secondary: spasticity, muscle spasms, bladder problems, tremor, pain, disability, cognition, mood, sleep, fatigue	All NS except: **Disability** (GNDS$^{\Delta}$): +1.81, p=0.048 **Spasticity** (VAS$^{\ni}$): -22.79, p=0.001 **Sleep quality** (VAS$^{\ni}$): -7.10, p=0.047	**Dizziness:** THC:CBD 26 (32.5%), placebo 10 (12.5%) **Headache:** THC:CBD 7 (8.8%), placebo 13 (16.3%) **Fatigue:** THC:CBD 12 (15%), placebo 3 (3.8%) **Nausea:** THC:CBD 7 (8.8%), placebo 5 (6.3%)
Wade *et al.*[19]	24 patients with neurological diagnosis, including 18 MS patients	THC alone (data not shown), CBD alone (data not shown), THC:CBD,◊ or placebo; 2 weeks open-label plus 2 weeks on each regimen (cross-over design); previous medication allowed	Pain, muscle spasms, spasticity, impaired bladder control, coordination	All NS except: **Muscle spasm** (VAS$^{\Psi}$): +8.5, p<0.05 **Spasticity** (NSS•): -1.3, p<0.05	**Feeling of intoxication:** °VAS mean difference +8.3, p<0.05 **Patients with ≥1AE:** THC:CBD 6 out of 20 (30%), placebo 10 out of 21 (47.6%)

AE=adverse events; NS=statistically non-significant

*Each spray delivers 2.7 mg THC and 2.5 mg CBD for oromucosal administration.

†BS-11=box scale 11-point scale (0=best imaginable, 10=worst imaginable); a two-point difference would be considered a clinically significant change; a positive mean difference favours placebo.

‡4-point categorical scale (none, once, twice, more than twice)

**NPS=Neuropathic Pain Scale (10 items, 100 points)

§NRS=numerical rating scale (0=none, 10=worst)

ΔGNDS=Guy's Neurological Disability Scale; a positive mean difference favours placebo

∋VAS=visual analogue score (0=no symptoms, 100=worst symptoms)

◊Each spray delivers 2.5 mg THC and/or 2.5 mg CBD for sublingual administration.

ΨVAS=visual analogue score (0=worst possible, 100=best possible)

•NSS=numerical symptom scale (0=good, 10=bad)

°VAS=visual analogue scale (0=none, 100=severe)

Implementation Issues

Possible factors that may affect the implementation of THC:CBD spray include its unknown potential for dependence, abuse, misuse and diversion, and the clinical impact of some AEs (e.g., dizziness on the risk of falls). As THC:CBD spray is used as an add-on therapy, it will not replace existing treatment.

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