

Review

# Cannabinoids in medicine: A review of their therapeutic potential

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## Abstract

In order to assess the current knowledge on the therapeutic potential of cannabinoids, a meta-analysis was performed through Medline and PubMed up to July 1, 2005. The key words used were cannabis, marijuana, marihuana, hashish, hashich, haschich, cannabinoids, tetrahydrocannabinol, THC, dronabinol, nabilone, levonantradol, randomised, randomized, double-blind, simple blind, placebo-controlled, and human. The research also included the reports and reviews published in English, French and Spanish. For the final selection, only properly controlled clinical trials were retained, thus open-label studies were excluded.

Seventy-two controlled studies evaluating the therapeutic effects of cannabinoids were identified. For each clinical trial, the country where the project was held, the number of patients assessed, the type of study and comparisons done, the products and the dosages used, their efficacy and their adverse effects are described. Cannabinoids present an interesting therapeutic potential as antiemetics, appetite stimulants in debilitating diseases (cancer and AIDS), analgesics, and in the treatment of multiple sclerosis, spinal cord injuries, Tourette's syndrome, epilepsy and glaucoma. © 2006 Elsevier Ireland Ltd. All rights reserved.

*Keywords:* Cannabinoids; Cannabis; Therapeutic potential; Controlled clinical trials; Efficacy; Safety

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## 1. Introduction

Originating from Central Asia, cannabis is one of the oldest psychotropic drugs known to humanity. The beginnings of its use by humans are difficult to trace, because it was cultivated and consumed long before the appearance of writing. According to archeological discoveries, it has been known in China at least since the Neolithic period, around 4000 BC (McKim, 2000).

There are several species of cannabis. The most relevant are *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*. *Cannabis sativa*, the largest variety, grows in both tropical and temperate climates. The two main preparations derived from cannabis are marijuana and hashish. Marijuana is a Mexican term initially attributed to cheap tobacco but referring today to the dried leaves and flowers of the hemp plant. Hashish, the Arabic name for Indian hemp, is the viscous resin of the plant (Ben Amar and Léonard, 2002).

The Emperor of China, Shen Nung, also the discoverer of tea and ephedrine, is considered to be the first to have described the properties and therapeutic uses of cannabis in his compendium of Chinese medicinal herbs written in 2737 BC (Li, 1974). Soon afterwards, the plant was cultivated for its fibre, seeds, recreational consumption and use in medicine. It then spread to India from China (Mechoulam, 1986).

In 1839, William O'Shaughnessy, a British physician and surgeon working in India, discovered the analgesic, appetite stimulant, antiemetic, muscle relaxant and anticonvulsant properties of cannabis. The publication of his observations quickly led to the expansion of the medical use of cannabis (O'Shaughnessy, 1838–1840). It was even prescribed to Queen Victoria for relief of dysmenorrhea (Baker et al., 2003).

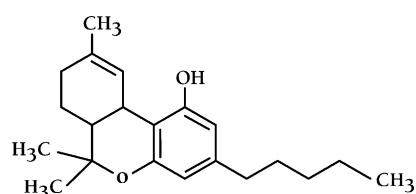
In 1854, cannabis is listed in the United States Dispensatory (Robson, 2001). It is sold freely in pharmacies of Western countries. It would be available in the British Pharmacopoeia in extract and tincture form for over 100 years (Iversen, 2000).

However, after prohibition of alcohol was lifted, the American authorities condemned the use of cannabis, making it responsible for insanity, moral and intellectual deterioration, violence and various crimes. Thus, in 1937, under pressure from the Federal Bureau of Narcotics and against the advice of the American Medical Association, the U.S. Government introduced the *Marihuana Tax Act*: a tax of \$1 per ounce was collected when marijuana was used for medical purposes and \$100 per ounce when it was used for unapproved purposes (Solomon, 1968; Carter et al., 2004). In 1942, cannabis was removed from the United States Pharmacopoeia, thus losing its therapeutic legitimacy (Fankhauser, 2002).

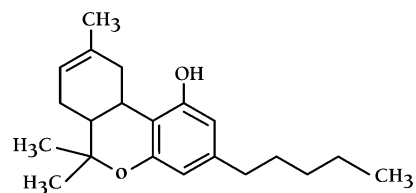
Great Britain and most European countries banned cannabis by adopting the 1971 Convention on Psychotropic Substances instituted by the United Nations.

Cannabis contains more than 460 known chemicals, more than 60 of which are grouped under the name cannabinoids (Ben Amar, 2004). The major psychoactive ingredient of cannabis is delta-9-tetrahydrocannabinol, commonly known as THC. Other cannabinoids present in Indian hemp include delta-8-tetrahydrocannabinol ( $\Delta^8$ THC), cannabinal (CBN), cannabidiol (CBD), cannabicyclol (CBL), cannabichromene

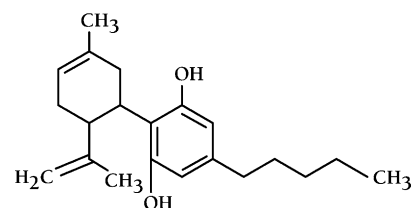
(CBC) and cannabigerol (CBG), but they are present in small quantities and have no significant psychotropic effects compared to THC (Smith, 1998; McKim, 2000). However, they may have an impact on the product's overall effect (Ashton, 2001). Cannabinoids exert their actions by binding to specific receptors: the CB<sub>1</sub> cannabinoid receptors, discovered by Devane et al. (1988), then cloned by Matsuda et al. (1990) and the CB<sub>2</sub> cannabinoid receptors, identified by Munro et al. (1993). Both cannabinoid receptors are part of the G-protein coupled class and their activation results in inhibition of adenylate cyclase activity. The identification of agonists (anandamide and 2-arachidonylglycerol, the most studied endocannabinoids, participate in the regulation of neurotransmission) and antagonists of these receptors has stimulated interest in the medical uses of cannabis (Baker et al., 2003; Iversen, 2003; Di Marzo et al., 2004).



$\Delta^9$  - tetrahydrocannabinol (THC)



$\Delta^8$  - tetrahydrocannabinol



Cannabidiol (CBD)

Despite its illegality, patients have continued to obtain cannabis on the black market for self-medication. In 1978, in response to the success of a lawsuit filed by a glaucoma patient (Robert Randall) who had begun treating himself by smoking marijuana after losing a substantial part of his vision, the U.S. Government created a compassionate program for medical marijuana: 20 people suffering from debilitating diseases legally received marijuana cigarettes from the National Institute on Drug Abuse (NIDA), after approval by the Food and Drug Administration (FDA). This program was closed to new candidates in 1991 by President Bush, but still recently seven people continued to receive their marijuana (Mirken, 2004).

In Canada, 14 years after the 1988 arrest of Terrance Parker (an Ontario patient who had discovered that marijuana con-

sumption relieved his epileptic attacks, contrary to conventional drugs) and 1 year after the Ontario Court of Appeal ruled that discretionary regulation of marijuana use for medical purposes was contrary to the principles of the Canadian Charter of Rights and Freedoms, the Government of Canada decided to draft new regulations (Hoey, 2001). Thus, since July 30, 2001, the *Marihuana Medical Access Regulations* (MMAR) allow Canadian patients suffering from a serious disease to be eligible for therapeutic marijuana consumption. As of April 2005, 821 people were thus authorized to possess marijuana for medical purposes and 363 physicians had supported a request for authorization of possession (Health Canada, 2005).

The therapeutic applications of cannabis and its derivatives have been studied by various world bodies, including the Scientific Committee of the House of Lords in Great Britain (1998), the Institute of Medicine in the United States (1999) and the Senate Special Committee on Illegal Drugs in Canada (Nolin et al., 2002). Since 2003, medicinal cannabis, in standard cannabinoid concentrations, is sold in pharmacies in the Netherlands by medical prescription (Gorter et al., 2005). It is presently available in two dosages: cannabis flos, variety Bedrocan, containing 18% dronabinol and 0.8% cannabidiol and cannabis flos, variety Bedrobinol, containing 13% dronabinol and 0.2% cannabidiol (Office of Medicinal Cannabis, 2005). Various Western countries have authorized and conducted clinical trials on cannabis and its derivatives. Thus, for example, since 1999, Health Canada, in collaboration with the Canadian Institutes of Health Research, has established a Medical Marijuana Research Program (Health Canada/CIHR, 1999).

To date, there are a multitude of anecdotal reports and a certain number of clinical trials evaluating the therapeutic applications of cannabis and its derivatives. This review reports on the most current data available on the therapeutic potential of cannabinoids.

## 2. Methodology

A systematic search was performed in Medline and PubMed up to July 1, 2005. The key words used were cannabis, marijuana, marihuana, hashish, hashich, haschich, cannabinoids, tetrahydrocannabinol, THC, dronabinol, nabilone, levonantradol, randomised, randomized, double-blind, simple blind, placebo-controlled, and human.

After initial sorting, all articles and reviews including clinical protocols or a summary of the literature evaluating the therapeutic potential of cannabinoids in humans were read. For the final selection, only properly controlled clinical trials were retained. Thus, open-label studies were excluded.

The list of references of all the relevant articles was also studied to include all reports and reviews related to the subject. The research included the works and data available in English, French and Spanish.

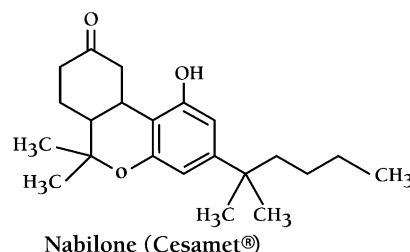
For each clinical study, the country where the project was held, the number of patients assessed, the type of study and comparisons made, the products and the dosages used, their efficacy and their adverse effects were identified.

## 3. Results

The meta-analysis identified 10 pathologies in which controlled studies on cannabinoids have been published: nausea and vomiting associated with cancer chemotherapy, loss of appetite, pain, multiple sclerosis, spinal cord injuries, Tourette's syndrome, epilepsy, glaucoma, Parkinson disease and dystonia.

### 3.1. Antiemetic effect

Cancer chemotherapy frequently causes nausea and vomiting which vary in intensity, but which can sometimes be severe and prolonged. In the 1970s and 1980s, the most widely used antiemetics were prochlorperazine, metoclopramide, chlorpromazine, domperidone, thiethylperazine and haloperidol. During this same period, various controlled studies evaluating the antiemetic effects of nabilone and dronabinol described the efficacy of these two cannabinoids (Table 1). Nabilone is a synthetic analog of THC and dronabinol is synthetic THC. The two substances were administered orally in clinical trials.



In the 15 controlled studies in which nabilone was compared to a placebo or an antiemetic drug, a total of 600 patients suffering from various types of cancers received this cannabinoid. Nabilone turned out to be significantly superior to prochlorperazine, domperidone and alizapride for treating nausea and vomiting associated with cancer chemotherapy. On the other hand, the patients clearly favoured nabilone for continuous use. The results led Health Canada to approve the marketing of this product. Marketed under the name Cesamet®, nabilone has been available in Canada since 1982. It is presented in the form of 1 mg pulvules. The recommended dosage is 2–6 mg per day (CPA, 2005).

With dronabinol, 14 controlled studies involving a total of 681 patients suffering from various types of cancers demonstrated that this cannabinoid exhibits an antiemetic effect equivalent to or significantly greater than chlorpromazine and equivalent to metoclopramide, thiethylperazine and haloperidol. All of these data led to the approval and marketing of dronabinol in the United States in 1985 and in Canada in 1995. Available under the name Marinol®, it is presented in the form of capsules of 2.5, 5 and 10 mg of THC. The recommended dosage as an antiemetic for nausea and vomiting induced by cancer chemotherapy is 5–15 mg/m<sup>2</sup>/dose, without exceeding 4–6 doses per day (CPA, 2005).

Nonetheless, the efficacy of nabilone and dronabinol as antiemetic agents is eclipsed by the high and sometimes severe incidence of their undesirable reactions. On the other hand, their interest has declined considerably since the advent of

Table 1  
Controlled studies evaluating the antiemetic effects of cannabinoids in patients receiving cancer chemotherapy

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Sallan et al. (1975)	United States	20 adults with various tumors (ages: 18–76)	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 15 mg or 10 mg/m <sup>2</sup> × 3 times	Antiemetic effect of THC significantly superior to placebo	Drowsiness in 2/3 of the patients; euphoria in 13 patients
Chang et al. (1979)	United States	15 patients with osteogenic sarcoma (ages: 15–49)	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 10 mg/m <sup>2</sup> × 5 times or smoked: one marijuana cigarette containing 1.93% THC (in the case of a vomiting episode, oral THC is replaced by a marijuana cigarette for the subsequent doses)	Oral THC alone or the combination of oral and smoked THC had an antiemetic effect significantly superior to placebo	Sedation in 80% of the patients
Frytak et al. (1979)	United States	116 adults with gastrointestinal tumors (median age: 61 years)	Randomized, double-blind, placebo-controlled, parallel groups	Oral THC: 15 mg × 3 times: 38 patients; oral prochlorperazine 10 mg × 3 times: 41 patients; placebo: 37 patients	Antiemetic effect equivalent with THC and prochlorperazine and superior to placebo	More frequent and more severe with THC than with prochlorperazine; 12 patients receiving THC and 1 patient receiving prochlorperazine dropped out of the study due to intolerable central nervous system toxicity
Kluin-Neleman et al. (1979)	The Netherlands	11 adults with Hodgkin or non-Hodgkin lymphoma (ages: 21–53)	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 10 mg/m <sup>2</sup> × 3 times	Antiemetic effect of THC significantly superior to placebo	Dizziness (82%), hallucinations (45%), euphoria (36%), drowsiness (36%), derealization (18%), concentration disorders (18%); some severe effects of THC resulted in stoppage of the clinical trial
Herman et al. (1979)	United States	113 patients with various tumors (ages: 15–74)	Randomized, double-blind, crossover	Oral nabilone: 2 mg × 3 or 4 times; oral prochlorperazine: 10 mg × 3 or 4 times	Antiemetic effect of nabilone significantly superior to prochlorperazine; the patients clearly favoured nabilone for continuous use	Drowsiness, dry mouth and dizziness observed with both products but twice as frequent and often more severe with nabilone; four patients taking nabilone exhibited undesirable effects which required medical attention: hallucinations in three patients and hypotension in one patient; euphoria associated with nabilone was infrequent (16% of cases) and mild

Table 1 (Continued)

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Orr et al. (1980)	United States	55 adults with various tumors (ages: 22–71)	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 7 mg/m <sup>2</sup> × 4 times; oral prochlorperazine: 7 mg/m <sup>2</sup> × 4 times	Antiemetic effect of THC significantly superior to prochlorperazine; the antiemetic effect of prochlorperazine was not statistically better than that of placebo	THC: euphoria (82%), sedation (28%), transient loss of emotional or physical control (21%); prochlorperazine: sedation (26%), dizziness (22%), dry mouth (11%)
Sallan et al. (1980)	United States	73 patients with various tumors (ages: 9–70)	Randomized, double-blind, crossover	Oral THC: 15 mg or 10 mg/m <sup>2</sup> × 3 times; oral prochlorperazine: 10 mg × 3 times	Antiemetic effect of THC significantly superior to prochlorperazine; most patients preferred THC to prochlorperazine; increase in food intake more frequent with THC	Euphoria with THC frequent but well tolerated
Colls et al. (1980)	New Zealand	35 adults with solid tumors	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 12 mg/m <sup>2</sup> × 3 times; oral thiethylperazine: 6.6 mg/m <sup>2</sup> × 3 times; metoclopramide IV: 4.5 mg/m <sup>2</sup> × 1 time	Antiemetic effect equivalent with all three products	Adverse effects, primarily of a neuropsychiatric nature, more frequent and severe with THC than with thiethylperazine or metoclopramide
Steele et al. (1980)	United States	37 adults with various tumors (ages: 19–65)	Randomized, double-blind, crossover	Oral nabilone: 2 mg × 2 times; oral prochlorperazine: 10 mg × 2 times	Antiemetic effect of nabilone superior to prochlorperazine	Nabilone: drowsiness (47%), dizziness (36%), dry mouth (25%), euphoria (19%), postural hypotension (17%). These side effects were severe enough to prohibit or modify the use of nabilone in 25% of patients; prochlorperazine: drowsiness (35%), dizziness (9%), dry mouth (5%). These side effects were mild
Chang et al. (1981)	United States	8 patients with various tumors (ages: 17–58)	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 10 mg/m <sup>2</sup> × 5 times or smoked: one marijuana cigarette containing 1.93% THC (in the case of a vomiting episode, oral THC is replaced by a marijuana cigarette for the subsequent doses)	No antiemetic effect of THC in this group of patients receiving cyclophosphamide or doxorubicin	Euphoria (75%) and short lasting episodes of tachycardia
Neidhart et al. (1981)	United States	36 patients with various tumors (median age: 45 years)	Randomized, double-blind, crossover	Oral THC: 10 mg × (4–8) times; oral haloperidol: 2 mg × (4–8) times	Antiemetic effect equivalent with THC and haloperidol	THC: toxicity in 94% of the patients. The most frequent manifestations were drowsiness (58%), feeling faint (55%), euphoria (40%), spasms or tremors (15%). Toxicity interfered with function in 25% of the cases; haloperidol: toxicity in 79% of the patients. The most frequent manifestations were drowsiness (36%), euphoria (30%) and spasms or tremors (18%). Toxicity interfered with function in 6% of the cases

Table 1 (Continued)

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Einhorn et al. (1981)	United States	80 patients with various tumors (ages: 15–74)	Randomized, double-blind, crossover	Oral nabilone: 2 mg × 4 times; oral prochlorperazine: 10 mg × 4 times	Antiemetic effect of nabilone significantly superior to prochlorperazine; 75% of patients preferred nabilone for continuous use	Hypotension, euphoria, drowsiness and lethargy more pronounced with nabilone
Ungerleider et al. (1982)	United States	172 adults with various tumors (ages: 18–82)	Randomized, double-blind, crossover	Oral THC: 7.5–12.5 mg × 4 times; oral prochlorperazine: 10 mg × 4 times	Antiemetic effect equivalent with THC and prochlorperazine	Drowsiness, dizziness, concentration disorders, spatial-time distortions, euphoria, loss of activity and reduction of social interactions more frequent with THC than with prochlorperazine
Johansson et al. (1982)	Finland	18 adults with various tumors (ages: 18–70)	Randomized, double-blind, crossover	Oral nabilone: 2 mg b.i.d.; oral prochlorperazine: 10 mg b.i.d.	Antiemetic effect of nabilone significantly superior to prochlorperazine; 72% of patients preferred nabilone for continuous use	More frequent and more severe with nabilone than with prochlorperazine. Main side effects: nabilone: postural hypotension (42%), dizziness (23%), mood disorders (8%); prochlorperazine: headaches (13%), postural hypotension (9%), dizziness (9%)
Wada et al. (1982)	United States	84 adults with various tumors (ages: 18–81)	Randomized, double-blind, crossover, placebo-controlled	Oral nabilone: 2 mg × 2 times	Antiemetic effect of nabilone significantly superior to placebo	Frequent: dizziness (40%), drowsiness (34%), dry mouth (28%), euphoria (25%), dysphoria (10%); generally mild or moderate except in 11 patients who reported severe reactions which led 8 of them to terminate the study
Jones et al. (1982)	United States	24 adults with various tumors	Randomized, double-blind, crossover, placebo-controlled	Oral nabilone: 2 mg × 2 times	Antiemetic effect of nabilone significantly superior to placebo	Frequent: dizziness (65%), drowsiness (51%), dry mouth (31%), sleep disorders (14%); 11 patients dropped out of the study due to side effects caused by nabilone
Levitt (1982)	Canada	36 patients with various tumors (ages: 17–78)	Randomized, double-blind, crossover, placebo-controlled	Oral nabilone: 2 mg × 2 times	Antiemetic effect of nabilone significantly superior to placebo	Frequent: vertigo (67%), drowsiness (61%), depersonalization (35%), dry mouth (24%), disorientation (16%); five patients dropped out of the study due to side effects caused by nabilone



Table 1 (Continued)

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
George et al. (1983)	France	20 women with advanced gynaecological tumors (median age: 54 years)	Randomized, double-blind, crossover	Oral nabilone: 1 mg × 3 times; chlorpromazine IM: 12.5 mg × 1 time	Antiemetic effect equivalent but insufficient with nabilone and chlorpromazine at doses used	More frequent with nabilone than with chlorpromazine but their extent never required specific treatment. Main side effects: nabilone: dry mouth (80%), drowsiness (60%), inebriated sensations (40%), postural hypotension (35%); chlorpromazine: dry mouth (40%), drowsiness (27%)
Ahmedzai et al. (1983)	Scotland	26 patients with lung cancer (ages: 27–72)	Randomized, double-blind, crossover	Oral nabilone: 2 mg b.i.d.; oral prochlorperazine: 10 mg t.i.d.	Antiemetic effect of nabilone significantly superior to prochlorperazine; 62% of patients preferred nabilone for continuous use	More frequent with nabilone than with prochlorperazine. Main side effects: nabilone: drowsiness (57%), postural dizziness (35%), euphoria (21%), drunk-feeling (18%), lightheadedness (18%); prochlorperazine: drowsiness (27%)
Hutcheon et al. (1983)	Great Britain	108 patients with various tumors (ages: 17–80)	Randomized, single blind, parallel groups	Levonantradol IM (synthetic cannabinoid): 0.5 mg × 4 times: 27 patients; 0.75 mg × 4 times: 28 patients; 1 mg × 4 times: 26 patients; chlorpromazine IM 25 mg × 4 times: 27 patients	Antiemetic effect of levonantradol (0.5 mg) significantly superior to chlorpromazine (25 mg); higher doses of levonantradol did not increase its efficacy and were accompanied by a greater toxicity	Levonantradol (0.5 mg) and chlorpromazine (25 mg) were reasonably well tolerated: they mainly cause drowsiness and dizziness with equivalent frequency; 0.75 mg and 1 mg doses of levonantradol induce significant, sometimes unacceptable toxicity
Gralla et al. (1984)	United States	30 adults with various tumors (ages: 39–72)	Randomized, double-blind, parallel groups	Oral THC: 10 mg/m <sup>2</sup> × 5 times: 15 patients; metoclopramide IV: 10 mg/m <sup>2</sup> × 5 times: 15 patients	Antiemetic effect of metoclopramide significantly superior to THC	The two products induced frequent but generally well tolerated side effects. Main adverse reactions: THC: sedation (86%), dry mouth (80%), dizziness (80%), orthostatic hypotension (53%), euphoria (20%); metoclopramide: sedation (93%), dry mouth (33%), dizziness (7%), euphoria (7%)
Levitt et al. (1984)	Canada	20 adults with various tumors (ages: 28–78)	Randomized, double-blind, crossover, placebo-controlled	One marijuana cigarette + placebo oral THC × 4 times; oral THC: 15 mg + placebo marijuana cigarette × 4 times	The treatments were effective only in 25% of the patients; 35% of the subjects preferred oral THC, 20% preferred smoked marijuana and 45% had no preference	Seven persons exhibited distortions of time perception or hallucinations: four with THC alone, two with marijuana alone and one with both
Niiranen and Mattson (1985)	Finland	24 adults with lung cancer (ages: 48–78)	Randomized, double-blind, crossover	Oral nabilone: 1 mg × 2–4 times; oral prochlorperazine: 7.5 mg × (2–4) times	Antiemetic effect of nabilone significantly superior to prochlorperazine; 2/3 of the patients preferred nabilone to prochlorperazine	More frequent with nabilone than with prochlorperazine; three patients dropped out of the study due to decreased coordination and hallucinations induced by nabilone; main side effects of nabilone: vertigo (48%), dry mouth (26%); prochlorperazine only induced drowsiness in one patient

Table 1 (Continued)

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Dalzell et al. (1986)	Great Britain	18 patients with various tumors (ages: 10 months to 17 years)	Randomized, double-blind, crossover	Oral nabilone: 1–3 mg; oral domperidone: 15–45 mg	Antiemetic effect of nabilone significantly superior to domperidone; most patients or their parents preferred nabilone for continuous use	More frequent with nabilone than with domperidone but generally well tolerated. Main side effects: nabilone: drowsiness (55%), dizziness (36%), mood changes (14%); domperidone: drowsiness (27%), dizziness (5%), mood changes (5%)
Pomeroy et al. (1986)	Ireland	38 adults with various tumors (ages: 21–66)	Randomized, double-blind, parallel groups	Oral nabilone: 1 mg $\times$ 3 times: 19 patients; oral domperidone: 20 mg $\times$ 3 times: 19 patients	Antiemetic effect of nabilone significantly superior to domperidone	More frequent with nabilone than with domperidone but generally well tolerated. Main side effects: nabilone: drowsiness (58%), dizziness (58%), dry mouth (53%), postural hypotension (21%), euphoria (11%), headaches (11%), lightheadedness (11%); domperidone: drowsiness (47%), dry mouth (42%), dizziness (21%), headaches (16%)
Niederle et al. (1986)	Germany	20 adults with testicular cancer (ages: 19–45)	Randomized, double-blind, crossover	Oral nabilone: 2 mg $\times$ 2 times; oral alizapride: 150 mg $\times$ 3 times	Antiemetic effect of nabilone significantly superior to alizapride; 50% of the patients preferred nabilone, 35% preferred alizapride and 15% expressed no preference	More frequent with nabilone than with alizapride. Main side effects: nabilone: drowsiness (80%), hypotension or tachycardia (70%), dry mouth (65%), apathy (15%), euphoria (10%), decreased concentration (10%); alizapride: drowsiness (20%), extrapyramidal effects (20%), headaches (10%)
Crawford and Buckman (1986)	Great Britain	32 patients with ovarian cancer or germ cell tumors	Randomized, double-blind, crossover	Oral nabilone: 1 mg $\times$ 5 times; metoclopramide IV: 1 mg/kg $\times$ 5 times	Antiemetic effect equivalent but insufficient with nabilone and metoclopramide	Main side effect of nabilone: drowsiness; main side effect of metoclopramide: diarrhea
Chan et al. (1987)	Canada	30 patients with various tumors (ages: 3.5–17.8)	Randomized, double-blind, crossover	Oral nabilone: 1–4 mg; oral prochlorperazine: 5–20 mg	Antiemetic effect of nabilone significantly superior to prochlorperazine; 66% of the patients preferred nabilone, 17% preferred prochlorperazine and 17% expressed no preference; lower doses of nabilone had equivalent efficacy and did not induce major side effects	More frequent with nabilone than with prochlorperazine but generally well tolerated. Main side effects: nabilone: drowsiness (67%), dizziness (50%), mood disorders (14%); prochlorperazine: drowsiness (17%), mood disorders (11%)
McCabe et al. (1988)	United States	36 adults with various tumors (ages: 18–69)	Randomized, crossover	Oral THC: 15 mg/m <sup>2</sup> $\times$ 7 times; oral prochlorperazine: 10 mg $\times$ 7 times	Antiemetic effect of THC significantly superior to prochlorperazine	Frequent but transient dysphoria with THC
Lane et al. (1991)	United States	54 adults with various tumors (ages: 20–68)	Randomized, double-blind, parallel groups	Oral THC: 10 mg $\times$ 4 times: 17 patients; oral prochlorperazine: 10 mg $\times$ 4 times: 20 patients; oral THC (10 mg $\times$ 4 times) + oral prochlorperazine (10 mg $\times$ 4 times): 17 patients	Antiemetic effect of THC significantly superior to prochlorperazine; the combination of THC and prochlorperazine was significantly more effective as an antiemetic than monotherapy	Adverse reactions, essentially related to the CNS, were more frequent with THC than with prochlorperazine; bitherapy reduced the frequency of dysphoric symptoms observed with THC alone

Reviews on cannabis and emesis: British Medical Association (1997; pp. 21–27), Tramer et al. (2001) and Bagshaw and Hagen (2002).



5-HT<sub>3</sub> receptor antagonists such as dolasetron, granisetron, ondansetron, palonosetron and tropisetron. These agents are more potent, do not exhibit significant psychotropic effects and can be administered intravenously (Iversen, 2000; Robson, 2001; Söderpalm et al., 2001; Jordan et al., 2005).

Levonantradol, a synthetic cannabinoid administered intramuscularly, has also proved its antiemetic efficacy in a controlled study. In 108 patients suffering from various tumors, it turned out to be significantly superior to chlorpromazine to relieve nausea and vomiting related to antineoplastic chemotherapy. However, its adverse central effects limit its utility (Hutcheon et al., 1983; British Medical Association, 1997).

Only three controlled studies have evaluated the efficacy of smoked marijuana to alleviate nausea and vomiting accompanying cancer chemotherapy (Chang et al., 1979, 1981; Levitt et al., 1984; Table 1): the first two used smoked marijuana which substituted oral THC, only in case of failure with dronabinol (Chang et al., 1979, 1981), the third compared smoked marijuana to oral THC (Levitt et al., 1984). In this third case, during a randomized, double-blind, crossover, placebo-controlled clinical trial, conducted in Canada on 20 adults suffering from various tumors and receiving cancer chemotherapy, Levitt et al. (1984) evaluated the antiemetic effects of smoked marijuana and oral THC (Table 1). The treatments only turned out to be effective in 25% of the patients. While questioning the 20 subjects, 35% preferred oral dronabinol, 20% preferred smoked marijuana and 45% did not express a preference. In addition, seven individuals experienced distortions of time perception or hallucinations: four with oral THC alone, two with smoked marijuana alone and one with both substances.

Despite the existence of many clinical trials with cannabinoids against nausea and vomiting associated with cancer chemotherapy, none have compared their efficacy against newer generation agents such as the 5-HT<sub>3</sub> receptor antagonists and the more recent neurokinin-1-receptor-antagonists (Jordan et al., 2005).

### 3.2. Appetite stimulation

Anorexia (loss of appetite) and a progressive weight loss are observed in patients suffering from advanced stages of cancer or HIV infection. In the case of AIDS, cachexia (extreme weight loss) may be accompanied by chronic diarrhea and weakness (Iversen, 2000).

Two controlled studies have demonstrated that oral THC stimulates appetite and helps retard chronic weight loss in adults suffering from various advanced cancers (Table 2). On the other hand, a clinical trial conducted on 139 patients suffering from AIDS and a weight loss of 2.3 kg or more illustrated that, compared to placebo, oral THC induced a marked, statistically significant stimulation of appetite after 4–6 weeks of treatment. THC tended to stabilize weight, while patients on placebo continued to lose weight. This effect persisted in the subjects who continued to receive dronabinol after the end of the study (Beal et al., 1995).

In a randomized, double-blind, parallel-group clinical trial of 469 individuals suffering from advanced cancer accompanied by

weight loss of 2.3 kg or more in the past 2 months and/or a daily intake of less than 20 calories/kg of body weight, Jatoi et al. (2002) compared the effects of oral THC at a 2.5 mg b.i.d. dose (152 patients), oral megestrol, a synthetically derived progesterone, at a 800 mg/day dose (159 patients) and the association of the two products at the aforesaid dosages (158 patients) on the anorexia of these subjects. The authors found that at these doses, megestrol alone stimulated appetite in 75% of the subjects and induced a weight gain in 11% of the subjects, while oral THC alone stimulated appetite in 49% of the patients and produced a weight gain in 3% of the patients. These two differences were statistically significant. Moreover, the combined therapy did not confer additional benefits. The toxicity of these two substances was comparable, except for an increased incidence of impotence in men receiving megestrol (Table 2). This study was criticized for the use of a low dosage of dronabinol (Roncoroni, 2003).

Indeed, a recent study conducted in the United States on 67 HIV-infected adults using a higher dosage of oral THC (2.5 mg t.i.d.) made it possible to obtain more interesting results (Abrams et al., 2003). Comparing smoked marijuana (one to three cigarettes per day containing 3.95% THC), oral THC and placebo, the clinical trial illustrated that after 21 days of treatment, smoked THC and oral THC induced a statistically greater weight gain than placebo (Table 2). The study also showed that during the treatment period, THC administered by intrapulmonary or oral routes did not affect neither the viral load nor the number of CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes. Moreover, the two forms of THC did not interfere with the protease inhibitors (indinavir or nelfinavir) taken by the patients (Abrams et al., 2003).

Health Canada has approved oral THC (Marinol<sup>®</sup>) as an appetite stimulant for the treatment of anorexia and weight loss associated with AIDS. This synthetic THC or dronabinol (Marinol<sup>®</sup>) is available in the form of 2.5, 5 and 10 mg THC capsules. The recommended dosage for this therapeutic indication is 2.5–20 mg per day (CPA, 2005).

### 3.3. Analgesia

Several cannabinoids proved to be effective analgesics in acute and chronic pain animal models (Segal, 1986; Consroe and Sandyk, 1992; Iversen, 2000; Duran et al., 2004). The literature review identified 14 controlled studies (Table 3) evaluating the effects of cannabinoids on human beings suffering from acute pain (postoperative or experimental pain) or chronic pain (cancerous, neuropathic or of various origins). The substances analyzed were oral THC in capsules (four studies) or in extract form (one study), THC in sublingual spray (two studies), intravenous THC (one study), cannabidiol in sublingual spray (two studies) and the following synthetic analogs: oral benzopyranoperidine (three studies), oral CT-3 (one study) and intramuscular levonantradol (one study).

Two controlled studies performed on a total of 46 patients demonstrated the analgesic efficacy of oral THC in 10, 15 and 20 mg doses on their cancerous pains. However, drowsiness and confusion were frequent (Noyes et al., 1975a,b). In contrast, oral THC at the 5 mg dosage did not show an analgesic effect

Table 2  
Controlled studies evaluating the appetite stimulant effects of cannabinoids in cancer or HIV/AIDS patients

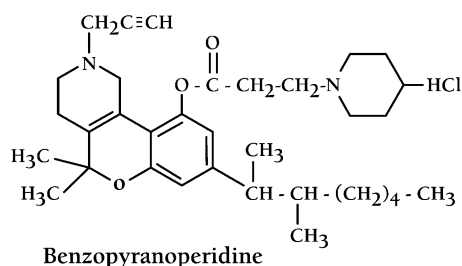
Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Regelson et al. (1976)	United States	54 adults with advanced cancer (ages: 21–73)	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 0.1 mg/kg t.i.d., i.e. 5–22.5 mg/day	THC stimulated appetite and helped retard chronic weight loss associated with cancer: on THC: total weight gain of 1.25 lb; on placebo: total weight loss of 21.25 lbs	The side effects limiting the use of THC in 25% of the patients were dizziness, confusion, drowsiness and dissociation
Struwe et al. (1993)	United States	12 men with symptomatic HIV infection and weight loss of 2.3 kg or more	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 5 mg b.i.d.	THC stimulated appetite but the weight variation observed on THC and on placebo was statistically insignificant: on THC: median weight gain of 0.5 kg; on placebo: median weight loss of 0.7 kg	Two patients exhibited sedation and mood disorders and withdrew from the study
Beal et al. (1995)	United States	139 patients with AIDS and weight loss of 2.3 kg or more	Randomized, double-blind, parallel groups, placebo-controlled	Oral THC: 2.5 mg b.i.d.: 72 patients; placebo: 67 patients	THC induced a marked, statistically significant stimulation of appetite. It tended to stabilize weight, while patients on placebo continued to lose weight	Generally minor or moderate. Main side effects: euphoria (12.5%), dizziness (7%), confusion (7%), drowsiness (6%)
Jatoi et al. (2002)	United States	469 adults with advanced cancers, weight loss of 2.3 kg or more over the past 2 months and/or intake of less than 20 calories/kg/day	Randomized, double-blind, parallel groups	Oral THC: 2.5 mg b.i.d.: 152 patients; oral megestrol (synthetically derived progesterone): 800 mg die: 159 patients; oral THC: 2.5 mg b.i.d. + oral megestrol 800 mg die: 158 patients	In monotherapy, megestrol stimulated appetite in 75% of the subjects and induced a weight gain in 11% of the subjects, while oral THC stimulated appetite in 49% of the patients and caused a weight gain in 3% of the patients. These two differences were statistically significant; combined therapy did not confer additional benefits	Main side effects: THC: drowsiness (36%), confusion (24%), loss of coordination (15%); megestrol: drowsiness (33%), confusion (21%), male impotence (18%), fluid retention (18%), loss of coordination (16%); THC + megestrol: drowsiness (39%), confusion (21%), loss of coordination (18%), male impotence (14%), fluid retention (13%)
Abrams et al. (2003)	United States	67 adults with HIV infection	Randomized, double-blind for oral THC or placebo, parallel groups, placebo-controlled	Smoked THC: one to three marijuana cigarettes per day containing 3.95% THC <i>n</i> = 21 patients; oral THC: 2.5 mg t.i.d. <i>n</i> = 25 patients; placebo: <i>n</i> = 21 patients	Weight gain equivalent with smoked THC and oral THC and statistically superior to placebo after 21 days of treatment: smoked THC group: average weight gain of 3.0 kg; oral THC group: average weight gain of 3.2 kg; placebo group: average weight gain of 1.1 kg; smoked THC and oral THC did not affect the viral load nor the number of CD4 <sup>+</sup> and CD8 <sup>+</sup> lymphocytes for the duration of treatment; smoked THC and oral THC did not interfere with the protease inhibitors taken by the patients (indinavir or nelfinavir)	Generally well tolerated; one patient in the smoked THC group dropped out of the study due to grade 2 neuropsychiatric troubles; two patients in the oral THC group dropped out of the study due to side effects: grade 2 paranoia (one patient), persistent headache and nausea (one patient)

Reviews on cannabis and anorexia: British Medical Association (1997; pp. 45–49), Iversen (2000; pp. 147–155) and Bagshaw and Hagen (2002).

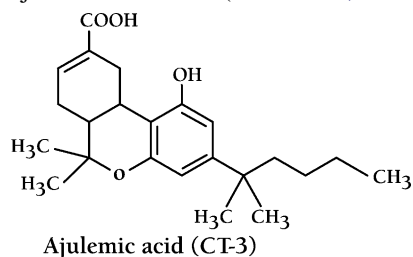
on postoperative pain in 40 women who had undergone elective abdominal hysterectomy (Buggy et al., 2003), nor did oral THC at a 20 mg dose manifest antinociceptive properties in 12 healthy subjects under experimental pain conditions (Naef et al., 2003).

In two recent studies conducted on 34 subjects suffering from chronic pain (Notcutt et al., 2004) and 48 patients exhibiting central neuropathic pain (Berman et al., 2004), THC in sublingual spray (2.5 or 2.7 mg, respectively), whether alone or combined to cannabidiol in sublingual spray (2.5 mg), exhibited pain relief and improvement in sleep quality (Berman et al., 2004; Notcutt et al., 2004), while cannabidiol alone, in this same sublingual spray format, turned out to be ineffective (Notcutt et al., 2004). Nor did oral cannabidiol show an analgesic effect in 10 patients suffering from chronic neuropathic pain (Lindstrom et al., 1987). Intravenous THC in 0.22 and 0.44 mg/kg doses also appeared to be ineffective in treatment of postoperative pain in 10 healthy volunteers undergoing molar extractions (Raft et al., 1977).

On the other hand, benzopyranoperidine, a synthetic nitrogen analog of THC, administered orally in the 4 mg dose, manifested an analgesic effect in a total of 45 patients suffering from cancerous pains (Staquet et al., 1978). Nonetheless, the beneficial effect of benzopyranoperidine was absent in a group of 35 subjects suffering from chronic pain (Jochimsen et al., 1978). The major undesirable effect of benzopyranoperidine was drowsiness.



Furthermore, oral CT-3 (ajulemic acid), a synthetic analog of 11-hydroxy-THC, showed analgesic efficacy in a study of 21 patients suffering from chronic neuropathic pain, without exhibiting major adverse effects (Karst et al., 2003).



Finally, levonantradol, a synthetic cannabinoid administered intramuscularly in 1.5, 2, 2.5 and 3 mg doses to 56 patients suffering from postoperative pain, manifested significant analgesic efficacy in the four dosages used. Analgesia persisted for more than 6 h with the 2.5 and 3 mg doses of levonantradol. Drowsiness was frequent but few other psychoactive effects were reported (Jain et al., 1981).

Recently, after completion of this review, Blake et al. (2005) published a study on the efficacy and the safety of a mixture of 2.7 mg THC and 2.5 mg CBD delivered via an oromucosal spray (Sativex®) and used against pain caused by rheuma-

toid arthritis. In a randomized, double-blind, parallel groups, placebo-controlled trial, the authors compared Sativex® ( $n = 31$ ) to a placebo ( $n = 27$ ) over 5 weeks of treatment. They concluded that Sativex® produced statistically significant improvements in pain on movement, pain at rest, quality of sleep and disease activity. There was no effect on morning stiffness, although baseline scores were low. The cannabis-based medicine (CBM) had mild or moderate side effects in the large majority of patients and none of them had to withdraw from the study due to adverse reactions in the CBM group (Blake et al., 2005).

### 3.4. Multiple sclerosis

Multiple sclerosis is a neurodegenerative disease which is accompanied by spasticity (muscle rigidity), painful muscle cramps, chronic pain in the extremities, tingling and prickling of the fingers of the hands and feet, as well as ataxia, tremors and vesical and intestinal dysfunctions (Petro, 1997; Smith, 1998; Iversen, 2000). Current symptomatic therapies for this demyelinating pathology of the central nervous system are in some cases ineffective and may present a risk of serious adverse effects. This has led some patients to self-medicate with cannabis, which anecdotal reports suggest may be beneficial to control some symptoms such as spasticity, tremor, pain and bladder dysfunction (Croxford and Miller, 2004).

Thirteen controlled studies evaluated the effects of cannabinoids on this pathology. The preparations studied were smoked marijuana and hashish, oral THC in capsule form, oral extracts of *Cannabis sativa* administered in capsules or sublingual spray and containing THC, cannabidiol or a combination of the two, and oral nabilone.

The results of these clinical trials are mixed: in some cases only, patients reported an improvement in spasticity, muscle spasms, pain, sleep quality, tremors and their general condition (Table 4). The most reliable conclusions on the efficacy and innocuousness of cannabinoids in the treatment of multiple sclerosis should be taken from two clinical trials recently conducted in Great Britain and covering the largest population samples (Zajicek et al., 2003; Wade et al., 2004).

Thus, in a randomized, double-blind, parallel group trial (the CAMS study), evaluating a total of 630 patients suffering from multiple sclerosis, 206 individuals received oral THC in capsules, 211 subjects consumed an oral cannabis extract in capsules containing 2.5 mg of THC, 1.25 mg of cannabidiol and less than 5% other cannabinoids per capsule and 213 persons took a placebo (Zajicek et al., 2003). The total duration of the study was 14 weeks. The authors reported the absence of beneficial effects of cannabinoids on spasticity, estimated by means of the Ashworth scale, while noting after the fact the limitations of this scale in measuring the highly complex symptoms of spasticity. However, they observed an objective improvement in mobility with oral THC and a subjective improvement in spasticity, muscle spasms, pain, sleep quality and general condition, as well as a decrease in hospitalizations for relapses with the two types of cannabinoids. The reported adverse effects were generally mild and well tolerated (Zajicek et al., 2003). Recent data from the CAMS study provide a longer term information on the efficacy

Table 3  
Controlled studies evaluating the analgesic effects of cannabinoids in humans

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Noyes et al. (1975a)	United States	36 patients with cancer pain	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 10 and 20 mg (capsules); oral codeine: 60 and 120 mg	Pain relief equivalent with 10 mg of THC and 60 mg of codeine, as well as with 20 mg of THC and 120 mg of codeine	THC, 10 mg: well tolerated; THC, 20 mg: drowsiness, dizziness, ataxia, confusion and frequent mental disorders
Noyes et al. (1975b)	United States	10 patients with cancer pain	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 5, 10, 15 and 20 mg (capsules)	Pain relief with the 15 and 20 mg doses	Frequent drowsiness and confusion
Raft et al. (1977)	United States	10 healthy volunteers undergoing dental extractions (4 molars for each patient)	Randomized, double-blind, crossover, placebo-controlled	THC IV: 0.22 and 0.44 mg/kg; diazepam IV: 0.157 mg/kg	No analgesic effect of THC on postoperative pain	0.22 mg/kg dose of THC: euphoria/dysphoria; 0.44 mg/kg dose of THC: anxiety
Staquet et al. (1978)	Belgium, United States	30 patients with cancer pain	Randomized, double-blind, crossover, placebo-controlled	Oral benzopyranoperidine in 4 mg capsules (synthetic analog of THC); oral codeine (50 mg capsules)	Equivalent pain relief with benzopyranoperidine and codeine and superior to placebo	Drowsiness in 40% of the patients treated with benzopyranoperidine and in 44% of the patients treated with codeine
Staquet et al. (1978)	Belgium, United States	15 patients with cancer pain	Randomized, double-blind, crossover, placebo-controlled	Oral benzopyranoperidine in 4 mg capsules (synthetic analog of THC); oral secobarbital (50 mg capsules)	Superior pain relief with benzopyranoperidine compared to secobarbital and placebo; secobarbital did not exhibit analgesic properties	Drowsiness in 40% of the patients treated with benzopyranoperidine and in 33% of the patients treated with secobarbital
Jochimsen et al. (1978)	United States	35 patients with chronic pain due to malignancies	Randomized, double-blind, crossover, placebo-controlled	Oral benzopyranoperidine: 2 and 4 mg (synthetic analog of THC); oral codeine: 60 and 120 mg	No analgesic effect of benzopyranoperidine	Sedation equivalent with benzopyranoperidine and codeine
Jain et al. (1981)	United States	56 patients with postoperative or trauma pain	Randomized, double-blind, parallel groups, placebo-controlled	Levonantradol IM 1.5; 2; 2.5 and 3 mg (synthetic cannabinoid); 1.5 mg, 10 patients; 2 mg, 10 patients; 2.5 mg, 10 patients; 3 mg, 10 patients; placebo, 16 patients	Pain relief with the four doses; analgesia persisted for more than 6 h with the 2.5 and 3 mg doses	Frequent drowsiness (18 patients on levonantradol)
Lindstrom et al. (1987)	Sweden	10 patients with chronic neuropathic pain	Randomized, double-blind, crossover, placebo-controlled	Oral cannabidiol: 450 mg/day in three split doses for 1 week	No analgesic effect of cannabidiol	Sedation in seven patients
Holdcroft et al. (1997)	Great Britain	1 patient with severe chronic gastrointestinal pain (Mediterranean fever)	Double-blind, crossover, placebo-controlled	Oral cannabis extract containing 10 mg of THC $\times$ 5 times/day for 3 weeks	Statistically significant reduction in morphine consumption with THC intake	Nausea and vomiting
Karst et al. (2003)	Germany	21 patients with chronic neuropathic pain	Randomized, double-blind, crossover, placebo-controlled	Oral CT-3 (10 mg capsules): 40 mg/day for the first 4 days followed by 80 mg/day for the next 3 days (synthetic analog of 11-hydroxy-THC)	CT-3 in both doses was more effective than placebo in relieving pain, with greater pain-reducing effects at 3 h after intake than at 8 h	No major adverse effects

Table 3 (Continued)

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Buggy et al. (2003)	Great Britain	40 women with postoperative pain (hysterectomy)	Randomized, double-blind, parallel groups, placebo-controlled	Oral THC: 5 mg; 20 patients; placebo: 20 patients	No analgesic effect of THC on postoperative pain	Increased awareness of surroundings
Naef et al. (2003)	Switzerland	12 healthy cannabis-naïve volunteers under experimental pain conditions (heat, cold, pressure, single and repeated transcutaneous electrical stimulation)	Randomized, double-blind, crossover, placebo-controlled	THC: 20 mg (capsules); morphine: 30 mg (capsules); THC: 20 mg + morphine 30 mg (capsules). The three regimens were administered as single oral doses	THC did not significantly reduce pain in any test compared to placebo; in the cold and heat tests, THC even produced hyperalgesia which is completely neutralized by THC–morphine; THC–morphine had a slight additive analgesic effect in the electrical stimulation test; THC–morphine had no analgesic effect in the pressure test	Sleepiness (12), dry mouth (12), vertigo (11), altered perception (10), euphoria (9), confusion (7) and strange thoughts (7) are common but usually mild
Notcutt et al. (2004)	Great Britain	34 patients with chronic pain	Randomized, double-blind, crossover, placebo-controlled	THC: 2.5 mg in sublingual spray for 4 weeks; cannabidiol (CBD) 2.5 mg in sublingual spray for 4 weeks; THC: 2.5 mg + CBD 2.5 mg in sublingual spray for 4 weeks	Pain relief and improvement of sleep quality with THC alone and the THC–CBD combination; CBD alone ineffective	Dry mouth, drowsiness, euphoria/dysphoria, dizziness
Berman et al. (2004)	Great Britain	48 patients with central neuropathic pain associated with brachial plexus root avulsion	Randomized, double-blind, crossover, placebo-controlled	THC: 2.7 mg in sublingual spray or THC: 2.7 mg + CBD 2.5 mg in sublingual spray for three periods of 2 weeks	Statistically significant decrease in pain and statistically significant improvement in sleep quality with THC alone and the THC–CBD combination	Three patients dropped out of the study, including two due to adverse effects of THC; side effects generally mild to moderate in the other patients

Reviews on cannabis and pain: British Medical Association (1997; pp. 39–45), Campbell et al. (2001) and Beaulieu and Ware (2004).

and safety of cannabinoids in multiple sclerosis. During a 1-year follow-up of this trial, in which 502 (80%) of the initial 630 patients decided to continue the study, overall objective improvements of both spasticity (illustrated by a small benefit in the Ashworth scale) and general disability indices were observed. These improvements were objectively confined to patients taking THC alone, although patients reported beneficial effects with both THC alone (Marinol<sup>®</sup>) and the combination of THC and CBD (Cannador<sup>®</sup>). Indeed, subjectively, rating scales showed highly significant favourable effects on spasticity, spasms, pain, tiredness and sleep with both Marinol<sup>®</sup> and Cannador<sup>®</sup>. Overall, no major safety concerns were observed and minor adverse events were reported by 109 patients on THC, 125 on cannabis extract and 127 on placebo (Zajicek et al., 2005).

In another randomized, double-blind, parallel groups, placebo-controlled study, conducted on 160 subjects suffering from multiple sclerosis, Wade et al. (2004) evaluated the effects of a cannabis extract containing almost equal quantities of THC (2.7 mg) and cannabidiol (2.5 mg) administered in sub-

lingual spray at 2.5–120 mg per day doses of each constituent for a period of 6 weeks. In terms of efficacy, this preparation (Sativex<sup>®</sup>) exhibited the following properties:

- a statistically significant reduction in spasticity with the cannabis extract compared to placebo, evaluated by means of the VAS scores (objective evaluation);
- a statistically significant subjective improvement in sleep quality with the cannabis extract compared to placebo;
- a statistically insignificant objective improvement in mobility and vesical dysfunction with the cannabis extract compared to placebo.

In terms of toxicity, the undesirable effects observed were generally mild and well tolerated (Wade et al., 2004).

A recent report, published after July 1, 2005, confirmed some of the beneficial effects of Sativex<sup>®</sup> in multiple sclerosis (Rog et al., 2005). During a randomized, double-blind, parallel groups, placebo-controlled trial, conducted in Great Britain and which



Table 4  
Controlled studies evaluating the effects of cannabinoids on multiple sclerosis in humans

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Petro and Ellenberger (1981)	United States	9	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 5 or 10 mg; single dose	Significant decrease in spasticity in four patients with both doses of THC (objective evaluation)	Minimal
Clifford (1983)	United States	8	Single blind, placebo	Oral THC: 5 mg/6 h; maximum three doses	Objective improvement in tremors and motor coordination in two patients; subjective improvement in tremors and well-being in five patients	Euphoria in all patients with the highest dose used; dysphoria in two patients
Ungerleider et al. (1987)	United States	13	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 2.5–15 mg/day for 5 days	Subjective improvement in spasticity from the 7.5 mg dose; 2.5 and 5 mg doses ineffective	Frequent from the 7.5 mg dose
Greenberg et al. (1994)	United States	10	Randomized, double-blind, parallel groups, placebo-controlled; control group of 10 healthy volunteers	One marijuana cigarette smoked over 10 min (1.54% THC)	Subjective feeling of clinical improvement in some patients; impairment of posture and balance in the 10 patients with multiple sclerosis	Euphoria in all patients smoking marijuana
Martyn et al. (1995)	Great Britain	1	Double-blind, crossover, placebo-controlled	Oral nabilone 1 mg/2 days for two periods of 4 weeks	Significant improvement in muscle spasms, pain, general health status and frequency of nocturia (objective evaluation)	Minor sedation
Killestein et al. (2002)	The Netherlands	16	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 2.5 mg capsules b.i.d. or 5 mg b.i.d. for 4 weeks; oral <i>Cannabis sativa</i> extract in capsules providing 2.5 mg b.i.d. or 5 mg b.i.d. of THC with 20–30% CBD and <5% other cannabinoids, for 4 weeks	No benefits on spasticity; treatment with THC or plant extract worsened the patients' global impression	More frequent with the cannabis extract but tolerated
Wade et al. (2003)	Great Britain	18	Randomized, double-blind, crossover, placebo-controlled	<i>Cannabis sativa</i> extract containing THC (2.5 mg), CBD (2.5 mg) or THC + CBD in equal quantities (2.5 mg + 2.5 mg) administered in sublingual spray in doses of 2.5–120 mg/day for four periods of 2 weeks	Statistically significant reduction in spasticity, muscle spasms and pain with THC compared to the placebo (objective evaluation with the VAS scores); statistically significant reduction in pain with CBD compared to placebo; statistically significant reduction in muscle spasms and statistically significant improvement in sleep quality with the THC–CBD combination compared to placebo	Four patients dropped out of the study due to non-tolerated side effects
Zajicek et al. (2003)	Great Britain	630	Randomized, double-blind, parallel groups, placebo-controlled, oral THC: 206 patients; oral cannabis extract: 211 patients; placebo: 213 patients	Oral THC in capsules or oral cannabis extract in capsules containing 2.5 mg of THC, 1.25 mg of cannabidiol and less than 5% other cannabinoids per capsule. Maximum dose: 25 mg of THC/day; duration: 14 weeks	No beneficial effects of cannabinoids on spasticity when evaluated by the Ashworth scale (the authors note the limitations of this scale in measuring the highly complex symptoms of spasticity); objective improvement in mobility with oral THC; subjective improvement in muscle spasms, pain, sleep quality and general condition with both types of cannabinoids; decrease in hospitalizations for relapses with both types of cannabinoids	Generally mild and well tolerated



Table 4 (Continued)

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Fox et al. (2004)	Great Britain	14	Randomized, double-blind, crossover, placebo-controlled	Oral extracts of <i>Cannabis sativa</i> containing 2.5 mg THC per capsule; dose: 5–10 mg of THC b.i.d.; duration: 14 days	No beneficial effects on tremors	Generally mild and well tolerated
Vaney et al. (2004)	Switzerland	50	Randomized, double-blind, crossover, placebo-controlled	Oral extracts of <i>Cannabis sativa</i> containing 2.5 mg of THC and 0.9 mg of CBD per capsule; dose: 15–30 mg of THC/day; duration: 14 days	No beneficial effects of cannabinoids on spasticity when evaluated by the Ashworth scale; reduction in spasm frequency; improvement in mobility and sleep quality; significant improvement in the patients' general condition	Generally mild and well tolerated
Wade et al. (2004)	Great Britain	160	Randomized, double-blind, parallel groups, placebo	Cannabis extract containing almost equal quantities of THC (2.7 mg) and CBD (2.5 mg) administered in sublingual spray at 2.5–120 mg/day doses of each constituent for 6 weeks (Sativex <sup>®</sup> ); cannabis extracts: 80 patients; placebo: 80 patients	Statistically significant reduction in spasticity with the cannabis extract compared to placebo, evaluated by the VAS scores (objective evaluation); statistically significant subjective improvement in sleep quality with the cannabis extract compared to placebo; statistically insignificant objective improvement in mobility and vesical dysfunction with the cannabis extract compared to placebo	Generally mild and well tolerated
Svendsen et al. (2004)	Denmark	24	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 2.5–10 mg per day for 18–21 days	Statistically significant decrease in central pain with oral THC compared to placebo	Central and musculoskeletal side effects which required a reduction of the THC dose in four patients

Reviews on cannabis and multiple sclerosis: British Medical Association (1997; pp. 27–39), Pertwee (2002), Beard et al. (2003), Killestein et al. (2004), Croxford and Miller (2004), Smith (2004) and Pryce and Baker (2005).

lasted 4 weeks, patients received either a mixture of 2.7 mg THC and 2.5 mg CBD administered by oromucosal spray ( $n = 32$ ) or a placebo ( $n = 32$ ). The authors showed that the cannabis-based medicine (CBM) was statistically superior to placebo in reducing the mean intensity of pain and sleep disturbance. They noted that CBM was generally well tolerated, although more patients on CBM than placebo reported dizziness ( $n = 18$  for CBM;  $n = 5$  for placebo), dry mouth ( $n = 4$  for CBM;  $n = 0$  for placebo) and somnolence ( $n = 3$  for CBM;  $n = 0$  for placebo). Cognitive adverse reactions were limited to long-term memory storage (Rog et al., 2005).

### 3.5. Spinal cord injuries

People suffering from spinal cord injuries often exhibit symptoms similar to those of multiple sclerosis, including spasticity, painful muscle spasms and urinary incontinence (British Medical Association, 1997). The available data on cannabinoids for this therapeutic application are limited because they concern a very small number of subjects.

Three controlled studies, one on five patients (Hanigan et al., 1986), the second on one patient (Maurer et al., 1990), and the third on four patients (Wade et al., 2003), are reported in the literature (Table 5). These studies observed that oral THC or *Cannabis sativa* extracts containing THC, cannabidiol or a combination of the two, administered in sublingual spray, may, in some patients, lead to an improvement in spasticity, muscle spasms, pain, vesical dysfunction and sleep quality.

### 3.6. Gilles de la Tourette's syndrome

Gilles de la Tourette's syndrome is a neurobehavioral dysfunction characterized by motor and verbal tics, as well as a spectrum of behavioral and cognitive disorders. A team of German researchers was particularly interested in the effects of cannabinoids on patients suffering from this problem. In two randomized, double-blind, placebo-controlled studies, one crossover (12 patients), the other with parallel groups (24 initial patients, 7 of whom received oral THC and completed the study), Müller-Vahl et al. (2002a, 2003a) showed that oral THC

Table 5  
Controlled studies evaluating the effects of cannabinoids on spinal cord injuries in humans

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Hanigan et al. (1986)	United States	5	Double-blind, crossover, placebo-controlled	Oral THC: 35 mg/day over a period of 20 days	Objective and significant decrease in spasticity in two patients; no objective improvement in spasticity in two other patients	One patient withdrew from the study due to psychological side effects
Maurer et al. (1990)	Switzerland	1	Double-blind, crossover, placebo-controlled	Oral THC 5 mg; oral codeine 50 mg; placebo administered 18 times over 5 months	Pain relief, reduced vesical dysfunction and improvement in sleep quality equivalent with THC and codeine and superior to placebo; decrease in spasticity noted only with THC	None
Wade et al. (2003)	Great Britain	4	Randomized, double-blind, crossover, placebo-controlled	<i>Cannabis sativa</i> extracts containing THC (2.5 mg), CBD (2.5 mg) or THC + CBD in equal quantities (2.5 mg + 2.5 mg) administered in sublingual spray at 2.5–120 mg/day doses for four periods of 2 weeks	Statistically significant decrease in spasticity, muscle spasms and pain with THC compared to placebo (objective evaluation with the VAS scores); statistically significant reduction in pain with CBD compared to placebo; statistically significant reduction in muscle spasms and statistically significant improvement in sleep quality with the THC–CBD combination compared to placebo	Generally mild and well tolerated

Reviews on cannabis and spinal cord injuries: British Medical Association (1997; pp. 27–39) and Consroe (1999).

reduced tics compared to placebo. There were no major undesirable effects in most of the patients (Table 6).

During their latest clinical trial, the researchers also reported that THC did not impair neuropsychological performances: treatment with up to 10 mg oral THC over a 6-week period and immediately as well as 5–6 weeks after withdrawal of THC use had no detrimental effects on learning, interference, recall and recognition of word lists, immediate visual memory and divided attention. To the contrary, the authors even found a trend towards a significant improvement during and after therapy while eval-

uating immediate verbal memory span. They concluded that treatment with oral THC in patients suffering from Tourette's syndrome did not impair their cognitive function and might even improve it (Müller-Vahl et al., 2003b; Müller-Vahl, 2003).

### 3.7. Epilepsy

Epilepsy affects about 1% of the world's population. It is estimated that 20–30% of epileptics are not adequately controlled with conventional drugs (Robson, 2001). Cannabidiol appeared

Table 6  
Controlled studies evaluating the effects of cannabinoids on Tourette's syndrome in humans

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Müller-Vahl et al. (2002a)	Germany	12 patients	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 5, 7.5 or 10 mg in a single dose	Significant decrease in tics with THC compared to placebo; significant improvement in obsessive-compulsive behavior with THC compared to placebo	No serious adverse effects; five patients experienced mild transient adverse reactions on the nervous system
Müller-Vahl et al. (2003a)	Germany	24 patients (7 patients dropped out or were excluded)	Randomized, double-blind, parallel groups, placebo-controlled; THC: 7 patients; Placebo: 10 patients	Oral THC up to 10 mg/day for 6 weeks	Decrease in tics with THC compared to placebo; THC reached efficacy after about 3 weeks of treatment; this efficacy persisted or increased after more than 4 weeks up to the end of the study (6 weeks)	THC did not impair cognitive functions; no major adverse effects in most patients; one patient dropped out of the study due to side effects such as anxiety and agitation

Reviews on cannabis and Tourette's syndrome: Müller-Vahl et al. (2002b) and Müller-Vahl (2003).

Table 7  
Controlled study evaluating the anticonvulsant effects of cannabinoids in humans

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Cunha et al. (1980)	Brazil	15 patients with generalized epilepsy inadequately controlled by standard drugs (ages: 14–49)	Randomized, double-blind, parallel groups, placebo-controlled	Oral cannabidiol 200–300 mg/day for 8–18 weeks; <i>n</i> = 8 patients; placebo: seven patients	Of the eight patients receiving cannabidiol, four subjects remained virtually convulsion-free for the duration of the study and three other subjects exhibited a clinical improvement	Drowsiness reported by four patients on cannabidiol

Reviews on cannabis and epilepsy: British Medical Association (1997; pp. 49–53) and Iversen (2000; pp. 169–171).

to be the most promising cannabinoid in the animal studies. It had a powerful anticonvulsant activity and minimal neurotoxicity (Mechoulam, 1986).

Several anecdotal reports (including the case of Terrance Parker, at the origin of the amendments to the Canadian regulations) suggest that cannabis has anticonvulsant properties and would be effective in treating partial epilepsies and generalized tonicoclonic seizures, still known as grand mal. They are based, among other factors, on the fact that in individuals who smoke marijuana to treat their epilepsy, stopping use of cannabis precipitates the reemergence of convulsive seizures, while resuming consumption of this psychotropic drug controls epilepsy; these results are reproducible (Consroe et al., 1975; Ellison et al., 1990; Grinspoon and Bakalar, 1997; Gurley et al., 1998).

However, only one controlled clinical study exists for this therapeutic application (Cunha et al., 1980). Fifteen patients suffering from secondary generalized epilepsy inadequately controlled by standard drugs, while continuing to take their regular therapy, were subjected to a randomized, double-blind, parallel group study: eight patients received, in addition, oral cannabidiol at 200–300 mg per day for 8–18 weeks and the other seven individuals had their regimen augmented with a placebo. Of the eight patients receiving cannabidiol, four subjects remained virtually convulsion-free for the duration of the study and three other subjects exhibited a clinical improvement. In the group also receiving the placebo, the condition of six out of seven

patients remained unchanged. Drowsiness was reported by four patients on cannabidiol (Table 7).

These results were not confirmed by other controlled clinical studies.

### 3.8. Glaucoma

Glaucoma is an eye affliction characterized by an increase in intraocular pressure. It can lead to blindness if it is not treated effectively. Several anecdotal reports observe that cannabis has the power to reduce the fluid pressure within the eye (Hepler et al., 1976; Green, 1984; Grinspoon and Bakalar, 1997). Nonetheless, only two controlled studies evaluating the effects of THC on glaucoma patients are reported in the literature (Table 8).

In a randomized, double-blind, crossover, placebo-controlled clinical trial, Merritt et al. (1980) administered one marijuana cigarette containing 2% THC to 18 adults suffering from glaucoma. Marijuana then induced a significant reduction in intraocular pressure but exhibited the following main adverse effects: various sensory alterations (100% of the cases), tachycardia and palpitations (44% of the cases) and postural hypotension (28%).

In another randomized, double-blind, parallel group study against placebo, conducted 1 year later, Merritt et al. (1981) instilled eye drops containing 0.01, 0.05 or 0.1% THC in eight individuals suffering from glaucoma and hypertension (one eye received THC and the other one placebo). They then observed a

Table 8  
Controlled studies evaluating the anti-glaucoma effects of cannabinoids in humans

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Merritt et al. (1980)	United States	18 adults with glaucoma (ages: 28–71)	Randomized, double-blind, crossover, placebo-controlled	One marijuana cigarette containing 2% THC	Significant reduction in intraocular pressure	Main side effects: various sensory alterations (100%), tachycardia and palpitations (44%), postural hypotension (28%)
Merritt et al. (1981)	United States	8 patients with glaucoma and hypertension (average age: 65)	Randomized, double-blind, parallel groups, placebo-controlled	Eye drops containing 0.01% (two patients), 0.05% (three patients) or 0.1% (three patients) THC	Significant reduction in intraocular pressure with 0.05% and 0.1% topical solutions of THC; no effect with the 0.01% topical solution of THC	Mild hypotension with the 0.1% topical solution of THC; no psychotropic effects with the 3 THC concentrations administered topically

Reviews on cannabis and glaucoma: British Medical Association (1997; pp. 53–59), Iversen (2000; pp. 164–169) and Järvinen et al. (2002).

Table 9  
Controlled studies evaluating the effects of cannabinoids on Parkinson disease in humans

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Sieradzan et al. (2001)	United Kingdom	7	Randomized, double-blind, crossover, placebo-controlled	Oral nabilone: 0.03 mg/kg in two split doses 12 and 1 h before levodopa administration	Nabilone had no antiparkinsonian effect per se; nabilone had no effect on the antiparkinsonian action of levodopa; significant reduction in total levodopa-induced dyskinesia with nabilone compared to placebo	Two patients withdrew from the study, one because of vertigo, the other one due to postural hypotension; five patients experienced transient side effects of mild sedation, "floating sensation", dizziness, hyperacusis, partial disorientation and formed visual hallucinations
Carroll et al. (2004)	United Kingdom	19	Randomized, double-blind, crossover, placebo-controlled	<i>Cannabis sativa</i> extract containing 2.5 mg THC and 1.25 mg CBD per capsule in a 4-week dose escalation study; maximum dose: 0.25 mg/kg of THC per day	The cannabis extract had no pro- or antiparkinsonian effect; the cannabis extract had no effect on levodopa-induced dyskinesia as assessed by the UPDRS, or any of the secondary outcome measures	No serious adverse events reported; main side effects: drowsiness/lethargy (nine patients), dry mouth (four patients), detachment (four patients). All adverse effects were improved by dose reduction

significant reduction in intraocular pressure with 0.05 and 0.1% topical solutions of THC. The 0.1% topical solution of THC induced a mild hypotension but no psychotropic effects were observed with the three locally administered THC concentrations.

Even though these results are interesting, the use of cannabis against glaucoma is unsatisfactory, because its beneficial effects are limited by its short-term action (a few hours), by the incidence of undesirable central and peripheral reactions, especially noticeable in the elderly, and by the possibility of using other more effective and less toxic drugs (Hartel, 1999; Institute of Medicine, 1999).

### 3.9. Parkinson disease

Two controlled clinical trials have evaluated the antiparkinsonian action of cannabinoids as well as their effect on levodopa-induced dyskinesia (Table 9).

In a randomized, double-blind, crossover, placebo-controlled study ( $n = 7$ ), conducted in the United Kingdom, Sieradzan et al. (2001) noted that oral nabilone had no antiparkinsonian action

per se when assessed in the practically defined off state and it did not have an influence on the antiparkinsonian effect of levodopa. However, nabilone significantly reduced total levodopa-induced dyskinesia compared with placebo.

In another trial of similar design, performed also in the United Kingdom on 19 patients suffering from Parkinson disease and levodopa-induced dyskinesia, Carroll et al. (2004) showed that the oral administration of a cannabis extract (2.5 mg of THC and 1.25 mg of cannabidiol per capsule) resulted in no objective or subjective improvement in parkinsonism or dyskinesias.

### 3.10. Dystonia

In a randomized, double-blind, crossover, placebo-controlled trial carried on 15 patients afflicted with generalized and segmental primary dystonia, oral nabilone did not show a significant reduction in total dystonia movement scale score compared to placebo (Table 10). The authors stated that lack of effect of nabilone might have reflected the insufficient dose employed (Fox et al., 2002).

Table 10  
Controlled study evaluating the effects of one cannabinoid on dystonia in humans

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Fox et al. (2002)	United Kingdom	15 patients with generalized and segmental primary dystonia	Randomized, double-blind, crossover, placebo-controlled	Oral nabilone: 0.03 mg/kg in a single dose	No significant reduction in dystonia with nabilone compared to placebo	Two patients experienced sedation and postural hypotension

Further research will be necessary to determine the impact of cannabinoids in the management of different forms of dystonia.

#### 4. Discussion

The summary of the clinical trials conducted with nabilone and dronabinol reveals that these two cannabinoids have a significant antiemetic efficacy, generally equivalent or superior to that of first-generation antiemetic drugs to relieve nausea and vomiting associated with cancer chemotherapy. Unfortunately, this interest has largely faded since the marketing of new, more potent and less toxic antiemetic drugs. Thus, the existing oral formulations are not recommended as first-line antiemetics.

Nonetheless, cannabinoids could be useful in the 10–20% of cancer patients whose nausea and vomiting are not well controlled by serotonin antagonists or by the more recent neurokinin-1-receptor-antagonists (Jordan et al., 2005). Clinical trials should thus be envisioned to compare the antiemetic effects of cannabinoids to those agents and evaluate the efficacy of their association, not only in cancer chemotherapy but to treat severe nausea and vomiting of various origins.

THC shows to be useful in stimulating appetite and preventing weight loss in cancer and AIDS patients. Its use in these debilitating diseases raises reservations, because some authors report immunosuppressive properties of cannabinoids (Cabral and Dove Pettit, 1998; Zhu et al., 2000; Roth et al., 2002; Pacifici et al., 2003), while others do not (Killestein et al., 2003; Kraft and Kress, 2004). In this regard, work conducted with HIV-1 infected patients has not proved that smoked marijuana or oral THC affects the viral load, the number of CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes or the progression of the disease (Kaslow et al., 1989; Abrams et al., 2003; Furler et al., 2004). For a definitive elucidation of the question of the safety of long-term use of cannabinoids in immunodepressed subjects, in-depth studies are still necessary.

The results of the clinical trials on the antinociceptive efficacy of cannabinoids are equivocal. THC, benzopyranoperidine, CT-3 (ajulemic acid) and levonantradol exhibit analgesic effects against certain forms of pain. Other types of pain do not respond as well to cannabinoids. No controlled study has evaluated the analgesic power of smoked cannabis.

In animal and human studies, it has been proved that cannabinoids and opiates have synergistic actions on pain control (Iversen, 2003; Lynch and Clark, 2003; Maldonado and Valverde, 2003). Controlled clinical trials evaluating the combined analgesic effects of these two types of psychotropic drugs would thus be suitable.

Cannabinoids exhibit some antispasmodic and muscle relaxant properties which could be used beneficially to relieve certain symptoms of multiple sclerosis and spinal cord injuries. Considering all of the results obtained, it can be said that cannabinoids do objectively show a small noticeable beneficial effect on the spasticity of individuals suffering from these pathologies. They can also lead to a subjective improvement of this same spasticity and a moderate, albeit significant, improvement in the patients' motor capacity and general well-being (Derkinderen et al., 2004). Future clinical trials should improve quantitative

assessments of spasticity and elude, if possible, the Ashworth scale due to its limitations in evaluating spasticity. Indeed, this method might not be sufficiently sensitive to detect clinically beneficial effects induced by cannabinoids (Pryce and Baker, 2005).

The results obtained with oral THC in the treatment of Tourette's syndrome are promising and suggest that it is effective and well tolerated for this pathology. Clinical trials provide evidence that THC reduces motor and vocal tics of Tourette's syndrome as well as its associated behavioral problems such as obsessive-compulsive disorders. It remains to be specified which cannabinoids are the most effective and what routes of administration should be privileged.

With only one controlled study available, the role of cannabinoids in the treatment of epilepsy remains speculative. Cannabidiol presents an interesting therapeutic potential but additional research on its anticonvulsant properties, whether alone or in association with the standard drugs, is necessary and justified. It is surprising to observe that such work has not yet been done, in view of this cannabinoid's absence of psychoactive effects.

Even though THC may offer some interest as an anti-glaucoma agent, there are currently several more effective and less toxic drugs to treat this pathology. There are no controlled clinical trials comparing the beneficial and undesirable effects of cannabinoids to the existing conventional drugs. Cannabinoids should be preferably applied topically and produce a sustained reduction in intraocular pressure without exhibiting unacceptable central and systemic effects. It should be possible to administer them in the long-term without developing a tolerance. It should also be possible to determine whether cannabinoids have additive effects with the anti-glaucoma agents available in order to also consider their eventual use as an adjuvant therapy.

Cannabinoids do not demonstrate an antiparkinsonian effect per se in controlled studies, nor do they provide convincing evidence of their effectiveness to treat dystonia.

Regarding other therapeutic applications, there is a growing interest in evaluating the potential of cannabinoids as anti-inflammatory (Burstein et al., 2004; Perrot, 2004) and anticancer agents (Bifulco and Di Marzo, 2002; Walsh et al., 2003; de Jong et al., 2005), as well as in the treatment of psychotropic drug dependence (Labigalini et al., 1999; De Vries et al., 2001; Piomelli, 2001; Robson, 2001; Yamamoto et al., 2004; Arnold, 2005). However, apart from the recent work of Blake et al. (2005) on rheumatoid arthritis, controlled clinical trials are lacking so far and, therefore, there is no solid evidence supporting their efficacy in such pathologies.

Until recently, two cannabinoids were marketed in Canada: nabilone (Cesamet<sup>®</sup>) and oral THC or dronabinol (Marinol<sup>®</sup>). On April 19, 2005, Health Canada approved Sativex<sup>®</sup> for the symptomatic relief of neuropathic pain in adults suffering from multiple sclerosis. This cannabis extract is administered via a spray into the mouth and contains 2.7 mg of THC and 2.5 mg of CBD per spray. It is available under prescription in the pharmacies of Canada since June 20, 2005. Nabilone (Cesamet<sup>®</sup>) and dronabinol (Marinol<sup>®</sup>) are not very popular in clinical practice, since the gap between the effective doses and the doses exhibit-



ing side effects on the central nervous system is rather narrow (Iversen, 2003). Although the adverse reactions reported are not generally considered serious, drowsiness, euphoria, dysphoria, dizziness and some other central effects limit the use of these two drugs in some patients. As for Sativex<sup>®</sup>, in view of its more recent use, its efficacy and toxicity profiles still have to be specified in the pathologies in which it will be used.

Compared to the intrapulmonary route, orally administered cannabinoids have a slower onset of action, a more erratic absorption and lower peak concentrations of drug. These three negative aspects explain why more and more patients turn to smoking marijuana for self-medication, which provides them with a more rapid and increased relief from the symptoms (Söderpalm et al., 2001). Furthermore, some patients who are experienced smokers find that this route of administration allows them to titrate more adequately the appropriate dose to control their symptoms and stop when the desired effect is obtained (Chang et al., 1979; Clark, 2000; Iversen, 2000; Abrams et al., 2003). Finally, inhaled THC is absorbed better than oral THC and cannabis contains other substances which increase the effects of THC and which could modulate its toxic effects (British Medical Association, 1997; Baker et al., 2003; Roncoroni, 2003; Wade et al., 2003; Carter et al., 2004). For all these reasons, smoked cannabis is preferred and considered more effective by many patients (Baker et al., 2003; Duran et al., 2004; Wingerchuk, 2004; Gorter et al., 2005).

Unfortunately, a marijuana cigarette is more harmful to health than oral THC. In theory, it can cause as many pulmonary problems as 4–10 regular cigarettes (Fehr et al., 1983; Kleber et al., 1997). Cannabis smokers are at greater long-term risk of suffering from pharyngitis, rhinitis, asthma, bronchitis, emphysema and lung cancer (van Hoozen and Cross, 1997; Hall and Solowij, 1998). This consideration is less important in the case of palliative care provided to terminally ill patients. Furthermore, the psychoactive effects of marijuana are likely to limit its clinical usefulness in the general population (Söderpalm et al., 2001).

In view of the current knowledge on cannabis and cannabinoids, the following methodological considerations should be pointed out:

1. Bioavailabilities and other pharmacokinetic parameters might conditionate the route of administration and the efficacy and toxicity of the treatment.
  - Cannabis is generally taken by smoking or ingestion. When inhaled, the bioavailability of THC varies from 18 to 50%, the onset of action is rapid (3–5 min), maximal effects are obtained within 30–60 min and euphoria is intense and might last 2–4 h. When cannabis is administered orally, the bioavailability ranges from 6 to 20%, the onset of action is slow (30–60 min), euphoria is less pronounced and effects are progressive and last longer (Ben Amar and Léonard, 2002).
  - Nabilone (synthetic analogue of THC) or Cesamet<sup>®</sup>, dronabinol (synthetic THC) or Marinol<sup>®</sup> and THC + CBD or Sativex<sup>®</sup>, the three current pharmaceutical preparations approved for medicinal use, have different pharmaco-

kinetic profiles. Nabilone (Cesamet<sup>®</sup>) is administered orally and has a bioavailability of 60%. Dronabinol (Marinol<sup>®</sup>), also used orally, has a bioavailability of 10–20%. Sativex<sup>®</sup> is taken sublingually as an oromucosal spray; its bioavailability is not well documented (CPA, 2005).

2. Placebo-controlled clinical trials involving cannabis or cannabinoids are problematic: although placebo is designed to match the appearance, smell and taste of the active formulation, the specific psychoactive properties of cannabinoids make many patients aware whether they are receiving the drug or placebo. This might influence the outcome, the statistical analysis and the value of the results. To mitigate this difficulty, the degree of blinding should be formally assessed in each study.
3. Side effects should be carefully taken into account depending on the population studied. Acute administration of cannabis should be pondered in elderly patients and sensitive individuals while psychotic or particularly vulnerable patients should avoid chronic use of cannabinoids. Although chronic psychosis induced by cannabis or cannabinoids remains controversial (Phillips et al., 2002; Degenhardt et al., 2003; Macleod et al., 2004), the possibility of such event should be seriously considered (Arseneault et al., 2002; van Os et al., 2002; Zammit et al., 2002; Fergusson et al., 2003) as well as other chronic toxic effects (i.e. respiratory and cardiovascular problems).
4. Rating of adverse reactions should be intuitively categorized. Depending on the disease treated and the interpretation of the evaluator, the same side effect may be considered “minor” or “major”. The lack of a standard scale that qualifies and quantifies the nature and severity of some toxic events related to cannabinoids raises the possibility of an underestimation of such events. Hence, a statement that there are no “major” side effects might be problematic, particularly if the research is funded by interested parties.
5. Drug interaction factors should also be analyzed. In some trials, more than one cannabinoid is evaluated and in other cases, the cannabinoid is administered in addition to the treatment drug. This might affect the efficacy and toxicity of the treatment applied. For example, the synergistic analgesic and sedative actions of cannabinoids and opiates are well documented (Lynch and Clark, 2003) while CBD has anticonvulsant and analgesic activities of its own and has the power to modulate the effects of THC (Rog et al., 2005).

To maximize the benefits (efficacy) and reduce the undesirable effects (toxicity), new formulations for administering and delivering cannabinoids are currently under investigation. These are smokeless oral inhalers (aerosols), sublingual preparations, nasal sprays, transdermal patches and rectal suppositories. The intravenous route is excluded because cannabinoids are insoluble in water. The sublingual spray is a compromise between the inhaled and oral routes: compared to the oral administration, it reduces the first-pass metabolism, thus increasing the bioavailability of the drug and allowing a greater dose-titration (Pryce and Baker, 2005).



Whatever the case may be, few controlled studies have been performed to date with smoked marijuana to evaluate rigorously the advantages and inconveniences of this pharmaceutical form. Comparative studies of smoked marijuana and various cannabinoids administered via different routes are necessary to specify the role that smoked cannabis may play in various therapeutic applications. Relaxation of the regulations on access to cannabis for medical purposes and a greater interest from the pharmaceutical industry in including this type of preparation in their research protocols would facilitate the realization of such clinical trials.

## 5. Conclusion

The progress achieved over the past 15 years in understanding the action mechanisms of THC and other cannabinoids has revived the therapeutic interest in these substances.

The relaxation of the regulatory norms for therapeutic cannabis and the accomplishment of a greater number of controlled clinical trials make it possible to affirm that cannabinoids exhibit an interesting therapeutic potential as antiemetics, appetite stimulants in debilitating diseases (cancer and AIDS), analgesics, as well as in the treatment of multiple sclerosis, spinal cord injuries, Tourette's syndrome, epilepsy and glaucoma.

However, based on the available data, oral cannabinoids should not be used as first-line antiemetics. They may, however, prove effective to treat refractory emesis and have their place as adjuvants to other antiemetic medications. There is insufficient evidence on the efficacy of cannabis and its derivatives to control epilepsy. Further clinical trials, well-designed, carefully executed and powered for efficacy, are essential to clearly define the role of cannabinoids as appetite stimulants, as well as in the treatment of multiple sclerosis, spinal cord injuries, Tourette's syndrome and glaucoma.

For each pathology, it remains to be determined what type of cannabinoid and what route of administration are the most suitable to maximize the beneficial effects of each preparation and minimize the incidence of undesirable reactions.

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Review

# Review on clinical studies with cannabis and cannabinoids 2005-2009

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## Abstract

To date, a large number of controlled clinical trials have been done evaluating the therapeutic applications of cannabis and cannabis-based preparations. In 2006, an excellent review was published, discussing the clinical trials performed in the period 1975 to June 2005 [Ben Amar 2006]. The current review reports on the more recent clinical data available. A systematic search was performed in the scientific database of PubMed, focused on clinical studies that were randomized, (double) blinded, and placebo-controlled. The period screened was from July 1, 2005 up to August 1, 2009.

The key words used were: cannabis, marijuana, marihuana, hashish, cannabinoid(s), tetrahydrocannabinol, THC, CBD, dronabinol, Marinol, nabilone, Cannador and Sativex. For the final selection, only properly controlled clinical trials were retained. Open-label studies were excluded, except if they were a direct continuation of a study discussed here.

Thirty-seven controlled studies evaluating the therapeutic effects of cannabinoids were identified. For each clinical trial, the country where the project was held, the number of patients assessed, the type of study and comparisons done, the products and the dosages used, their efficacy and their adverse effects are described. Based on the clinical results, cannabinoids present an interesting therapeutic potential mainly as analgesics in chronic neuropathic pain, appetite stimulants in debilitating diseases (cancer and AIDS), as well as in the treatment of multiple sclerosis.

**Keywords:** cannabinoids, cannabis, therapeutic potential, controlled clinical trial, efficacy, safety

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## Introduction and Method

There is a growing number of clinical studies that indicate that cannabis or single cannabinoids may have medicinal value for certain diseases and under certain conditions. In the period from 1975 to current, at least 110 controlled clinical studies have been published, assessing well over 6100 patients suffering from a wide range of illnesses. Also the mechanisms of action are becoming increasingly clear since the discovery of the endocannabinoid system and its physiological functions.

In 2006, the Canadian researcher Ben Amar published a review discussing the results of clinical trials per-

formed with cannabis and cannabinoids over the period 1975 to June 2005. The review presented here reports on the period following this, discussing the clinical trials published since then. Together, these two reviews can provide a convenient overview of clinical studies over the last 34 years.

The methodology of this review has been adopted from Ben Amar [2006]. In order to assess the current knowledge on the therapeutic potential of Cannabis, phyto-cannabinoids, and medicinal preparations directly based on phyto-cannabinoids, a systematic search was performed in the scientific database of *PubMed*. Hosted by the U.S. National Library of Medicine, this database contains about 20 million scientific publica-



tions from the field of life sciences and biomedical information.

The period screened was from July 1, 2005 up to August 1, 2009. Clinical data from the period up to July 2005 has been previously reviewed by Ben Amar [2006]. The search focused on clinical studies that were randomized, (double) blinded, and placebo-controlled. The key words used were: *cannabis*, *marijuana*, *marihuana*, *hashish*, *cannabinoid(s)*, *tetrahydrocannabinol*, *THC*, *CBD*, *dronabinol*, *Marinol*, *nabilone*, *Cannador* and *Sativex*.

After initial sorting, all articles and reviews including clinical protocols or a summary of the literature evaluating the therapeutic potential of cannabinoids in humans were read. For the final selection, only properly controlled clinical trials were retained, thus open-label studies were excluded, except when they were a direct continuation of a clinical trial discussed in this paper. The research included the works and data available in English, but also other languages (2x German, 1x Danish).

A range of different cannabis-based products are described in the studies presented in this review. For the ease of the less experienced reader, these preparations are briefly discussed below:

**Cannabis** refers to the dried flowertops of the female plant of Cannabis. This herbal product is also commonly known as marijuana or marihuana. The main way to administer cannabis is by smoking, which is also the way most medicinal users consume it. For clinical trials, most often these materials are standardized for their content (in % of dry weight) of THC.

**THC**, or delta-9-tetrahydrocannabinol, is the pharmacologically and toxicologically most relevant constituent found in the Cannabis plant, producing a myriad of effects in animals and humans. The most well-established palliative effect of THC is the inhibition of chemotherapy-induced nausea and vomiting, mainly in cancer patients. Pure THC can be derived from natural sources (extraction from cannabis plants) or produced synthetically. Chemically, THC belongs to a group of closely related compounds known as cannabinoids, and they are commonly considered the main bioactive components of Cannabis. Up to date, more than 100 different cannabinoids have been described, but only a few of the major ones have been characterized for biological activities, including cannabidiol (CBD, see below) and cannabinol (CBN).

**Dronabinol** is the INN (international non-proprietary name) of the isomer of delta-9-tetrahydrocannabinol that is present in the cannabis plant, the (-)-trans-isomer. This is the only naturally occurring of the four isomers. Oral capsules containing synthetically manufactured dronabinol are available under the name Marinol (see below).

**CBD**, or cannabidiol, is the major non-psychoactive cannabinoid found in Cannabis. It has shown anti-epileptic, anti-inflammatory, anti-emetic, muscle relaxing, anxiolytic, neuroprotective and anti-psychotic activity and reduces the psychoactive effects of THC [Russo

2006]. The mode of action of cannabidiol is not fully understood and several mechanisms have been proposed: (1) CBD acts as antagonist at the central CB<sub>1</sub> receptor and was able to inhibit several CB<sub>1</sub> mediated THC effects [Zuardi et al. 1982]. In a study by Petitot et al. (1998), CBD considerably reduced the receptor activation by the potent classical CB<sub>1</sub> receptor agonist CP55940. (2) CBD stimulates the vanilloid receptor type 1 (VR<sub>1</sub>) with a maximum effect similar in efficacy to that of capsaicin [Bisogno et al. 2001]. (3) CBD inhibits the uptake and hydrolysis of the endocannabinoid anandamide, thus increasing its concentration [Bisogno et al. 2001, Mechoulam & Hanus 2002]. (4) Finally, CBD may also increase the plasma THC level [Bornheim et al. 1995] by inhibiting hepatic microsomal THC metabolism through inactivation of the cytochrome P-450 oxidative system [Bornheim et al. 1998, Jaeger et al. 1996]. However, there was no or minimal effect of CBD on plasma levels of THC in man [Aguirell et al. 1981, Hunt et al. 1981]. Further mechanisms have been described.

**Marinol®** (Solvay Pharmaceuticals, Belgium) is a synthetic version of dronabinol. It is formulated as a capsule containing synthetic dronabinol in sesame oil. In the US it is indicated for the treatment of anorexia associated with weight loss in patients with AIDS and nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. The patent on Marinol will expire in 2011, opening the way for the development of generic preparations of synthetic, as well as naturally-derived, THC.

**Nabilone** (Valeant Pharmaceuticals International, USA) is a synthetic analogue of THC which binds to the cannabinoid CB<sub>1</sub> receptor. In Canada, the United States, the United Kingdom and Mexico, nabilone is marketed as Cesamet®. It is registered for treatment of chemotherapy-induced nausea and vomiting that has not responded to conventional antiemetics. It is also used for other medical conditions.

**Sativex®** (GW Pharmaceuticals, UK) is a cannabis-based pharmaceutical product containing delta 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:1 ratio, delivered in an oromucosal (into the mouth) spray. Because of the use of whole extracts, non-standardized amounts of ballast components are also present, such as minor cannabinoids and terpenoids. Sativex has been approved in Canada as adjunctive treatment for neuropathic pain in adults with multiple sclerosis (MS) and in cancer pain. Registration is pending in several European countries.

**Cannador®** (Society for Clinical Research, Germany) is an oral capsule containing a whole plant extract, with standardized THC content and a CBD amount controlled to lie within a fixed narrow range with a THC:CBD ratio of about 2:1. It has been used in several clinical trials. It has been clinically tested for reduction of muscle stiffness, spasms and associated pain in Multiple Sclerosis, for cachexia in cancer patients and for post-operative pain management.

**Table 1:** Number of studies and patients reviewed

Pathology	# of studies found	Total # of patients included
1. Neuropathic or chronic pain:	11	631
2. Experimental pain:	4	63
3. Multiple sclerosis and spasticity:	9	1300
4. HIV/AIDS:	4	118
5. Glaucoma:	1	6
6. Intestinal dysfunction:	2	82
7. Nausea/vomiting/appetite:	2	228
8. Schizophrenia:	2	55
Other indications:	2	80
<b>Total</b>	<b>37</b>	<b>2563</b>

## Results

The review identified 8 main pathologies in which controlled studies on cannabinoids have been published: they are listed below. A number of other illnesses have been grouped under 'other indications'. Although experimentally induced pain is obviously not a pathological condition, it has been included in this review because it may add to our understanding of the use of cannabis for pain control.

In total, 37 controlled studies evaluating the therapeutic effects of cannabis or cannabinoids were identified. For each clinical trial, the country where the project was held, the number of patients assessed the type of study and comparisons done, the products and the dosages used, and their efficacy are described. Noteworthy adverse and side effects for each study are discussed in the text.

## Summary of the clinical trials

### Neuropathic, chronic and acute pain

A range of studies has been done to determine the effect of nabilone on different types of pain. Based on the analgesic effects of cannabinoids in animal studies, it was hypothesized that nabilone would decrease morphine consumption, pain scores, nausea and vomiting following major surgery. [Beaulieu 2006] tested this hypothesis in a double-blind, randomized, placebo-controlled, parallel-group pilot trial with three doses of 1 or 2 mg of nabilone in the 24 hours after different types of major surgery. Surprisingly, and contrary to the main hypothesis, pain scores at rest and on movement were actually significantly higher in the 2 mg nabilone group compared to the other groups. Also, nabilone administration was not associated with a decrease in morphine consumption in patients. The most common adverse effects of nabilone were dry mouth, nausea and vomiting, respiratory depression, sedation and pruritus. No serious adverse events were observed. It is concluded from animal experiments that cannabinoid receptor and mu-opioid receptor agonists act synergistically with respect to antinociception. In order to demonstrate this effect under clinical conditions, a

study was performed with oral THC on patients after radical prostatectomy [Seeling 2006]. It was expected that patients receiving THC required significantly less of the synthetic opioid analgesic piritramide to control their pain compared to patients on placebo. From the evening before the operation until the morning of the second postoperative day, patients received eight oral doses of either placebo or 5 mg THC, which is a significant amount of THC for any clinical trial. However, neither synergistic effect nor even an additive antinociceptive interaction with the combination of THC and piritramide was found, even though plasma concentrations of THC were measurable in all patients in the verum group.

In another study on postoperative pain, Holdcroft et al. [2006] aimed to investigate whether a single oral dose of Cannador could provide pain relief with minimal side effects. Sixty-five patients received a single dose of 5, 10, or 15 mg Cannador when they had at least moderate pain after stopping patient-controlled analgesia. Pain relief, pain intensity, and side effects were recorded over 6h after administration. Rescue analgesia was requested by all 11 patients (100%) receiving 5 mg, 15 of 30 patients (50%) receiving 10 mg, and 6 of 24 patients (25%) receiving 15 mg Cannador. There was a significant dose-response effect for decreasing pain intensity at rest, and increasing sedation. The number needed to treat (NNT) to prevent one rescue analgesia request for the 10-mg and 15-mg doses, relative to 5 mg, were 2.0 and 1.3, respectively, which is equivalent to many routinely used analgesics. The majority of adverse events affected the central nervous (14 of 26) or cardiovascular (6 of 26) systems, but none persisted after the study. The study was terminated because of a serious vasovagal adverse event in one patient receiving 15 mg.

In a study with nabilone, focusing on chronic pain, results were more promising. [Pinsger 2006] investigated the effect of an add-on treatment with nabilone on patients with chronic therapy-resistant pain in causal relationship with a pathologic status of the skeletal and locomotor system. From the results, it was obvious that the nabilone treatment (up to 1 mg per day) was superior, resulting in a decrease in several different

**Table 2:** Studies on neuropathic or chronic pain

Study	Country	Indication	Type of study	Product	Patients assessed	Efficacy
Skrabek et al. (2008)	Canada	Fibromyalgia	Randomized, double-blind, placebo-controlled trial	Nabilone (oral)	40 fibromyalgia patients having continued pain despite the use of other oral medications.	Nabilone improved symptoms and was well-tolerated.
Wilsey et al. (2008)	United States	Neuropathic pain	Double-blind, placebo-controlled, crossover study	Cannabis (smoked)	38 patients with complex regional pain syndrome (CRPS type I), spinal cord injury, peripheral neuropathy, or nerve injury.	Significant improvement of neuropathic pain.
Narang et al. (2008)	United States	Chronic pain	Phase I: randomized, single-dose, double-blind, placebo-controlled, crossover trial; Phase II: extended open-label titrated trial.	Dronabinol (oral)	30 patients with severe chronic noncancer pain, taking stable doses of opioid analgesics for longer than 6 months.	THC (in combination with opioids) reduced pain & pain bothersomeness, and increased satisfaction. No difference was observed between 10-20mg THC.
Frank et al. (2008)	Great Britain	Chronic neuropathic pain	Randomised, double blind, crossover trial	Nabilone (oral)	96 patients with chronic neuropathic pain.	Dihydrocodeine provided better pain relief than Nabilone.
Nurmikko et al. (2007)	Great Britain	Neuropathic pain, allodynia	Randomised, double-blind, placebo-controlled, parallel-group trial	Sativex (sublingual)	125 patients with a current history of unilateral peripheral neuropathic pain and allodynia.	Significant improvement in pain by Sativex.
Holdcroft et al. (2006)	Great Britain	Postoperative pain	Multicenter dose-escalation study	Cannador (oral)	65 Postoperative patients experiencing at least moderate pain, after stopping patient controlled analgesia.	The optimal dose was 10 mg Cannador, effectively reducing postoperative pain without serious side effects.
Pinsger et al. (2006)	Austria	Chronic pain	Placebo-controlled, double-blind pilot study	Nabilone (oral)	30 patients with chronic therapy-resistant pain in causal relationship with a pathologic status of the skeletal and locomotor system.	Nabilone caused a significant reduction in pain and improvement of quality of life.
Blake et al. (2006)	Great Britain	Pain in rheumatoid arthritis	Placebo-controlled, randomized, double-blind, parallel group study	Sativex (sublingual)	58 patients with active arthritis not adequately controlled by standard medication.	Sativex produced improvements in pain and sleep.
Ware et al. (2006)	Canada	Chronic pain	Randomized, controlled, crossover trial	Cannabis (smoked)	8 experienced and authorized (Canada) cannabis users with chronic pain.	Medical cannabis users can appreciate differences in herbal cannabis products.
Seeling et al. (2006)	Germany	Postoperative pain	Randomized, double blind trial	THC (oral)	100 patients after radical prostatectomy.	No synergistic or additive interaction between THC and piritramide.
Beaulieu et al. (2006)	Canada	Postoperative pain	Double-blind, randomized, placebo-controlled, parallel-group pilot trial	Nabilone (oral)	41 patients undergoing gynecologic, orthopedic or other surgery.	Nabilone did not reduce 24h morphine consumption or improve effects of morphine. Nabilone did increase pain scores.

**Table 3:** Studies on experimental pain

<b>Study</b>	<b>Country</b>	<b>Indication</b>	<b>Type of study</b>	<b>Product</b>	<b>Patients affected</b>	<b>Efficacy</b>
Kraft et al. (2008)	Austria	Acute inflammatory pain and hyperalgesia	Double-blind, placebo-controlled, crossover study	Cannador (oral)	18 healthy female volunteers without a history of cannabis use.	No analgesic or antihyperalgesic activity observed for the cannabis extract. However, Cannador did lead to hyperalgesic effect.
Redmond et al. (2008)	Canada	Experimental heat pain	Double-blind, placebo controlled, crossover study	Nabilone (Oral)	17 healthy volunteers.	Nabilone failed to produce analgesic effect, and it did not interact with descending pain inhibitory systems. Significant difference was observed in effects between men and women.
Wallace et al. (2007)	United States	Pain: capsaicin-induced and hyperalgesia	Randomized, double-blind, placebo-controlled, crossover trial	Cannabis (smoked)	15 healthy volunteers.	A medium dose of cannabis reduced pain, while a high dose increased pain induced by capsaicin.
Roberts et al. (2006)	United States	Analgesia, synergy with morphine	Double-blind, four treatment, four period, four sequence, crossover trial	THC (oral)	13 healthy volunteers.	There was a synergistic effect between THC and morphine on the affective component of pain but not on the sensory component.

**Table 4:** Studies on multiple sclerosis and spasticity

Study	Country	Indication	Type of study	Product	Patients affected	Efficacy
Aragona et al. (2009)	Italy	MS: psycho-pathological and cognitive effects	Double-Blind, placebo-controlled, crossover trial	Sativex (sublingual)	17 cannabis-naïve MS patients	Cannabinoid treatment did not induce psychopathology and did not impair cognition in cannabis-naïve patients
Conte et al. (2009)	Italy	MS: pain	Randomized, double-blind, placebo-controlled, cross-over study	Sativex (sublingual)	18 patients with secondary progressive MS	Results provide objective neurophysiological evidence that cannabinoids modulate the nociceptive system in patients with MS
Collin et al. (2007)	Great Britain	MS: spasticity	Randomized, placebo-controlled trial	Sativex (sublingual)	189 MS patients with spasticity.	Significantly reduction in spasticity.
Rog et al. (2007)	Great Britain	MS: neuropathic pain (Open label extension of Rog 2005)	Uncontrolled, open-label trial	Sativex (sublingual)	63 MS patients with central neuropathic pain.	Sativex was effective, with no evidence of tolerance, in these select patients with CNP and MS who completed approximately 2 years of treatment (n = 28). Ninety-two percent of patients experienced side effects, the most common of which were dizziness and nausea.
Kavia et al. (2006)	Great Britain	MS-associated detrusor overactivity	Double blind, randomized, placebo controlled parallel group trial	Sativex (sublingual)	135 MS patients with an overactive bladder.	Sativex has a beneficial effect on the symptoms of overactive bladder.
Freeman et al. (2006)	Great Britain	MS: urge incontinence	Multicentre, randomised placebo-controlled trial	Cannador (oral); dronabinol (oral)	630 MS patients with muscle spasticity.	Cannabis and THC caused a significant reduction in incontinence.
Wissel et al. (2006)	Austria	Spasticity related pain	Double-blind placebo-controlled cross-over trial.	Nabilone (oral)	11 patients with chronic upper motor neuron syndrome (UMNS).	Significant reduction of pain, but not of spasticity, motor function, or activities of daily living.
Wade et al. (2006)	Great Britain	MS: spasticity (Open label extension of Wade 2004)	Open label continuation after placebo-controlled study	Sativex (sublingual)	137 MS patients with symptoms not controlled satisfactorily using standard drugs.	Long-term use of an oromucosal CBM (Sativex) maintains its effect in those patients who perceive initial benefit. The precise nature and rate of risks with long-term use, especially epilepsy, will require larger and longer-term studies.
Katona et al. (2005)	Great Britain	MS: cytokine profile	Randomised, placebo-controlled trial at 33 UK centers	Sativex (sublingual)	100 MS patients with muscle spasticity.	No evidence for cannabinoid influence on serum levels of cytokines.

**Table 5:** Studies on HIV/AIDS

Study	Country	Indication	Type of study	Product	Patients affected	Efficacy
Ellis et al. (2009)	United States	Neuropathic pain	Phase II, double-blind, placebo-controlled, crossover trial	Cannabis (smoked)	28 patients with documented HIV infection and neuropathic pain refractory to a least two previous analgesics.	Significant pain relief with cannabis.
Haney et al. (2007)	United States	HIV: caloric intake, mood, sleep	Placebo-controlled within-subjects study	Dronabinol (oral); Cannabis (smoked)	10 patients taking at least 2 antiretroviral medications, currently under the care of a physician for HIV management, and smoking marijuana at least twice weekly for the past 4 weeks.	THC and cannabis caused an increase in caloric intake and weight.
Abrams et al. (2007)	United States	HIV: sensory neuropathy	Prospective randomized placebo-controlled trial	Cannabis (smoked)	50 patients with HIV infection and symptomatic HIV-associated sensory neuropathy.	Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy.
Haney et al. (2005)	United States	HIV: caloric intake, mood	Randomized, within-subject, staggered, double-dummy design	Dronabinol (oral); Cannabis (smoked)	30 HIV-positive patients smoking marijuana.	THC and cannabis cause increased caloric intake.

**Table 6:** Studies on glaucoma

Study	Country	Indication	Type of study	Product	Patients affected	Efficacy
Tomida et al. (2006)	Great Britain	Glaucoma: intraocular pressure	Randomized, double-blind, placebo-controlled, 4 way crossover study	2 cannabis extracts rich in THC or CBD (sublingual)	6 patients with ocular hypertension or early primary open angle glaucoma.	Significant reduction of intraocular pressure.

**Table 7:** Studies on Intestinal dysfunction

Study	Country	Indication	Type of study	Product	Patients affected	Efficacy
Esfandiyari et al. (2007)	United States	Colonic motor and sensory functions	Randomized, placebo-controlled study	Dronabinol (oral)	52 healthy volunteers.	THC relaxes the colon and reduces postprandial colonic motility.
Esfandiyari et al. (2006)	United States	Gastrointestinal transit and postprandial satiation	Double-blind, randomized, placebo-controlled, parallel group study	Dronabinol (oral)	30 healthy volunteers.	Dronabinol retards gastric emptying in humans; effects are gender-related. Dronabinol also increases fasting gastric volumes in males.



**Table 8:** Studies on nausea/vomiting/appetite

Study	Country	Indication	Type of study	Product	Patients affected	Efficacy
Meiri et al. (2007)	United States	Chemotherapy-induced nausea and vomiting	Double-blind, placebo-controlled study	Dronabinol (oral)	64 patients receiving moderately to highly emetogenic chemotherapy.	Dronabinol or ondansetron was similarly effective for the treatment of CINV. Combination therapy with dronabinol and ondansetron was not more effective than either agent alone. Active treatments were well tolerated.
Strasser et al. (2006)	Switzerland	Cancer: anorexia-cachexia	Multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial	Cannador (oral); THC (oral)	164 patients with advanced cancer, Cancer-Related Anorexia-Cachexia Syndrome, and severe weight loss.	Insufficient difference between Cannador, THC and placebo on appetite or quality of life.

**Table 9:** Studies on schizophrenia

Study	Country	Indication	Type of study	Product	Patients affected	Efficacy
Leweke et al. (2007)	Germany	Schizophrenia	Double-blind, controlled clinical trial	CBD (oral), amisulpride (oral)	42 patients suffering from acute paranoid schizophrenia and schizophreniform psychosis.	CBD significantly reduced psychopathological symptoms of acute psychosis. CBD was as effective as amisulpride, a standard antipsychotic.
D'Souza et al. (2005)	United States	Schizophrenia	Double-blind, randomized, placebo-controlled study	THC (intravenous)	13 stable, antipsychotic-treated schizophrenia patients.	THC is associated with transient exacerbation in core psychotic and cognitive deficits in schizophrenia. These data do not provide a reason to explain why schizophrenia patients use cannabis in self-treatment.

**Table 10:** Studies on other indications

Study	Country	Indication	Type of study	Product	Patients affected	Efficacy
Guzmán et al. (2006)	Spain	Cancer: recurrent glioblastoma multiforme	pilot phase I trial	THC (intra-tumoral)	9 patients with recurrent glioblastoma multiforme	THC inhibited tumour-cell proliferation in vitro and decreased tumour-cell Ki67 immunostaining when administered to two patients
Sylvestre et al. (2006)	United States	Hepatitis C	prospective observational study	Cannabis (smoked)	71 patients, being recovering substance users	Modest cannabis use may offer symptomatic and virological benefit to some patients undergoing HCV treatment by helping them maintain adherence to the challenging medication regimen

pain-parameters (VAS), and an increase in quality of life ( $\Delta$ QOL score). Although typical side effects of nabilone were commonly observed, such as dizziness, fatigue, dry mouth and sleepiness, the study concluded that a majority of patients classified nabilone intake in addition to the standard treatment as a positive measure. Thus, this kind of treatment may be an interesting and attractive enrichment of analgesic therapy.

Also **Frank et al. [2008]** focused on the potential analgesic effects of nabilone in neuropathic pain. Objective of this study was to compare the analgesic efficacy and side effects of this synthetic cannabinoid with those of the weak opioid dihydrocodeine for chronic neuropathic pain in 96 patients aged 23-84 years. It was found that the opioid was a better analgesic than nabilone. However, the clinical significance of the difference was small, and in fact the majority of patients had no clinically relevant drop in their pain score on either treatment. Nabilone was associated with more sickness than dihydrocodeine, while dihydrocodeine was associated with more tiredness and nightmares. No major adverse events occurred with either drug and both drugs were equally well tolerated. Although a dose of only 2 mg of nabilone was used in this study, the observed side effect profile argues against giving higher doses of the drug.

In patients with fibromyalgia, the first randomized, controlled trial to assess the benefit of nabilone on pain reduction and quality of life improvement was done only recently [**Skrabek 2008**]. It has been suggested that a clinical endocannabinoid deficiency may be involved in the etiology of fibromyalgia. As no treatment has been specifically approved for management of this condition, further research into treatment strategies is important. Nabilone (up to 1 mg BID) appeared to be a beneficial, well-tolerated treatment option for fibromyalgia patients, with significant benefits in pain relief and functional improvement. The most common side effects reported by subjects in the nabilone group included drowsiness (7/15), dry mouth (5/15), vertigo (4/15), and ataxia (3/15). No serious adverse events occurred during the study. There was a significant, but transient, increase in the weight of subjects treated with nabilone over the 8 weeks of the trial (mean 1.13 kg). Nabilone did not appear to have any lasting benefit in subjects when treatment was discontinued. During the study, subjects were asked to continue any current treatment for fibromyalgia, including breakthrough pain medications. Future studies could be done using nabilone as a single agent to determine its effect on pain and quality of life alone.

The efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy was assessed by [**Narang 2008**] in a study combining a phase I (double-blind, single dose) and phase II (Open-label, multi-dose) trial. Results of the phase I study showed that patients who received dronabinol (10 or 20 mg) experienced decreased pain intensity and increased satisfaction compared with placebo. No differences in pain relief were found between the active treatments.

According to the authors, a lack of an active placebo may have contributed to unblinding. Phase II was an extended open-label titrated trial of dronabinol as add-on medication to patients on stable doses of opioids. In this phase, titrated dronabinol contributed to significant relief of pain, reduced pain bothersomeness, and increased satisfaction compared with baseline. Overall, the use of dronabinol was found to result in additional analgesia among patients taking opioids for chronic noncancer pain. Subjects also showed improvements in quality of sleep. The most frequently reported side effects, compared to placebo, were dry mouth, tiredness, sleepiness, and drowsiness. Despite these side effects, subjects' overall satisfaction with treatment was significantly higher (54%) on active doses than placebo. The results imply that dronabinol may be a useful adjuvant analgesic for patients with persistent pain in spite of taking stable doses of opioids. Future studies need to examine whether the benefits and the side effects of THC among chronic pain patients change with prolonged use.

The majority of patients using cannabis for self-medication administer it by smoking, but there is currently no significant experience within the pharmaceutical world with the preparation and composition of cannabis cigarettes. As a result, it may be difficult to evaluate the experience of self-medicating patients, and to prove or disprove the medicinal effects of smoked cannabis. A unique study by [**Ware 2006**] addressed this issue by testing a range of different cannabis cigarettes in a randomized controlled crossover trial. Four different herbal cannabis preparations were tested among 8 experienced and authorized cannabis users with chronic pain. Preparations were varied with respect to grind size, THC content and humidity. The product with highest THC content (12%), highest humidity (14%) and largest grind size (10 mm) was rated highest overall. Significant differences were noted between preparations on overall appearance and color. While the small size of the study precludes broad conclusions, the study shows that medical cannabis users can appreciate differences in herbal product. A more acceptable cannabis product may increase recruitment and retention in clinical studies of medical cannabis.

[**Wilsey 2008**] studied the effects of smoked cannabis on patients with central and peripheral neuropathic pain. A standardized procedure was used for smoking either high-dose (7%), low-dose (3.5%), or placebo cannabis. The amount of THC consumed was estimated to be 19 mg during the low-dose sessions and 34 mg during the high-dose sessions. Results indicated that cannabis may be effective at ameliorating neuropathic pain, and may be an alternative for patients who do not respond to, or cannot tolerate, other drugs. There was no apparent correlation of cannabinoid serum levels with analgesia. It was concluded that, as with opioids, cannabis does not rely on a relaxing or tranquilizing effect (e.g., anxiolysis) but rather reduces both the core component of nociception and the emotional aspect of the pain experience to an equal degree.

Undesirable consequences of smoking cannabis were clearly identifiable, but no participant dropped out because of an adverse event related to an experimental intervention.

In a first ever controlled trial of a cannabis preparation in rheumatoid arthritis, a significant analgesic effect was observed and disease activity was significantly suppressed following Sativex treatment [Blake 2006]. In comparison with placebo, a significant analgesic effect was observed and disease activity was significantly suppressed. Sativex produced statistically significant improvements in pain on movement, pain at rest, quality of sleep and inflammation (DAS28). The suppression of pain on movement, the primary endpoint, suggests a peripheral analgesic action, while the suppression of pain at rest may suggest a more central effect. The modest suppression of the present gold standard inflammation activity measure, the DAS28, might indicate an influence on the immune effector system. Importantly, the trial did not demonstrate significant toxicity and Sativex was generally well tolerated. The large majority of adverse effects were mild or moderate, and there were no adverse effect-related withdrawals or serious adverse effects in the active treatment group. About a quarter of patients receiving Sativex experienced transient dizziness at some point, though in all cases this was rated as mild.

A study by [Nurmikko 2007] demonstrated that Sativex is effective in the relief of peripheral neuropathic pain when given in addition to existing stable analgesia. A self-titrating regimen was used to optimise drug administration. Greater than 30% improvement in pain intensity, generally considered as clinically meaningful [Farrar 2000], was reported by 26% of subjects receiving Sativex, compared with 15% of patients taking placebo. A self-titration regimen permitted individual patients to optimize their dose on the basis of their own efficacy and tolerability response. Both experimental and human volunteer studies suggest that tolerance to some of the side effects of cannabis occurs within days of its repeated administration [Guy 2003, Jones 2002]. A self-titration regimen allows for this to occur, further optimizing the therapeutic response. An open-label extension study showed that the initial pain relief was maintained without dose escalation or toxicity for 52 weeks. The majority of patients took far less than the highest allowable dosage. Fifty-seven (91%) patients in the Sativex group experienced at least one adverse event (AE) during the course of the study compared with 48 (77%) patients in the placebo group. The AEs reported by the patients were mostly gastrointestinal, central nervous system related or topical. While reported gastrointestinal AEs were more common in the Sativex group, central nervous system AEs were not. Most were observed at onset of treatment, and in the majority described as mild. Intoxication scores remained low throughout the study. At recruitment, all patients were either non-responders to several conventional neuropathic analgesics, or were in severe pain despite taking appropriate therapy. Considering the re-

fractory nature of their pain, and that patients remained on their existing analgesia, the improvement of the ongoing pain in those on the active drug is encouraging.

### Experimental pain

Co-administration of various cannabinoids with morphine has been found to produce a greater-than-additive effect with respect to antinociception in mice [Smith 1998], and crosstalk between the endocannabinoid- and endorphin-systems has been shown [Corchero 2004]. Therefore, the synergistic affective analgesic interaction between THC and morphine was determined in a double-blind, four treatment, crossover design [Roberts 2006]. Subjects received THC (5 mg orally) or placebo and 90 min later morphine (0.02 mg/kg) intravenously, or placebo. Fifteen minutes later subjects rated the pain associated with the application of thermal stimuli to skin. Neither morphine nor THC had a significant effect at the doses used, and there was no significant interaction between the two. A small, but non-significant synergy was found only for the affective component of pain. Subjects described a variety of mild euphoric or dysphoric effects, but no serious or unexpected toxicities occurred. The study concluded that future studies of THC or other cannabinoids in combination with opiates should focus upon clinical rather than experimental pain.

Based on the results of preclinical studies, another study [Wallace 2007] hypothesized that inhaled cannabis would reduce capsaicin-induced pain and hyperalgesia, and change the affective quality of pain in a dose-dependent manner. In 19 healthy volunteers, the concentration-response effects were evaluated of low-, medium-, and high-dose smoked cannabis (respectively 2%, 4%, and 8% THC by weight). Only the medium dose cannabis significantly decreased capsaicin-induced pain. Interestingly, as has been observed in other studies [e.g. Kraft 2008], a significant *increase* in capsaicin-induced pain occurred with the high dose. The authors suggested that there is a window of modest analgesia for smoked cannabis, with lower doses decreasing pain and higher doses increasing it. There was a significant correlation between plasma levels of THC and metabolites with decrease in pain, but no correlation between the high-dose plasma levels and increase in pain. This suggests that there may be another compound within the cannabis used that was not measured but that was responsible for the increased pain at the high dose. Mild to moderate side effects were experienced by 7 of 19 subjects, primarily at the highest dose of cannabis, but no serious AEs occurred.

The double-blind, placebo-controlled, crossover study performed by Kraft *et al.* [2008] was designed to detect a potential analgesic activity of Cannador by two different and well-established human models of acute inflammatory pain and hyperalgesia. Only female volunteers were included, because animal studies using the same models have suggested a more pronounced effect of cannabinoids in females compared with males

[Tseng 2004, Craft 2005]. The dose of THC in each cannabis administration was standardized to 20 mg. Also a significant amount of CBD was present (about 10 mg per administration). No analgesic or antihyperalgesic activity of this cannabis extract was found, even though the high levels of THC and its metabolites detected in the plasma of study subjects, and the occurrence of psychotropic side effects, argue for a sufficient bioavailability. In contrast, the results actually seem to support the impression that high doses of cannabinoids may cause hyperalgesia in certain acute pain conditions. One subject experienced acute psychotic symptoms after Cannador, but all symptoms spontaneously disappeared after 4 hours. Despite the standardized conditions, a broad variability in peak plasma levels for all measured cannabinoids was observed, possibly indicating the difficulties of standardizing the administration of orally used cannabis products.

One way cannabinoids may act to dampen the intensity of nociceptive signals in prolonged pain models is through their potentiating actions on descending inhibitory systems, which at least partly depends on the release of endogenous opioids. Descending inhibitory systems originate in the brainstem and are dynamically triggered following prolonged noxious insult [Millan 2002]. A double-blind, placebo-controlled, crossover study explored the analgesic and antihyperalgesic properties of the synthetic cannabinoid nabilone on long-lasting experimental heat pain, as well as its effects on descending pain inhibitory systems [Redmond 2008]. Single doses of 0.5 and 1 mg nabilone were administered to 10 men and 10 women. Primary outcome measures included average heat pain, temporal summation of heat pain, and drug-induced changes in the strength of descending analgesia. Administration of low-dose Nabilone did not act as an analgesic agent. However, a significant antihyperalgesic effect was observed in women only. No important AEs were observed during testing, and the most commonly observed side effects were dry mouth, red eyes, mild sedation, and euphoria.

### Multiple sclerosis and spasticity

Although cannabinoids have been used mainly to alleviate symptoms of multiple sclerosis, there is also experimental evidence to suggest that they may be immunomodulatory. Cannabinoids are believed to be anti-inflammatory, mainly through activation of the CB2 receptor, which is principally located peripherally, especially on leucocytes. CB2 activation may be associated with a Th1 to Th2 shift. Consequently, there is some evidence that cannabinoids may be therapeutically useful in treating multiple sclerosis, which is generally believed to be an autoimmune condition. A clinical study [Katona 2005] investigated the nature of potential cannabinoid immunomodulation on serum samples obtained from patients with MS taking part in the CAMS study [Zajicek 2003, 2005]. Cannador and THC were used as study medication. With 657 patients recruited, this is to date the largest clinical trial per-

formed with any cannabis-based medicine. Serum samples of 100 subjects were available for analysis. Results did not demonstrate any significant effects of cannabinoids on the cytokine profiles examined, which included interferon-gamma (IFN- $\gamma$ ), interleukin (IL)-10, IL-12 and C-reactive protein. However, the standard deviations were large, so that relatively small but possibly clinically useful effects cannot be excluded from these results.

In 2004, Wade *et al.* performed a 10-week placebo-controlled study with 160 MS patients, administering Sativex using a self-titration dosing regimen. The study suggested that Sativex is an effective treatment for spasticity associated with MS, but the supporting data was not very strong. Therefore, the investigation was continued as an open label trial to monitor the safety and efficacy of long-term use of Sativex. A total of 137 MS patients who perceived to benefit from treatment entered the extension trial [Wade 2006]. Patients were assessed every eight weeks and were followed for an average of 434 days. This study concluded that patients with MS who derive symptom relief from Sativex in the first 10 weeks, generally maintain that relief over an extended period of treatment without any increase in dose. Patients tended to stabilize at a dose of approximately 11 sprays daily (equivalent to 30 mg THC and 28 mg CBD). Unwanted effects were common but rarely troublesome, and the majority was found to be unrelated to the treatment. Four patients experienced seizures, but all four were also taking other potentially epileptogenic drugs. Nevertheless, the relationship between Sativex (or other cannabis based medicines) and seizures warrants further investigation. Although only 67% of the initial number of subjects could be followed for at least one year on the medication, the obtained data nevertheless provides a large body of safety and tolerability data. A number of subjects who had received Sativex for at least one year were asked to participate in a planned abrupt interruption of the study medication for up to 14 days, in order to explore the possibility of a withdrawal syndrome and to determine whether MS-related symptoms would reappear. Of 25 patients participating, five resumed Sativex before the end of 14 days because of reemergence of marked MS symptoms. There was no consistent withdrawal syndrome on abrupt cessation, although just under half the patients experienced new symptoms that may have been related to withdrawal.

A study by Rog *et al.* [2005] compared the efficacy, safety, and tolerability of Sativex with placebo in relieving central neuropathic pain in 64 patients with MS. Patients could gradually self-titrate and the median dose used by subjects was equal to 25 mg of THC. The study concluded that Sativex is effective in reducing pain and sleep disturbance in the population studied. Patients in this study were taking, on average, two other medications, with limited efficacy given their baseline pain scores. Therefore, as adjunctive analgesic treatment, Sativex had a significant treatment effect. The numbers needed to treat (NNT) to achieve a 50%



reduction in central pain in at least one patient was 3.7, similar to the value of 3.5 obtained in a previous dronabinol trial [Svendsen 2004]. The same group [Rog 2007] continued their study with a long-term extension, treating MS patients for neuropathic pain with Sativex in an uncontrolled, open-label trial. Patients remained on a self-titration scheme, while maintaining their existing analgesia as required. Of 64 patients completing the original trial, 28 patients completed the extension with a mean duration of treatment of 839 days. In this group a relatively small but sustained reduction in pain was observed. Seventeen patients withdrew due to AEs; the most common of which were nausea, dizziness, weakness, and fatigue. Only two serious AEs were judged to be treatment-related. The mean dose of Sativex, and number of patients experiencing intoxication remained stable throughout the follow-up trial.

Lower urinary tract symptoms (LUTS) are very common symptoms of MS and are mainly due to neurogenic detrusor overactivity [Goldstein 1982], and often lead to bladder dysfunction. Anecdotal reports from MS patients have suggested that cannabis might have a beneficial effect on LUTS [Brady 2002]. Therefore, the effect of Cannador and pure THC on urge incontinence in patients with multiple sclerosis was determined in a multicentre, randomised placebo-controlled trial [Freeman 2006]. The data for this substudy was collected from the patient population of the CAMS study [Zajicek 2003], by asking subjects to complete incontinence diaries. Finally, 255 patients could be fully evaluated. Both Cannador and THC treatments showed significant effects over placebo in urge incontinence episodes. The authors hypothesized that cannabinoids relax the detrusor smooth muscle during filling, thereby improving neurogenic detrusor overactivity. Further support for a positive treatment effect comes from the measurement of lower volumes of involuntary urine loss in the active treatment groups. Because this was an “add-on” study to the CAMS study, which was assessing spasticity, patients were selected on this symptom rather than on incontinence. A proper trial set up specifically to test for incontinence may therefore yield more robust results. Nevertheless, it has been shown that even a modest 25% reduction in urge incontinence might be clinically significant [Coyne 2005].

Another, smaller, study was performed to determine the effects of Sativex treatment on the overactive bladder in MS [Kavia 2006]. Patients were treated over a period of 8 weeks, in order to detect an improvement in urgency incontinence. Although the study failed to show a reduction in *daily* incontinence at the end of the study, Sativex was superior to placebo for nocturia. This effect was greater for more severe disease, and a substantial number of patients became nocturia free on the active treatment. Patients on Sativex were three times more likely to report an improvement of >30% compared to placebo. Active treatment was well tolerated, and the most common adverse effects were dizziness, urinary tract infection, and headache.

Because THC was reported to add benefit in the treatment of pain in patients with MS, the question arose whether synthetic cannabinoids with lower potential for psychotropic side effects could be effective as well. A double-blind, placebo-controlled, cross-over trial was performed to evaluate the safety and efficacy of low dose treatment with nabilone (1 mg per day) on spasticity-related pain [Wissel 2006]. Patients all suffered from chronic upper motor neuron syndrome (UMNS) not sufficiently correctable by conventional treatment. Results showed a significant decrease of pain under nabilone after 4 weeks of treatment, while spasticity, motor function and activities of daily living did not change. Although one patient dropped out because of weakness of lower limbs which could be attributed to nabilone, the other side effects observed in the present study were stated as mild and easily tolerable, or not related to the treatment. The study also assessed neuropsychological parameters relevant for driving ability in a subset of patients [Kurtzhaler 2005], but no cognitive side effects were found in domains of attentional performance, psychomotor speed, and mental flexibility.

In a randomized, placebo-controlled trial on the efficacy and tolerability of Sativex, 189 subjects with definite MS and spasticity were treated over a 6 week period. Subjects were allowed to self-titrate their daily dose, which resulted in a mean dose of ca. 25 mg of THC and of CBD (9.4 sprays) per day. Results rated Sativex significantly more effective than placebo in relieving spasticity [Collin 2007]. Of the Intention to Treat (ITT) population, 40% of the subjects achieved >30% improvement from baseline. The secondary outcomes did not achieve statistical significance but were all in favour of Sativex. The low rate of subject withdrawal due to AEs in this study may seem surprising given that the dose of THC, present in the cannabis extract, was being taken in mean daily doses in excess of 25 mg, considerably more than was given in most other published studies. However, this may reflect the presence of CBD, which is known to modify some of the psychoactive effects of THC, so that THC as part of a cannabis extract may become better tolerated than THC as a single molecule [Zuardi 1982].

In a group of 18 patients with secondary progressive MS, a study was performed to identify the neurotransmitter system involved in the pain control by cannabinoids in MS [Conte 2009]. The flexion reflex method was used, an objective tool for assessing pain threshold, pain pathways and the neurotransmitter system involved in pain control [Sandrini 1993]. After administration of Sativex, at a mean dose of 8 sprays daily (ca. 20 mg THC and CBD), a significant effect was observed on the parameters recorded. Also the patients' VAS pain scores decreased, although not significantly. It was concluded that cannabinoids modulate human pain perception mainly by acting at the pre-motorneuronal level in the spinal cord. Cannabinoids, like opioids, could act by decreasing neurotransmitter release.

Although no significant cognitive deficits were reported in frequent but moderate users of cannabis [Jager 2006] the persistent effects of cannabis on cognition remain uncertain [Verdejo-Garcia 2004]. Therefore, the primary aim of a double-blind, placebo controlled, crossover study performed by **Aragona *et al.* [2009]** was to explore the onset of psychopathological symptoms and cognitive deficits in cannabis-naïve patients with MS treated with Sativex for relieving their spasticity. The mean daily dose used by self-titration corresponded to ca. 22 mg of THC. The effects on psychopathology were evaluated after 3 weeks of treatment. During the study, plasma levels of THC and CBD were monitored. Cannabinoid treatment did not induce psychopathology and did not impair cognition in subjects. Also the effects of cannabinoids on quality of life, fatigue, and motor function of MS patients were non-significant; however, the positive correlation between plasma levels of THC and psychopathological scores suggests that at dosages higher than those used in therapeutic settings, interpersonal sensitivity, aggressiveness, and paranoid features might arise. All subjects finished the study. Safety and tolerability were generally good, drug tolerance and dose increasing were not reported during the trial, and desire for Sativex or abuse was not present at follow-up.

#### HIV/AIDS

In two studies, Haney *et al.* demonstrated that smoked cannabis, and oral dronabinol, stimulates appetite in already experienced cannabis smokers. In the first study [**Haney 2005**], using only acute doses, it was found that for experienced cannabis smokers with clinically significant wasting, both dronabinol (at acute doses at least four to eight times the current recommendation) and cannabis produced substantial and comparable increases in food intake without causing major adverse effects. Caloric intake was only increased in the group with significant wasting, but not in a control group of HIV patients without signs of wasting. Only the highest dose of dronabinol (30 mg) was poorly tolerated, producing at least one adverse effect (e.g., headache, nausea, overintoxication) in 20% of the participants, suggesting that this (oral) dose may be too high, even among regular cannabis smokers.

The second study [**Haney 2007**] showed that also repeated long-term doses of both dronabinol (up to 10 mg daily) and smoked cannabis (up to 3.9% THC) were well tolerated and produced substantial and comparable increases in food intake. Both drugs dose-dependently increased daily caloric intake and body weight, without causing disruptions in psychomotor functioning. For the high-dose dronabinol and cannabis conditions, this resulted in a significant increase in body weight within 4 days (>1 kg). Both active treatments increased daily food intake by increasing the number of times participants ate throughout the day, without altering the number of calories consumed during each eating occasion. Increased food intake paralleled increased ratings of intoxication (generally rated

as positive by patients) for all cannabinoid conditions, except for the low dose of dronabinol (5 mg).

HIV-associated sensory neuropathy is the most common peripheral nerve disorder complicating HIV-1 infection, most often defined by hyperalgesia and allodynia. **Abrams *et al.* [2007]** determined the effect of smoked cannabis on this condition. Patients were randomly assigned to smoke either cannabis or identical placebo cigarettes three times daily for 5 days. It was found that smoked cannabis reduced daily pain significantly compared to placebo; the number needed to treat (NNT) in order to achieve a >30% pain reduction (commonly seen as a clinically relevant improvement) among all completing patients was 3.6. These findings are comparable to oral drugs routinely used for chronic neuropathic pain, such as Gabapentin [Backonja 1998]. Cannabis also reduced some types of experimentally induced hyperalgesia in the same patients. Although the active treatment was well tolerated, side effects ratings were higher in patients in the cannabis group for anxiety, sedation, disorientation, confusion, and dizziness. No serious AEs were reported, and no patient withdrew from the study because of AEs.

Despite management with opioids and other pain modifying therapies, neuropathic pain continues to reduce the quality of life and daily functioning in HIV-infected individuals. In a randomized cross-over trial, smoked cannabis at maximum tolerable dose (1-8% THC), significantly reduced neuropathic pain intensity in HIV-associated distal sensory predominant polyneuropathy (DSPN) compared to placebo when added to stable concomitant analgesics [**Ellis 2009**]. Among the completers, pain relief was greater with cannabis than placebo. Using verbal descriptors of pain magnitude from the Descriptor Differential Scale (DDS), cannabis was associated with an average reduction of pain intensity from 'strong' to 'mild to moderate'. Also, cannabis was associated with a sizeable (46%) and compared to placebo (18%) significantly greater proportion of patients who achieved a >30% reduction in pain. Smoked cannabis was generally well tolerated and effective when added to concomitant analgesic therapy in these patients. The frequency of some non-treatment-limiting side effects was greater for cannabis than placebo. These included concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst. Although most side effects were mild and self-limited, two subjects experienced treatment-limiting toxicities.

#### Glaucoma

There is increasing evidence suggesting that cannabinoids may lower IOP primarily by influencing aqueous humor production and outflow, through activation of the CB1 receptor. In glaucoma, the final pathway leading to visual loss is the selective death of retinal ganglion cells through apoptosis. Recent studies have documented the neuroprotective properties of cannabinoids independently of their effect on IOP [listed in Tomida 2006]. But despite these promising results, in



recent years only a single clinical trial has been added to the scientific literature.

**Tomida *et al.* [2006]** performed a pilot study to assess the effect on IOP, and the safety and tolerability of a low dose of THC and CBD. Although topical administration (eye drops) of cannabinoids would be ideal for glaucoma, this type of application has been associated with irritation and corneal damage [Jay 1983]. Therefore, an oromucosal spray was used because it has been shown to have a satisfactory pharmacokinetic profile and has been well tolerated in clinical studies [Guy 2003]. Patients with ocular hypertension or early primary open angle glaucoma received single dose standardized cannabis extracts, containing either 5 mg THC, 20 mg CBD, 40 mg CBD, or placebo. Two hours after administration of THC, the IOP was significantly lower than after placebo, returning to baseline level after 4 hours. CBD administration did not reduce the IOP at any time with either of the two doses studied. Instead, the higher dose of CBD (40 mg) produced a transient elevation of IOP at 4 hours after administration. One patient experienced mild psychotropic side effects, but there were no serious AEs.

#### Intestinal dysfunction

Two controlled clinical trials have been performed in the period covered by this review. The first study [**Esfandyari 2006**] evaluated the effects of dronabinol on gastrointestinal transit, gastric volume and satiation in healthy volunteers, who were randomly assigned to receive three doses of THC (5 mg) or placebo over a period of 24h. The results suggested that THC administration was associated with a significant delay in gastric emptying of a standard solid and liquid meal, and there was a suggestion of a gender effect: THC significantly slowed gastric emptying in females, but not in males, which is consistent with earlier findings [Bateman 1983]. In contrast, THC increased fasting gastric volumes specifically in males. The data obtained suggested that the antiemetic effect of cannabinoids may not be due to a direct effect on gastric accommodation or sensation, but rather to a central modulation of perception.

A second study by the same group [**Esfandyari 2007**] aimed to compare the acute effects of single dose dronabinol (7.5 mg) versus placebo on colonic sensory and motor functions in healthy adults. The study demonstrated that THC was associated with relaxation of the colon and inhibition of the increase in tone after the meal. It was concluded that the potential for CB agonists to modulate colonic motor function in diarrheal disease such as irritable bowel syndrome deserves further study. As in the previous trial [Esfandyari 2006], the study observed greater effect of THC on gastric emptying prolongation in female volunteers than in males. The significance of the observed gender-related differences is unclear.

#### Nausea-vomiting-appetite

The purpose of the placebo-controlled study by

**Strasser *et al.* [2006]** was to compare the effects of Cannador and THC on appetite and quality of life in patients with cancer-related anorexia-cachexia syndrome (CACS). Adult patients with significant weight loss were treated with Cannador (standardized for 2.5 mg THC and 1 mg CBD) or THC (2.5 mg) twice daily for 6 weeks. Appetite, mood, and nausea were monitored daily. Cannador at the oral dose administered was well tolerated by the study subjects. Results showed no significant differences between the three arms for appetite, quality of life, or cannabinoid-related toxicity. Increased appetite was reported by 73%, 58%, and 69% of patients receiving Cannador, THC, or placebo, respectively. Finally, an independent data review board recommended termination of recruitment because of insufficient differences between study arms. A large number of adverse effects were observed, but there were no differences between treatment arms, and only a minority of adverse effects was found to be linked to study medication. Authors assumed that the study medications were underdosed.

Delayed chemotherapy-induced nausea and vomiting (CINV), defined as nausea and vomiting occurring more than 24 hours after chemotherapy and lasting for up to 1 week, is common, with at least 50% of patients experiencing it following moderately emetogenic chemotherapy. The impaired quality of life imparted by CINV can affect treatment outcomes when patients refuse chemotherapy because of severe AEs. A recent study [**Meiri 2007**] evaluated the efficacy of dronabinol versus ondansetron in delayed CINV. Over the course of 2-5 days after receiving chemotherapy, subjects received an increasing dose of up to 20 mg dronabinol daily, either alone, or in combination with ondansetron. Efficacy of dronabinol alone was comparable with ondansetron, and combination therapy did not provide benefit beyond that observed with either agent alone. Nevertheless, specifically on day 1 after chemotherapy, significantly greater efficacy on intensity of nausea was demonstrated in the combined active treatment group versus placebo. Active treatments were well tolerated. The highest rate of CNS-related AEs (dizziness and fatigue) was found in patients receiving combination therapy, while the incidence of these events in the THC group was low. Also, it was found that quality of life was most improved in patients receiving dronabinol compared with patients in the other treatment groups.

#### Schizophrenia

An explorative, 4-week, double-blind, controlled clinical trial was performed by **Leweke [2007]** on the antipsychotic properties of CBD in acute schizophrenia compared to the standard antipsychotic amisulpride. Furthermore, side-effects and anxiolytic capabilities of both treatments were investigated. Forty-two patients fulfilling DSM-IV criteria of acute paranoid schizophrenia or schizophreniform psychosis participated in the study. Both treatments were associated with a significant decrease of psychotic symptoms after 2 and 4

weeks. However, there was no statistical difference between both treatment groups. In contrast, cannabidiol induced significantly less side effects (EPS, increase in prolactin, weight gain) when compared to amisulpride. It was concluded that CBD proved substantial antipsychotic properties in acute schizophrenia.

In another clinical study [D'Souza 2005], the behavioral, cognitive, motor, and endocrine effects of up to 5 mg intravenous THC were characterized in stable, antipsychotic-treated schizophrenia patients. These data were compared with effects in healthy subjects reported elsewhere. It was found that THC transiently exacerbated a range of positive and negative symptoms, perceptual alterations, cognitive deficits, and medication side effects associated with schizophrenia without producing any obvious "beneficial" effects. The data do not provide a reason to explain why schizophrenia patients use or misuse cannabis. Furthermore, schizophrenia patients were more vulnerable to THC effects on learning and memory than healthy subjects. The enhanced sensitivity to the cognitive effects of THC warrants further study into whether brain cannabinoid receptor dysfunction contributes to the pathophysiology of the cognitive deficits associated with schizophrenia.

#### Other indications

The effects of intratumoral THC [Guzmán 2006] were studied on 9 patients with recurrent glioblastoma multiforme. A dose escalation regimen for THC administration was assessed. Cannabinoid delivery was safe and could be achieved without overt psychoactive effects. The treatment was found to inhibit tumour-cell proliferation *in vitro* and to decrease tumour-cell Ki67 immunostaining in two patients. The fair safety profile of THC, together with its possible antiproliferative action on tumour cells reported here and in other studies, may set the basis for future trials aimed at evaluating the potential antitumoral activity of cannabinoids.

[Sylvestre 2006] performed a study on 71 patients suffering from hepatitis C, all being recovering heroin users consuming cannabis on their own account. It was found that modest use of smoked cannabis may offer symptomatic and virological benefit to some patients undergoing viral treatment by helping them maintain adherence to the challenging medication regimen. The lack of dose response in this study argues against specific receptor- or metabolism-related effects, and suggests instead that cannabis exerted its benefit by non-specific improvements in symptom management. It must be noted that the authors point out a number of limitations that warrant caution in the interpretation of this study.

#### Discussion

This review is intended to support the discussion on the question whether there is currently enough clinical data to accept cannabis and cannabinoids as drugs in certain indications. In the review by Ben Amar [2006], a

therapeutic potential of cannabinoids was concluded for a range of disorders. Based on the data presented here, covering the period 2005-2009, it is possible to confirm that cannabinoids exhibit a strong therapeutic potential mainly as analgesics in chronic neuropathic pain, appetite stimulants in debilitating diseases (cancer and AIDS), as well as in the treatment of multiple sclerosis. For each of the 8 main indications discussed in this review, the general conclusions are discussed below.

It may be interesting to note that in the last few years, some well-designed studies on the effects of smoked cannabis have been released, mainly on HIV/AIDS. This is of specific interest because most patients administer their medicinal cannabis by smoking. The studies particularly show a benefit on neuropathic pain and appetite. Obviously, the noxious pyrolytic byproducts released through combustion remain a public health deterrent to the use of smoked cannabis. However, specific herbal vaporizers have been devised to provide a safer and more efficient delivery system for inhaling cannabis. It is reasonable to assume that future clinical trials will utilize this alternative delivery method.

#### Pain

Although cannabinoid-induced analgesia is now well-recognized in animal models, evidence of its analgesic properties in humans is less conclusive. Interestingly, trials involving pain patients with neuropathic-like features (e.g. multiple sclerosis, neuropathic pain and fibromyalgia) have produced mostly positive results, whereas studies measuring the efficacy of cannabinoids for acute pain (e.g. postoperative pain) have generated mostly negative results. For that reason, experimental pain and chronic (neuropathic) pain are discussed in separate sections. It has been demonstrated that endocannabinoids produced in the spinal cord can enhance pain by dampening the synapses of inhibitory interneurons that usually prevent the perception of innocuous stimuli as painful [Christie and Mallet 2009]. The pain-promoting action of endocannabinoids wanes during the development of chronic pain that is induced by inflammation or nerve injury. This can explain the differences observed in clinical studies with cannabinoids on acute and chronic pain.

The results of the clinical trials on chronic and neuropathic pain conditions are equivocal. A wide range of cannabis-based medicines exhibit analgesic effects on different forms of pain. THC, nabilone, Sativex, Canador and even smoked cannabis have been used in these studies, either alone or in addition to existing analgesia. The large majority of adverse effects were mild or moderate. Chronic neuropathic pain is a common and difficult to treat condition that has limited treatment options. As a consequence, even modest clinical effects may be relevant. Studies with cannabinoids should therefore be regarded as highly significant for the intended patient population. Clearly, the optimal type of cannabinoids and administration route may

differ for each indication.

Acute types of pain did not respond as well to cannabinoids. For postoperative pain management, the use of THC or nabilone did not reveal a positive effect on pain scores and a higher dose of nabilone (2 mg) actually increased pain scores. The use of Cannador, a standardized extract containing both THC and CBD, was more successful, and dose-dependently decreased postoperative pain. The presence of CBD may modulate the effects of THC (e.g. by changing the pharmacokinetic profile of THC and its metabolites), and it may also be possible that CBD has an effect on pain by itself as shown in an animal model of neuropathic pain [Costa et al. 2007].

A crucial caveat in the study of cannabis or cannabinoids in experimental pain models is that the data is mainly collected with healthy, regular marijuana users who smoke acute doses in a controlled laboratory situation and are exposed to artificial pain stimuli. Obviously, it is not possible to predict whether chronically ill patients taking cannabinoids for pain relief would respond similarly. The respective mechanisms underlying the whole variety of chronic pain syndromes may considerably differ from acute nociception. It has previously been reported that in rats, cannabinoid CB1 receptors are upregulated in chronic neuropathic pain and therefore could lead to an increased analgesic effect of THC in chronic pain [Siegling 2001]. It is interesting to note that a selective effect on women was observed in some pain studies. This may be an indication that certain cannabinoids may help alleviate chronic pain conditions which predominantly affect women, such as fibromyalgia.

Experimental pain studies often show that THC-induced analgesia is accompanied (and outlasted) by side-effects such as sedation. At doses producing substantial biological exposure, the antinociceptive effects of cannabis - although statistically significant - are often rather weak compared with motor-impairing and subjective effects. Nevertheless, in certain groups of chronically ill patients with severe enough symptoms, and without further options for treatment, even this weak effect on pain may be significant enough.

In previous animal and human studies, it has been shown that cannabinoids and opioids have synergistic actions on pain control [Iversen 2003; Lynch and Clark 2003; Maldonado and Valverde 2003], but for chronic pain this could not be firmly confirmed in the clinical trials reported here. More study is needed to evaluate the combined analgesic effects of both types of drugs.

### **Multiple sclerosis and spasticity**

In clinical trials, more patients have been treated with cannabinoids for MS than for any other indication. Symptomatic therapy for MS often provides inadequate relief and can be limited by toxicity. As a consequence, people with multiple sclerosis have experimented with many alternative therapies, including cannabis, to ease their physical problems. There is much anecdotal suggestion that cannabis and cannabinoids, have beneficial

effects on disease-related pain, bladder symptoms, tremor, and particularly spasticity, but until recently, little scientific evidence existed for their efficacy. In the period covered by this review, nine studies have been released on the effect of cannabinoids on MS symptoms. Most studies were done with Sativex, which is currently approved only in Canada, and the largest studies have been conducted with Cannador and dronabinol.

MS is one of the few conditions where long-term extension studies have been performed with cannabis-based medicines. When assessing clinical results, it should be acknowledged that the degree of evidence for many of the commonly used drugs to combat MS symptoms is weak. A Cochrane review [Shakespeare 2003] of antispasticity agents for multiple sclerosis concluded that the paucity of evidence meant no recommendations could be made to guide prescribing, and that better outcome measures need to be developed. It may therefore not be surprising that it has proven hard to collect evidence for the efficacy of cannabis in the treatment of MS.

The current studies presented in this review provide us with cautious optimism that Sativex, but also Cannador, THC and nabilone, can improve the symptoms of spasticity in MS sufferers, specifically for the treatment of spasticity, pain and incontinence. Often the improvements were gained over and above the concomitant anti-spasticity medication being taken by the subjects during the study. In those patients perceiving initial benefit from their medication, the positive effects often persisted in longer term extension trials without tolerance. This is representative of clinical practice, where only patients who consider a treatment beneficial will continue taking it. Cannador or THC did not show any detectable effects on a range of cytokines that influence inflammation in serum samples of MS patients.

### **HIV/AIDS**

The primary constituent of cannabis, THC, is approved by the Food and Drug Administration (FDA) for oral administration as appetite stimulant in the case of anorexia associated with weight loss in patients with HIV/AIDS. Studies on the effects of cannabinoids in patients with HIV are particularly important given that they constitute one of the largest groups using dronabinol and cannabis for medicinal reasons [Institute of Medicine 1999], and a considerable proportion of those with HIV currently smoke cannabis. Reasons for smoking cannabis cited by patients include countering the nausea, anorexia, stomach upset, and anxiety associated with the disease and with antiretroviral therapy.

The four studies presented here all used smoked cannabis, but also THC, and clearly showed the beneficial effects on pain, appetite and weight gain. Although cannabinoids tend to increase fat rather than the more wanted lean muscle mass [Abrams 2003], HIV patients who are able to maintain stable weight often report improved quality of life [Beal 1995]. Overdosing ef-

fects were relatively common, because the exact dose of cannabinoids is relatively difficult to control in smoked studies, compared to oral administration.

### Glaucoma

Glaucoma is one of the leading causes of blindness in the world, affecting about 70 million people worldwide. As glaucoma is a chronic disease lacking a cure, the quest for new ocular hypotensive agents is important for its treatment, and these agents are likely to remain frontline therapy for the foreseeable future. Since the early 1970s, it was reported that smoking cannabis cigarettes could lower intraocular pressure (IOP) by up to 45% [Hepler & Frank 1971]; later works showed that THC lowered IOP when given intravenously, orally or by inhalation [Ben Amar 2006]. Since these early observations, numerous studies have been conducted confirming that different cannabinoids, including THC, CBD, cannabigerol, endogenous cannabinoids, and some synthetic cannabinoids, can reduce IOP when administered systemically and topically [listed in Tomida 2006]. In addition to the reduction of IOP THC may increase blood circulation in the retina, which was demonstrated in an open study [Plange et al. 2007], and is known to be neuroprotective, which both may increase survival of the optical nerve. Only one single controlled clinical study was added to the literature in the past years. The modest reduction of IOP observed after oromucosal administration of THC was not deemed to be clinically relevant. An important goal of further research may be to determine the additive effects of cannabinoids with the anti-glaucoma agents available.

### Intestinal dysfunction

Cannabinoid receptor (CB) stimulation inhibits colon motility and increases food intake in rodents. However, effects of CB stimulation in human gastrointestinal (GI) tract are largely unclear. *In vitro* studies have suggested that cannabinoids delay transit in human colon and ileum [Manara 2002]. In general, reports of effects of cannabinoids on GI transit and sensation in humans *in vivo* are sparse, and the role of stomach function in the appetite-stimulating and anti-emetic effects of cannabinoid agonists is unclear. The two studies discussed here indicate that THC administration was associated with a significant delay in gastric emptying, relaxation of the colon and inhibition of the increase in tone after the meal. The obtained data may help to better understand the effects of cannabinoids in nausea, vomiting and appetite. In both studies, a greater effect of THC was observed on gastric emptying prolongation in female volunteers than in males. The significance of the observed gender-related differences is yet unclear.

### Nausea, vomiting and appetite

Besides the use as an appetite stimulant for AIDS patients, THC is FDA approved in the USA as an antiemetic for cancer patients undergoing chemotherapy.

One study showed no significant effect of either Canador (containing THC and CBD) or THC on appetite and nausea in cancer patients, but study medications were obviously underdosed since there was no difference of side-effects compared to placebo. A second study demonstrated an effect in delayed chemotherapy-induced nausea and vomiting (CINV), and this effect was comparable to the standard drug ondansetron. The data suggest that the addition of THC directly before and after chemotherapy may offer more benefit than the standard regimen alone taken before chemotherapy.

### Schizophrenia

The human endocannabinoid system interacts with various neurotransmitter systems and the endocannabinoid anandamide was found significantly elevated in CSF and inversely correlated to psychopathology in patients with schizophrenia [Giuffrida 2004] providing a link to the neurobiology of the disease. The major herbal cannabinoid compound CBD was suggested recently to be a re-uptake inhibitor of anandamide. In a study using purified CBD, it was found that this non-psychoactive compound shows substantial antipsychotic properties in acute schizophrenia, with an efficacy comparable to amisulpride. This is in line with the suggestion of an adaptive role of the endocannabinoid system in paranoid schizophrenia, and raises further evidence that endocannabinoid system may represent a valuable target for antipsychotic treatment strategies. Another study using high doses of intravenous THC caused schizophrenia-like symptoms.

### Other indications

Most of the experiments performed so far in animal models of cancer have evidenced a tumour growth-inhibiting action of cannabinoids (Guzmán, 2003). The study by Guzmán *et al.* described in this review was the first clinical study aimed at evaluating cannabinoid antitumoral action. Owing to obvious ethical and legal reasons, this pilot study was conducted in a cohort of terminal patients harbouring actively growing recurrent tumours. In view of the fair safety profile of THC, together with its possible antiproliferative action on tumour cells reported here and in other studies (Guzmán, 2003), it would be desirable that additional trials – on various types of tumours – were run to determine whether cannabinoids – as single drugs or in combination with established antitumoral drugs – could be used, other than for their palliative effects, to inhibit tumour growth.

Another indication that was clinically studied for the first time in recent years was hepatitis C. Although hepatitis C virus (HCV) treatment outcomes have improved dramatically over the past decade, the intolerance of interferon/ribavirin combination therapy remains a barrier to treatment success. Faced with severe treatment-related side-effects that respond inadequately to conventional medications, some patients turn to cannabis for symptom relief. Although widespread restrictions limit the ease with which medicinal



cannabis use can be formally studied, the pervasive use of cannabis by patients during HCV treatment provided a means for an observational study of its potential risks and benefits. Despite its shortcomings, the study by Sylvestre *et al.* [2006] begins to answer some of the key questions that arise about the use of cannabis during HCV treatment. The results of this observational study suggest that at least moderate use of cannabis during HCV treatment can improve adherence by increasing the duration of time that patients remain on therapy. However, because the benefits of heavy cannabis use were less apparent, the authors could not rule out the possibility that detrimental biological or immunological mechanisms may be relevant at higher levels of consumption.

A series of studies have previously [Ben Amar 2006] shown promising effects of THC on tics associated with Tourette's syndrome as well as its associated behavioral problems such as obsessive-compulsive behavior, providing a reason for careful optimism in the treatment of this poorly understood condition. However, no new data has been published in recent years. Also no new clinical studies were released in recent years on the use of cannabinoids for epilepsy.

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# Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action

## Canabidiol: de um canabinóide inativo a uma droga com amplo espectro de ação

Antonio Waldo Zuardi<sup>1</sup>

### Abstract

**Objective:** The aim of this review is to describe the historical development of research on cannabidiol. **Method:** This review was carried out on reports drawn from Medline, Web of Science and SciELO. **Discussion:** After the elucidation of the chemical structure of cannabidiol in 1963, the initial studies showed that cannabidiol was unable to mimic the effects of Cannabis. In the 1970's the number of publications on cannabidiol reached a first peak, having the research focused mainly on the interaction with delta9-THC and its antiepileptic and sedative effects. The following two decades showed lower degree of interest, and the potential therapeutic properties of cannabidiol investigated were mainly the anxiolytic, antipsychotic and on motor diseases effects. The last five years have shown a remarkable increase in publications on cannabidiol mainly stimulated by the discovery of its anti-inflammatory, anti-oxidative and neuroprotective effects. These studies have suggested a wide range of possible therapeutic effects of cannabidiol on several conditions, including Parkinson's disease, Alzheimer's disease, cerebral ischemia, diabetes, rheumatoid arthritis, other inflammatory diseases, nausea and cancer. **Conclusion:** In the last 45 years it has been possible to demonstrate that CBD has a wide range of pharmacological effects, many of which being of great therapeutic interest, but still waiting to be confirmed by clinical trials.

**Descriptors:** Cannabidiol; Cannabis; Cannabinoids; History; Therapeutic uses

### Resumo

**Objetivo:** O objetivo desta revisão é descrever a evolução histórica das pesquisas sobre o canabidiol. **Método:** Esta revisão foi conduzida utilizando-se bases de dados eletrônicas (Medline, Web of Science e SciELO). **Discussão:** Após a elucidação de sua estrutura química, em 1963, os estudos iniciais do canabidiol demonstraram que ele não foi capaz de mimetizar os efeitos da maconha. Na década de 70, o número de publicações sobre o canabidiol atingiu um primeiro pico, com as investigações centrando-se principalmente na sua interação com o delta9-THC e nos seus efeitos antiepiléptico e sedativo. As duas décadas seguintes apresentaram um menor nível de interesse e as propriedades terapêuticas potenciais do canabidiol investigadas foram, principalmente, as ansiolíticas, antipsicóticas e seus efeitos sobre as doenças motoras. Os últimos cinco anos têm demonstrado um notável aumento de publicações sobre o canabidiol, principalmente estimulado pela descoberta dos seus efeitos anti-inflamatório, anti-oxidativo e neuroprotetor. Estes estudos têm sugerido uma vasta gama de possíveis efeitos terapêuticos da canabidiol em várias condições, incluindo doença de Parkinson, doença de Alzheimer, isquemia cerebral, diabetes, náusea, câncer, artrite reumatóide e outras doenças inflamatórias. **Conclusão:** Nos últimos 45 anos, foi possível demonstrar uma vasta gama de efeitos farmacológicos do canabidiol, muitos dos quais são de grande interesse terapêutico, que ainda necessitam ser confirmados por estudos clínicos.

**Descritores:** Canabidiol; Cannabis; Canabinóides; História; Usos terapêuticos

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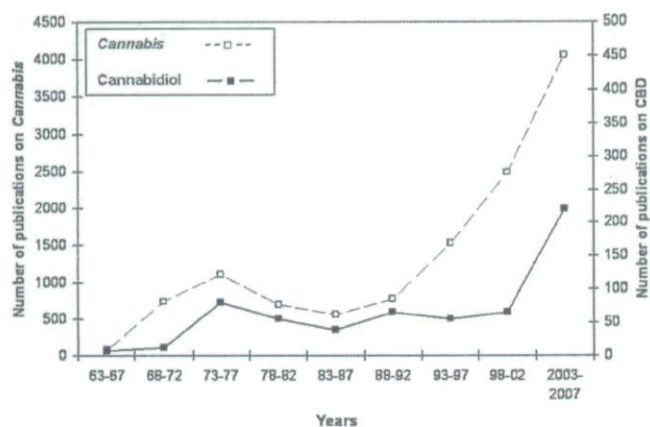
## Introduction

In the tip of secreting hairs located mainly on female-plant flowers and, in a smaller amount, in the leaves of *cannabis* plant, there are resin glands that have a considerable amount of chemically related active compounds, called cannabinoids. In some varieties of *cannabis* the main cannabinoid is the psychoactive component of the plant, delta9-tetrahydrocannabinol (delta9-THC). *Cannabis* varieties typically bred for fiber are nearly always relatively low in delta9-THC, cannabidiol (CBD) being the predominant cannabinoid in these plants.<sup>1</sup>

Although CBD was isolated from marijuana extract in 1940 by Adams et al.,<sup>2</sup> for almost 25 years no further work has been reported, except for a few early works about its isolation. Only in 1963 its exact chemical structure was elucidated by Mechoulam and Shvo.<sup>3</sup> Over the following few years Mechoulam's group was responsible for the structure and stereochemistry determination of the main cannabinoids, which opened a new research field on pharmacological activity of *cannabis* constituents.<sup>4,5</sup>

The evolution of the number of publications on CBD since 1963, in comparison with publications on *cannabis* in general, is shown in Figure 1. Only a few pharmacological studies on CBD were reported before the early 1970's, showing that CBD had no *cannabis*-like activity.<sup>6</sup> The number of publications increased in this decade and reached a first peak around 1975. In this period, a Brazilian research group led by Carlini, gave an important contribution, especially about the interactions of delta9-THC with other cannabinoids, including CBD.<sup>7</sup> Then, the number of publications declined and remained stabilized until a few years ago. The interest in studies about *cannabis* was renewed in the early 1990's, by the description and cloning of specific receptors for the cannabinoids in the nervous system and the subsequent isolation of anandamide, an endogenous cannabinoid.<sup>8</sup> Afterwards, the number of publications about *cannabis* has been continuously growing, but the reports on CBD remained stable until the early 2000's. In the last five years there has been an explosive increase in publications on CBD, with the confirmation of a plethora of pharmacological effects, many of them with therapeutic potential.

There are some recent and very good reviews on CBD.<sup>9-12</sup> As historical aspects have so far not been yet emphasized, the aim of the present review is to describe the development of this research field which transformed our view about CBD from an inactive cannabinoid to a drug with multiple actions.



**Figure 1** - Number of *cannabis* and cannabidiol-related publications in the last 45 years. The source used was the 'ISI Web of Knowledge' with the keywords: *Cannabis* and cannabidiol.

## Inactive cannabinoid that interact with delta9-THC (1970's)

The early pharmacological tests on isolated cannabinoids had evidenced that except for delta9-THC, no other major psychotomimetically active compounds were present in *cannabis*.<sup>13</sup> During this period, several reports attested that CBD was unable to mimic the effects of *cannabis* both in animals<sup>14</sup> and in humans,<sup>15,16</sup> leading to the thought that it was an inactive cannabinoid.

This thought began to change with the observation that the activity in animals of several samples of *cannabis* differed widely, a fact which could not be attributed only to the different delta9-THC contents of the samples.<sup>17,18</sup> It was then hypothesized that other cannabinoids, among them CBD, could be interfering with the delta9-THC effects.

Many interactive studies between CBD and delta9-THC were accomplished by different groups, producing seemingly contradictory results both in animals,<sup>19-21</sup> and in humans.<sup>22-24</sup> Different schedules of drug administration used in these studies may help explain the contradictions. It seems that CBD administered before delta9-THC potentiates the effects of the latter compound. However, concomitant use of both compounds suggests that CBD antagonizes delta9-THC effects.<sup>25-27</sup> This difference could be explained by pharmacokinetic or pharmacodynamic interactions between the two cannabinoids.

CBD has been found to be a potent inhibitor of hepatic drug metabolism.<sup>28,29</sup> Pre-treatment of mice with high doses of CBD causes an increase in delta9-THC level in the brain.<sup>30</sup> Recently, evidence that CBD also inhibits the metabolic hydroxylation of delta9-THC in human volunteers<sup>31</sup> has been obtained. This pharmacokinetic interaction could explain the increased effects of delta9-THC by CBD pretreatment. On the other hand, CBD is not able to change delta9-THC blood level with co-administration of both compounds in rats<sup>32</sup> or humans volunteers.<sup>33</sup> Therefore, it has been suggested that CBD can antagonize delta9-THC effects pharmacodynamically.<sup>34</sup>

## Early evidence (1970's) on CBD pharmacological activity

### 1. Antiepileptic action

The first pharmacological actions of CBD described were the antiepileptic and the sedative ones. In 1973, a Brazilian group reported that CBD was active in reducing or blocking convulsions produced in experimental animals by a variety of procedures,<sup>35,36</sup> which was confirmed by another group one year later.<sup>37</sup> At the end of that decade, the same Brazilian group has tested CBD as a treatment for intractable epilepsy in 16 grand-mal patients. Each patient received, in a double-blind procedure, 200 to 300 mg daily of CBD or placebo for as long as four and a half months. Throughout the experiment, the patients did not stop taking the antiepileptic drugs prescribed before the experiment (which had not eliminated their seizures). Only one of the eight patients getting CBD showed no improvement, while among the patients who received the placebo, 1 improved and 7 remained unchanged.<sup>38</sup> In a less successful study, no significant improvement in seizure frequency was observed among 12 epileptic patients who received 200-300 mg of cannabidiol per day, in addition to standard antiepileptic drugs.<sup>39</sup> No further clinical trials with CBD have been published since then. Therefore, the clinical efficacy of CBD on epilepsy is still uncertain.

### 2. Sedative action

In the early 1970's, suggestive evidence of a sedative action appeared, based on the observation that CBD reduced ambulation in



rats<sup>40</sup> and, with higher doses, operant behavior in rats and pigeons.<sup>41</sup> Few years later, Monti<sup>42</sup> reported sleep-inducing effects of CBD in rats, with an increase in total sleeping time, increment of slow-wave sleep (SWS) and decrease of SWS latency. In humans with insomnia, high doses of CBD (160 mg) increased sleep duration compared to placebo.<sup>43</sup> Sedative effect was also observed in healthy volunteers with high CBD dose (600 mg).<sup>44</sup> This effect of CBD may be biphasic, since in low doses (15 mg) the cannabinoid appears to have alerting properties in healthy volunteers, as it increases wakefulness during sleep and counteracts the residual sedative activity of 15 mg THC.<sup>45</sup> Previous reports of subjective feelings by healthy volunteers after CBD (1 mg/Kg) showed a significant increase in "clear minded" and "quick-witted" feelings, in contrast with THC (0.5 mg/Kg) that induced an increase in "muzzy"<sup>46</sup> feelings. In agreement with the two last observations, intracerebroventricular administration of CBD in rats during the lights-on period increased wakefulness (W) and decreased rapid eye movement sleep (REMS), probably through increased dopamine release.<sup>47</sup>

### CBD effects on anxiety, psychoses and movement disorders (1980's and 1990's)

After the peak of reports on CBD in the 1970's, the next two decades the publication rate remained stabilized, indicating a lower degree of interest on the study of therapeutic actions of CBD. The reports in this field were maintained mainly by Brazilian researchers investigating the anxiolytic and antipsychotic properties of CBD and by a few studies about its effects in motor diseases conducted by Consroe et al.<sup>48,49</sup>

#### 1. Anxiolytic action

In 1974, an interactive study between CBD and THC, *per os*, in healthy volunteers, gave the first clue that CBD could act as an anxiolytic drug.<sup>22</sup> This study showed that CBD (60 mg), added to delta9-THC (30 mg), changed the symptoms induced by delta9-THC alone in such a way that the subjects receiving the mixture showed less anxiety and more pleasurable effects. In 1982, a study with appropriate rating scales confirmed that CBD (1 mg/kg), co-administered with delta9-THC (0.5 mg/kg), significantly reduced anxiety indexes in healthy volunteers.<sup>46</sup>

The anxiolytic properties of CBD have been demonstrated by several pre-clinical studies that employed different paradigms such as the conditioned emotional response,<sup>50</sup> the Vogel conflict test<sup>51</sup> and the elevated plus-maze.<sup>52,53</sup> In the latter study,<sup>53</sup> the effective doses of CBD ranged from 2.5 to 10 mg/kg, and the drug produced an inverted U-shaped dose-response curve, the higher doses being no longer effective. This could explain the negative results obtained with high doses of CBD (above 100 mg/kg) in a previous study employing the Geller-Seifter conflict test.<sup>54</sup> A recent study showed that the anxiolytic effect of CBD in the Vogel test was not mediated by benzodiazepine receptors.<sup>55</sup>

In order to evaluate a possible anxiolytic effect of CBD in humans, a double-blind study was conducted on healthy volunteers submitted to a simulation of the public speaking test. CBD (300 mg, *po*) was compared to ipsapirone (5 mg), diazepam (10 mg) or placebo. The results showed that both CBD and the two other anxiolytic compounds attenuated the anxiety induced by the test.<sup>56</sup> The anxiolytic-like effect of CBD in healthy volunteers was also observed in a more recent double-blind study that investigated its effects on regional cerebral blood flow by single-photon emission computed tomography. Because the procedure itself can be interpreted as

an anxiogenic situation, it allows the evaluation of anxiolytic drug action. CBD induced a clear anxiolytic effect and a pattern of cerebral activity compatible with an anxiolytic activity.<sup>57</sup> Another study, using functional magnetic resonance imaging (fMRI) to investigate the neurophysiologic basis of the effects of cannabis on human anxiety, showed that CBD affected activation when subjects were processing intensely fearful stimuli, attenuating responses in the amygdala and cingulate cortex. The suppression of the amygdalar response was correlated to the drug effect of reducing fluctuations of skin conductance.<sup>58</sup> Therefore, similar to the data obtained in animal models, results from studies in healthy volunteers strongly suggest an anxiolytic action of CBD.

#### 2. Antipsychotic action

The first evidence that CBD could have antipsychotic effects was obtained in the interactive study of CBD and delta9-THC in healthy volunteers published in 1982.<sup>46</sup> This study demonstrated that CBD could inhibit THC-induced subjective changes that resembled symptoms of psychotic diseases such as: disconnected thought, perceptual disturbance, depersonalization and resistance to communication. In the same year, it was observed that patients admitted to a psychiatric hospital in South Africa, after the use of a variety of cannabis virtually devoid of CBD, showed much higher frequency of acute psychotic episodes than in other countries.<sup>59</sup> These lines of evidence led to several investigations of a possible antipsychotic action of CBD.

As a first step to investigate antipsychotic-like properties of CBD in animal models, the drug was compared to haloperidol in rats.<sup>60</sup> Both drugs reduced the apomorphine-induced stereotyped behavior (such as sniffing and biting), in a dose-related manner. Even though these drugs also increased the plasma level of prolactin, CBD needs higher doses (120 and 240 mg/kg) to show such an effect. Moreover, contrary to haloperidol, CBD did not induce catalepsy, even at doses as high as 480 mg/kg. These results suggest that CBD may exhibit a profile similar to atypical antipsychotic drugs. Recently, a study tested CBD effects both in dopamine-based and glutamate-based models predictive of antipsychotic activity in mice.<sup>61</sup> In this study CBD was compared to haloperidol and clozapine, an atypical antipsychotic drug. CBD inhibited the hyperlocomotion induced by amphetamine in a dose-related manner, in agreement with the data obtained with another dopamine-based model, and also attenuated the hyperlocomotion induced by ketamine, extending its antipsychotic-like action to a glutamate-based model. As expected, while both haloperidol and clozapine inhibited hyperlocomotion, only haloperidol induced catalepsy within the dose range used. Therefore, similar to clozapine, CBD did not induce catalepsy with doses that inhibited hyperlocomotion. Strengthening these results, CBD reversed the disruption of prepulse inhibition (PPI) of the startle response in mice caused by MK-801, a glutamate receptor antagonist, as did clozapine, further supporting the idea that this compound may act as an atypical antipsychotic drug.<sup>62</sup> Consistent with the behavioral data, both CBD and clozapine, but not haloperidol, induced Fos immunoreactivity (Fos) in the prefrontal cortex, while only haloperidol increased Fos in the dorsal striatum.<sup>63,64</sup>

Even in human models of psychotic symptoms induced in healthy volunteers, the antipsychotic-like activity of CBD can be demonstrated. In the perception of binocular depth inversion, used to evaluate the antipsychotic effects of new drugs,<sup>65</sup> the impairment of



the perception of illusory image induced by nabilone was attenuated by CBD, suggesting an antipsychotic-like effect of this compound.<sup>66</sup> Another model used to evaluate antipsychotic-like activity of drugs in healthy volunteers is the administration of sub-anesthetic doses of ketamine that induce a psychotic reaction mimicking both positive and negative symptoms of schizophrenia.<sup>67</sup> A double-blind crossover procedure using this model was performed to compare the effects of CBD (600 mg) and placebo in nine healthy volunteers.<sup>68</sup> CBD attenuated the effects of ketamine on the depersonalization factor of a dissociative rating scale, further reinforcing the antipsychotic-like properties of CBD.

The therapeutic use of CBD in psychotic patients was tested for the first time in 1995. In a case study, a schizophrenic patient, who presented serious side effects after treatment with conventional antipsychotics, received oral doses of CBD (reaching 1500 mg/day) for 4 weeks.<sup>69</sup> A significant improvement was observed during CBD treatment, while a worsening was observed when the administration was interrupted. More recently, CBD was administered to three schizophrenic patients who had not responded to typical antipsychotic drugs.<sup>70</sup> A partial improvement was observed in one patient, but only slight or no improvement in the other two, thus suggesting that CBD has little effect in patients resistant to typical antipsychotics. Confirming the suggestion of case-studies, a preliminary report from a 4-week double-blind controlled clinical trial, using an adequate number of patients and comparing the effects of CBD with amisulpride in acute schizophrenic and schizophreniform psychosis, showed that CBD significantly reduced acute psychotic symptoms after 2 and 4 weeks of treatment when compared to baseline. In this trial, CBD did not differ from amisulpride except for a lower incidence of side effects.<sup>71</sup> In conclusion, clinical studies suggest that CBD is an effective, safe and well-tolerated alternative treatment for schizophrenic patients.

### 3. Action on movement disorders

The possible therapeutic effect of CBD on movement disorders came from anecdotal accounts and preliminary reports of open trials, in the middle 1980's. CBD (100 to 600 mg/day) had antidystonic effects in humans when administered along with standard medication to five patients with dystonia, in an open study.<sup>48</sup> In Huntington's disease (HD), the effectiveness of CBD was investigated with a small number of patients (four) and a non-blinded design, showing some beneficial effects of CBD.<sup>72</sup> However, the latter finding was not confirmed by a study comparing the effects of oral CBD (10 mg/kg/day for 6 weeks) with placebo under a double-blind, randomized cross-over design. In this study, CBD at an average daily dose of about 700 mg/day was neither symptomatically effective nor toxic in neuroleptic-free patients with HD.<sup>49</sup>

Afterwards, this field of research was apparently abandoned until recently, when CBD's neuroprotective effects began to be reported in animal models of Parkinson's disease.

### CBD as a drug with a wide spectrum of action (2000's)

The interest in studies about *cannabis* was renewed in the early 1990's, with the description and cloning of specific receptors for the cannabinoids (CB<sub>1</sub> and CB<sub>2</sub>) in the nervous system and the subsequent isolation of anandamide, an endogenous cannabinoid.<sup>73</sup> After that, the number of publications about *cannabis* has been continuously growing, attesting the great interest in research involving the herb. However, the number of studies on CBD has increased only in the last five years (Figure 1), mainly stimulated

by discoveries of the anti-inflammatory, anti-oxidative and neuroprotective actions of CBD.

### 1. Anti-oxidative and neuroprotective actions

In the late 1990's, it was demonstrated that CBD reduced glutamate toxicity mediated by N-methyl-D-aspartate receptors (NMDAR), 2-amino-3-(4-butyl-3-hydroxyisoxazol-5-yl) propionic acid receptors (AMPA) or kainate receptors. The neuroprotection observed with cannabidiol was not affected by a cannabinoid receptor antagonist, indicating it is cannabinoid-receptor independent.<sup>74</sup> Previous studies had shown that glutamate toxicity may be prevented by antioxidants. In line with this, it was demonstrated that CBD can reduce hydroperoxide-induced oxidative damage as well as or better than other antioxidants. CBD was more protective against glutamate neurotoxicity than either ascorbate or  $\alpha$ -tocopherol, indicating that this drug is a potent antioxidant.<sup>74</sup>

The anti-oxidative action of CBD can be responsible for the neuroprotection reported in animal models of Parkinson's disease (PD). Daily administration of CBD during 2 weeks may produce a significant waning in the magnitude of toxic effects caused by a unilateral injection of 6-hydroxydopamine into the medial forebrain bundle,<sup>75</sup> probably due to receptor-independent actions. In this model of PD, CBD led to an up-regulation of mRNA levels of Cu/Zn-superoxide dismutase, a key enzyme in endogenous defense against oxidative stress. The conclusion was that the antioxidant properties of CBD can provide neuroprotection against the progressive degeneration of nigrostriatal dopaminergic neurons that occur in PD.<sup>76</sup> This is reinforced by the observation that CBD reduced the striatal atrophy caused by 3-nitropropionic acid, *in vivo*, through mechanisms independent of the activation of cannabinoid, vanilloid TRPV1 and adenosine A<sub>2A</sub> receptors.<sup>77</sup> The neuroprotective action of CBD in the human basal ganglia was suggested by the strong positive correlation of N-acetylaspartate/total creatine ratio and CBD in the putamen/globus pallidum found in recreational cannabis users. This could reflect an enhancement of neuronal and axonal integrity in these regions by CBD.<sup>78</sup> Considering the relevance of these preclinical data and the possible antipsychotic effect of CBD, a recently study evaluated, for the first time, the efficacy, tolerability and safety of CBD in PD patients with psychotic symptoms.<sup>79</sup> In an open-label pilot study, six consecutive outpatients with the diagnosis of PD and who also had psychosis for at least 3 months, have received a flexible-dose regimen of CBD administration (starting with an oral dose of 150 mg/day) for four weeks, in addition to their usual therapy. The psychotic symptoms significantly decreased along the CBD treatment, and the scale used to follow up the PD course exhibited a significant decrease of the total score. These preliminary data suggest that CBD may have a beneficial action in PD.<sup>79</sup>

The possible neuroprotective actions of CBD highlight the importance of studies on the therapeutic potential of this compound in Alzheimer's disease (AD). AD is widely associated with oxidative stress due in part, to the membrane action of beta-amyloid peptide (beta-A) aggregates. A marked reduction in the cell survival was observed following exposure of cultured rat pheochromocytoma PC12 cells to beta-A peptide. Treatment of the cells with CBD prior to beta-A exposure significantly elevated the cell survival, probably by a combination of neuroprotective, anti-oxidative and anti-apoptotic actions against beta-A toxicity. In addition, CBD inhibited caspase 3 generation from its inactive precursor, pro-caspase 3, an effect that is involved in the signaling pathway for this neuroprotection.<sup>80</sup> In the search for the molecular mechanism of this CBD-induced



neuroprotective action it was reported that CBD inhibits hyperphosphorylation of tau protein in beta-A-stimulated PC12 neuronal cells, which is one of the most representative hallmarks of AD.<sup>81</sup> A possible anti-inflammatory action may be involved in this CBD effect, since CBD inhibited both nitrite production and nitric oxide synthase (iNOS) protein expression induced by beta-A.<sup>82</sup> These results of *in vitro* studies were confirmed *in vivo* with a mouse model of AD-related neuroinflammation. Mice were inoculated with human beta-A into the right dorsal hippocampus, and treated daily with vehicle or CBD (2.5 or 10 mg/kg, i.p.) for 7 days. In contrast to vehicle, CBD dose-dependently significantly inhibited mRNA for glial fibrillary acidic protein and the protein expression in beta-A injected animals. Moreover, under the same experimental conditions, CBD impaired iNOS and IL-1beta protein expression, and the related NO and IL-1beta release.<sup>83</sup> The possibility of CBD inhibiting beta-A-induced neurodegeneration is very promising to AD prevention.

Recently it has been suggested that CBD may protect neurons against the multiple molecular and cellular factors involved in the different steps of the neurodegenerative process, which takes place during prion infection.<sup>84</sup> Prion diseases are transmissible neurodegenerative disorders characterized by the accumulation in the CNS of the protease-resistant prion protein, a structurally misfolded isoform of its physiological counterpart.<sup>84</sup>

## 2. Anti-inflammatory action

In 2000, a few previous reports showing that CBD can modulate tumor necrosis factor *in vitro* and suppress chemokine production by a human B cell,<sup>85-87</sup> motivated the study of CBD as a therapeutic agent in collagen-induced arthritis, a model for rheumatoid arthritis.<sup>88</sup> This model is based on immunizing mice with type-II collagen. CBD, administered i.p. or orally, has blocked the progression of arthritis. Dose-dependency was shown by a bell-shaped curve, with an optimal effect at 5 mg/kg per day (i.p.), or at 25 mg/kg per day (orally). In addition, CBD has suppressed T cell responses and has decreased the release of bioactive tumor necrosis factor (TNF) from synovial cells isolated from arthritic knee joints of treated mice. Data of this study suggest that the antiarthritic effect of CBD is due to a combination of immunosuppressive and anti-inflammatory actions.<sup>10,12</sup> A CBD anti-inflammatory effect was observed in acute inflammation induced by intraplantar injection of 0.1 ml carrageenan in rats.<sup>89</sup> Oral CBD (5-40 mg/kg) once a day for 3 days after the onset of acute inflammation had a beneficial action on edema and hyperalgesia. CBD also proved effective in chronic neuropathic (sciatic nerve chronic constriction) painful states in rats, reducing hyperalgesia to mechanical stimuli. This effect was prevented by the vanilloid antagonist capsaizepine, but not by cannabinoid receptor antagonists.<sup>90</sup> In these models of inflammation, decreases in prostaglandin E2 (PGE2) plasma levels, tissue cyclooxygenase (COX) activity and production of nitric oxide (NO)<sup>89,90</sup> have been observed. The suppressive effects of CBD on cellular immune responses and on the production of pro-inflammatory mediators may indicate its usefulness in several inflammatory diseases.

## 3. Action on ischemia

The anti-oxidative and anti-inflammatory properties of CBD have led to the research of its possible activity in preventing damage caused by cerebral ischemia. CBD (1.25-20 mg/kg) was administered to freely-moving gerbils 5 min after bilateral carotid-

artery occlusion for 10 minutes. Seven days after the ischemia, CBD antagonized electroencephalographic flattening, showing a dose-dependent bell-shaped curve. The best neuroprotective effect was observed at 5 mg/kg. Histological examination showed the complete survival of CA1 neurons in CBD-treated gerbils.<sup>91</sup> A similar effect has been reported by another research group in mice, after middle cerebral artery occlusion; the neuroprotective action of CBD being unaffected by CB<sub>1</sub> receptor blockade.<sup>92</sup> The same research group has verified that this effect was inhibited by WAY100135, a serotonin 5-hydroxytryptamine 1A (5-HT<sub>1A</sub>) receptor antagonist, but not by capsazepine, a vanilloid receptor antagonist, suggesting that the neuroprotective effect of CBD may be due to the increase in cerebral blood flow mediated by the serotonergic 5-HT<sub>1A</sub> receptor.<sup>93</sup> Experimental evidence has suggested that beyond this action on the 5-HT<sub>1A</sub> receptor, the protective effect of CBD on ischemic injury is also secondary to its anti-inflammatory action.<sup>94</sup> In another study, the same research group reported that, while repeated treatment with delta9-THC leads to the development of tolerance for this neuroprotective effect, this phenomenon is not observed with CBD.<sup>95</sup>

CBD has been studied for ischemic heart diseases in rats.<sup>96</sup> The left anterior descending coronary artery was transiently obstructed for 30 min, and the rats were treated for 7 days with CBD (5 mg/kg, ip) or vehicle. Cardiac function was studied by echocardiography and showed preservation of shortening fraction in CBD-treated animals. Infarct size was reduced by 66% in CBD-treated animals and this effect was associated with reduction of myocardial inflammation and reduction of IL-6 levels. In isolated hearts, no significant difference was detected between rats that received CBD or vehicle regarding: infarct size, left ventricular developed pressures during ischemia and reperfusion, or coronary flow. This study shows that CBD induces a substantial cardioprotective effect, but only *in vivo*.

## 4. Action on diabetes

The potent anti-inflammatory effect of CBD, with reduction of cytokines production (IFN- $\gamma$  and TNF- $\alpha$ ) and inhibition of T cell proliferation observed in experimental arthritis,<sup>88</sup> led to investigation of the possible CBD effects on others autoimmune diseases.<sup>12</sup> Type 1 diabetes mellitus (insulin-dependent) is an autoimmune disease that results in the destruction of insulin-producing pancreatic  $\beta$  cells. The initial lesion of insulin-dependent diabetes mellitus is an inflammation of the islands of Langerhans, during which leukocytes, lymphocytes in particular, surround and infiltrate the islets. That way Mechoulam's group investigated CBD action on non-obese diabetic (NOD) mice. They found that CBD treatment of NOD mice before the development of the disease reduced its incidence from 86% in the non-treated control mice to 30% in CBD-treated mice. CBD treatment also resulted in significant reduction of plasma levels of the pro-inflammatory cytokines, IFN- $\gamma$  and TNF- $\alpha$ . Histological examination of the pancreatic islets of CBD-treated mice revealed significant reduction of the inflammation.<sup>97</sup> It was also observed that administration of CBD to 11-14 week old female NOD mice, which were either in a latent diabetes stage or had initial symptoms of diabetes, ameliorated the manifestations of the disease. In addition, the level of the pro-inflammatory cytokine IL-12 produced by splenocytes was significantly reduced, whereas the level of the anti-inflammatory IL-10 was significantly elevated after CBD treatment.<sup>98</sup> This data have suggested that CBD can possibly be used as a therapeutic agent for the treatment of type 1 diabetes.



CBD has also been proven useful for possible complications of diabetes. The majority of diabetic complications are associated with pathophysiological alterations in the vasculature. Microvascular complications involve retinopathy and nephropathy while the atherosclerosis is the most common macrovascular complication of diabetes. The protective effects of CBD were studied in experimental diabetes induced by streptozotocin in rats. CBD treatment prevented retinal cell death and vascular hyperpermeability in the diabetic retina. In addition, it significantly reduced oxidative stress, decreased the levels of TNF- $\alpha$ , vascular endothelial growth factor, and intercellular adhesion-molecule.<sup>99</sup> It has also been suggested that CBD has significant therapeutic benefits against other diabetic complications and atherosclerosis, since it attenuated several effects of high glucose, including the disruption of the endothelial function.<sup>100</sup>

### 5. Antiemetic action

The treatment of nausea and vomiting associated with chemotherapy was one of the first therapeutic uses of cannabis and cannabinoids that has been evaluated with clinical trials. In the mid 1970's, a clinical trial indicated that delta9-THC was effective as an anti-nausea agent in patients receiving cancer chemotherapy.<sup>101</sup> In 1990, a survey of the members of the American Society of Clinical Oncology found that more than 44% of the respondents reported that they had already recommended the use of marijuana for the control of emesis to at least one cancer chemotherapy patient.<sup>102</sup>

Although the anti-emetic action has been associated to delta9-THC, many users claim that marijuana suppresses nausea more effectively than oral delta9-THC.<sup>103</sup> These observations led a Canadian group to investigate whether CBD can suppress nausea in the conditioned rejection model in rats. The association between a flavor and an emetic drug results in altered affective reactions, called conditioned rejection reactions, which reflect nausea.<sup>10</sup> In this model, rats were injected with a low dose (5 mg/kg i.p.) of CBD, a synthetic dimethylheptyl homolog of CBD, or vehicle 30 min prior to a pairing of saccharin solution and lithium chloride (20 ml/kg of 0.15 M LiCl) or saline. The rejection reactions (gapes, chin rubs and paw treads) that were elicited by lithium chloride and by a flavor paired with lithium chloride were suppressed by CBD and its synthetic dimethylheptyl homolog.<sup>104</sup> Since rats are incapable of vomiting, a better model for vomiting was found with a mouse species (*Suncus murinus*), which both vomits and expresses nausea.<sup>12</sup> These animals were injected with vehicle or one of two cannabinoids, THC (1-20 mg/kg) or CBD (2.5-40 mg/kg), 10 min prior to an injection of LiCl (390 mg/kg of 0.15 M) and were then observed for 45 min. delta9-THC produced a dose-dependent suppression of Li-induced vomiting while CBD produced a biphasic effect, having lower doses produced suppression and higher doses produced enhancement of Li-induced vomiting. The suppression of Li-induced vomiting by delta9-THC, but not by CBD, was reversed by SR-141716, a CB<sub>1</sub> antagonist, suggesting that both cannabinoids are effective treatments for Li-induced vomiting, however, only delta9-THC acts through the CB<sub>1</sub> receptor.<sup>105</sup> CBD was effective also in the conditioned retching reaction, which is a model of anticipatory nausea. Following three pairings of a novel distinctive contextual cue with the emetic effects of an injection of lithium chloride, the context acquired the potential to elicit conditioned retching in the absence of the toxin. The expression of this conditioned retching reaction was completely suppressed by CBD and delta9-THC, but not by ondansetron, a 5-HT<sub>3</sub> antagonist that interferes with acute vomiting in this species.<sup>106</sup> A similar effect

of CBD on anticipatory nausea was observed with a rat model of nausea (conditioned gaping).<sup>107</sup> These results support anecdotal claims that marijuana may suppress the expression of anticipatory nausea experienced by chemotherapy patients, resistant to current anti-nausea treatments.

### 6. Anticancer action

In the mid 1970's, several cannabinoids, including CBD, were studied in cancer cells and the results observed with CBD were not promising. However, these experiments were performed with extremely high doses (e.g., 200 mg/kg) and it is unlikely that these observations are relevant to the usual doses of CBD.<sup>12</sup>

In 2000, the interest in CBD as a potential anticancer drug was renewed with an investigation of its effect on glioma cells. In this study, CBD produced a modest reduction in the cell viability of C6 rat glioma cells, only evident after 6 days of incubation with the drug and only in a serum-free condition.<sup>108</sup> A further study has demonstrated that CBD, *in vitro*, caused a concentration-related inhibition of the human glioma cell viability that was already evident 24 h after the CBD exposure and significantly inhibited the growth of subcutaneously implanted human glioma cells in nude mice. The authors also showed for the first time that the antiproliferative effect of CBD was correlated to induction of apoptosis, as determined by cytofluorimetric analysis and single-strand DNA staining, which was not reverted by cannabinoid and vanilloid receptor antagonists.<sup>109</sup> CBD also caused apoptosis in human myeloblastic leukemia cells.<sup>110</sup> In addition, CBD inhibits the migration of U87 human glioma cells *in vitro* and this effect was also not antagonized by either selective CB<sub>1</sub> or CB<sub>2</sub> receptor antagonists.<sup>111</sup> A study of the effect of different cannabinoids on eight tumor cell lines, *in vitro*, has clearly indicated that, of the five natural compounds tested, CBD was the most potent inhibitor of cancer cell growth. In this study, two different tumor cell lines transplanted to hairless mice were half as big as those of the untreated group, and both breast- and lung-cancer cells injected to paws showed approximately three times less metastatic invasion.<sup>112</sup> An inhibitor of basic helix-loop-helix transcription factors (Id1) has recently been shown to be a key regulator of the metastatic potential of breast and additional cancers. CBD could down-regulate the Id-1 expression in aggressive human breast cancer cells, and the concentrations effective at inhibiting Id-1 expression correlated with those used to inhibit the proliferative and invasive phenotype of breast cancer cells.<sup>113</sup>

The precise mechanisms underlying CBD effects on apoptosis and tumor growth are not clear, and have recently been discussed in a review by Mechoulam.<sup>12</sup>

#### CBD: a drug with multiple mechanisms of action

The plethora of CBD effects described above can be explained by its multiple mechanisms of action. The description and cloning of specific receptors for the cannabinoids in the nervous system have been a great contribution to the understanding of the mechanism of actions of cannabinoids. However, in contrast to delta9-THC, CBD has little affinity to CB<sub>1</sub> and CB<sub>2</sub> receptors.<sup>114</sup>

#### 1. Actions on the cannabinoid system

In spite of its low affinity for CB<sub>1</sub> and CB<sub>2</sub> receptors, experimental evidence has shown that CBD is capable of antagonizing CB<sub>1</sub>/CB<sub>2</sub> receptor agonists at reasonably low concentrations.<sup>115</sup> This unexpected effect of CBD raises the possibility that this antagonism is non-competitive in nature, a hypothesis that has been discussed



by Pertwee.<sup>116</sup> Recently, the cloning and protein sequence of the human, mouse and rat new cannabinoid receptor (GPR55) that can be activated by the established CB<sub>1</sub>/CB<sub>2</sub> receptor agonists, such as delta9-THC and endogenous cannabinoids, has been described. The activation of the GPR55 receptor is antagonized by CBD at a concentration that is below any concentration at which it displaces agonists from CB<sub>1</sub> or CB<sub>2</sub> receptors.<sup>117</sup> Other actions of CBD on the cannabinoid system are the blockade of anandamide uptake and the inhibition of its enzymatic hydrolysis.<sup>118</sup>

## 2. Action on the vanilloid receptor type 1

CBD stimulated vanilloid receptors (VR1) with EC<sub>50</sub> = 3.2 ± 3.5 mM and with a maximal effect similar in efficacy to that of capsaicin, the natural agonists of this receptor.<sup>118</sup> Although VR1 is involved in inflammatory hyperalgesia, the stimulation of this receptor by capsaicin and some of its analogues leads to rapid desensitization, with subsequent paradoxical analgesic and anti-inflammatory effects. CBD desensitized VR1 to the action of capsaicin, thus opening the possibility that this cannabinoid exerts an anti-inflammatory action in part by desensitization of sensory nociceptors.<sup>118</sup>

## 3. Action on the 5-HT<sub>1A</sub> receptor

CBD displaces the agonist [3H]8-OHDPAT from the cloned human 5-HT<sub>1A</sub> receptor in a concentration-dependent manner. In signal-transduction studies, CBD acts as an agonist at the human 5-HT<sub>1A</sub> receptor.<sup>119</sup> This CBD action is probably involved in the protective effect of CBD on ischemia<sup>93</sup> and in its anxiolytic-like effects.<sup>120</sup>

## 4. Action on adenosine signaling

CBD decreases the uptake of [3H] adenosine in both murine microglia and macrophages, and binding studies show that CBD binds to the equilibrative nucleoside transporter.<sup>121</sup> The enhancement of adenosine signaling through inhibition of its uptake can provide a non-cannabinoid receptor mechanism by which CBD can decrease inflammation.

## 5. Anti-oxidant action

As mentioned above, CBD prevents hydroperoxide (H<sub>2</sub>O<sub>2</sub>)-induced oxidative damage equally well, or better than ascorbate (vitamin C) or tocopherol (vitamin E).<sup>74</sup> This action may be related to the neuroprotective effect of CBD.

## 6. Immunosuppressive and anti-inflammatory actions

The effects of CBD on pro-inflammatory cytokines and related compounds as well as its immunosuppressive effect have been reviewed above.

## Conclusion

In the last 45 years it has been possible to demonstrate that CBD has a wide range of pharmacological effects, many of which being of great therapeutic interest, but still waiting to be confirmed by clinical trials. It is important to highlight that many effects of CBD draw a bell-shaped dose-response curve, suggesting that the dose is a pivotal factor in CBD research. The wide range of CBD effects can be explained by the multiple mechanisms through which CBD acts, although further research is needed to clarify the precise mechanisms that underlie some of the potentially beneficial effects of CBD.

## Disclosures

Writing group member	Employment	Research grant <sup>1</sup>	Other research grant or medical continuous education <sup>2</sup>	Spekcar's honoraria	Ownership interest	Consultant/ Advisory board	Other <sup>3</sup>
Antonio W. Zuardi	FMRP-USP	CNPq FAPESP	—	—	—	—	—

\* Modest

\*\* Significant

\*\*\* Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.

Note: FMRP-USP = Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; FAPESP = Fundação de Amparo à Pesquisa do Estado de São Paulo.

For more information, see Instructions for authors.

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