

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.
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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).

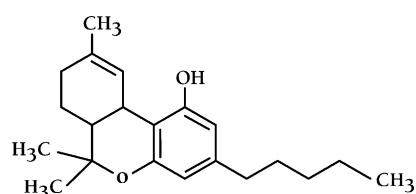
In 1854, cannabis is listed in the United States Dispensatory (Robson, 2001). It is sold freely in pharmacies of Western countries. It would be available in the British Pharmacopoeia in extract and tincture form for over 100 years (Iversen, 2000).

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).

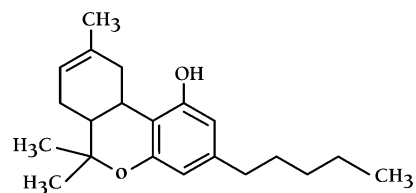
Great Britain and most European countries banned cannabis by adopting the 1971 Convention on Psychotropic Substances instituted by the United Nations.

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 (Δ^8 THC), cannabinal (CBN), cannabidiol (CBD), cannabicyclol (CBL), cannabichromene

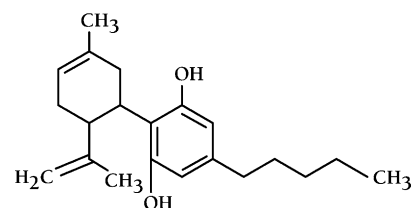
(CBC) and cannabigerol (CBG), but they are present in small quantities and have no significant psychotropic effects compared to THC (Smith, 1998; McKim, 2000). However, they may have an impact on the product's overall effect (Ashton, 2001). Cannabinoids exert their actions by binding to specific receptors: the CB₁ cannabinoid receptors, discovered by Devane et al. (1988), then cloned by Matsuda et al. (1990) and the CB₂ 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).



Δ^9 - tetrahydrocannabinol (THC)



Δ^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.

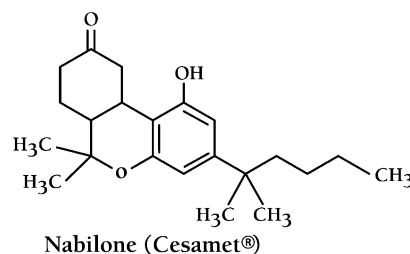
For each clinical study, the country where the project was held, the number of patients assessed, the type of study and comparisons made, the products and the dosages used, their efficacy and their adverse effects were identified.

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/m²/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 ² × 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 ² × 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 ² × 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 ² × 4 times; oral prochlorperazine: 7 mg/m ² × 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 ² × 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 ² × 3 times; oral thiethylperazine: 6.6 mg/m ² × 3 times; metoclopramide IV: 4.5 mg/m ² × 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 ² × 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 ² × 5 times: 15 patients; metoclopramide IV: 10 mg/m ² × 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 ² \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-HT₃ 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-HT₃ 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⁺ and CD8⁺ 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[®]) as an appetite stimulant for the treatment of anorexia and weight loss associated with AIDS. This synthetic THC or dronabinol (Marinol[®]) 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

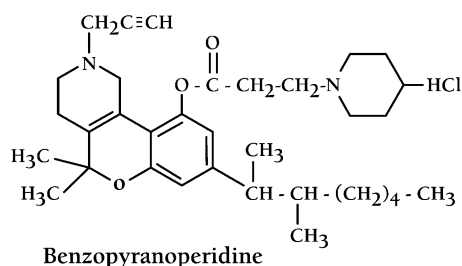
Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Regelson et al. (1976)	United States	54 adults with advanced cancer (ages: 21–73)	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 0.1 mg/kg t.i.d., i.e. 5–22.5 mg/day	THC stimulated appetite 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 ⁺ and CD8 ⁺ 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).

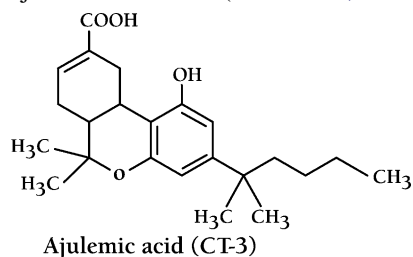
on postoperative pain in 40 women who had undergone elective abdominal hysterectomy (Buggy et al., 2003), nor did oral THC at a 20 mg dose manifest antinociceptive properties in 12 healthy subjects under experimental pain conditions (Naef et al., 2003).

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®) and the combination of THC and CBD (Cannador®). Indeed, subjectively, rating scales showed highly significant favourable effects on spasticity, spasms, pain, tiredness and sleep with both Marinol® and Cannador®. 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®) 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® 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 [®]); 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⁺ and CD8⁺ 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[®]) and oral THC or dronabinol (Marinol[®]). On April 19, 2005, Health Canada approved Sativex[®] 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[®]) and dronabinol (Marinol[®]) 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[®], 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[®], dronabinol (synthetic THC) or Marinol[®] and THC + CBD or Sativex[®], the three current pharmaceutical preparations approved for medicinal use, have different pharmaco-

kinetic profiles. Nabilone (Cesamet[®]) is administered orally and has a bioavailability of 60%. Dronabinol (Marinol[®]), also used orally, has a bioavailability of 10–20%. Sativex[®] 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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