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Review

Cannabinoids in medicine: A review of their therapeutic potential

Mohamed Ben Amar

Substance Abuse Program, Faculties of Continuing Education and Graduate Studies, University of Montreal, C.P. 6128, succursale Centre-ville, Montreal, Que. H3C 3J7, Canada

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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.

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

Contents

E-mail address: mohamed.ben.amar@umontreal.ca.

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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).

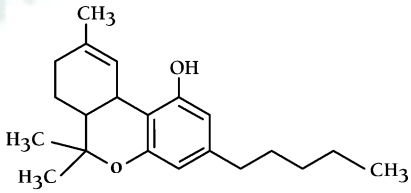
In 1839, William O'Shaughnessy, a British physician and surgeon working in India, discovered the analgesic, appetite stimulant, antiemetic, muscle relaxant and anticonvulsant properties of cannabis. The publication of his observations quickly led to the expansion of the medical use of cannabis (O'Shaugnessy, 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).

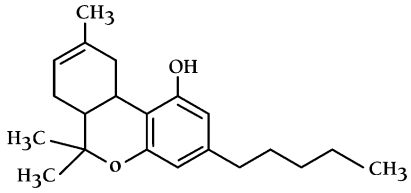
However, after prohibition of alcohol was lifted, the American authorities condemned the use of cannabis, making it responsible for insanity, moral and intellectual deterioration, violence and various crimes. Thus, in 1937, under pressure from the Federal Bureau of Narcotics and against the advice of 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.

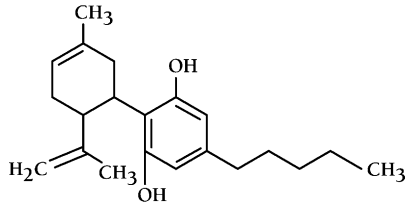
Cannabis contains more than 460 known chemicals, more than 60 of which are grouped under the name cannabinoids (Ben Amar, 2004). The major psychoactive ingredient of cannabis is delta-9-tetrahydrocannabinol, commonly known as THC. Other cannabinoids present in Indian hemp include delta-8-tetrahydrocannabinol (Δ^8THC), cannabinol (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_1 cannabinoid receptors, discovered by Devane et al. (1988), then cloned by Matsuda et al. (1990) and the CB_2 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 Marihuana 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.

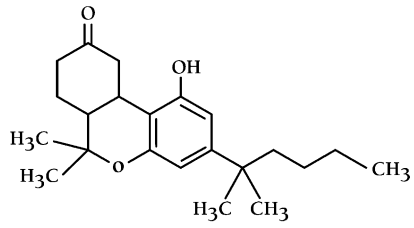
For each clinical study, the country where the project was held, the number of patients assessed, the type of study and comparisons made, the products and the dosages used, their efficacy and their adverse effects were identified.

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.



Nabilone (Cesamet®)

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^2/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 × 3 times: 19 patients; oral domperidone: 20 mg × 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 × 2 times; oral alizapride: 150 mg × 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 × 5 times; metoclopramide IV: 1 mg/kg × 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% prefered 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 × 7 times; oral prochlorperazine: 10 mg × 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 × 4 times: 17 patients; oral prochlorperazine: 10 mg × 4 times: 20 patients; oral THC (10 mg × 4 times) + oral prochlorperazine (10 mg × 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_3 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 antineoplasic 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_3 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 $n = 21$ patients; oral THC: 2.5 mg t.i.d. $n = 25$ patients; placebo: $n = 21$ 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).