

REVIEW ARTICLE

Recent Developments in the Therapeutic Potential of Cannabinoids

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Objective. To examine the recent evidence that marijuana and other cannabinoids have therapeutic potential.

Methods. Literature published since 1997 was searched using the following terms: cannabinoid, marijuana, THC, analgesia, cachexia, glaucoma, movement, multiple sclerosis, neurological, pain, Parkinson, trial, vomiting. Qualifying clinical studies were randomized, double-blind, and placebo-controlled. Selected open-label studies and surveys are also discussed.

Results. A total of 15 independent, qualifying clinical trials were identified, of which only three had more than 100 patients each. Two large trials found that cannabinoids were significantly better than placebo in managing spasticity in multiple sclerosis. Patients self-reported greater sense of motor improvement in multiple sclerosis than could be confirmed objectively. In smaller qualifying trials, cannabinoids produced significant objective improvement of tics in Tourette's disease, and neuropathic pain. A new, non-psychotropic

cannabinoid also has analgesic activity in neuropathic pain. No significant improvement was found in levodopa-induced dyskinesia in Parkinson's Disease or post-operative pain. No difference from active placebo was found for management of cachexia in a large trial. Some immune system parameters changed in HIV-1 and multiple sclerosis patients treated with cannabinoids, but the clinical significance is unknown. Quality of life assessments were made in only three of 15 qualifying clinical trials.

Conclusion. Cannabinoids may be useful for conditions that currently lack effective treatment, such as spasticity, tics and neuropathic pain. New delivery systems for cannabinoids and cannabis-based medicinal extracts, as well as new cannabinoid derivatives expand the options for cannabinoid therapy. More well-controlled, large clinical tests are needed, especially with active placebo.

Key words: Cannabinoids, Movement disorders, Spasticity, Pain.

Marijuana is a psychoactive drug that is widely used for its euphoric and hallucinogenic properties. Although marijuana is a Schedule I controlled drug, the 2003 National Survey on Drug Use and Health reported that over 40 percent of all US residents aged 12 years and older have used it at least once in their lifetime (1). Anecdotal evidence suggests that marijuana has medicinal properties, fueling the push for its re-legalization. Indeed, marijuana was listed in the US Pharmacopoeia until 1941. With the November elections of 2004, Montana became the eleventh state to approve a medical marijuana initiative, California being the first in 1996. The California Compassionate Use Act ensures that

seriously ill Californians have the right to obtain and use marijuana for medical purposes.

The therapeutic potential of marijuana was the topic of a scientific panel at the NIH in 1997 (2). At that time, the therapeutic potential was judged to lie in five areas: analgesia, neurological and movement disorders, nausea and vomiting associated with cancer chemotherapy, glaucoma, and appetite stimulation for anorexia associated with cancer. The present review examines clinical and experimental evidence of therapeutic efficacy of cannabinoids published from 1997 until December 2004. The literature search used the following terms: *cannabinoid, marijuana, THC, analgesia, appetite, glaucoma, movement, multiple sclerosis, nausea, neurological, pain, Parkinson,, vomiting*. Unless otherwise noted, clinical trials were randomized, double-blind, and placebo-controlled. Pertinent animal studies and surveys are also discussed,

Marijuana is a green, brown, or gray mixture of dried, shredded leaves, stems, seeds, and flowers of the hemp plant *Cannabis sativa*. More than 400 chemicals have been identified in marijuana preparations, of which more

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than 60 have been classified as cannabinoids. The principal psychoactive chemical, delta-9-tetrahydrocannabinol (THC), was identified in 1964 by Gaoni and Mesoulam (cited in 3). The concentration of THC in usual preparations of marijuana varies from 0.3 percent to 4 percent by weight, although specially-grown marijuana can contain 15 percent or more by weight. Thus a 1-g marijuana cigarette can contain as little as 3 mg or as much as 150 mg of THC. Other native cannabinoids include cannabidiol (CBD) and cannabinol (CBN). Some studies suggest that CBD can attenuate the psychological response to THC, and block the anxiety produced by high doses of THC (2).

Cannabinoid receptors. The actions of marijuana are produced by binding to and activating CB1 and CB2 cannabinoid receptors. CB1 receptors are present throughout the body, but are especially concentrated in the central nervous system. The highest levels of CB1 receptors are present on axons and nerve terminals in the extrapyramidal motor system, including the *globus pallidus*, and *pars reticulata* of the *substantia nigra*; high levels are also found in the hippocampus and cerebellum. Intermediate levels are present in the amygdala and hypothalamus, and low levels in the thalamus (3,4). The CB1 receptor is almost absent from areas related to respiration, consistent with marijuana's lack of respiratory toxicity. The CB2 receptor, only 48% homologous to CB1 (reviewed in 3, 4), is found on immune system cells. In humans, CB2 receptors are present on CD4⁺, CD8⁺, and B lymphocytes, macrophages, and natural killer cells in lymph nodes, spleen, tonsils and thymus.

Like opioid receptors, cannabinoid receptors are coupled through an inhibitory G-protein to intracellular effector pathways: adenylyl cyclase is inhibited, the G-protein dependent K-channel is activated, calcium conductances are closed and the calcium-and phospholipid-dependent protein kinase (PKC) is activated. Additional signaling pathways include activation of a focal adhesion-kinase, mitogen-activated protein kinase and phosphatidylinositol-3-kinase. Ceramide synthesis is increased and nitric oxide production is stimulated (3).

Endocannabinoids. Mechoulam and co-workers identified anandamide as the first of five endogenous ligands for the cannabinoid receptor (3). Anandamide is a lipid derived from arachidonic acid; the name is based on *ananda*, the Sanskrit word for "bliss". Anandamide is only a partial agonist for the CB1 receptor, and greater efficacy is produced by synthetic derivatives, such as CP55940, which led to the discovery of the CB1 receptor (4). Anandamide is released from presynaptic terminals. Like prostaglandins, anandamide is not stored, but synthesized on demand from arachidonic acid after its release from nerve terminal membranes (5). Anandamide is recycled

into the presynaptic terminal by a transporter protein, then rapidly hydrolyzed by a membrane-associated serine hydrolase enriched in brain and liver, fatty acid amide hydrolase (FAAH). FAAH is a potential therapeutic target; the activity of anandamide is strikingly increased in mice in which the enzyme has been genetically inactivated ("knockouts") (6).

Medicinal cannabinoid preparations. Marijuana is usually administered by smoking or by oral ingestion. By inhalation, marijuana produces detectable plasma levels within a few seconds and peak plasma levels within 3-10 minutes after the onset of smoking; pharmacological effectiveness parallels plasma levels. The bioavailability of smoked marijuana ranges from 10-35%. Absorption by the oral route is slow and erratic owing to the extremely hydrophobic nature of THC. Peak plasma levels are usually produced after 1-2 hours, but may lag as long as 6 hours. Oral bioavailability is also extremely low, ranging from 2-14% for commercial preparation of synthetic THC, with high inter-individual variation. Based on elimination half-lives for THC and its principal metabolites in the range of 20-30 hours (7), more than 99.9% should be eliminated in two weeks.

The first commercial preparation of synthetic THC in the United States, *dronabinol* (Marinol®), is marketed as round, soft gelatin capsules containing either 2.5 mg, 5 mg, or 10 mg dronabinol in sesame oil. Dronabinol is categorized as an antiemetic, and is indicated for nausea and vomiting produced by cancer chemotherapy; it is also approved as an appetite stimulant for patients with AIDS. Nabilone, chemically related to THC, is a synthetic cannabinoid with antiemetic properties approved for use during cancer chemotherapy. Absorption is nearly complete, and the plasma half-life is about two hours (7). Ajulemic acid (also known as CT-3) is a new cannabinoid derivative with analgesic activity, but little or no psychotropic activity (8).

GW Pharmaceuticals (United Kingdom) developed an oral spray containing extracts of marijuana plants with specific proportions of THC and CBD, termed cannabis-based medicinal extracts (CBME). The improved preparations provide rapid onset of activity without the risks of smoking; they also facilitate the use of double-blind tests, although frequent unmasking is still a problem owing to the psychotropic properties of THC (9). *Cannador* is a capsule containing an alcoholic extract of selected marijuana plants.

THERAPEUTIC POTENTIAL

Analgesia. THC has significant analgesic activity in many standard animal models of pain, including thermal

pain, inflammation-associated pain, and neuropathic pain (2). Campbell et al. (10) reviewed the literature through October 1999 and found nine randomized studies of cannabinoid analgesia compared to either a placebo or standard analgesic. Oral THC (5-10 mg) was about as effective as codeine 50-120 mg.

Neuropathic pain is relatively insensitive to opioids and is currently managed with anticonvulsants. Berman et al. (9) tested the effectiveness of cannabinoids in 48 patients with neuropathic pain due to brachial plexus root avulsion (Table 1). A three-period crossover design was used with 2-week treatment periods. The study medications were oral CBME sprays containing either THC, THC:CBD 1:1 or placebo. The daily dose was determined by self-titration. The greatest improvement was in sleep quality; pain was slightly reduced. Despite the small objective improvement, 45 patients elected to enter an open-label extension study using the THC:CBD preparation; no patients preferred THC alone.

quantitative sensory testing corresponding to at least one lesion in the central nervous system. The median spontaneous pain score was significantly lower at the end of dronabinol treatment compared to placebo, although the improvement was small.

Several small open-label studies have also reported limited success with cannabinoids for neuropathic pain. Notcutt et al. (12) tested oral sprays containing CBME THC, CBD, or a 1:1 mix of THC and CBD for efficacy in 34 chronic pain patients poorly responsive to other modalities of pain control, including 16 with multiple sclerosis. After an initial open-label period with THC:CBD, test drugs were used in a randomized, double-blind, placebo-controlled, crossover trial; each patient received each CBME and placebo for two separate 1-week periods. Extracts that contained THC proved most effective in symptom control; the most common side effects were dry mouth, drowsiness and dysphoria/euphoria. The THC:CBD combination was slightly preferred over THC

Table I. Qualifying Clinical Trials with Cannabinoids 2001-2004

Disease (symptom)	Cannabinoid ^a	Route ^b	n	Average age (range or SD ^c)	Dose	Reference #
Central neuropathic pain	CBME (THC:CBD 1:1)	M	48	39 (23-63)	22 mg THC (mean)	9
Multiple sclerosis (central pain)	CBME (High THC)					
Post-operative pain	Dronabinol	GI	24	50 (23-55)	2.5-10 mg/day (range)	11
Multiple sclerosis (spasticity)	THC	GI	40	46	5 mg (single dose)	15
Multiple sclerosis (tremor)	Dronabinol	GI	667	50	6-21 mg/day THC (range)	18
Multiple sclerosis (tremor)	Cannador (THC:CBD 2:1)					
Multiple sclerosis (tremor)	CBME (THC:CBD 1:1)	M	160	51 (27-74)	40 mg THC (mean)	20
Multiple sclerosis (tremor)	CBME (THC:CBD 2.8:1)	GI	57	55	7.5-27.5 mg THC (range)	21
Multiple sclerosis (spasticity)	Dronabinol	GI	16	46 (SD 7.9)	5-10 mg THC/day (range)	22
MS (tremor)	CBME (THC:CBD 2:1)					
Parkinson's disease	Cannador (High THC)	GI	14	45 (35-56)	2.5-10 mg THC bid (range)	23
Parkinson's disease (dyskinesia)	Nabilone	GI	9	59 (49-69)	0.03 mg/kg (two doses in 24 h)	26
Parkinson's disease (dyskinesia)	Cannador (THC:CBD 2:1)	GI	19	67 (51-78)	0.034-0.25 mg/kg/day (range)	27
Primary dystonia	Nabilone	GI	15	47 (28-63)	0.03 mg/kg (single dose)	29
Tourette's disease (tics)	THC	GI	24	33 (18-68)	2.5 - 10 mg THC (range)	32
Cancer (anorexia)	Dronabinol	GI	469	66	2.5 mg bid	37
AIDS (Immune function)	Marijuana	I	67	43 (26-80)	35 mg THC tid (as tolerated)	41
Multiple sclerosis (Immune function)	Dronabinol	GI			2.5 mg THC tid	
Multiple sclerosis (Immune function)	CBME (THC:CBD 2:1)	GI	16	46 (SD 7.9)	10 mg THC/day	42
Multiple sclerosis (Immune function)	Dronabinol					

a) CBME= cannabis-based medicinal extract; CBD = cannabidiol; THC = delta-9-tetrahydrocannabinol. b) GI = swallowed capsule; M = oromucosal spray; I = inhaled cigarette smoke. c) SD = standard deviation.

Svendsen et al. (11) tested the efficacy of oral THC (*dronabinol*) or vehicle in 24 multiple sclerosis patients with central pain, defined as pain in a body territory with abnormal sensation evaluated at the bedside or

alone; no patient preferred either CBD or placebo.

In contrast, Attal et al. (13) concluded that dronabinol provided no overall benefit in a 4-month trial in eight patients with long-term, refractory neuropathic pain. The

most common side effects were somnolence and fatigue. Only 2 patients could tolerate the maximal dose of 25 mg tid. Average Visual Analog Scale (VAS) scores for spontaneous ongoing pain, maximal spontaneous pain, and paresthesias trended down (n=5), but allodynia scores increased; there was no improvement in quality of life scores.

A long-standing goal has been the discovery of a potent cannabinoid with diminished psychotropic effects. *Ajulemic acid* (AJA), a derivative of the major THC metabolite, is free of psychotropic properties. In a placebo-controlled cross-over study of 21 patients with chronic neuropathic pain (14), ajulemic acid was significantly more effective than placebo in reducing VAS scores for pain. Tiredness and dry mouth were reported significantly more often when AJA was administered, but no major psychological or physical events were observed.

Buggy et al. (15) reported a single-dose, double-blind trial of oral THC or placebo in 40 women undergoing elective abdominal surgery (Table 1). Randomization took place on the second post-operative day after discontinuing standard patient-controlled analgesia with morphine. Women requesting additional analgesia were given a single oral capsule containing either THC or placebo. Pain was evaluated hourly for 6 h using a VAS. There were no significant difference in pain scores between groups. This study demonstrates no effect of THC at this relatively low dosage in postoperative pain.

Movement disorders. Very high levels of CB1 receptors are found in the basal ganglia, giving rise to the hypothesis that cannabinoids may be useful in a variety of movement disorders (3).

Multiple sclerosis. A relatively large subset of studies have been reported for treatment of multiple sclerosis symptoms. Spasticity, a motor disorder characterized by exaggerated tendon jerks that result from hyperexcitability of the stretch reflex, is a significant problem for many multiple sclerosis patients. Present medications such as baclofen, diazepam, dantrolene and tizanidine fail to adequately control spasticity, and have side effect profiles that limit their usefulness. Cannabinoids have been reported to improve motor function and reduce inflammation in the mouse model of multiple sclerosis, Theiler's murine encephalomyelitis virus-induced demyelinating disease (16, 17).

Zajicek et al. (18) reported a large (630 patients), multi-center randomized placebo-controlled trial of cannabinoids for treatment of spasticity and other problems of multiple sclerosis (Table 1). Active treatments were *cannador* (THC:CBD 1:1) and *dronabinol*; placebo capsules contained only the vegetable oil vehicle. Medications were taken twice daily with food for 15 weeks. Ten muscle groups

on each side of the body were assessed by a doctor or physiotherapist using the Ashworth scale of biological impairment. There was a small, but non-significant improvement in Ashworth scores with both active treatments. Nonetheless, patients self-reported significant improvement in several symptoms, i.e., pain, sleep quality, spasms and spasticity, with no improvement in irritability, depression, tiredness, tremor or energy. The principal adverse effects were located to the gastrointestinal tract, vision, and feeling dizzy or light-headed. Although there was a significant tendency for patients to correctly surmise that they were receiving active treatment (77% active treatment vs 50% placebo), the result suggests that performance parameters that are important to the patients were not evaluated objectively.

An additional unexpected result was a significant reduction in hospital admissions for relapses when compared to placebo (9). Since multiple sclerosis is an autoimmune disease and cannabinoid receptors are present on immune cells, the authors speculated that their result might be related to the immunosuppressive properties of *cannabinoids* (reviewed in 19).

Wade et al. (20) reported a randomized double-blind, placebo-controlled study of 160 MS patients using an oral CBME spray or placebo for a total of ten weeks (Table 1). Objective assessments were made by a research nurse. Each patient also filled a weekly record using a VAS for spasm frequency, feelings of intoxication, and severity of their primary symptom. Improvement of spasticity was highly significant on the VAS, but not on the objective Ashworth scale. Significant objective improvement was noted for the 10-M time and the Guy's Neurological Disability Scale. Primary symptoms with no improvement on the self-reported record were spasms and bladder dysfunction. The principal treatment-related adverse effects were dizziness and application site discomfort. Vaney et al. (21) reported a significant improvement in the frequency of muscle spasms, mobility and sleep in 57 multiple sclerosis patients given oral CBME capsules (THC:CBD) for 2 weeks in a single cross-over trial (Table 1).

Lack of effect has also been reported. Killestein et al. (22) administered dronabinol, CBME or placebo to 16 multiple sclerosis patients for 4 weeks, with a 4-week washout period between treatments (see Table 1). Muscle tone was not significantly altered, and objective worsening of brain stem function was noted. The quality of life assessment improved significantly, but was offset by a worsening in the self-rated global impression score. Fox et al. (23) also found no significant difference in tremor index in a 14-patient study placebo-controlled cross-over study with oral *cannador* (see Table 1).

Bladder dysfunction develops in 90% of multiple sclerosis patients after 10 years of disease. Brady et al. (24) reported the results of an open-label quantitative study to test the efficacy of oral CBME sprays (THC or THC:CBD) for alleviation of bladder spasticity. Urinary frequency, the number and volume of incontinence episodes, and nocturia all decreased significantly compared to baseline values. Patients' self-assessment of pain, spasticity and quality of sleep all improved significantly, with pain improvement continuing up to a median of 35 weeks.

Overall, these studies provide evidence of a therapeutic potential for cannabinoids in multiple sclerosis. Although neurological improvement has not been large, self-assessment scores suggest a significant improvement in well-being that is not being objectively assessed. Adverse effects were generally mild.

In *Parkinson's and Huntington's diseases*, high levels of CB1 receptors are normally found presynaptically on GABA terminals of the striatopallidal pathway. Expression of the CB1 receptor is markedly reduced in globus pallidus and putamen of patients dying from Parkinson's disease compared to controls dying from cardiovascular diseases (25). A small, randomized, placebo-controlled cross-over pilot study (26) reported that oral *nabilone* reduced dyskinesia induced by a single dose of levodopa in Parkinsonian patients without altering the antiparkinsonian action of levodopa; the best-on scores were not significantly different, nor was the latency of switching on (Table 1).

Subsequently, Carroll et al. (27) reported a longer-term study of the effect of *cannador* on levodopa-induced dyskinesia; treatment periods were of 4-weeks duration separated with a 2-week washout period (Table 1). No evidence was found of significant reduction in the dyskinesia score (derived from the Unified Parkinson's Disease Rating scale (UPDRS)), pain, or quality of life, but patients reported significant subjective improvement in tremor and sleep.

The origin of levodopa-induced dyskinesias is controversial. Mesnage et al. (28) probed the contrary hypothesis that dyskinesias can be improved by cannabinoid antagonists. Investigators administered oral cannabinoid antagonists (4 patients) or placebo (16 patients) once daily at one hour before the first intake of levodopa for 16 days. At the dose tested, the cannabinoid antagonist did not improve motor disability,

All these studies have not provided evidence that cannabinoid drugs have therapeutic potential in Parkinson's disease.

Primary dystonias involve underactivity of the output regions of the basal ganglia, in particular the medial *globus pallidus*, and overactivity of motor cortical areas.

Cannabinoids might potentially reduce dystonia by enhancing GABAergic transmission in the lateral *globus pallidus* (GPI) and, as a consequence, reducing inhibition produced by overactivity of the GPI. In an acute neuropharmacological challenge of patients with primary dystonia (29), a single dose of oral nabilone capsules failed to reduce dystonia when observed up to three hours after drug administration (Table 1).

Huntington's disease is an inherited neurodegenerative disease caused by a CAG expansion in the Huntington gene. Early disease is characterized by a major loss of CB1 receptors in the basal ganglia, with almost complete loss in advanced disease; dopamine D2 and adenosine A2 receptors are also reduced in early disease (30). Aiken et al. (31) screened 1040 drugs for efficacy in reducing death of PC12 cells transfected with Huntington gene containing the expansion; only four cannabinoids and caspase inhibitors were effective. No clinical trials have been reported.

Other neurological disorders: Gilles de la Tourette syndrome is an inherited, neurological disorder characterized by repeated and involuntary body movements (tics) and uncontrollable vocal sounds. Muller-Vahl et al. (32) performed a 6-week, randomized double-blind placebo-controlled crossover trial with 24 patients to test the effectiveness of oral THC (Table 1). Significant improvement was found on three objective assessment scales, as well as the self-reported assessment.

Blepharospasm is a painful, involuntary convulsive contraction of the *orbicularis oculi* muscle that is thought to be caused by dysfunction of the basal ganglia dopamine system. Gauter et al. (33) reported a single case of severe blepharospasm probably of psychogenic origin that was resistant to standard injections of botulinum toxin (Botox®). After 5 weeks with *dronabinol* (30 mg/day in three divided doses), the self-rated pain score had declined to a tolerable level, providing evidence for the usefulness of cannabinoids in a psychogenous-derived movement disorder.

Amtmann et al. (34) reported an anonymous survey of alternative therapies used by persons with amyotrophic lateral sclerosis, a neurodegenerative disorder with few treatment options. Of 131 validated responses, 13 reported using marijuana. The symptoms that responded best were depression, appetite loss, pain, weakness, spasticity, and drooling. Marijuana was reported to be ineffective for speech, swallowing, and sexual dysfunction.

Nausea and Vomiting. *Dronabinol* was originally marketed as an anti-emetic, but has not been highly successful since its low bioavailability and slow absorption makes it difficult for patients to titrate the dose to their needs. Tramer et al. (35) reviewed the literature to 2000 on

the utility of cannabinoids for control of chemotherapy-induced nausea and vomiting. In thirty randomized studies, cannabinoids were found to be more effective than prochlorpromazine, thiethylperazine, metoclopramide, haloperidol, domperidone and alizapride, but not effective with very low or very highly emetogenic chemotherapy agents. More recently, serotonin antagonists such as ondansetron have been found to be highly effective in controlling chemotherapy-induced nausea and vomiting. No clinical studies have been found comparing dronabinol and ondansetron, but Kwiatkowska et al. (36) reported that both were effective in an animal model of cisplatin-induced vomiting. Moreover, a combination of both drugs at sub-effective dose levels was also effective, suggesting that dronabinol may potentiate the effectiveness of ondansetron.

Appetite stimulation / cachexia. The appetite-stimulating effect of marijuana is widely known. Both food intake and body weight are increased, but fat, not lean body mass, is the beneficiary (2). *Megestrol acetate*, a semi-synthetic progestational steroid with appetite-stimulating activity, has become an established treatment for malnutrition in patients with AIDS and non-hormone responsive cancers. Jatoi et al. (37) reported a large clinical trial comparing the activity of oral megestrol vs dronabinol or a combination of both agents in terms of weight gain and appetite improvement in 465 patients with advanced cancer (Table 1). A significantly greater percentage of megestrol-treated patients reported appetite improvement (79% vs 49%) and weight gain (11% vs 3%). The combination of *dronabinol* and *megestrol* was not significantly different from megestrol alone. The results do not support a therapeutic role for oral THC in ameliorating cachexia and anorexia, although the dose used was relatively low.

Glaucoma. Marijuana has been found to be effective in lowering intraocular pressures in patients with glaucoma who do not respond well to standard medications, but the degree of ocular hypotensive effect obtained is paralleled by the generation of euphoria (2). Flach et al. (38) reported an open-label test of *dronabinol* (2.5 mg qid to 17.5 mg qid) in uncontrolled intraocular pressure despite using maximally-tolerated medication. Intraocular pressure decreased significantly in all patients (n=9), although only four successfully met the therapeutic goal. Tolerance to both therapeutic and adverse effects developed during the study (range 3-36 weeks). All patients elected to discontinue treatment within one to nine months. The ocular hypotensive effect of marijuana is accompanied by significant postural syncope in a subpopulation of human volunteers (39).

Owing to the presence of ocular cannabinoid receptors,

topical application of cannabinoids is also effective and does not produce systemic hemodynamic effects. The CBI cannabinoid agonist WIN 55212-2 was found to be effective topically, producing a long-lasting reduction in intraocular pressure with twice-daily application to glaucomatous rhesus monkeys (40). The effect was mediated through a reduction in aqueous humor flow. No clinical trials are available.

Immune system. Cannabinoids have significant immune suppressive activity (19). Since many immune-suppressed HIV-patients in California use medical marijuana, Abrams et al. (41) tested the safety of marijuana cigarettes, oral THC, and placebo in 62 HIV-1 patients during a three-week controlled study (Table 1). No significant effects were found in HIV mRNA levels or CD4⁺ cell count, although the CD8⁺ cell count increased slightly. Killestein et al. (42) also examined immune system parameters in 16 multiple sclerosis patients treated with dronabinol, oral CBME-THC or placebo (Table 1). TNF- α increased significantly, but no changes in leukocyte subsets were noted. Nonetheless, the subgroup that experienced the greatest adverse effects (n=7) also had increased levels of IL-12p40, consistent with a possible proinflammatory effect in multiple sclerosis patients.

Adverse effects. The cannabinoids were generally well-tolerated, and most side-effects were minor, including dizziness, fatigue, drowsiness, dry mouth, hypotension, nausea, constipation and diarrhea. Of 1176 patients enrolled in the qualifying studies, only 22 withdrew because of intolerance of the medication; intolerance data were not reported for one large study (37). Three patients, one of whom was in the placebo phase, reported severe anxiety that required withdrawal from the study.

Conclusions

Cannabinoids may be useful in management of movement disorders that currently lack effective treatment, such as spasticity in multiple sclerosis and Tourette's disease, as well as neuropathic pain syndromes. Possible utility as a palliative in amyotrophic lateral sclerosis is suggested. Currently available cannabinoids are not more useful than standard medications in three of the five originally identified areas, e.g., nausea and vomiting in cancer chemotherapy, anorexia/cachexia (at least at low doses) and glaucoma. When available, the combination of THC:CBD was preferred over THC alone. A new cannabinoid derivative separates therapeutic from intoxicating and hypotensive effects. Continued development of new derivatives with reduced psychotropic properties is important. Few trials currently include quality of life assessment, an important issue for

patients with chronic, under-treated health problems. The possibility of immune system toxicity needs further study.

Resumen

Este artículo pretende examinar la evidencia reciente del potencial terapéutico de la marihuana.

Se buscó la literatura listada en *Medline* desde el 1997 usando los siguientes términos: *cannabinoid, marijuana, THC, analgesia, cachexia, glaucoma, movement, multiple sclerosis, neurological, pain, Parkinson, trial, vomiting*. Los estudios clínicos que cualificaban eran escogidos al azar, doble-ciego, y controlados con placebos. También se discuten algunos estudios de rotulo-abierto y encuestas.

Se identificaron un total de 15 estudios, de los cuales solo tres tenían mas de 100 pacientes. En dos estudios grandes se encontró que los cannabinoides eran significativamente mejores que el placebo en el manejo de ciertos aspectos de espasticidad en esclerosis múltiple, aunque un estudio mas pequeño no encontró mejoría. Los pacientes informaron un mayor sentido de mejoría que podía ser confirmado objetivamente. Los cannabinoides produjeron una mejoría significativa de *tics* in la enfermedad de Tourette y en dolor neuropático. Un nuevo derivado sin actividad sicotrópica el ácido ajulémico, tiene actividad en dolor neuropático. No se detectó mejoría significativo en las disquinesias inducidas por levodopa en la enfermedad de Parkinson, ó en dolor pos-operativo. No hubo diferencia entre canabinoide y placebo activo en el manejo de caquexia. Algunos de los parámetros inmunológicos cambiaron en pacientes de HIV-1 y esclerosis múltiple tratados con cannabinoides, pero no se sabe cual es su significado clínico. Solo tres estudios incluyeron un asesoramiento de calidad de vida. Se concluye que los cannabinoides pueden ser útiles para condiciones que actualmente carecen de tratamiento efectivo, tales como la espasticidad en esclerosis múltiple, *tics*, y el dolor neuropático. Tanto los nuevos sistemas de administración de cannabinoides y los extractos medicinales basados en cannabis así como los nuevos derivados pueden aumentar las opciones de terapia con cannabinoides. Es importante enfatizar que son necesarias mas pruebas clínicas controladas, especialmente con placebo activo.

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